UNIVERSITÀ DEGLI STUDI DI PADOVA

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Direttore: Chiar.mo prof. Umberto Cillo

TESI DI LAUREA

COLORECTAL LIVER METASTASES TREATMENT IN A HIGH VOLUME, EUROPEAN CENTRE

Relatore: Chiar.mo prof. Umberto Cillo
Correlatore: Prof. Francesco Enrico D'Amico

Laureanda: Francesca Fistarol

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ABSTRACT

This study was conducted to evaluate the impact of different neoadjuvant chemotherapy regimens on morbidity and mortality after resection or ablation for colorectal liver metastases (CRLM). Specifically, the aim was to determine if the use of the triplet FOLFOXIRI, because of its higher cytotoxicity compared to its doublet counterparts, could be associated with worse surgical outcomes.

Chemotherapy can have numerous side effects, some of which directly affect the liver, while others can indirectly impact it. This hepatotoxicity can complicate CRLM (colorectal liver metastasis) surgery by inducing liver parenchyma changes such as steatosis, hepatic vascular injuries, and nodular regenerative hyperplasia. These alterations can lead to an increased risk of bleeding, inflammation, cholestasis, and postoperative complications.

Doublet therapies, such as FOLFOX (5-FU and Oxaliplatin) and FOLFIRI (5-FU and Irinotecan), have long been utilized and studied as neoadjuvant treatments. It is well-established that the triplet therapy FOLFOXIRI (5-FU, Oxaliplatin, and Irinotecan) provides a more substantial oncological benefit due to the broader drug combination. However, this enhanced therapeutic effect comes with a higher risk of hepatotoxicity and, consequently, an increased likelihood of postoperative complications. The potential for severe hepatotoxicity may outweigh the benefits of an aggressive neoadjuvant regimen, particularly if the associated risks are high.

Patients and methods

A court of one hundred and ninety-two patients who, after a single line of chemotherapy, had been subjected to their first CRLM resection or ablation between 2015 and 2023 was analyzed.

Fifty-eight patients (30,2%) had been treated with FOLFOXIRI, while the remaining one hundred and thirty-four (69,8%) had taken a doublet therapy, which was represented by either FOLFOX (76%) or FOLFIRI (24%).

Subsequently, relevant data was collected from various hospitalization documents, including information on the patient's comorbidities, primary tumor excision, metastatic disease characteristics, chosen surgical procedure, in-hospital and early postoperative complications, and follow-up care.

Results

There was no significant difference between the two groups in terms of gender distribution, height, weight, BMI, or smoking status, which helps confirm the comparability of the two populations. However, the median ages of the two groups and their comorbidity scores were significantly different, with the FOLFOXIRI cohort including younger and fitter patients to compensate for the added toxicity of the drug.

The analysis revealed no statistically significant increase in complications for patients treated with the more aggressive triplet regimen compared to doublet therapies. Specific postoperative events like ascites, reintervention rates, percutaneous drainage, and blood transfusion needs were similarly distributed across the two groups.

Median overall survival (OS) was longer in the triplet group (19.1 months vs. 14.1 months), though this difference did not reach statistical significance (p=0.15).

While certain complications, such as hypertensive peaks, showed borderline significance (p=0.077) and were more frequent in triplet-treated patients, overall complication rates between the two groups were similar. Concerns about the higher hepatotoxicity of the triplet regimen did not translate into worsened surgical outcomes.

Conclusion

The analysis showed no statistically significant impact of the therapy regimen on postoperative complications. The findings suggest that FOLFOXIRI is safe for use in appropriate candidates, as it does not significantly increase the risk of postoperative complications. However, patient selection remains crucial, and doublet therapy remains a safer option for patients with comorbidities.

As for the impact on survival, despite a slight advantage in median survival in the triplet cohort, the statistical significance was not sufficient to affirm a clear superiority of this treatment over the other.

INTRODUCTION

COLORECTAL CANCER

EPIDEMIOLOGY

Distribution

Colorectal cancer (CRC) is one of the most widespread and dangerous types of malignant neoplasms. According to the World Health Organization GLOBOCAN database, it reaches as high as third place in the global ranking of most commonly diagnosed cancers in males, and second place in its female counterpart.

Although this is true as a worldwide outlook, in Italy specifically its incidence rate is slightly different from the global average, placing this type of cancer as the second most frequent even in males. (1)

Worldwide, age-standardized incidence and mortality rates are both noticeably different between sexes, with the male population being almost 50% more at risk in both aspects, although the disparity in incidence is slightly less than the one in mortality. (2)

Incidence rates can also vary substantially depending on the observed location, with Europe, Australia and North America representing the most affected areas, and Africa and South Asia as those least touched by the disease. This phenomenon can be attributed to the stark differences between each continent regarding environmental pollution, lifestyle and dietary traditions, average socioeconomic status and access to screening programs, on top of a diverse background of genetic susceptibility. (3) (4) This was corroborated by a recent epidemiologic study regarding the USA population, which has also found some grade of correlation between ethnicity and the probability of developing this disease, revealing that black Americans are more exposed to this risk than white people of the same sex and age. (5)

While the global incidence has seen a slight increase of diagnosed cases, the situation is very different from country to country. While the US has been seeing a slow decline of the trend in recent years, with an initial 2% decrease that has slowed to 1,2% between 2014 and 2018, most other western countries have not been as fortunate. Many have not registered any improvement in CRC's burden and some historically low risk countries have even reported an unexpected and sudden increase in cases, such as Spain and Eastern Europe states. (6)

Localization

While rectal and distal colic lesions were the most common diagnoses up until the last decades, in recent years the anatomic distribution of most CRCs has gradually shifted from the left side of the colic tract to the proximal end. This is most likely due to the greater efficacy of colonoscopies in the diagnosis and removal of distal-located polyps, but another theory is that it can also be linked to the higher prevalence in right-side lesions of the BRAF V600E mutation, which is correlated with the growth of serrated polyps, harder to spot especially in the often murkier setting of the proximal colon.

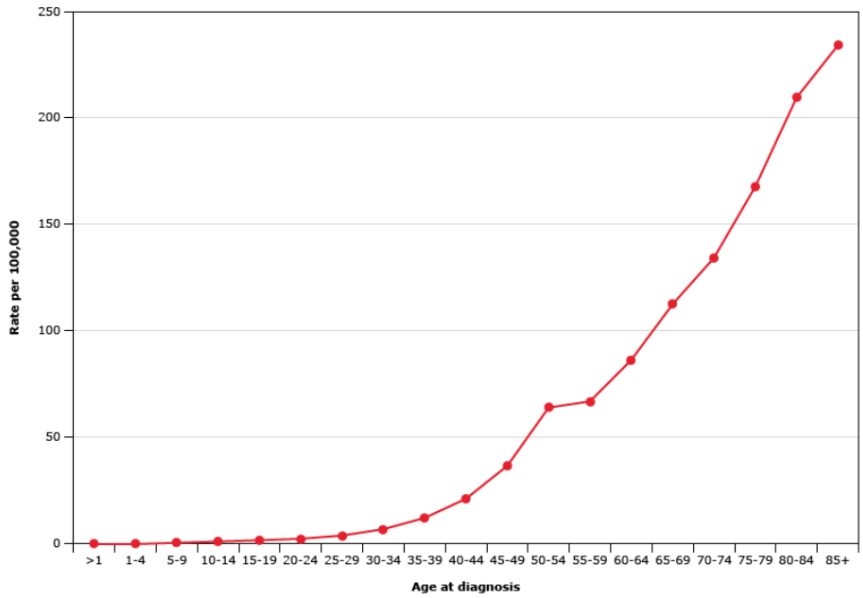
Early-Onset Colon Cancer

Although the most common types of colon cancer are sporadic, which means that they are not linked to any hereditary condition and as such their incidence is correlated with the increasing age of patients, a worrying trend is represented by the recent shift towards early onset colon cancer (EOCRC). This kind of tumor is defined by its insurgence in people under the age of 50, and it's predominantly represented by lesions that are located in the left colic tract, the sigma and rectum. Furthermore, these neoplasms appear to be more aggressive, with a greater prevalence of signet ring histology, poorer cell differentiation and a more advanced stage at the time of diagnosis. These patients are often symptomatic, which makes the theory that the receding diagnostic age may be linked to a more efficient screening system much less likely.

RISK FACTORS

Immutable risk factors

Age is a major risk factor in the development of sporadic CRC, as the somatic driving mutations are often the result of cell senescence, an imperfect DNA-repairing system and a weaker immune response. Therefore, it's very uncommon to diagnose this kind of cancer in patients under 40. Between 40 and 50 years of age, the incidence rate rises significantly, and every decade after is correlated to an increasing risk of cancer. (7) This age-specific distribution of the disease has been applied in practice to set the screening guidelines for the general population.



The age-specific incidence of colorectal cancer was measured between 2017 and 2021 in males and females of all races and ethnicities.

Sex and ethnicity, as touched upon earlier, are also key components. In the US, the highest rates of incidence of CRC and EO-CRC can be found in black and native Americans, while white Americans and other minorities generally experience a lower frequency and an older age of insurgence.

Hereditary CRC syndromes are another important risk factor, and they are mainly associated with EOCRC. Even then, only about 30% of all early onset colorectal cancers are caused by hereditary mutations, while another 20% are familial CRCs. The remaining 50% are sporadic cases, which remain to be further examined in order to find the underlying cause. (8)

These genetic predispositions can be categorized into two groups: Polyposic and Non-polyposic syndromes. The two most common ones, which make up approximately 5% of CRC cases if combined, are Familial Adenomatous Polyposis (FAP), associated with APC mutation, and Lynch Syndrome, which is caused by mutations in the mismatch repair genes. (5)

Even in the absence of determining genetic mutations, history of CRC in a first-degree relative is reason enough to keep a close eye on the patient even before the 50 years mark, as it doubles their chance of developing the disease.

Family history is not the only thing to consider: an even more important information to acquire is the presence of a personal history of colonic polyps or CRC. Large adenomatous polyps, especially if histologically dysplastic, raise the relative risk of cancer to 3,5-6,5. Furthermore, a diagnosis of CRC, even after resection, increases substantially the risk of developing another metachronous primary cancer. In the five years after the first disease, up to 3% of patients are diagnosed with a CRC relapse. (9)

Modifiable risk factors

Metabolic dysregulation is another strong component in the stratification of risk; this includes factors such as obesity, hypertension, NAFLD, insulin resistance and hypercholesterolemia. These aspects are not only correlated with a higher chance of CRC, but also with an earlier presentation of the disease since they were found to be statistically significant factors in EOCRC cases. (10) Furthermore, they also impacts prognosis, as obese and metabolic syndrome patients have a higher mortality rate than the average.

Because of this, lifestyle choices such as the excessive intake of red meat, sedentariness, alcohol abuse, smoking and general unhealthy eating patterns are something to be careful of even after diagnosis, as they greatly impact patients' life expectancy.

Inflammatory bowel diseases provide the optimal background for the development of dysplastic lesions, as inflammatory cytokines give damaged cells a prolonged proliferative boost, favoring the build-up of small DNA mutations that can eventually lead to neoplasia.

Ulcerative colitis in particular has been vastly studied in its association with colorectal cancer, finding that its extent, duration and activity of disease are primary determinants of risk. While pancolitis raises the likelihood of CRC by up to 15 times that of the average person, left-bound colitis is more moderate in its action but still causes a triplication of the risk. It's important to note that, if successfully treated, ulcerative colitis can be almost innocuous, so there can be a reduction in frequency of the surveillance. (11)

Crohn's Disease's more scattered distribution makes the association with CRC more variable and difficult to study, but most guidelines recommend higher surveillance if more than a third of colonic mucosa is compromised. Being less susceptible to pharmacological treatment, this condition is harder to control than Ulcerative Colitis. (11)

Another crucial factor to consider is if the patient has ever been subjected to abdominopelvic radiation. This is often the case in childhood cancer survivors, a group that needs to be especially kept under surveillance because of the cytotoxic therapies administered: not just radiation, but procarbazine and platinum drugs all independently constitute a risk factor for gastrointestinal neoplasms, and particularly colorectal cancer. (12)

Finally, cystic fibrosis is a less known risk element for this disease, but the cost-benefit ratio of extra screening in these patients is still a topic of research and discussion.

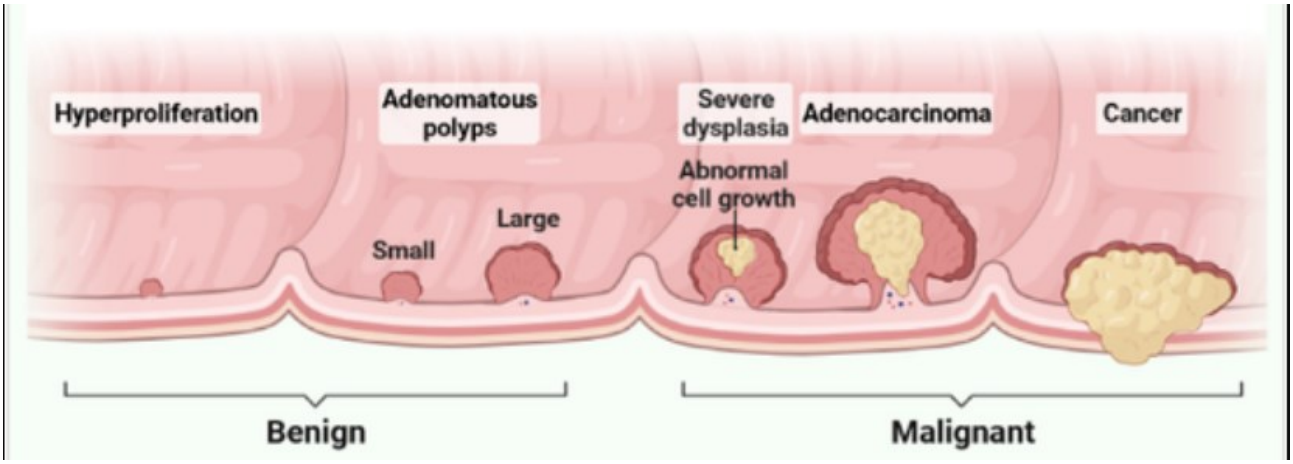
Other elements that indicate a higher risk and therefore have to be examined more closely with increased screening are acromegaly (13) and renal transplantation. (14)

On the other hand, many established risk factors don't require earlier or more frequent colonoscopies.

PATHOGENESIS

Most CRC develop from adenomatous polyps, which can grow from small lesions under 8 mm to large excrescences. Once identified, a polyp must be biopsied in order to differentiate between an adenomatous and a hyperplastic one. While the former is the first step in carcinogenesis, the second brings virtually no neoplastic risk.

On average, the progression from adenomatous polyp to colon cancer takes approximately 10 years, but every case is different, and histology and dimensions of the growth play a big part in determining the speed of the cancerization process. (15)



The transformation from normal colonic epithelium to invasive cancer takes many steps, and specific genetic changes that can be inherited or acquired with time. Germline mutations underlie the common

inherited syndromes such as FAP or Lynch syndrome, while sporadic cancers result from the gradual accumulation of multiple somatic mutations. Most cancers are sporadic, their mutations are somatic, and give the cell selective growth advantage, resulting in an uncontrolled proliferation of the original clone. The rapid duplication of cells, along with their damaged control systems, favour the accumulation of even more mutations which eventually give the cancer the ability to metastasize and invade other tissues.

This pathogenic pathway is common between different cancers, but CRC represents the ideal model for the observation of the various steps both because of its accessibility and slow growth, and also because its transformation stages are particularly sequential and neat: from healthy mucosa to adenomatous polyps, to dysplastic polyps, to cancer and metastasization.

Several molecular pathways to tumorigenesis have been described.

The CIN (Chromosomal Instability) Pathway is driven by APC mutation and gain of function mutations regarding oncogenes and antiapoptotic pathways. It's typified by FAP, in which the mutation is inherited, but it can be, and most often it is, sporadic. Cells are characterized by gross chromosomal abnormalities such as insertions, deletions, and loss of heterozygosity.

The MMR (Mismatch Repair) Pathway is correlated with serrated adenomas as well as adenomatous polyps, and it's implicated in Lynch syndrome tumors. This pathway is based on the loss of function of DNA mismatch repair proteins, codified by MLH1, MSH2, MSH6 and PMS2 genes. This allows several random mutations to pile up every time the cell duplicates or gets damaged, defects that are especially found in microsatellites, short sequences of nucleotide bases that are repeated hundreds of times which favour errors in polymerase activity.

High levels of this microsatellite instability are found in almost 15% of sporadic CRCs, and are often due to silencing by hypermetilation of MMR proteins' gene promoter. Affected cells are characterized by a heavy antigenic burden, therefore they are the most easily identified by the immune system once uninhibited.

The Hypermethylation (CIMP+) Pathway is characterized by a high frequency of methylation of CpG islands. This phenomenon can silence the expression of certain genes, specifically oncosuppressor genes. This last group is partially intersecting with those CRC with microsatellite instability caused by hypermetilation.

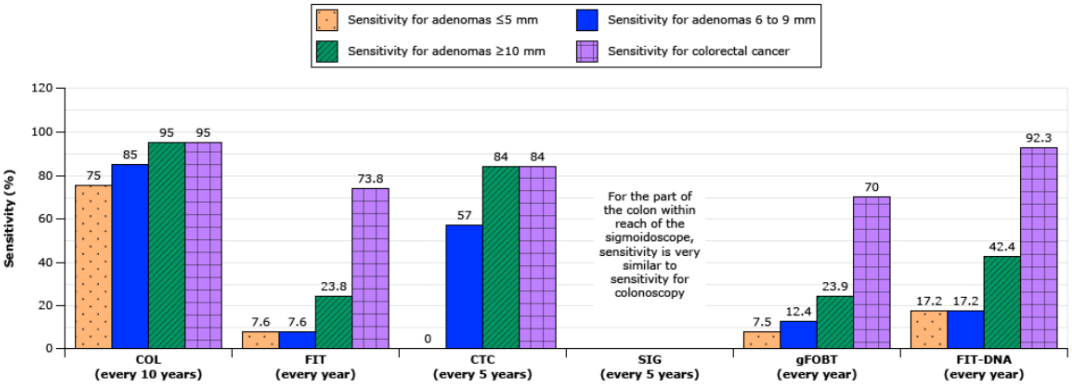
Specific mutated genes are correlated with each of these pathways.

Activating mutations in the BRAF gene are almost exclusive to somatic microsatellite instability and are never present in Lynch-related CRCs. These, on the contrary, are especially affected by KRAS mutations. (16)

SCREENING

Colorectal cancer (CRC) screening is a crucial aspect of healthcare, as early detection significantly enhances patient prognosis and can even eliminate the risk entirely if pre-cancerous lesions are found.

There are various screening strategies available, and research indicates that while their overall efficacy is similar, they differ in terms of sensitivity and specificity in the detection of polyps.



	COL (every 10 years)	FIT (every year)	CTC (every 5 years)	SIG (every 5 years)	gFOBT (every year)	FIT-DNA (every year)
Test specificity	86	96.4	88	87	92.5	89.8
Colorectal cancer deaths averted per 1000 40-year-olds (n)*	22 to 24	20 to 23	16 to 24	16 to 21	20 to 23	21 to 24

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

Recommendations

The cost of the various screening methods ranges from a few US dollars to over a thousand. Given the need to apply this procedure to a large population, it's essential to plan the screening appropriately to minimize costs while maintaining effectiveness.

The U.S. Preventive Services Task Force (USPSTF), the American College of Gastroenterology, the European Council and the American Cancer Society recommend starting screening at age 45. However, their recommendation to begin at age 50 is much stronger, as it has a more evident positive impact on the population.

In Europe, including Italy, the screening typically starts at age 50 for those at average risk. People between 50 and 69 years of age (or up to 74, depending on the region) are invited to undergo a fecal occult blood test (FOBT) every two years in order to identify those who may need further examination by colonoscopy. (17)

Stool tests

To test the presence of blood in the stool there are several methods. The fecal immunochemical test (FIT) is convenient and requires only one sample of fecal matter, but it can give false positives in case of upper GI bleeding. The guaiac-based occult blood test (gFOBT) requires three different samples, and it’s also susceptible to false positives, but it’s cheaper than the former. Finally, the multitarget DNA test is easy and can be done less frequently, but it’s quite costly. (18)

Since stool tests are generally cheap and have a good sensitivity, the standard practice for screening is to begin by submitting the whole age-appropriate population to those tests, and to then examine those who tested positive with a colonoscopy, which is characterized by high sensitivity and specificity but is severely more invasive and expensive.

Colonoscopy

As all medical procedures, screening and diagnostic strategies need to be cost effective and the benefits need to outweigh the risks, and while that is certainly true for CRC screening, it's important to remember that colonoscopy can, although rarely, bring harm to the patient since it's an invasive procedure.

Adverse events during colonoscopy can be due to different reasons. Sedation can bring cardiopulmonary complications, bowel preparations can cause electrolyte disturbances, nausea, vomiting, and abdominal pain. The risk of bleeding is usually associated with polypectomy, with rates varying from 1 to 2% depending on the site of removal and the lesion size, but also on personal characteristics such as thrombocytopenia or coagulopathies. During diagnostic colonoscopies bleeding is almost null, but the risk increases slightly if other therapeutic maneuvers such as stricture dilation are performed.

Perforation is usually the worst case scenario as a colonoscopy complication. It can occur by one of three mechanisms: excessive mechanical pressure exerted by the colonoscope on the colic wall, barotrauma or an overly large resection during polypectomy. As with bleeding, perforation rates vary with the performed procedure: while a strictly diagnostic colonoscopy has a maximum risk of 0,1%, a mucosal resection goes up to 5%, and an anastomotic stricture dilation arrives at 6%. Overall, the mortality rate from iatrogenic perforation ranges from 0 to 0,65%. (19)

Despite this, it's considered the gold standard for early CRC or polyps' detection, with its high sensitivity and specificity.

In the general population, it's recommended every 10 years if the initial stool results are negative, while in patients with a family history of colorectal cancer it should be performed every 5 years; in patients with Lynch syndrome or FAP, annual colonoscopy if there hasn't been a prophylactic colectomy is often recommended.

Other procedures

Although colonoscopy is the gold standard, some cases can require a different approach, either because of an obstruction, or because of an elevated risk of complications.

These alternative options include a wireless video endoscopy capsule called Pill Cam Colon 2, flexible sigmoidoscopy, and CT Colonography, which is very useful as it has nearly the same sensitivity as colonoscopy but does not give the option to remove any of the visualized lesions. Therefore, a positive CT Colonography still must be followed by a colonoscopy.

Other methods of screening have been studied, but none is sufficiently sensitive or specific: anemia is hardly indicative of CRC, as it can stem from many different sources, while CEA, along with other serum markers like carbohydrate antigen 19-9 (CA 19-9), has limited diagnostic ability for detecting primary CRC due to low sensitivity and overlap with benign conditions. A meta-analysis found that CEA's sensitivity for CRC is only 46%, with a specificity of 89%. Elevated CEA levels can result from non-cancerous conditions such as gastritis, liver disease, and smoking. Therefore, CEA and similar markers should not be used for CRC screening or diagnosis.

Starting age

While the general population can begin with stool testing between 45 and 50 years of age, people at higher risk are generally advised to start earlier or to get tested more frequently, depending on the risk factor involved.

Table 4. Risk Categories for Family History with CRC

Category	Description	Screening recommendation
Category 1 Average risk	No family history and age >50 years	• Perform IFOBT (refer to **Algorithm A**). • Stop screening at age 75.[9, level III]
Category 2 Moderate risk	Family history of CRC either: • >1 FDR • 1 FDR and >1 SDR • >3 and one of them must be FDR	• FDR with CRC diagnosed at age <60 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger). If normal, repeat every 3-5 years. • FDR with CRC diagnosed at ≥60 years, colonoscopy should be performed at age 40 years. If normal, repeat every 10 years. • Stop screening at age 75.[9, level III]
Category 3 High risk	Family history of: • CRC at age <50 years • FAP • HNPCC (Lynch Syndrome) • Peutz-Jegher Syndrome • Juvenile polyposis • MAP	• For family history of CRC diagnosed at age <50 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger). If normal, repeat every 3-5 years. Stop screening at age 75. • For hereditary colorectal cancer syndromes, refer to **Table 5**.

For people with one or more first-degree relatives affected by CRC, for example, colonoscopy-based screening should be performed since 40 years of age, or alternatively 10 years before the earliest age of diagnosis in the family, and repeated every five years independently of the earlier results, although if patients are unwilling to participate in the colonoscopy, a more frequent FIT or gFOBT exam is also acceptable.

Lynch syndrome-related cancers generally occur much earlier than average, with patients as young as 30-40 years old, and FAP-related neoplasms can begin even earlier, in their mid-20s, with a 100% chance of developing a CRC before 50 years of age. (20)

For these two conditions, even early screening isn't very efficient, and besides the heavy burden on the patient's life, it can only push back the age of insurgence of the disease. Therefore, people affected by these syndromes are often good candidates for prophylactic colectomy. (21)

DIAGNOSIS AND STAGING

Patients affected by colorectal cancer (CRC) may present in three ways: through suspicious symptoms, as asymptomatic individuals discovered via routine screening, or as emergency cases with severe complications like intestinal obstruction or perforation. In most cases, early-stage CRC patients show no symptoms and are diagnosed through routine screening, while the majority that sees symptoms appear, is already affected by an advanced disease (70-90%).

Symptoms

Typical symptoms include changes in bowel habits, rectal bleeding, abdominal pain, and iron deficiency anemia due to a slow but steady blood loss. Less common ones can be nausea or vomiting. The clinical presentation can change depending on tumor location, with left-sided CRC more likely to cause changes in bowel habits, and right-sided CRC often associated with iron deficiency anemia.

The presence of symptoms typically indicates more advanced disease and a poorer prognosis. Obstruction or perforation in particular are generally linked to worse outcomes, while tumors presenting with rectal bleeding, which is often detected at an earlier stage, have a relatively better prognosis. Advanced CRC can also metastasize to organs like the liver and lungs, causing local complications and affecting the patient's outcome.

While some abdominal symptoms are strongly associated with CRC, they are not highly sensitive or specific. Positive fecal occult blood tests are more predictive of CRC than any single symptom, and therefore screening cannot be replaced by a "watchful waiting" approach.

Differential diagnosis

Since the signs and symptoms of colorectal cancer (CRC) are nonspecific, it's important to make an accurate differential diagnosis, especially in patients with abdominal pain and rectal bleeding. Many conditions, both malignant and benign, can present similar symptoms to CRC. These include hemorrhoids, diverticulitis, infections, and inflammatory bowel disease.

Even a colonic mass seen in radiographic or endoscopic studies can be misleading, as it might be caused by various benign and malignant conditions. Some rare malignancies that may affect the large bowel include: Kaposi Sarcoma, often associated with AIDS, non-Hodgkin lymphomas, colonic carcinoid tumors, GISTs and metastases, often coming from ovarian cancers.

In summary, the differential diagnosis of CRC includes a variety of other conditions, necessitating careful evaluation to determine the correct one. Because of this, the official diagnosis of colorectal cancer can only be made through the histologic examination of a biopsy of the suspected lesion, typically obtained through a colonoscopy.

Staging system

Once diagnosed, the disease has to be accurately studied in order to properly plan the following therapeutic measures. The TNM staging system, which accounts for primary extension, affected lymph nodes and the presence of distant metastases, represents the fundamental basis for prognostic estimates.

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres¶ to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres¶ to adjacent organs or structures
* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina). ¶ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: ▪ Subserosa ▪ Mesentery ▪ Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

To detect metastases and evaluate the clinical stage, several diagnostic options can be implemented, such as imaging, physical examination and blood markers. Physical evaluation must take into account

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

the presence of ascites, hepatomegaly and lymphadenopathy; blood tests are often used to check for CEA levels and liver enzymes, which are not particularly sensitive to liver metastases but can help detect them especially through variations of serum alkaline phosphatase levels.

Standard practice in most institutions dictates that a CT scan be performed before resection, in order to have a baseline image of CRC extension, but other imaging methods such as MRI or PET-TC can also be associated.

CT is better at detecting distant metastases than lymph node involvement, and it isn't very reliable in the detection of peritoneal implants, pelvic MRI is the gold standard for rectal cancer staging, contrast-enhanced liver MRI can be used to visualize more clearly eventual hepatic metastases, and PET scans are mostly utilized to identify sites of disease recurrence in patients with rising CEA levels.

This system can be applied with different accuracy in various stages of the diagnosis. While the initial

Distant metastasis (M)			
M category	**M criteria**		
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)		
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified		
M1a	Metastasis to one site or organ is identified without peritoneal metastasis		
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

clinical assessment is based on radiographic and endoscopic findings, the more accurate pathologic stage (termed pT, pN and pM) requires colic resection and histologic examination. This type of staging requires the specification of the positive number of lymph nodes in relation to the total and is therefore much more sensitive than the clinical one in the determination of the N parameter.

Prognostic parameters

TNM staging is not the only determining factor for prognosis, though. Some very important characteristics to account for are: CEA levels, which are not diagnostic but can represent a good indicator of cancer regression or resurgence if elevated at diagnosis, lymphovascular and perineural invasion, tumor regression score after neoadjuvant therapy, and molecular characterization.

This last feature is not only prognostic, but it's predictive of the cancer's response to treatment, as some mutations can be targeted by specific drugs and some others render cancerous cells immune to the standard therapies.

The most important characteristics to look for are microsatellite instability, which indicates resistance to fluoropyrimidine therapy, and the mutation status of KRAS, NRAS and BRAF, which are associated with immunity to agents that target the epidermal growth factor receptor (EGFR), such as antibodies Cetuximab and Panitumumab. Microsatellite instability is caused by mutations in the mismatch repair enzymes, and despite the resistance to 5-FU it's a good sign of susceptibility to checkpoint inhibitor therapies because of its high antigenic burden.

Despite not being diagnostic, CEA has significant prognostic value. Elevated preoperative CEA levels (>5 ng/mL) are associated with a worse prognosis, and if CEA levels do not normalize after surgery, it may indicate persistent disease.

Monitoring CEA levels post-surgery is recommended for up to five years in patients with stage II and III CRC, as increasing levels may suggest recurrence and warrant further investigation. (22)

LIVER METASTASES

The liver is the main metastatic site for patients with colorectal cancer, as almost all of the colorectal veins drain in the vena porta, which directly leads to the liver and therefore favors the seeding of metastatic cells in this site. Because of this, approximately 25% of all patients suffering from CRC present with colorectal liver metastases at diagnosis, and another 25-30% develop metachronous CRLM later on.

Although two-thirds of metastatic patients also present with extrahepatic metastases, some have disease confined solely to the liver. For these patients, regional treatment approaches can be considered as an alternative or in combination with systemic chemotherapy. Most patients with isolated liver metastases are not eligible for surgical resection and are referred for palliative chemotherapy. However, for some individuals with a limited number of small lesions who are unsuitable for resection due to tumor location, impaired health status, or an insufficient future liver remnant, nonsurgical locoregional liver-directed treatments are an appropriate alternative to initial systemic chemotherapy.

In patients with potentially resectable metastases, resection is the preferred treatment when possible. Among those with four or fewer isolated liver lesions, five-year survival rates range from 24 to 58%, with an average of 40%, and many of these patients may be cured through the surgical intervention.

Systemic chemotherapy is an important component of treatment for patients with resectable liver metastases and is often given either pre or post-operatively.

Some patients who are candidates for surgery may receive initial systemic chemotherapy with delayed resection. This approach is beneficial in synchronous metastatic disease as it helps understand the disease's natural progression before potentially non-curative surgery. Additionally, initial chemotherapy may be considered for patients with isolated, initially unresectable liver metastases,

making them possible candidates for surgery if their metastases shrink. In that case, a re-evaluation after sufficient chemotherapy cycles is necessary to determine the following procedure.

CHEMOTHERAPY

MOLECULAR ANALYSIS

Most patients with metastatic colon cancer are treated with systemic chemotherapy. Many different agents can be used, both in monotherapy and combined, ranging from immunotherapy to cytotoxic drugs, to anti angiogenic factors.

Many patients with mCRC are treated with first line combination systemic therapy, particularly those whose metastases might be potentially resectable after an initial response to chemotherapy. This approach must take into account the potential toxicities of combination therapy, which can in some cases even determine an interruption of treatment.

Since the toxicity of these drugs is very impactful, it's in the patient's best interests to verify potential resistances, immunities or susceptibilities by analyzing the cancer's molecular characteristics. These predictive biomarkers are therefore often used to guide first line therapy for metastatic CRC. Gene profiling through next-generation sequencing should always be done after an mCRC diagnosis to identify these alterations, which influence treatment decisions.

RAS/BRAF Mutations

RAS testing is essential for patients eligible for EGFR inhibitors, with tumor tissue tested for KRAS and NRAS mutations. Depending on RAS status, which can be classified as wild-type or mutated, the tumor can be vulnerable to EGFR-targeting therapies or not.

Tumor tissue remains the gold standard for assessing RAS mutations, though circulating tumor DNA testing is emerging as an alternative, despite some discrepancies between ctDNA and tissue results. However, in some settings, rebiopsy of metastases for RAS mutation analysis may be warranted, since in patients with colorectal cancer that assessed RAS mutations in the primary tumor versus recurrent tumors, the rate of discordant results was estimated at 20%.

Another necessary test is whether BRAF V600E is wild-type or mutated, as gain of function alterations of this gene bypass the EGF receptor, making its inhibition useless.

EGFR inhibitors such as Cetuximab and Panitumumab are therefore only applied in RAS wild-type and BRAF V600E wild-type tumors, as otherwise they would only be detrimental to the patient. The only exception to this rule is that in some BRAF V600E-mutated cases EGFR inhibitors can be used in combination with BRAF inhibitors, therefore blocking the whole pathway but inevitably causing the patients more side effects.

By contrast, EGFR amplification is thought to be linked to a greater response to these target therapies, but it's not yet a standard predictive biomarker due to insufficient data and technological limitations.

Microsatellite instability

Another important characteristic to check for is high microsatellite instability, as tumors with mismatch repair deficiency are very responsive to immune checkpoint inhibitors, such as Nivolumab, Avelumab and Atezolizumab. These drugs target PD1 and PDL-1, subsequently neutralizing the tumor's ability to sedate the natural immune response to its antigens.

HER2 and NTRK

HER2 testing is also useful, as a small percentage of CRC over expresses this molecule and is responsive to HER2-targeted therapies, such as Trastuzumab. This type of target therapy is usually saved for second-line treatment, but in the absence of more aggressive first-line alternatives it can also be suggested as an initial systemic approach. Despite making up only about 4% of cases, the benefits that this treatment brings make testing for this condition worthwhile. (23)

Finally, testing for NTRK gene fusions, although rare, gives the option to target cells with hyperactive TRK through inhibitors like Entrectinib and Larotrectinib, eliciting a good tumor response. (24)

REGIMEN STRATEGIES

Resectable vs unresectable disease

Accordingly to the clinical scenario, physicians must set reasonable and attainable goals and subsequently choose the most appropriate therapy. In most patients, the main purpose of treatment is to prolong overall survival and improve the quality of life for as long as possible, thus representing a palliative approach.

For patients with potentially resectable disease, on the contrary, it's possible to aim for complete recovery. This set of patients is usually selected between those with liver-limited metastases, provided that the remaining liver after resection is sufficient for survival. If that is not initially the case, patients can undergo chemotherapy and be re-evaluated for surgery after enough cycles.

Neoadjuvant therapy is the term used for preoperative chemotherapy in patients who present upfront with resectable disease, since the surgery is guaranteed to happen; conversion therapy is instead used for initially unresectable patients, and the main parameter for regimen selection in this case is response rate, as the objective is to render the patient eligible for surgery. (25)

In unresectable patients, the choice of therapy is based on other criteria. Asymptomatic patients are generally treated to delay tumor progression as much as possible while maintaining the least number of side effects possible. These patients gain greater benefit from having access to all active agents rather than from the specific sequence in which these treatments are administered, with a significant improvement in median survival in the first scenario. (26) Because of this, there is not a universally preferred regimen and the singular agents' efficacy is harder to estimate.

Systemic fluorouracil based chemotherapy significantly improves median survival and progression-free survival (PFS), with the greatest benefits seen in regimens that include irinotecan or oxaliplatin.

Median survival with these chemotherapy combinations consistently exceeds two years, whereas median survival with best supportive care alone is around five to six months. Long-term survival has improved with the introduction of more effective anticancer agents. For example, in older trials using FU plus leucovorin, only 1.1% of patients survived five years. However, in the FIRE-3 trial, patients with RAS wild-type tumors treated with FOLFIRI plus cetuximab had a five-year survival rate of about 20%. (27)

Although initiating chemotherapy in asymptomatic unresectable patients can seem counterintuitive because of the high chance of side effects, seeing as improvement of the quality of life is one of the main goals, treatment deferral is not recommended.

Indeed, some studies show that an early start with 5-FU is associated not only with prolonged survival, but also a longer symptom-free period, with an overall improvement in quality of life despite eventual adverse events, but if this can be inferred to other chemotherapeutic treatments is still unclear. (28)

As for doses, although there is not specific proof, many centers tend to adopt a policy of routine dose reduction for obese patients, in order to avoid potential extra toxicity. The available data, though, does not support this method, as nothing has been proven regarding a superior susceptibility to chemotherapeutic side effects in overweight patients. Therefore, it is always preferable to administer full weight-adjusted doses of cytotoxic chemotherapy. (29)

Additionally, duration of treatment is also to be carefully considered, as the optimal duration of initial chemotherapy for unresectable metastatic colorectal cancer is still debated. The decision to allow treatment breaks for patients responding to therapy should be personalized, considering factors such as the chemotherapy regimen, individual tolerance, disease characteristics, symptoms, and patient preference.

Intermittent therapy

For many patients with chemotherapy-responsive disease without bulky or severely symptomatic tumors, intermittent therapy might reduce treatment-related toxicity without negatively impacting overall survival. When fluorouracil (FU) was the only treatment option, patients could stay on therapy until disease progression or intolerable toxicity, typically receiving treatment for four to six months before moving to supportive care alone, with a median survival of about one year. Now, newer combination therapies have improved median survival to around two years but are more toxic, particularly oxaliplatin-containing regimens, which are associated with cumulative neurotoxicity.

Therefore, in patients treated with oxaliplatin, a full break from therapy may be a valid alternative to maintenance therapy with a fluoropyrimidine-based regimen, especially for those with a complete clinical response or minimal metastatic disease. Thus, intermittent therapy could potentially reduce toxicity, improve outcomes, and lower costs.

However, it may not be suitable for all patients: those that maintain stable disease for extended periods may tolerate chemotherapy-free intervals, potentially responding to treatment for many years; but patients with bulky tumors, poor performance, or those at risk of complications like bowel obstruction, might benefit more from continuous chemotherapy. Furthermore, irinotecan-based

therapies are not in need of chemotherapy-free breaks, as this drug is not associated with significant cumulative toxicities.

Often, some form of maintenance therapy is favored over a complete break in therapy in patients who are responding or have stable disease. However, while maintenance therapy prolongs PFS compared with no maintenance therapy, this approach is not associated with better overall survival compared with a complete break in therapy. (30)

Tumor response

Overall, many different factors have to be taken into consideration while deciding on a chemotherapy regimen, and even after its administration it's necessary to consistently monitor the patient in order to accurately adjust the treatment.

This is achieved through periodic measurement of serum carcinoembryonic antigen (CEA) levels if elevated at diagnosis, and regular radiographic evaluations, usually every 8 to 12 weeks. Persistently rising CEA levels often indicate disease progression, but confirmatory radiologic studies are recommended before changing treatment, except in cases of confirmed peritoneal carcinomatosis, which is not easily measured radiographically.

Radiographically, tumor response is usually assessed using RECIST (Response Evaluation Criteria in Solid Tumors). For patients with microsatellite instability, usually treated with immune checkpoint inhibitors, immune-modified RECIST (imRECIST) criteria are used due to the possibility of pseudo progression.

A significant decline of 50% or more in CEA levels after initial chemotherapy can predict non-progression and favorable outcomes, but caution is needed when interpreting rising CEA levels during the first 4-6 weeks of new therapy, as false elevations can occur, particularly with oxaliplatin. (31)

CYTOTOXIC DRUGS

5-FU

5-Fluorouracil is part of the fluoropyrimidine drug category. It works as an analog antimetabolite that interferes with DNA and RNA synthesis: after its activation, F-UMP is incorporated into RNA to replace uracil and inhibit cell growth by inhibiting thymidylate synthetase and depleting thymidine triphosphate, which is a necessary component of DNA synthesis.

Some of its adverse effects include: bone marrow suppression, cardio, GI, and neurotoxicity, hyperammonemic encephalopathy, and hand-foot syndrome. Another important element is its interaction with anticoagulant drugs such as warfarin, which has to be adequately adjusted in its doses.

It's usually administered in association with Leucovorin, a supplement of folinic acid, and chemotherapy regimens often see it used in combination with either oxaliplatin (FOLFOX), irinotecan (FOLFIRI), or both. (32)

Oxaliplatin

Oxaliplatin is an alkylating agent. The platinum compound binds to DNA following intracellular hydrolysis, forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Because of this mechanism, cytotoxicity is cell-cycle nonspecific.

Before its use, it's recommended to correct hypokalemia and hypomagnesemia. It's also necessary to check for congenital long QT syndrome, as it represents a contraindication for the usage of this drug, along with renal impairment, peripheral sensitive neuropathy and pregnancy. Additionally, this drug is associated with delayed nausea and vomiting; antiemetics are recommended to prevent those side effects.

Most importantly, oxaliplatin is associated with dose-dependent hepatic sinusoidal injury, a side effect which can be radiographically identified by the development of splenomegaly due to an increase in portal venous pressure. The potential clinical impact is mostly seen in patients undergoing hepatic metastasectomy for colorectal cancer liver metastases; patients who receive preoperative oxaliplatin have increased bleeding risk and postoperative morbidity. Allegedly, the association with Bevacizumab seems to lessen this collateral effect.

Because of its many and significant side effects, oxaliplatin administration has to be adjusted depending on the patient's reaction, either decreasing its dose, increasing the infusion time, delaying the injection or suspending the treatment entirely.

In colon cancer treatments, it's usually combined with fluoropyrimidines such as 5-FU (FOLFOX), or Capecitabine (CAPOX), but more recently the double combination with 5-FU and Irinotecan has been very successful. (33)

Irinotecan

Irinotecan and its active metabolite bind reversibly to the Topoisomerase I - DNA complex, preventing religation of the cleaved DNA strand. This results in the accumulation of cleavable complexes and double-strand DNA breaks. Since mammalian cells cannot efficiently repair these breaks, their death during the S-phase cell cycle leads to termination of cellular replication.

Its dosing can prove to be a challenge, as it's characterized by a marked interpatient variability in pharmacokinetics that correlates poorly with body surface area-based dosing, unlike oxaliplatin. Besides, irinotecan also has higher rates of metabolic effects in overweight patients, in which it has been associated with steatosis, steatohepatitis, and hepatic vascular damage.

The most frequent side effects include: alopecia, abdominal pain, anorexia and constipation, anemia, leukopenia and neutropenia, asthenia, cholinergic syndrome, fever and increased serum bilirubin. Since irinotecan is associated with a moderate emetic potential, premedication with dexamethasone and a 5-HT3 blocker is recommended 30 minutes prior to administration; additionally, patients should be advised to keep Loperamide on hand in order to manage the common side effect of late diarrhea. (34)

Capecitabine

The other commonly used cytotoxic agent is capecitabine, another fluoropyrimidine, usually combined with oxaliplatin. Its action is phase specific for the G1 and S phases of the cell cycle, and adverse effects are similar to those related to 5-FU, with a particular tendency to increase bilirubin serum levels.

It's not commonly used in neoadjuvant CRLM regimens, but it can frequently appear in CRC post-colectomy adjuvant therapies and as a maintenance drug.

DOUBLETS AND TRIPLETS

The advantages and disadvantages of combining three different drugs instead of two, thus creating a more impactful line of treatment, are a subject of great interest.

For patients in good health who can tolerate intensive therapy, especially those with a high tumor burden or needing conversion therapy for liver metastases, an initial 3-6 month course of FOLFOXIRI (a triplet therapy combining irinotecan, oxaliplatin, fluorouracil, and leucovorin) is recommended. This is favored over doublet therapy like FOLFOX, CAPOX, or FOLFIRI, because of its aggressiveness towards the tumor.

However, for less fit patients, the decision should be based on a discussion of the benefits and the additional toxicity of the triplet therapy, as the survival advantage is relatively small.

The choice between FOLFOX and FOLFIRI depends mainly on the patient's history: FOLFIRI may be preferred in patients with a precedent of oxaliplatin-related neuropathy, while FOLFOX is favored for those without significant antecedent contraindications. CAPOX is a reasonable alternative to the FOLFOX regimen, particularly when the continuous infusion of 5-FU is impractical.

The possible side effects also differ between FOLFIRI and FOLFOX and have to be evaluated in relation to the patient's pre-existing comorbidities. XELIRI is not routinely recommended as a substitute for FOLFIRI due to significant toxicity concerns, particularly higher rates of severe diarrhea. FOLFIRI is more likely than FOLFOX to cause diarrhea and fatigue, while FOLFOX is associated with neuropathy and liver toxicity. CAPOX may result in higher incidences of hand-foot syndrome, nausea, and neuropathy compared to FOLFOX, which is in turn more likely to cause neutropenia. Furthermore, the presence of specific genetic markers, like UGT1A1 polymorphisms, can also influence the side effects of irinotecan-based therapies, sometimes necessitating dose adjustments.

Many studies comparing the FOLFOXIRI regimen with others show mixed results. Some trials found that FOLFOXIRI provides better response rates and progression-free survival, but with higher toxicity, such as neuropathy and neutropenia. Another trial found that initial FOLFOXIRI associated with Bevacizumab led to longer overall survival and better disease control compared to sequential use of the same drugs. However, another trial found no significant survival benefit.

Other possible regimens, although rarely used, are: SOX, an alternative first-line option mainly for Asian patients, showing noninferiority to CAPOX with a distinct toxicity profile; UFT (Tegafur+Uracil) combined with oxaliplatin or irinotecan, and IROX, used primarily in patients who cannot tolerate fluoropyrimidines.

In conclusion, the choice of regimen should be tailored to the patient's overall health, treatment goals, and tolerance for side effects. (35)

TARGET THERAPIES

The addition of a biologic agent to the chemotherapy scheme is common practice. It can achieve additional efficacy in some patients, all the while reducing the needed dose of cytotoxic drugs and therefore its toxicities, but it’s important to remember that it can give important side effects of its own.

Therefore, as is true for all treatments, the potential benefits need to be weighed against the negative aspects.

The main options for biologic agents are VEGF-inhibitors, particularly Bevacizumab, and EGFR-inhibitors Cetuximab and Panitumumab. The selection is based on primary tumor site, patient preference, and most importantly predicted efficacy, as EGFR inhibitors are only effective in RAS/BRAF V600E wild type tumors.

VEGF Inhibitors

Bevacizumab is a humanized monoclonal antibody targeting the vascular endothelial growth factor A (VEGF-A), thus inhibiting the tumor’s ability to induce angiogenesis. Its efficacy has been confirmed through several studies, with improvements in both overall survival and progression free survival rates if added to a chemotherapy backbone.

These benefits come at the price of various, although not common, potential side effects, including hypertension, proteinuria, bowel perforation, thromboembolic events and bleeding. Despite their rarity, Bevacizumab-treated patients discontinue treatment more often because of toxicity than disease progression.

Overall, though, the addition of Bevacizumab to FOLFOX or FOLFIRI is a valid treatment option that can prolong the median survival of several months. While several studies were executed in order to compare FOLFOX or FOLFIRI alone versus that same doublet and Bevacizumab, with an overall benefit in the second category, the same cannot be said for FOLFOXIRI, for which there is virtually no data.

For patients with RAS and BRAF wild-type tumors, an important question is whether a bevacizumab-containing regimen provides superior outcomes as compared with an initial regimen that contains an EGFR inhibitor. Data suggest that first-line Bevacizumab containing regimens may provide superior outcomes for patients with RAS/BRAF wild-type with a primary tumor site in the right colon.

As for contraindications, they include recent hemoptysis of >2.5 mL and major surgery within 28 days of treatment, as it impairs wound healing. The use of Bevacizumab in patients with brain metastases is controversial, as it's been linked to a potential increase in the risk of intracerebral hemorrhage, and clinicians also tend to avoid it in older adult patients with a history of an arterial thromboembolic event within six months and consider the use of aspirin in other high-risk patients.

In case of any serious adverse event, Bevacizumab should be discontinued.

EGFR Inhibitors

Cetuximab and Panitumumab are respectively a chimeric and a humanized monoclonal antigen, and they target the epidermal growth factor receptor, thus inducing receptor dimerization and internalization. This blocks EGFR's effect in the cell.

Choosing to administer a therapy with an EGFR inhibitor, either alone or in conjunction with cytotoxic chemotherapy, is an appropriate option for individuals with RAS/BRAF wild-type tumors, especially with a left-sided primary. If an EGFR inhibitor is chosen, the choice between Cetuximab and Panitumumab is empiric. The available evidence suggests that antitumor efficacy of single agent Panitumumab is similar to that of Cetuximab, and that the two drugs might be interchangeable, with the only difference that Panitumumab has fewer infusion reactions since it's not a chimeric, but a human antibody.

If Cetuximab or Panitumumab are chosen, the chemotherapy backbone should contain infusional FU. Triplet combinations of an EGFR inhibitor plus FOLFOXIRI may also be appropriate in patients who can tolerate more intensive therapy, while the addition of EGFR antibodies to oxaliplatin-based regimens in which non infusional fluoropyrimidines are used, such as Capecitabine has not resulted in any benefit, and it's therefore not recommended.

Furthermore, it's contraindicated to simultaneously use Bevacizumab and an EGFR-inhibitor, as the results of two trials demonstrated that the combination was associated with a worse clinical outcome for the patient.

Various studies have been conducted to explore the benefit of adding EGFR inhibitors to FOLFIRI rather than FOLFOX, and results seem to show a substantial increase in progression free and overall survival by using irinotecan, contrarily to oxaliplatin, despite the higher risk of adverse effects diarrhea, skin toxicity, and infusion reactions.

In some studies, the addition of cetuximab to a FOLFOX treatment was even found to be irrelevant or damaging. In particular, the advisability of combining Cetuximab with an oxaliplatin-based regimen in patients with potentially resectable colorectal cancer liver metastases continues to have disparate results from published trials.

The most common adverse effects associated with EGFR inhibitors are weakness, malaise, an acneiform rash in up to two thirds of the cases, nausea, electrolyte disorders, and infusion reactions in up to 25% of patients treated with Cetuximab. Pruritus is an irritating side effect most associated with Panitumumab.

One particularity of these agents is that their efficacy depends on the primary tumor's location: left side cancers showed to be susceptible to these treatments, while right side ones showed no response despite being RAS/BRAF wt. Patients with a right-sided tumor who are ineligible for Bevacizumab may be offered chemotherapy alone, as the addition of EGFR inhibitors does not offer benefits.

Combining one of the aforementioned treatments with immunotherapy is still controversial. For most metastatic colorectal cancers, which are proficient in mismatch repair, the benefit of immunotherapy, specifically immune checkpoint inhibitors, is not yet established unless the tumors have a high tumor mutational burden or specific mutations like POL-E.

Ongoing trials are exploring whether combining checkpoint inhibitors with other agents can enhance the immune response in these cases. However, whether this combined approach will be beneficial remains uncertain and is still under investigation.

For patients without MMR deficiency who are not candidates for an intensive first-line standard-dose oxaliplatin- or irinotecan-based regimen because of age, poor performance status or associated comorbidity, but who are fit enough to tolerate some form of systemic therapy, options include dose-reduced FOLFOX, a fluoropyrimidine alone or, for patients with no contraindication, a fluoropyrimidine plus Bevacizumab. Additionally, non-chemotherapy options can also be considered for patients with RAS/BRAF wild-type cancers, and HER2-targeted therapy can be considered for the small proportion of susceptible patients.

PD-1/PDL-1 Inhibitors

Immune checkpoint inhibitors are another drug category that has shown great efficacy in CRC treatment. These therapies are effective against mismatch repair deficient tumors, which make up about 4-6% of the total.

Nivolumab plus ipilimumab is a recommended combination for first-line treatment, as it improves progression free survival with an acceptable toxicity profile, and it can be administered without any other cytotoxic drug. A valid alternative to this option is Pembrolizumab or Dostarlimab.

Individuals treated with immune checkpoint inhibitors for any cancer, including dMMR/MSI-H mCRC, can have pseudo progression within the first several months of treatment. Therefore, patients should be closely monitored for pseudo progression versus early disease progression.

In other cases, checkpoint inhibitors can be associated with chemotherapy to improve outcome: Avelumab, Atezolizumab and Nivolumab are some of the most frequently used. (35)

SURGICAL TREATMENT

Surgery provides a potentially curative option for selected patients with limited metastatic disease. Long-term survival can be achieved with metastasectomy in as many as 50% of cases, and an aggressive surgical approach to both the primary and the metastatic sites is warranted in conjunction with systemic chemotherapy.

PRIMARY TUMOR

Benefits

Management of the primary tumor in patients with metastatic colorectal cancer is very debated, with no clear guidance from prospective randomized studies. Treatment decisions generally depend on the presence of symptoms and the resectability of metastases:

For patients with synchronous metastatic disease and local symptoms like obstruction, bleeding, or perforation, surgery to remove the primary tumor is recommended. Even if the metastatic disease is incurable, surgical palliation can relieve symptoms and increase quality of life for the patient, which is the main objective in advanced stage patients. Even if surgery isn't an option due to patient condition or preference, other palliative measures, such as endoluminal stent placement or laser ablation, may be used.

In asymptomatic, but unresectable patients, surgery is unnecessary and thus not recommended.

For patients with symptomatic primary tumors, surgery is considered based on the specific symptoms and the extent of metastatic disease. Alternatives like self-expanding metal stents can be used for bowel obstruction. If the patient is not fit for surgery, nonsurgical options are considered.

In asymptomatic primary tumors with resectable metastases, surgery may be part of an aggressive strategy aimed at curing the disease.In this case, then a radical surgical approach is warranted for both the primary and metastatic sites with the aim of curing the patient. However, if there are five or more simultaneous, potentially resectable hepatic metastases, extensive bilobar involvement, or if disease is borderline resectable due to location, initial chemotherapy followed by reassessment and delayed resection is probably a better strategy than upfront surgery.

Additionally, if there is widespread disease progression during chemotherapy, resection will likely provide no specific benefit. If, on the other hand, the disease has responded or is stable, resection of both the primary tumor and the metastatic disease could be attempted in either a single or separate operation.

Timing

Another debated subject is whether the surgery should be carried out simultaneously or colorectal resection first, then followed by hepatectomy, or a first hepatectomy followed by resection of the primary tumor. For most patients, simultaneous resection is clearly preferable as it takes away the additional stress of a second operation, and several surgical case series and meta-analyses have failed to confirm inferior survival or greater morbidity for patients who undergo a one-stage procedure compared with delayed hepatic stage, except in case of a major hepatic resection.

Factors that influence a decision on single operation versus a staged approach include the prospected complexity of the colectomy or proctectomy, the size of the future liver remnant, the likelihood of major blood loss or prolonged hepatic ischemic times, and patient comorbidities. For patients with metastatic CRC who are subjected to primary tumor resection, the risk of postoperative morbidity is between 20 to 30%, and the risk of perioperative mortality can be up to 6%. (36)

LIVER ABLATION

Techniques

Imaging-guided thermal ablation is currently widely offered as part of the modern armamentarium for treating patients with primary and secondary malignancies of the liver.

Cryoablation is a treatment for destroying tissue by the application of freezing temperatures around -160 C, alternated with thawing or slight heating, using cryoprobes.

Microwave (MW) ablation is a type of tumor destruction from electromagnetic energy sources. Currently available microwave ablation devices function at frequencies of 915 MHz or 2.45 GHz. MW applicators are called antennas.

Radiofrequency (RF) Ablation is a type of coagulation induction from electromagnetic energy sources with frequencies under 30 MHz. For tumor ablation purposes, the frequency in applicators, which are named electrodes, is usually in the range of 375–500 kHz.

Benefits

Local treatment can be used in various scenarios, with different purposes. At present time, liver disease is considered resectable as long as complete macroscopic resection is feasible while maintaining at least 30% future liver remnant or a remnant liver to bodyweight ratio of >0.5

In the case of patients with poor anatomical localization of their metastases for resection, ablative therapies may provide an alternative to resection, or they can be used in combination with resection, in order to obtain sufficient future liver remnants.

When an oligometastatic disease, which is usually defined as up to 5 metastases, is present, the role of local treatment becomes relevant in combination with systemic therapy. In these patients, the goal is not necessarily to cure, but to achieve long-term progression free survival, potentially contributing to overall survival. Finally, ablation may represent a salvage treatment for recurrences after hepatectomy.

Adverse events

Thermal ablation can be contraindicated in some cases. A tumor located at <1 cm from the main biliary duct, for example, brings an excessive risk of perforation or delayed stenosis of the structure; significant ascites along the applicator path can impede movement and ruin the operation.

Another impeding factor is the exophytic location of the tumor if its direct puncture is necessary, as the risk of seeding would be too high. An untreated coagulopathy would put the patient at severe bleeding risk, and finally, ablation of metastases larger than 3 cm presents a high risk of failure, regardless of the technology used.

As for side effects, post-ablation syndrome is described as a self-limiting flu-like illness with symptoms such as low-grade fever, nausea, and vomiting. This condition is believed to be caused by an inflammatory response to the necrotic tissue resulting from the ablation procedure. Another commonly reported side effect of thermal ablation is pain at the treatment site or in the right shoulder, which is typically mild and subsides within a few days. The size of the ablation and its proximity to the liver capsule have been associated with the frequency and intensity of post-ablation pain.

Like any medical treatment, each ablative technique carries the potential for complications. These can be categorized into puncture-related and thermal-related issues, with the overall rate of grade 2–6 (major) complications ranging from 2.2% to 3.1%.

Puncture-related complications include: intraperitoneal bleeding, pneumothorax, and hemothorax, which can be prevented or quickly resolved by checking the patient's coagulation status and selecting the safest path to reach the nodule. Tumor seeding is another puncture-related complication, occurring in about 0.5% of cases, that can be avoided as much as possible by ablating the needle track.

Thermal-related complications include: bowel perforation, portal vein thrombosis, liver abscess, bile duct injuries, and cholecystitis. Bowel perforations can be prevented by using procedures such as gas or hydro-dissection to protect nearby organs from heat damage. To minimize biliary complications, it's advised not to treat tumors located less than 1 cm from the main biliary tract unless biliary cooling is provided. A specific complication of cryoablation is cryo-shock, a syndrome characterized by coagulopathy and potentially fatal multiorgan failure, including acute renal failure and adult respiratory distress syndrome. This risk is proportional to the amount of liver tissue treated, and a similar mechanism to septic shock may play a role in this phenomenon.

Results

In conclusion, ablation is a valid procedure in the treatment of colorectal liver metastases. In non-surgical patients treated with thermal ablation, 5-year survival rates range from 25% to 55%, and radiofrequency (RF) ablation has shown results comparable to surgery for solitary CRC metastases smaller than 3 cm, since tumor size remains a great limitation for ablative therapies.

Additionally, a trial compared chemotherapy alone versus chemotherapy combined with percutaneous or intraoperative RF ablation for those with up to 10 metastases and found improved progression-free survival (22.3% vs. 2%) and overall survival (35.9% vs. 8.9%) in the combined treatment group at 8 years of follow-up.

Several cohort studies have evaluated the effectiveness of microwave ablation for CRC liver metastases, reporting 3-, 4-, and 5-year overall survival rates ranging from 35% to 79%, 35% to 58%, and 17% to 18%, respectively. (37)

LIVER RESECTION

Of all patients with metastatic colorectal cancer extended to the liver, approximately 20 percent will be candidates for a potentially curative hepatic resection. Long-term survival after surgery for

colorectal liver metastases (CRLMs) has improved dramatically, with five-year overall survival rates of almost 60 percent.

Liver physiology

The liver is divided into two lobar segments, right and left, and further subdivided into eight segments based upon vascular supply and bile duct distribution. The segmental anatomy of the liver is the basis for the various types of anatomic hepatic resections.

Liver regeneration is fundamental to the ability to perform more extensive hepatic resections, as remnant liver tissue has to be able to compensate for the activity of the lost liver area. The mechanisms responsible for this capability are an area of active research, but it's fairly accepted that angiogenesis inhibitors severely suppressed hepatic regeneration. Therefore, the use of Bevacizumab can have severe consequences in patients subjected to extensive liver resection. Furthermore, one small study suggested that liver regeneration in patients with body mass index >30 may be slower than in others.

In patients with focal or isolated disease, resection of liver metastases is associated with low rates of major perioperative morbidity and mortality, circa 3%.

Despite the good results, not everyone can be a candidate for resection, as patients with severe underlying functional liver disease such as cirrhosis, nonalcoholic steatohepatitis, are unfit for major liver resection. For patients with less severe disease, the degree to which the underlying liver disease constitutes an absolute rather than relative contraindication to hepatic resection depends upon the anticipated volume of liver remaining after resection.

Preoperative steps

It's imperative to evaluate the patient and assign an accurate Child Pugh score, in order to predict the risk of postoperative liver failure and death. Patients with a Child Pugh score of C, or B with future liver remnant <40% are completely unresectable, but even lower score patients can be excluded in some cases.

There are many different procedures for hepatic resection, and one of the first distinctions to make is whether the operation will be laparoscopic or a laparotomy.

Basically all elective liver resections for metastatic tumors begin with evaluation for extrahepatic disease, with a widespread use of intraoperative liver ultrasound imaging to evaluate the potential for complete resection and to define the relevant anatomy. If resection is feasible the operation can proceed, otherwise the choice is between a switch to ablation or the complete abandonment of the surgical option.

Surgical procedure

In open surgeries, an upper abdominal incision is made, and the liver is exposed. Cholecystectomy is usually performed first, followed by dissection of the porta hepatis to isolate and control the vascular and ductal structures.

Depending on the patient's body type and the location of the lesions, either a standard laparotomy or a bilateral subcostal incision is feasible to provide wide exposure and access to most areas of the liver and major blood vessels. For large right liver tumors or those located posteriorly, an inverted L incision is preferable. If needed, a superior midline extension can be used. When performing a synchronous resection of the non-hepatic primary tumor along with hepatic metastases, an extended midline incision is often favored. In rare cases, a right thoracoabdominal incision may be required to access the dome of the liver for resecting large tumors or those in segments VII or VIII.

To reduce blood loss during liver resections, particularly when vessels in the porta hepatis are not ligated, the hepatic artery and portal vein can be individually controlled. The Pringle maneuver, which involves clamping the hepatoduodenal ligament to occlude portal blood flow, significantly reduces blood loss and transfusion rates. Despite its benefits, the Pringle maneuver is rarely needed in elective hepatic resections due to advancements in surgical techniques and tools. After resection, intraoperative duplex ultrasound is used to confirm normal blood flow, especially if portal clamping was used.

Before the actual resection, the planned path of division must be marked. In major anatomic resections, the plane is defined by ligating the inflow structures of the affected segment or lobe. For less extensive procedures, intraoperative ultrasound helps identify and mark the dissection plane on the liver's surface using electrocautery. Vertical mattress sutures can also be placed to compress liver tissue and reduce bleeding.

Several tools assist in liver parenchymal dissection, such as ultrasonic vibration for superficial layers and microwave ablation for pre-coagulation along the resection plane. Some electrosurgical devices like monopolar electrocautery, or the clamp-crush technique where tissue is gently broken apart by hand, can be used for dissection.

With the remaining liver anchored to the abdominal wall by reattaching ligaments, hemostasis and bile leaks can be controlled at the end of the operation, by using electrocautery, surgical clips, or additional sutures. If needed, persistent bile leaks can be evaluated using cholangiography, which is performed by injecting gastrointestinal contrast. (38)

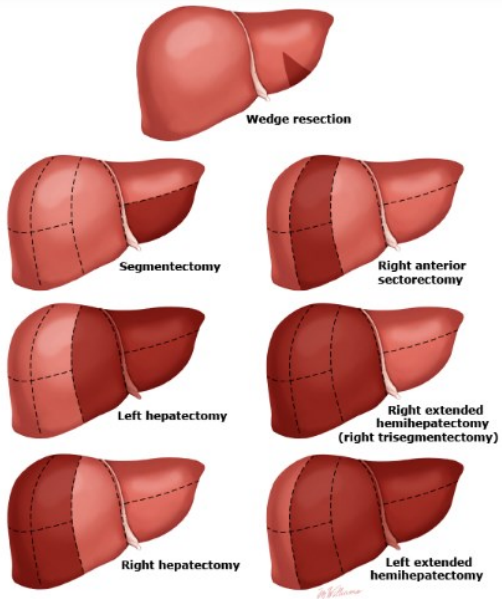
Laparoscopy

Laparoscopy as a technique in CRLM resections is expanding rapidly and can be a viable alternative to open surgery for small tumors, provided the surgeon has expertise in hepatic resection and advanced laparoscopic techniques. These approaches are suitable for small lesions, particularly those in accessible areas like the dome, peripheral regions, or the left lateral and lower right liver. A hand-assist port can be used for larger tumors or when training surgeons.

Because of it being minimally invasive, laparoscopic liver resection results in reduced blood loss and shorter hospital stays compared to open surgery, without differences in tumor clearance or recurrence rates. However, conversion from a minimally invasive approach to open surgery is generally linked to poorer outcomes, and larger randomized trials are needed to confirm equivalent oncologic results.

Resection types

The different types of liver resections include wedge resection, segmental resection (segmentectomy), hepatectomy (right or left), and extended hepatectomy (right or left), with caudate lobe resection as a separate procedure. Except for wedge resection, these are based on the liver's segmental anatomy.



The types of hepatic resection are based on the anatomic nomenclature. "Wedge resection" refers to any nonanatomic liver resection exclusive of biopsy. "Sectorectomy" refers to any one of the following: right anterior sectorectomy, right posterior sectorectomy, left medial sectorectomy, and left lateral sectorectomy.

The choice of resection depends on the lesion's location, ensuring an adequate liver remnant, and for malignant cases, achieving a tumor-free margin. While anatomic resections are more likely to achieve tumor-negative margins, nonanatomic resection may be necessary if an anatomic approach would leave insufficient liver volume.

Wedge resections use a "V" incision and are mostly used for peripheral lesions. The technique involves marking the limit of the planned resection on the surface of the liver in the shape of a large "V" using electrocautery, with the open part of the "V" located on the free edge of the liver. Alternatively, if the lesion is located near the dome of the liver, it’s necessary to mark a circle around the lesion and then resect.

Segmental resections focus on removing specific liver segments with intraoperative ultrasound guidance to ensure tumor-free margins. The main use of segmental resection is removal of an isolated lesion located at the center of a segment. Margins are defined by ligation of a hepatic artery branch and portal venous branch, which typically results in significant ischemic discoloration to that portion of the liver. Assuming the lesion of interest is confirmed present within the zone of ischemic tissue and no critical structure exists in the plane of demarcation as seen with ultrasound, then those demarcation lines are used as transection planes. In this type of technique, vascular structures are temporarily occluded and then divided using stapling devices for vessels and ducts.

Then there are sectorectomies, such as Anterior right sectorectomy, which removes segment V and VIII,

Major resections include left or right hemihepatectomy, where the respective liver half is removed, guided by ultrasound and ensuring adequate blood supply to the remaining liver. A common indication for extended right hepatectomy is a right hepatic colorectal cancer metastasis, extending into the medial segment of the left liver (segment IV), while left extended hepatectomy is useful for patients who have left-sided lesions that encroach on segments V and VIII. Due to the extent of the resection, it is important to evaluate the volume of the future liver remnant, which must be adequate to allow a reasonable probability of recovery. Hemostasis is achieved using topical agents, electrosurgical devices, or sutures.

Extended resections such as right or left extended hemihepatectomy involve removing additional segments or lobes, including the caudate lobe if necessary. These resections are more complex and require careful planning to ensure adequate liver remnant volume for recovery.

TWO-STEP HEPATECTOMY

As previously mentioned, one of the most important parameters to consider while evaluating the patient for surgery is the predicted amount of remaining liver. In some patients, especially if right hepatectomy is recommended, the parenchymal remains aren't sufficient to ensure an appropriate recovery and hepatic regeneration.

Therefore, two-step hepatectomies aim to enlarge the healthy portion of the liver before proceeding with the operation.

Portal vein embolization/ligation

Several strategies to increase the FLR volume preoperatively have been developed over the years, allowing more patients to undergo successful surgical resection.

The first one is PVE, which consists of embolizing the portal branches of the future resected liver 3–5 weeks before the scheduled hepatectomy. This method has a very low morbidity and is well tolerated with a high success rate. However, in 15–20% of patients after PVE, the planned hepatectomy cannot be performed either due to tumor progression or due to insufficient hypertrophy.

Then, there is a surgical equivalent technique which is portal vein ligation (PVL), which can be used especially when additional metastasectomies are to be performed on the FLR. With this surgery, one of the portal vein branches is ligated and can also be embolized with ethanol.

One other strategy has been explored in patients with insufficient liver volume gain four weeks after PVE by adding HVE, which has shown to add further liver regeneration. A major drawback of this approach is the delay between each procedure increasing the risk of liver or extrahepatic tumor progression. Four weeks are necessary to assess liver volumetric gain after PVE, which are then followed by another four weeks after HVE. (39)

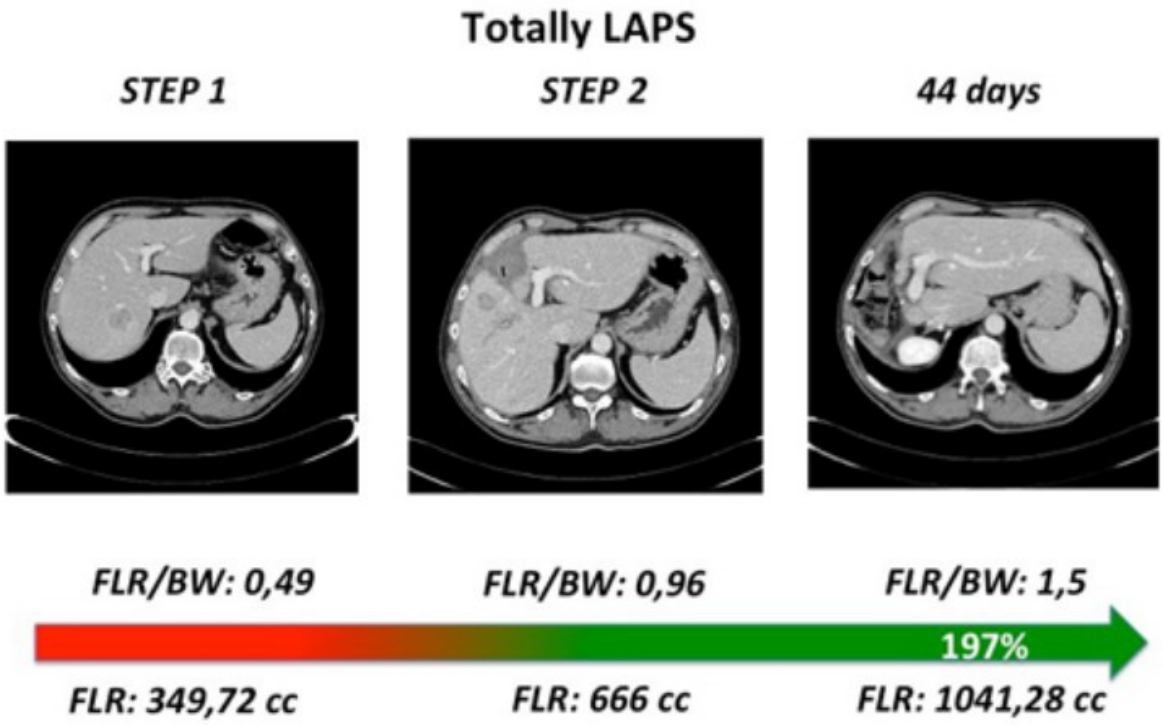
ALPPS

In order to reduce the risk of tumor progression, by decreasing the delay between liver preparation and resection, an aggressive surgical approach called ALPPS has been developed, associating right portal vein ligation and liver partition one week before hepatectomy. Despite the very rapid hypertrophy, a high morbidity and mortality rate was unexpectedly seen with this surgical strategy. One possible explanation for this is the fact that the function of the FLR does not necessarily mirror the volumetric gain and may even decrease. Preoperative FLR functional evaluation has thus been advised.

LAPS

Lastly, in the General Surgery department of Padua University, another method has been put into practice. LAPS (Laparoscopic ablation and portal vein ligation for staged hepatectomy) is in many ways similar to ALPPS but is characterized by a minimally invasive approach for the first stage of the whole procedure.

The operation begins with a standard exploratory laparoscopy, aimed to exclude the presence of extrahepatic disease, followed by an ultrasound to confirm resectability. The next step is portal vein ligation, associated with the ablation of any lesion in the FLR zone and of the future resection border. After 9 days, the patient is subjected to a CT scan in order to assess liver hypertrophy. In case of an adequate response, the following step is to complete the hepatic resection.



This technique brings several advantages, such as a simpler and faster procedure, a lighter first step without need of ICU stay, and a minimized risk of complications in comparison to ALPPS. (40)

SURGICAL COMPLICATIONS

Complications following hepatic resection occur in up to 40 percent of patients without cirrhosis, and even more frequently in those with cirrhosis. A review from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database reported perioperative morbidity rates of 21% for malignant lesions, not just CRLM.

Incidence

Morbidity was highest for extended hepatic resections (33%), compared to 25% for hemihepatectomy and 21% for partial hepatectomy.

Major complications, including bile leaks, pulmonary issues, acute kidney injury, and liver failure, occur in 10 to 20% of cases, especially affecting patients with risk factors such as advanced age and metabolic syndrome.

Bile leak occurs in fewer than 10% of patients and is classified into Grades A, B, or C depending on severity. Most leaks can be managed with endoscopic decompression and drainage. Risk factors include prolonged surgery and repeat hepatectomy.

Pulmonary complications are common due to the extent of the incision and retraction needed. In one study, pleural effusion and pneumonia occurred in 40 percent and 22 percent of cases, respectively. Independent risk factors for these include prolonged surgery, right hepatectomy, and diabetes.

Ascites is often found postoperatively in patients with liver disease, and severe cases may indicate portal vein thrombosis or liver failure.

Thrombotic complications, including portal vein and hepatic artery thrombosis, are rare but serious. Risk factors include prolonged Pringle maneuver and right hepatectomy.

Liver failure, the most severe complication, is characterized by impaired liver function, elevated INR, and hyperbilirubinemia, and it's favored by underlying liver disease and insufficient residual liver volume. Its mortality can be as high as 70 percent.

Mortality after hepatic resection is 1 to 3 percent at high-volume centers. Preexisting renal disease, cirrhosis-related complications, and ischemic heart disease are important risk factors. Nonalcoholic steatohepatitis (NASH), associated with obesity and diabetes, also increases perioperative risks.

Long-term survival in hepatic resection for colorectal metastases yields 1-, 5-, and 10-year survival rates of 93, 47, and 28%, respectively. (41)

Clavien-Dindo

The Clavien-Dindo classification for complications is widely utilized in every medical specialty, as it's not specific to any type of disease or apparatus. Scores are classified as a number ranging from 1 to 5, with some categories being further subdivided as "a" and "b".

Grade	
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions, antibiotics and total parenteral nutrition are also included.
3	Requiring surgical, endoscopic or radiological intervention
3a	Intervention under regional/local anesthesia
3b	Intervention under general anesthesia
4	Life-threatening complication requiring intensive care/intensive care unit management
4a	Single organ dysfunction
4b	Multi-organ dysfunction
5	Patient demise

While groups I and II indicate complications easily managed through common and non-invasive clinical practice such as drug administration, categories ranging from IIIa to IVb imply gradually more invasive and risky procedures, from local interventions to prolonged intensive care. A score of 5 indicates the patient's death.

The use of this classification provides a clear, standardized method for recording and comparing complications across studies and institutions, enhancing the consistency and reliability of postoperative outcome assessments.

Because of its precise definition of the different grades, it allows for a detailed evaluation of the severity of postoperative problems, facilitating communication among healthcare providers.

This system also has some drawbacks, as it does not account for the specific type of complication or its impact on the patient's overall health and recovery, potentially oversimplifying some complex clinical scenarios. Being a subjective grading system, it can also be variably interpreted despite the instructions.

Since it primarily focuses on immediate postoperative issues, it cannot give a full-fledged assessment of the patient's long term health.

Overall, despite being valuable for its structured approach to assessing postoperative complications, it should be used in conjunction with other clinical judgments and patient-specific factors to provide a comprehensive view of patient outcomes.

PROGNOSTIC FACTORS

Prognostic factors for CRC are numerous, but they can be more easily interpreted thanks to various scoring systems, which help calculate the patient's survival probability and overall prognosis with a good degree of accuracy.

The FONG score and the OSLO score are two clinical scoring systems used in surgical practice to predict outcomes and complications after liver surgery, especially in patients undergoing liver resections for colorectal liver metastases. Both are designed to help surgeons assess the risks and guide decision-making in liver resection procedures.

FONG Score

The FONG score (42), also known as the Clinical Risk Score (CRS), was introduced by Dr. Yuman Fong in 1999. It is used to predict recurrence and survival following hepatic resection of colorectal liver metastases. The score is based on five clinical factors:

1. Disease-free interval from primary tumor to liver metastases < 12 months.
2. Node-positive primary tumor.
3. More than one liver metastasis.
4. Largest liver metastasis > 5 cm.
5. Preoperative carcinoembryonic antigen (CEA) level > 200 ng/mL.

Each of these factors is valued as 1 point, and the total score can range from 0 to 5. A higher FONG score correlates with worse prognosis, higher risk of recurrence, and lower survival rates following surgery.

Another related variable is median survival, which ranges from 74 months (FONG 0) to 22 months (FONG 5)

Fong score	1-Year survival	3-Year survival	5-Year survival
0	93%	72%	60%
1	91%	66%	44%
2	89%	60%	40%
3	86%	42%	30%
4	70%	38%	25%
5	70%	27%	14%

OSLO Score

The OSLO score was instead developed based on a study from Oslo University Hospital and is focused on predicting the risk of postoperative complications after liver surgery. The score was originally designed for patients undergoing laparoscopic liver resections, but it is applicable more broadly in liver surgery. It takes into account the following four factors:

1. Male gender.
2. Extrahepatic disease.
3. Major liver resection (removal of 3 or more liver segments).
4. Blood loss greater than 500 mL during surgery.

Each factor contributes 1 point, giving a total score range from 0 to 4. A higher OSLO score indicates an increased risk of major complications following liver resection.

There are many differences in the use of these two indicators:

While the FONG score predicts long-term outcomes such as recurrence and survival after liver resection for colorectal liver metastases, The Oslo Score is used to estimate the short-term risk of postoperative complications, specifically after liver resections, especially those performed laparoscopically.

As for variables, the FONG score focuses on cancer-related factors, such as the nature of the metastases and primary tumor characteristics, along with the tumor burden.

The Oslo score focuses instead on surgical factors, such as blood loss, the extent of the liver resection, and patient characteristics like gender.

Therefore, the FONG score is widely used in patients with colorectal liver metastases to help determine prognosis and guide adjuvant therapy decisions; the Oslo score is more focused on evaluating the technical aspects of surgery and patient risk in the immediate postoperative period.

While both scores are important in liver surgery, they serve distinct purposes. The FONG score is valuable for assessing long-term cancer-related outcomes, whereas the OSLO score is helpful for predicting short-term surgical risks and complications.

CEA

CEA is used as a prognostic marker in several ways, helping clinicians assess the severity of the disease and guide treatment strategies:

Preoperative CEA Levels:

- High preoperative CEA levels (>200 ng/mL) are associated with worse outcomes in patients with CRLM. Elevated levels often indicate a higher tumor burden or more aggressive disease, correlating with:
    - Higher risk of recurrence after liver resection.
    - Shorter overall survival rates.

- Lower CEA levels (<5 ng/mL) before surgery are generally associated with better prognosis, indicating a lower likelihood of extensive disease or metastasis.

Predicting Tumor Aggressiveness:

- High CEA levels can indicate more aggressive tumor biology, reflecting factors such as:
    - Larger metastatic tumors.
    - Presence of multiple metastases.
    - Involvement of extrahepatic disease
    - More rapid disease progression, requiring more aggressive treatment strategies.

Postoperative CEA Trends:

Postoperative monitoring of CEA levels is crucial for detecting recurrence. Persistent or rising CEA levels after liver resection can indicate residual disease, early recurrence, or undetected metastases, prompting further investigation through imaging or additional interventions.

Patients with normalization of CEA postoperatively usually have a more favorable prognosis compared to those whose CEA levels remain elevated or rise again shortly after surgery. (22)

PURPOSE OF THE STUDY

The primary purpose of this study is to analyze whether administering a combination of two cytotoxic drugs (FOLFIRI or FOLFOX) as a first-line neoadjuvant treatment for colorectal liver metastases results in a lower risk of complications in the 90-day postoperative period compared to a three-drug regimen (FOLFOXIRI), independently of associated targeted therapies.

By focusing on early postoperative complications, the study aims to better understand the safety and risks associated with the surgical intervention after neoadjuvant chemotherapy. This understanding is crucial for improving patient management strategies.

Secondarily, the study seeks to determine whether the use of double chemotherapy provides any advantage in overall survival compared to the use of a triplet regimen.

Lastly, the study aims to identify the most significant predictors of overall survival by analyzing postoperative and intraoperative factors associated with patients' mortality in the following 5-year period.

PATIENTS AND METHODS

INCLUSION CRITERIA

For this study, the original data pool was sourced from the admissions database of the Hepato-Biliary Surgery Unit at the University of Padua, of which only the group with patients that were hospitalized from 2014 to 2024 was analyzed. This produced a starting base of 11.470 units, with many instances of recurring patient names as every entry represented a different hospital stay and not a univocal person.

The next step of the process was to include only the patients with an established diagnosis of CRLM, an information easily accessible by consulting the Galileo system. This operation left 1.370 available entries.

Subsequently, the database was further reduced to those admissions that had included an entry in the OR during the hospital stay, either programmed or in a state of emergency, for whichever reason; the 1.075 remaining hospitalizations were then divided between those who featured a liver metastasectomy and those that did not.

The next step entailed selecting only the first CRLM excision for every patient, therefore making every patient ID univocally bound to one hospitalization. In order to achieve this, every patient's hospital stays were numbered and only the rows corresponding with the first registered liver surgery of each subject were left, while the others were eliminated.

This initial part of the selection gave as a result a database of 681 patients.

The following phase required the retrieval of various information for each entry, such as the operation date, the type of surgical procedure, the presence of any record of previous metastasectomies, and the number and type of neoadjuvant therapies used, if any.

Regarding the first parameter, already restricted at the beginning of the whole research to be set between 2014 and 2024, there was further tightening of the criteria and all patients that were first operated before January 1st, 2015 or after December 31st, 2023, were eliminated.

As for the type of surgical procedure, the selection was not particularly restrictive, as all kinds of partial liver excision were included, from ablation, to resection, to two-step hepatectomies. The only exclusion criteria was the choice of liver transplantation as the therapeutic strategy.

Next, every patient's anamnesis was carefully searched for mentions of any previous CRLM resection or ablation. As already mentioned, part of the selection criteria for each entry was to be the patient's first instance of hepatic surgery, but the initial database only featured information stored in Padua's records. Therefore, a previous operation and its respective documents, had they been conducted in any other center, would not have been visible for the study.

Because of this, any mention of previous metastasectomies resulted in the elimination of the patient from the database, as the needed data from the first liver surgery would have been inaccessible from Galileo.

The final important inclusion criteria was the number of lines of therapy. For the purpose of this study, many lines of chemotherapy in the same patient would have represented a confounding factor, especially if containing different drug combinations. Because of this, anyone that was subjected to more than one line was excluded, with the only exception being patients treated with a maintenance regime after their first and only line of therapy.

Furthermore, the neoadjuvant treatment had to contain either a doublet or a triplet, thus any first line therapy containing only biologic agents was rejected, leaving in total one hundred and ninety-two subjects.

To summarize, the inclusion criteria for patients were:

- CRLM diagnosis
- Liver metastasectomy performed at any point
- No liver transplantation
- First liver surgery performed in Padua
- First liver surgery performed between 2015 and 2023
- Single line of neoadjuvant chemotherapy
- Neoadjuvant therapy containing a doublet or a triplet

ACQUIRED DATA

Having selected the final pool of 192 patients, the next step was to acquire significant data for the following analyses by researching on Galileo each patient’s O.R. logs, anamnesis, discharge letter and hospital stay diary.

BIOMETRIC DATA

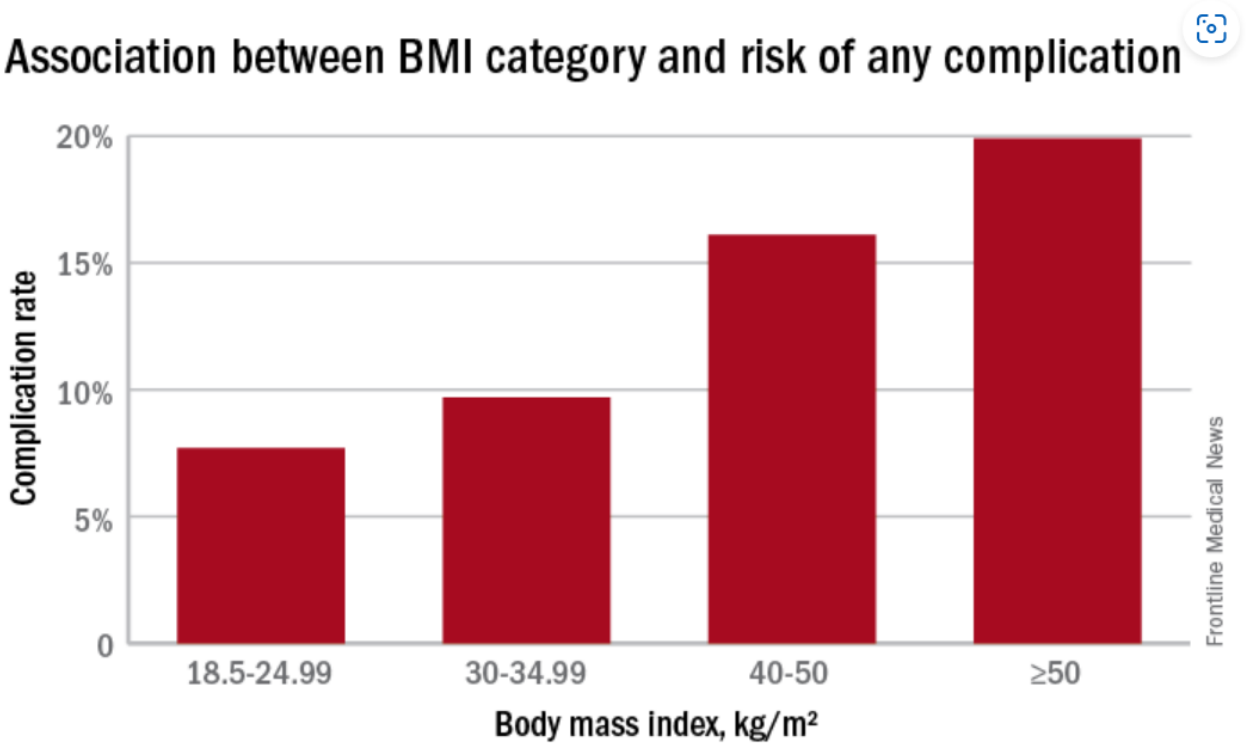
Biometrics are defined as body measurements and related calculations. They provide valuable information about an individual's physical characteristics and can be used to evaluate body composition and health risks.

In this case, the only required information was about height and weight, from which BMI can be then derived.

Both height (m) and weight (kg) were obtained from the patient's anamnesis, specifically from the anamnestic document associated with the hospitalization during which the first metastasectomy was performed.

BMI (kg/m²) was then calculated through the appropriate formula, and besides its exact value, patients were also categorized into two groups:

- People with BMI > 25 (tendentially overweight)
- People with BMI ≤ 25 (not overweight)



Note: The retrospective analysis involved 102,191 patients from the National Surgical Quality Improvement Program database.

Source: Surgery 2017 Sep 27. doi: 10.1016/j.surg.2017.07.025

This distinction was made because of the different postoperative risk that characterizes people with excessive BMI, which makes them more susceptible to chemotherapy side effects and surgical complications. By stratifying the group, patients with similar characteristics can be more easily compared without confounding factors.

COMORBIDITIES AND MEDICAL HISTORY

The next important set of data was the one regarding each patient's health status, lifestyle and comorbidities.

By searching through patients' anamnesis and discharge letter, relevant pieces of medical history were obtained and registered, with a particular focus on some elements.

First thing, patients were subdivided into three categories depending on their smoking status:

- Never smokers: people who have smoked less than a total of 100 cigarettes in their lifetime;
- Former smokers: people who have smoked more than 100 cigarettes in their life, but have then quit;
- Current smokers: people currently smoking that have also smoked more than 100 cigarettes.

Then, a binary categorization was used to divide patients with a silent medical history from those with comorbidities. The records of patients with comorbidity were subsequently examined to check

Table 3. CCI (Charlson comorbidity index) score.

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
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno-deficiency syndrome (AIDS)	6

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for notable diseases, including but not limited to those that contribute to the Charlson Comorbidity Index (ChCI), an indicator of 10-year survival probability.

This parameter can be calculated by adding up points from various elements, each multiplied by a specific coefficient. The presence of a history of each of the following factors was categorized as ‘1’, while its absence was codified as ‘0’.

Myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular accidents, including TIA, all had a coefficient of 1.

Other pathologies only counting as one point were dementia, chronic obstructive pulmonary disease, connective tissue disease, and peptic ulcer disease.

A coefficient of 2 was then assigned to columns regarding the presence of hemiplegia and moderate to severe chronic kidney disease, but also leukemia and lymphoma. On the other hand, a diagnosis of AIDS alone was counted as six points.

Parameters such as diabetes mellitus, liver disease and solid tumor were stratified based on their severity. Therefore, besides their presence or absence, a secondary column for each element was used to classify the advancement of the disease.

Diabetes mellitus:
- None/diet controlled→0
- Uncomplicated→1
- Complicated→2

Liver disease:
- None→0
- Mild→1
- Moderate to severe→3

Solid tumor:
- None→0
- Localized→2
- Metastatic→6

The last element needed to calculate the Charlson Comorbidity Index score was each patient's age, which was grouped into five categories: under 50 (0 points), 50-59 (1 point), 60-69 (2 points), 70-79 (3 points), 80 and over (4 points).

While the ChCI scores ranged from 6 to 12 between all patients, a stratification of the results was deemed necessary for a better analysis. Therefore, scores were divided into three groups:

- CCI = 6
- CCI = 7-8
- CCI >8

This consented to divide patients affected only by cancer (CCI 6) from patients with two comorbidities (CCI 7-8) and more (CCI>9).

Despite the minimal difference in the actual prediction, as 10-year survival with 6 or more comorbidities ranges from 0 to 2% only, the distinction between scores was kept because of its impact in shorter-term prognosis, such as 5 year survival.

Besides the aforementioned diseases, other important comorbidities were taken into account and marked as present (1) or absent (0), such as hypertension, hypercholesterolemia, pulmonary, renal and gastrointestinal disease, and the presence of other kinds of cancer.

Regarding surgical history, patients were first classified between those with no history of abdominal surgery and those who had been subjected to one or more. Then, another column was used to specify for each patient what kind of operations they had undergone.

PRIMARY TUMOR

The next inquiry concerned the primary tumor characteristics.

The date of first diagnosis, corresponding in most cases to a colonoscopy, was used to then calculate the age of insurgence of the tumor. In order to have a clearer picture of the age range distribution, patients were then sorted into two categories, those over and those under 65 years of age. This distinction was made according to the demographic standard that marks 65 as the threshold between the "adult" and "young elderly" categories.

Subsequently, several columns regarding data about the original tumor were compiled, in order to obtain an overview of the initial prognosis based on location, effective resection of the mass, lymph node involvement and delay between diagnosis and operation.

The primary tumor location was recorded based on anamnestic and radiographic findings. Four groups were defined to distinguish between CRC localization in the right colon, transverse colon, left colon, and rectum.

The difference between left and right cancers is partly due to their embryological origin. While the RCC is derived from the embryological midgut, including the proximal two-thirds of the transverse colon, ascending colon, and cecum. LCC is derived from the embryologic hindgut, which includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. Since it was not possible to distinguish between the proximal and distal transversum colon, it was registered as a separate entity from left and right.

As for the surgery on the colorectal neoplasm, patients were sorted between those who had been subjected to a resection at any point in time, and those who had the growth still in place at the time of death or last follow up. The proportion was heavily in favor of those who had undergone resection, while the other group included only six patients. In the next column, for each of the operated patients the exact date of the colectomy was registered, and subsequently the patient's age at the time of the surgery.

Using this data, another calculated parameter was the delay between the initial diagnosis and the operation, expressed in days. This was considered important, as a longer wait for surgery is generally associated with poorer outcomes and reduced life expectancy, with prognosis gradually worsening after a delay of four weeks. (43)

Then, by checking the histological findings from colic resection, or the radiographic estimates in absence of a primary surgery, lymph node positivity was codified as a binary parameter, independently of the proportion between affected nodes and healthy ones.

This element is one of the parameters used for the calculation of the Fong score, a prognostic indicator for 1 year and 5 year survival. The evidence of lymph node positivity alone is enough to lower the patient's life expectancy, with a 91% probability at 1 year and a 44% chance of survival at 5 years.

The next important detail to determine about the colectomy was its potential association with the hepatic metastasectomy, or the precedence of the latter over the former.

Finally, the last subject of inquiry was the administration of any kind of adjuvant therapy after the colectomy.

Each patient was thus divided between those who had and had not been subjected to a post operative treatment. This chemotherapy was then specified, in order to verify a possible interaction and interference with the following neoadjuvant chemotherapy results.

The only adjuvant options found both involved the fluoropyrimidine capecitabine, in two different regimes:

- Capecitabine only
- XELOX

The number of administered cycles was specified but then deemed not relevant and therefore ignored.

LIVER METASTASES

The most important prognostic data for surgical complications is the one regarding the metastatic nodules' characteristics.

Using anamnestic records in the patients' files, the date of diagnosis of the metastatic disease was registered, and then used to derive several different parameters:

- Patient's age at metastases diagnosis
- Months between the primary diagnosis and the first metastatic nodule appearance
- Months between colectomy and first metastatic disease diagnosis

The patient's age was fairly similar to the one calculated by taking into account the primary disease diagnosis, therefore it was not deemed necessary to further separate patients between adults and young elderly.

As for the months of delay between the primary diagnosis and the first metastatic nodule appearance, they were used to identify synchronous and metachronous metastases.

Synchronous metastases are defined as those that appear after less than six months from the original cancer, and despite being more receptive to chemotherapy they are generally associated with a slightly worse prognosis, especially if associated with a right-side primary. (44)

Metachronous metastases are instead associated with a longer survival, but they pose the problem of an evidently inadequate chemotherapy regimen, as the seeding of micrometastatic particles should have been prevented by the systemic treatment.

Besides this distinction, the time between primary and metastatic disease is also important as a prognostic factor in the previously mentioned FONG score.

Nodal status of primary tumor — positive
Disease-free interval from primary to detection of liver metastases < 12 mo
Number of lesions > 1
Preoperative carcinoembryonic antigen > 200 ng/mL
Size of largest tumour > 5 cm

In the FONG score, the cutoff is at one year, longer than the distinction between synchronous and metachronous cancer. Therefore, both synchronous and metachronous metastases that developed in less than a year from the initial diagnosis have a negative prognostic value.

As points in the score are equivalent, the 1-year and 5-year survival probabilities in case of positivity of this criterion alone are equal to those illustrated in regard to lymph node positivity.

After that, data about the metastatic nodules was collected:

- Number of hepatic metastases
- Localization of hepatic metastases
- Maximum size of the nodules

The number of hepatic nodules ranged from 1 to more than 15 micronodules, therefore, to better analyze the impact of this element, results were grouped together in three clusters:

- 1-5
- 6-10
- >10

Besides this categorization, another column was designated to distinguish between the presence of a singular nodule or multiple ones, as this is another fundamental criterion in the determination of the FONG score.

In case of multiple, synchronous metastases, for example, the FONG score is 2 and therefore the probability of 1-year survival is at 89%, while the one for 5-year survival is at 40%.

Localization was then researched by reading through various radiographic and postoperative reports, with a particular focus on TC and intraoperative ultrasound findings.

Patients were then categorized into three groups based on the CRLM affected hepatic segments and their position in the liver.

- Bilateral → Defined as either multiple nodules distributed in both the right and left liver, or even a single nodule affecting the hepatic hilum zone or the margins between the IV and VIII or IV and V segments. This did not require further specification.
- Unilateral → One or multiple nodules, all fairly confined to a specific half of the liver, most frequently the right one because of its size
    - Right
    - Left

This can have repercussions in case the metastatic burden is so heavy that it requires the removal of the affected liver half.

Since the right side is much more voluminous than the left, while a left hepatectomy can generally be performed without previous preparatory steps, right hepatectomies tendentially require an enlargement of the left side, in order to guarantee a sufficient functional remaining liver volume.

The final information was obtained from CT reports and radiographic estimates, specifically by considering the initial examinations performed either at the time of or shortly after the diagnosis of metastatic disease.

Aside from the specific diameters, expressed in millimeters, three categories were taken into account and patients were sorted into them based on the maximum size of the biggest nodule found in the liver.

- ≤ 30 mm
- 30-50 mm
- >50 mm

The most important cutoff is 50 mm, as it represents yet another factor in the FONG score calculation. Therefore, the first two categories have no theoretical repercussions, although a score of 0 still implies a 93% chance of survival at 1 year and 60% at 5 years, while the third group lowers the survival probability.

The 30 mm cutoff was instead chosen because of an earlier study that found associations between metastases' size and post operative complications.

NEOADJUVANT TREATMENT

The most important distinction of all, for the purpose of this study, was between those that had been treated with a doublet of chemotherapy and those who had been administered a triplet therapy regimen.

The next data revolved around the characteristics of the administered lines of therapy.

Because of the inclusion criteria, there was no need to specify if or with how many lines the patient had been treated, as everyone selected had to have received only one line of neoadjuvant chemotherapy, with the exception of the possible administration of a maintenance regime, often limited to biologic agents.

The first information collected about the line of therapy was the starting date, important to calculate timing and duration of the treatment.

While not present in every patient's anamnesis, the total number of cycles was also recorded, as many studies agree that up to a certain number, specific to a particular therapy regime, chemotherapy gives a survival advantage by eliciting a partial response, but after that threshold, the benefits of the treatment tend to decrease and the tumor burden remains stable, while the side effects continue to increase.

Therefore, an excessive number of cycles can be as noxious to the patient as the original disease, especially if it precludes them from undergoing an eventual curative surgery because of the extreme damage to the liver tissue. [45]

Once acquired the end date of the treatment, the total duration in months was easily calculated. Instead of analyzing it as continuous data, though, it was determined for each patient if their treatment had gone on for longer than 6 months or not.

The next step was determining the exact regimen the patient had been administered, therefore separate columns were used to pinpoint the drugs used, particularly:

- 5FU → Always present, as the selected regimes were FOLFOX, FOLFIRI and FOLFOXIRI
- Oxaliplatin
- Irinotecan

After examining the chemotherapeutic part of the treatment, data about the chosen biologic agents for target therapy was obtained, especially regarding:

- Bevacizumab →Anti-VEGF
- Cetuximab →Anti-EGFR
- Panitumumab →Anti-EGFR

Finally, the potential usage of immunotherapy was investigated, examining:

- Nivolumab
- Avelumab
- Atezolizumab

The line end date was also used to calculate the delay between the last chemotherapy administration and the surgery, which can be relevant since this kind of treatment leaves the liver more flaccid and favors bleeding. A longer wait can therefore allow the liver to slightly heal before the operation.

In order to better analyze this data, the calculated delay was sorted into one of two groups:

- > 6 months
- < 6 months

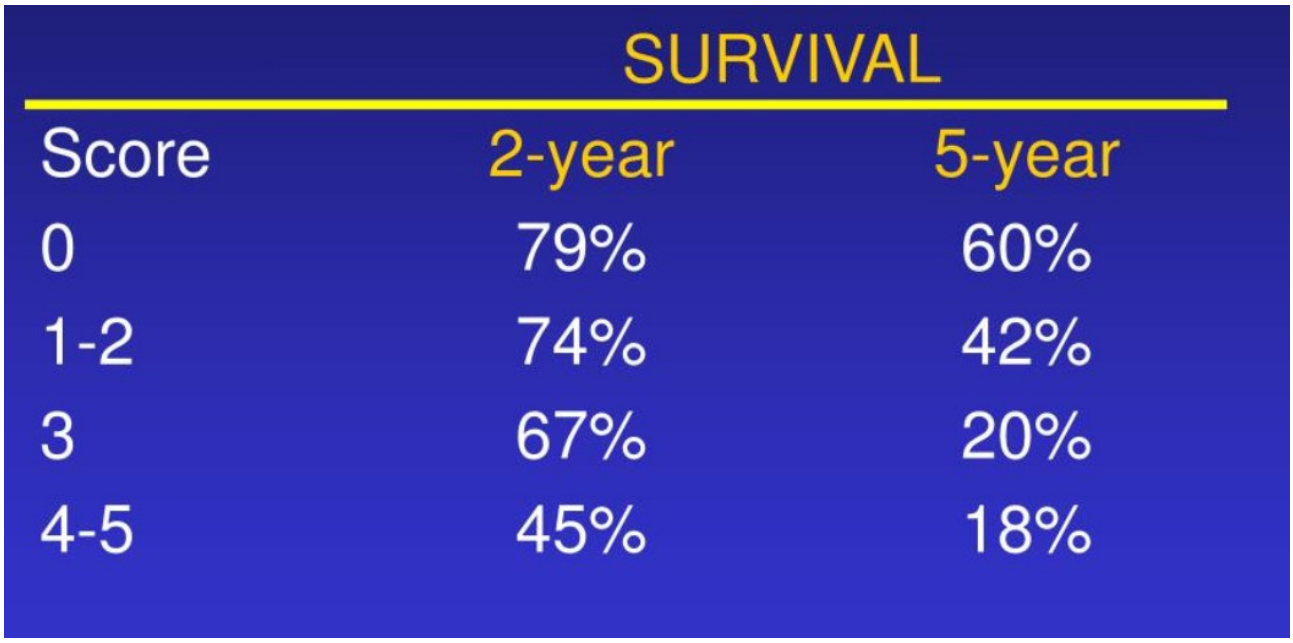
After the information on the first line of therapy, in case of maintenance treatment the same kind of data was acquired and appropriately cataloged.

The final research in the pre-operative field was about CEA levels after chemotherapy.

Besides the actual value of the carcino-embryonic antigen, another inquiry was carried out, determining whether its levels after the neoadjuvant treatment were above or below the cut-off line of 200 ug/l.

This was the final factor to determine FONG score, which as mentioned earlier helps in predicting the survival rate.

The cumulative points were thus summed up for each patient, obtaining the final score.



SURGERY DATA

The first information, found in discharge letters, was the operation date. For two-step hepatectomies, although not technically the patient's first surgery, the registered date was the one concerning the second step of the process, namely the left or right hepatectomy.

This was then used to calculate the patient's age at the time of the operation, which was subsequently divided between:

- Over 65
- Under 65

Another important calculation was the delay between the diagnosis of metastatic disease and the operation to eradicate it, expressed in days.

The next assessment registered, found in surgical reports or anamnestic records, was the ASA score.

The ASA score, or American Society of Anesthesiologists (ASA) Physical Status Classification System, is a system used to assess a patient's overall health before surgery. It helps predict the risk of perioperative complications based on the patient's physical status and comorbidities. The score ranges from 1 to 6:

- ASA 1: A healthy patient with no medical problems.
- ASA 2: A patient with mild systemic disease (for example controlled hypertension or diabetes).
- ASA 3: A patient with severe systemic disease that limits activity but is not incapacitating (poorly controlled diabetes or heart disease).
- ASA 4: A patient with severe systemic disease that is a constant threat to life (recent heart attack or severe respiratory failure).

- ASA 5: A moribund patient who is not expected to survive without the surgery.
- ASA 6: A patient declared brain-dead, whose organs are being removed for donation.

The ASA score helps anesthesiologists and surgeons assess surgical risks and plan perioperative care depending on the patient's comorbidity status.

Since patients were being electively operated, with potentially curative intent,there were no ASA scores over 4.

As the biggest difference in outcome is between ASA I-II and ASA III and upwards, patients of the first two grades were grouped together, as well as those with ASA III and IV.

Another relevant factor in the risk of complications is the concurrent resection of the primary mass. This, being a major surgery, has a big influence on the post-operative complications, therefore in the final statistical analysis patients must be divided between the liver-only and combined surgery groups.

The actual type of colic resection was also registered, using the indications "left hemicolectomy", "right hemicolectomy" or "rectal anterior resection". This information was not included in the final statistics, however, as it had no relation to the use of doublet or triplet therapy.

The following inquiries were all researched in the surgical report, as they devolved into more technical details.

First off, it was specified for every patient if they had been subjected to open or laparoscopic surgery. Then, for each of them was posed the question about the use of robotics during surgery, as the precision and control offered by robotic systems can lead to fewer complications, such as bile leaks and bleeding, which are significant concerns in liver surgery.

Since the number of patients who had been treated with a robotics approach was negligible, almost null in comparison to the total population, this distinction was scrapped as it could not bring any significant value to the study.

A fundamental parameter to research was, instead, the possible conversion of the surgery from laparoscopic to open, as it would indicate the presence of unexpected intra operative complications or a wider diffusion of the disease.

In any case, this feature indicates a worse prognosis for patients, either because of the disease burden or because of the added surgical complications.

The reason for said conversion was also specified in another, descriptive entry, but because of the wide variety of possible causes, which ranged from the need to extract a particularly voluminous surgical piece to the management of an intra operative hemorrhage, patients were nearly singled out by each entry.

Therefore, in order to avoid excessive fragmentation of the patient population, the specific causes were not taken into account in the final data analysis.

Afterwards, for each patient was registered the type of surgical technique used, specifically if they had been subjected to:

- Local treatment only→ Ablation techniques, which offer a minimally invasive alternative to surgical resection for treating liver metastases, with each method having its own advantages and limitations;
- Resection only→ Complete excision of the pathologic nodules, with a wider margin to ensure oncological radicality, and thus often more efficient in the prevention of recurrences than ablation;
- Resection+local treatment→ Excision of the major focal points of metastasis, combined with ablation of the smaller peripheral nodules, this combination can sometimes balance the pros and cons of both techniques.

The next stage was specifically targeted to those patients who had been candidates for two-step hepatectomy.

For this pool of patients, anamnestic records were used to determine if and when they had been subjected to portal vein embolization or portal vein ligation, also specifying the involved portal branch.

After that, a column was dedicated to the exact two-step procedure performed:

- ALPPS
- LAPS

Once terminated the section reserved to two-step hepatectomies, the next collected information was about the utilized types of resection, which were then codified through an abbreviation followed by the involved segments:

- W→ Wedge resection, which can be preferable if the nodules are superficial and localized at the margin between two segments;
- SEG→ Segmentectomy, which is based on the areas defined by independent vascularization and biliary drainage, and is most used when nodules are deeply embedded in the parenchyma of a few selected sections;
- R/C/L-H→ Right, central or left hepatectomy, which is a much more challenging operation as it removes at least four segments (counting IVa and IVb as separate entities) and therefore needs a careful evaluation of the functional remnant liver volume before proceeding with the surgery
- E-R/L-H→ Extended right or left hepatectomy, which is even more demanding than the former procedure as it extends into the contralateral liver.

To better classify the difficulty of each procedure, another column was registered, categorizing each surgery as:

- Major→ Resections involving more than three segments
- Technically major→ Resections involving the posterior side of the liver, although with less than three segments exported
- Minor→ Resections involving a maximum of three segments

After that, a column was dedicated to a binary check of Pringle maneuver execution, with the following one used to specify the total number of minutes passed during the portal clamping, although with free intervals.

Any eventual concurrent procedures were then listed, with the most common one being cholecystectomy, as it's often rendered necessary by the resection area or the metastatic disease. In case of different, more rare operations, these were lumped together in the category "Other procedures". These included instances of peritoneal nodules excision, adrenalectomy, adhesiolysis, and splenectomy.

Some particular procedures, though, were listed separately and checked as performed or not performed singularly. These are the practices most associated with specific liver complications, as they affect the vascular and lymphatic components of this organ:

- Hepatic hilar lymphadenectomy
- Biliary tract reconstruction →The type could be specified in the following column, but the only variant ever used was the Roux-en-Y hepatic-jejeunostomy, therefore this variable was deemed irrelevant
- Vascular reconstruction

Once the section about the resective procedure was terminated, the ablative techniques were taken into consideration.

The first question was if a local treatment had indeed been performed, followed by the specifics on every possible technique used.

The most common was MicroWave Ablation (MWA), as it's quick and effective for tumors up to 5 cm in size, differently from other ablative procedures. Some patients, although very few if compared with the whole pool, were subjected to either Ethanol Injection or Cryotherapy, some of them still combined with MWA. None of them, instead, was treated with RadioFrequency Ablation (RFA).

The last aspects examined were those regarding the final overview of the operation.

The duration of the surgical procedure was first considered as a continuous variable, the value expressed in minutes by calculating the difference between the declared finishing and starting time in the surgery report.

Then, in case the study called for a categorical distinction, these continuous values were grouped together in two categories:

- > 300 minutes
- ≤ 300 minutes

Blood loss was then found, either in the surgical report or written in the clinical diary, and subsequently registered, expressed in cc.

The final inquiry concerned intraoperative death, which luckily affected no one in this patients' pool.

COMPLICATIONS AND HOSPITALIZATION

The data collection for this aspect represented the focal point of the study.

The in-hospital course of convalescence was the starting point, deriving the information from both the clinical diary and the discharge letter.

First, patients were categorized between those who had and who had not experienced complications during their stay. Those subjects were automatically excluded from all further inquiries about their hospitalization morbidities.

Next, every patient's comorbidity was classified by type and location and grouped into gross macro categories:

- Infectious comorbidities → Low fever and high fever/sepsis
- Bleeding → Rectal bleeding, slow-onset anemia, and internal hemorrhage were the most prevalent events, leaving a few instances of various different complications, defined as "others";
- Cardiovascular complications → Hypertension and hypotension were the most frequent, while less represented ones were grouped as "others";
- Respiratory complications → Pleural effusion, pulmonary embolism and desaturation episodes were the only ones deemed relevant, while the anecdotal pulmonary densification or dysphonia were not specified;
- GI complications → Abdominal pain, intestinal disorders such as stipsis, diarrhea or slow peristalsis, vomit, and intestinal fistulae;
- GU complications → The only recurrent type was a slowed reprise in urination, often associated with simultaneous primary surgery;
- Liver complications → The relevant categories were hyperbilirubinemia, hepatic hematoma of any size, and most importantly an eventual biliary leak;
- Other complications → Here, systemic findings of any kind were grouped together, including complications such as ascites, hypokalemia, and anastomotic leaks or failures.

Every recorded complication, independently of their type, was assigned a Clavien-Dindo score based on the clinical diary description of the necessary steps for the complication management and resolution.

The Clavien-Dindo score is useful both as a singular value, as any complication exceeding the IIIa stage is considered as a major morbidity, and as a cumulative score, as it can be used to calculate the Comprehensive complication index.

Therefore, for each patient it was determined if their maximum Clavien-Dindo score was over or under the IIIa threshold:

- 0, I and II → Minor complications, not requiring a surgical or otherwise invasive procedure to be resolved;
- IIIa,b, and IVa,b → Major complications, needing at the very least a local anesthesia and intervention and at worst an intensive care unit stay to be managed;
- V → Patient death (this was never registered during the hospital stay)

Another important criterion recorded was the total number of complications, regardless of their severity. The data were subsequently categorized into two groups based on whether the total number of complications was greater than or less than two.

The next step involved the calculation of the aforementioned Comprehensive complication index (CCI).

This index does not operate as a straightforward additive process. Thus, a patient with two complications will not have a score equivalent to the sum of the individual complication grades' scores. Instead, the actual CCI value is calculated by taking the square root of the sum of the weighted scores for each complication and then dividing by two.

Clavien-Dindo classification (CDC)	Comprehensive Complication Index (CCI) CCI value	wC
I	8,7	300
II	20,9	1750
III a	26,2	2750
III b	33,7	4550
IV a	42,4	7200
IV b	46,2	8550
V	Always results in CCI score of 100	

$$CCI = \frac{\sqrt{wC1 + wC2 \ldots + wCx}}{2}$$

The final CCI score for each patient was analyzed both as a continuous variable and a categorical one, classified as either over or under the threshold of 30 points.

After this initial overview of all the different types of complication, the study focused on those that were specific to the liver.

The investigated variables were, particularly:

- Portal vein thrombosis
- Postoperative bile leak

    - Grade A→A small quantity of bile, which can only require observation and conservative management, such as drainage or supportive care;
    - Grade B→This can be managed with techniques like percutaneous drainage, endoscopic interventions, or other minor surgical procedures;
    - Grade C→An important amount of bile, which requires surgery and is often associated with sepsis or peritonitis.
- Post hepatectomy liver failure
    - Grade A
    - Grade B
    - Grade C
- Postoperative ascites

The next step required a report on any postoperative management treatment performed during the hospital stay, particularly:

- Re-intervention
- Percutaneous drainage →Usually associated with non-severe bile leaks, unspecified fluid masses near the liver or hematomas;
- Postoperative blood transfusion →The specific number of RBC units was then to be recorded.

The final part of information about the hospitalization aimed to analyze the differences in ICU and regular ward stay between different patients.

Through the clinical diary, the date of admission was registered, followed by the date of the main surgical procedure and the discharge date.

The next column was a binary query on the patient's admission to the intensive care unit after the operation room dismissal.

If the patient had been actually transferred to the ICU, the date of discharge was then registered in a separate column.

Afterward, the necessary calculations were made to obtain:

- Length of ICU stay
- Length of ward stay after surgery/ICU
- Total length of stay

The length of ICU stay was then categorized into two groups: people whose intensive care had taken less than two days, and those who instead had been kept under surveillance for two days and upwards.

Ultimately, the only remaining data to investigate was that regarding the after-discharge complications.

These were differentiated between immediate (30-day) and early (90-day) complications, and researched in all the admission reports following the one analyzed for the surgical process.

Besides the presence or absence of said complications, a descriptive category was used to determine the most common types of postoperative morbidity.

FOLLOW UP AND SURVIVAL

With the purpose of calculating overall survival and progression free survival, patients had to be monitored in their postoperative period.

The initial data collected focused on the occurrence of death within the first 90 days after surgery. This early postoperative mortality is often considered a potential indicator of complications directly related to the surgery itself, rather than solely attributable to the underlying tumor.

Overall, this approach helps in assessing the immediate impact of the surgery on patient outcomes and differentiating between issues related to the surgical procedure and those related to the progression of the disease.

The checked instances were:

- In-hospital mortality
- 30-day mortality
- 90-day mortality

Although patients from external centers could not be subjected to a strict follow-up and were therefore often lost after a short period of time, every patient who stayed in the Padua University records survived both the 30 and 90 day period, indicating the presence of a good standard of care enforced before and during this timeframe.

The date associated with the last follow-up of every patient was recorded, along with their oncological status at the time:

- AWD (Alive with disease)
- NED (No evidence of disease)

Besides this, by searching through the personal records of patients stored in the Veneto Database, the eventuality of death was registered on the database. Those who were pronounced dead were eliminated from the oncological status category.

Besides the “Deceased” or “Alive” status, the reported date of death was also registered.

This data allowed us to calculate for each patient the maximum time passed from their last follow up.

For deceased patients, the time since the last follow-up was calculated with their date of death as the endpoint. For patients who are still alive or lost to follow-up, the period without updates was measured using August 31, 2024, as the endpoint.

This was a good enough approximation, as the final check on patients’ status was carried out on September 4, 2024.

STATISTICAL METHOD

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 and survival was expressed as median (interquartile ranges). Survival curves were calculated using the Kaplan–Meier technique and compared with the log-rank test.

Prognostic factors of recurrence 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 (specificare la tabella delle analisi descrittive), 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. The covariates included are:

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).

RESULTS

The collected data was compared across two groups: one that had been administered the doublet therapy FOLFOX or FOLFIRI, and the other that had been treated with the triplet FOLFOXIRI.

The first analysis underlined the main criteria used in the decision to apply doublet or triplet therapy, and the comparability of the two populations.

Demographic analysis

Table 1: Demographic data in 192 patients undergoing liver resection for CRLM

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Gender				0.27
Female	78 / 192 (41%)	51 / 134 (38%)	27 / 58 (47%)	
Male	114 / 192 (59%)	83 / 134 (62%)	31 / 58 (53%)	
Height (m)	1.7 (1.6,1.8)	1.7 (1.6,1.8)	1.7 (1.7,1.8)	0.42
Weight (kg)	73.0 (62.0,82.0)	70.0 (63.5,80.0)	74.5 (61.8,85.5)	0.66
BMI (kg/m²)				0.82
<25	61 / 115 (53%)	43 / 80 (54%)	18 / 35 (51%)	
≥25	54 / 115 (47%)	37 / 80 (46%)	17 / 35 (49%)	
BMI (kg/m²)	24.7 (22.2,27.5)	24.7 (22.5,27.4)	24.7 (21.7,27.8)	0.95
Smoking status				0.29
Current smoker	19 / 192 (9.9%)	16 / 134 (12%)	3 / 58 (5.2%)	
Former smoker	33 / 192 (17%)	24 / 134 (18%)	9 / 58 (16%)	
Never smoker	140 / 192 (73%)	94 / 134 (70%)	46 / 58 (79%)	

Patients across the two groups did not present significant demographic differences.

The gender distribution was similar (p value=0,27), with both groups being composed of more males than females. This is consistent with the known epidemiology of the disease.

Height and weight, expressed through their median and quartile values, were also comparable. Consequently, BMI was found to be equally well distributed across the populations, with similar percentages of patients having values below or above 25 in both groups. (p=0,82).

Although there was a slight variation in the proportion of current, former, and never smokers, the differences were not statistically significant (p = 0.29). The "Triplet" group had a smaller percentage of current smokers, but all in all the smoking status was evidently uninfluential in the choice of treatment. It's therefore clear that the two groups are sufficiently homogeneous regarding demographical and lifestyle characteristics.

Comorbidities and Charlson Comorbidity index

Table 2: Comorbidity data in 192 patients undergoing liver resection for CRLM

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Comorbidity				0.001
No	85 / 192 (44%)	49 / 134 (37%)	36 / 58 (62%)	
Yes	107 / 192 (56%)	85 / 134 (63%)	22 / 58 (38%)	
Diabetes mellitus				0.083
No	175 / 192 (91%)	119 / 134 (89%)	56 / 58 (97%)	
Yes	17 / 192 (8.9%)	15 / 134 (11%)	2 / 58 (3.4%)	
Hypercholesterolemia				0.056
No	169 / 192 (88%)	114 / 134 (85%)	55 / 58 (95%)	
Yes	23 / 192 (12%)	20 / 134 (15%)	3 / 58 (5.2%)	
Arterial hypertension				<0.001
No	122 / 192 (64%)	75 / 134 (56%)	47 / 58 (81%)	
Yes	70 / 192 (36%)	59 / 134 (44%)	11 / 58 (19%)	
Myocardial infarction / Ischemic heart disease				0.18
No	186 / 192 (97%)	128 / 134 (96%)	58 / 58 (100%)	
Yes	6 / 192 (3.1%)	6 / 134 (4.5%)	0 / 58 (0%)	
Peripheral vascular disease				0.11
No	180 / 192 (94%)	123 / 134 (92%)	57 / 58 (98%)	
Yes	12 / 192 (6.3%)	11 / 134 (8.2%)	1 / 58 (1.7%)	
Liver disease				>0.99
No	185 / 192 (96%)	129 / 134 (96%)	56 / 58 (97%)	
Yes	7 / 192 (3.6%)	5 / 134 (3.7%)	2 / 58 (3.4%)	
GI disease				0.12

Gastritis	4 / 17 (24%)	2 / 14 (14%)	2 / 3 (67%)	
Peptic ulcer	13 / 17 (76%)	12 / 14 (86%)	1 / 3 (33%)	
Other significant comorbidity				0.16
No	136 / 192 (71%)	99 / 134 (74%)	37 / 58 (64%)	
Yes	56 / 192 (29%)	35 / 134 (26%)	21 / 58 (36%)	
Charlson Comorbidity Index				<0.001
6	40 / 192 (21%)	20 / 134 (15%)	20 / 58 (34%)	
7-8	138 / 192 (72%)	100 / 134 (75%)	38 / 58 (66%)	
9+	14 / 192 (7.3%)	14 / 134 (10%)	0 / 58 (0%)	
Previous extra hepatic abdominal surgery				0.81
No	110 / 192 (57%)	76 / 134 (57%)	34 / 58 (59%)	
Yes	82 / 192 (43%)	58 / 134 (43%)	24 / 58 (41%)	

The next analysis aimed at highlighting possible differences between the two groups in pre-operative morbidity.

In fact, the presence of comorbidities alone presented a strong association ($p=0.001$) with the use of a doublet rather than a triplet therapy, which is comprehensible given the higher systemic toxicity associated with the latter over the former.

The comorbidities with the highest statistical significance were hypercholesterolemia ($p=0.056$) and arterial hypertension ($p<0.001$). In both cases, the percentage of affected patients treated with FOLFOX or FOLFIRI was more than double that of those treated with FOLFOXIRI.

Other comorbidities, such as diabetes mellitus, although not statistically significant ($p=0.083$), showed a trend towards correlation with treatment choice, being more prevalent in the doublet group. Peripheral vascular disease was even less significant ($p=0.11$), but still appeared slightly more common in patients receiving doublet therapy.

In contrast, parameters such as liver disease and a history of extra-hepatic abdominal surgery were evenly distributed between the two groups of patients and, therefore, had no impact on the choice of therapy.

Finally, a highly significant correlation was found between Charlson Comorbidity Index (CCI) scores and the administration of doublet therapy ($p<0.001$). This indicates that not only the presence of comorbidities but also their number and type influence treatment selection. The extremely low p-value suggests that as the CCI score increases, there is a greater tendency to prescribe double rather than triple therapy.

Diagnosis and treatment of the primary tumor

Table 3: Primary CRC characteristics

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Age at CRC diagnosis	59.0 (50.0,65.0)	61.0 (54.0,67.0)	51.5 (48.0,61.8)	<0.001
CRC diagnosis age>65				0.009
Over 65	47 / 192 (24%)	40 / 134 (30%)	7 / 58 (12%)	
Under 65	145 / 192 (76%)	94 / 134 (70%)	51 / 58 (88%)	
Colon tumor localization				0.056
Left	94 / 192 (49%)	71 / 134 (53%)	23 / 58 (40%)	
Rectum	39 / 192 (20%)	29 / 134 (22%)	10 / 58 (17%)	
Right	49 / 192 (26%)	30 / 134 (22%)	19 / 58 (33%)	
Transversum	10 / 192 (5.2%)	4 / 134 (3.0%)	6 / 58 (10%)	
Positive lymph nodes				0.65
0	78 / 192 (41%)	53 / 134 (40%)	25 / 58 (43%)	
1	114 / 192 (59%)	81 / 134 (60%)	33 / 58 (57%)	
Age at first colectomy	59.5 (50.0,66.0)	61.0 (54.5,67.5)	51.0 (47.5,62.0)	<0.001
Liver first / same time				0.18
No	126 / 192 (66%)	92 / 134 (69%)	34 / 58 (59%)	
Yes	66 / 192 (34%)	42 / 134 (31%)	24 / 58 (41%)	
Diagnosis to colectomy	63.0 (9.0,213.0)	47.0 (0.0,212.5)	143.0 (29.0,217.0)	0.067
Adjuvant therapy				0.043
No	176 / 192 (92%)	119 / 134 (89%)	57 / 58 (98%)	
Yes	16 / 192 (8.3%)	15 / 134 (11%)	1 / 58 (1.7%)	
Type of adjuvant				0.35
CAPECITABINE	3 / 17 (18%)	3 / 16 (19%)	0 / 1 (0%)	
Non specificato	3 / 17 (18%)	2 / 16 (13%)	1 / 1 (100%)	
XELOX	11 / 17 (65%)	11 / 16 (69%)	0 / 1 (0%)	

Data concerning the primary CRC characteristics showcased especially the high correlation between patients' younger age and their eligibility for the more aggressive treatment.

Age was found to be equally relevant if calculated at the time of diagnosis or in correspondence with the colectomy.

By analyzing the median ages between groups, the significance was extremely relevant ($p<0.001$), and this was confirmed by the categorical comparison between the prevalence of adult versus young elderly patients in the two populations. The percentage of patients over 65 years of age that were considered "fit" for a triplet regimen was 12%, less than half its counterpart referred to doublets. (30%)

Another significant difference ($p=0.043$) was found in post colectomy adjuvant therapy administration, with fewer patients receiving it in the "Triplet" group than in the "Doublet" one.

Furthermore, there was a borderline statistically significant difference in tumor localization ($p=0.056$), with more tumors localized to the right side in the second and more left-sided tumors in the first group. Transversum located cancers, similarly to right-side ones, seemed to also push towards a more aggressive regimen choice, while the rectal distribution was similarly prevalent in both groups.

Of uncertain interpretation was the result that showed a borderline relevant ($p=0,067$) tendency of triplet patients to have longer intervals of time between CRC diagnosis and colectomy.

Notably, lymph node positivity was not associated with any specific treatment, showing an even distribution through the two groups, as was the choice to perform the liver treatment during or after the colectomy.

Diagnosis and preoperative characteristics of CRLM

Table 4: Metastatic disease characteristics

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Synchronous vs. Metachronous CRLM				0.006
Metachronous	40 / 192 (21%)	35 / 134 (26%)	5 / 58 (8.6%)	
Synchronous	152 / 192 (79%)	99 / 134 (74%)	53 / 58 (91%)	
Colectomy to CRLM (months)	-1.0 (-6.8,2.0)	0.0 (-6.0,5.0)	-4.0 (-7.0,0.0)	0.012
Number of metastases				0.11
>10	26 / 192 (14%)	14 / 134 (10%)	12 / 58 (21%)	
6-10	46 / 192 (24%)	31 / 134 (23%)	15 / 58 (26%)	
1-5	120 / 192 (63%)	89 / 134 (66%)	31 / 58 (53%)	
Single nodule				0.072
No	170 / 192 (89%)	115 / 134 (86%)	55 / 58 (95%)	
Yes	22 / 192 (11%)	19 / 134 (14%)	3 / 58 (5.2%)	
Localization				0.47

Bilateral	132 / 192 (69%)	90 / 134 (67%)	42 / 58 (72%)	
Unilateral	60 / 192 (31%)	44 / 134 (33%)	16 / 58 (28%)	
Side if unilateral				>0.99
Left	10 / 60 (17%)	7 / 44 (16%)	3 / 16 (19%)	
Right	50 / 60 (83%)	37 / 44 (84%)	13 / 16 (81%)	
Metastases' max size (mm)	31.5 (21.5,53.0)	30.5 (22.0,50.0)	33.0 (20.0,54.8)	0.90
Largest lesion				0.31
>30 mm	47 / 192 (24%)	37 / 134 (28%)	10 / 58 (17%)	
>50 mm	49 / 192 (26%)	33 / 134 (25%)	16 / 58 (28%)	
Max 30 mm	96 / 192 (50%)	64 / 134 (48%)	32 / 58 (55%)	

As for metastatic disease, the strongest association between its characteristics and the choice of neoadjuvant regimen was found in the categorization of synchronous versus metachronous CRLM nodules (p=0.006). Differentiating between single and multiple nodule patients showed a borderline significance of 0.072.

The exact number of metastases and their localization were found to be insignificant, with p values over 0.1. Their maximum size, although with a median difference of 3 mm, was also not significant (p=0.90)

Neoadjuvant regimen administered

Table 5: Neoadjuvant therapy

	ALL PATIENTS (192)	**DOUBLET (134)**	**TRIPLET (58)**	***p Value***
Number of cycles	8.0 (6.0,11.0)	8.0 (6.0,11.0)	8.0 (6.0,11.0)	0.66
Target therapies				0.19
No	26 / 192 (14%)	21 / 134 (16%)	5 / 58 (8.6%)	
Yes	166 / 192 (86%)	113 / 134 (84%)	53 / 58 (91%)	
Bevacizumab				<0.001
No	91 / 192 (47%)	76 / 134 (57%)	15 / 58 (26%)	
Yes	101 / 192 (53%)	58 / 134 (43%)	43 / 58 (74%)	
Panitumumab				0.050
No	156 / 192 (81%)	104 / 134 (78%)	52 / 58 (90%)	
Yes	36 / 192 (19%)	30 / 134 (22%)	6 / 58 (10%)	

Cetuximab				0.047
No	164 / 192 (85%)	110 / 134 (82%)	54 / 58 (93%)	
Yes	28 / 192 (15%)	24 / 134 (18%)	4 / 58 (6.9%)	
Immunotherapy				<0.001
No	183 / 192 (95%)	134 / 134 (100%)	49 / 58 (84%)	
Yes	9 / 192 (4.7%)	0 / 134 (0%)	9 / 58 (16%)	
CT end to surgery (months)				0.44
Over 6	18 / 192 (9.4%)	14 / 134 (10%)	4 / 58 (6.9%)	
Under 6	174 / 192 (91%)	120 / 134 (90%)	54 / 58 (93%)	
MAINTENANCE N°of cycles	3.0 (2.0;5.0)	3.0 (2.0;4.0)	3.0 (1.0;5.0)	0.89
LV5FU				0.29
Yes	9 / 17 (53%)	5 / 12 (42%)	4 / 5 (80%)	
Irinotecan				>0.99
Yes	1 / 17 (5.9%)	1 / 12 (8.3%)	0 / 5 (0%)	
Targeted therapies				>0.99
Yes	15 / 17 (88%)	10 / 12 (83%)	5 / 5 (100%)	
Bevacizumab				>0.99
Yes	8 / 17 (47%)	6 / 12 (50%)	2 / 5 (40%)	
Panitumumab				0.51
Yes	2 / 17 (12%)	1 / 12 (8.3%)	1 / 5 (20%)	
Cetuximab				>0.99
Yes	4 / 17 (24%)	3 / 12 (25%)	1 / 5 (20%)	
Immunotherapy				0.074
Avelumab	1 / 17 (5.9%)	0 / 12 (0%)	1 / 5 (20%)	
Nivolumab	1 / 17 (5.9%)	0 / 12 (0%)	1 / 5 (20%)	
No	15 / 17 (88%)	12 / 12 (100%)	3 / 5 (60%)	

Regarding combinations with target therapies, Bevacizumab is used significantly more often in the "TRIPLET" group, sporting a 74% in contrast to the 43% in the "DOUBLET" group ($p<0.001$), while the use of Panitumumab and Cetuximab is slightly less frequent in association to FOLFOXIRI rather than FOLFIRI or FOLFOX ($p=0.047$ and $p=0.05$).

Immunotherapy, too, was strongly associated with triplet administration, as no instances of its combination with doublets were recorded.

In regard to maintenance therapy, no statistically relevant data was found, with every category showing a p value of over 0.3.

Prognostic factors

Table 5: Pre-operative data

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
CEA ug/L	3.4 (0.0,11.9)	3.8 (0.0,11.4)	2.5 (0.0,12.4)	0.50
CEA > 200 ug/L				>0.99
No	185 / 192 (96%)	129 / 134 (96%)	56 / 58 (97%)	
Yes	7 / 192 (3.6%)	5 / 134 (3.7%)	2 / 58 (3.4%)	
FONG SCORE				0.18
0	4 / 192 (2.1%)	4 / 134 (3.0%)	0 / 58 (0%)	
1	11 / 192 (5.7%)	8 / 134 (6.0%)	3 / 58 (5.2%)	
2	63 / 192 (33%)	48 / 134 (36%)	15 / 58 (26%)	
3	88 / 192 (46%)	55 / 134 (41%)	33 / 58 (57%)	
4	25 / 192 (13%)	19 / 134 (14%)	6 / 58 (10%)	
5	1 / 192 (0.5%)	0 / 134 (0%)	1 / 58 (1.7%)	
Age at operation	61.0 (51.0,67.0)	62.5 (56.0,68.0)	53.5 (48.0,62.0)	<0.001
Age at operation				0.002
Over 65	56 / 192 (29%)	48 / 134 (36%)	8 / 58 (14%)	
Under 65	136 / 192 (71%)	86 / 134 (64%)	50 / 58 (86%)	
CRLM to operation (days)	259.5 (194.5,352.0)	271.0 (200.5,370.3)	227.0 (190.8,315.0)	0.11
ASA score				0.36
1-2	103 / 192 (54%)	69 / 134 (51%)	34 / 58 (59%)	
3-4	89 / 192 (46%)	65 / 134 (49%)	24 / 58 (41%)	

No preoperative data was found to be relevant, except for the age at the time of surgery, which had the same correlation to a regimen as the other previously examined ages. CEA, FONG score and ASA score were comparable across groups.

Surgical procedures and intraoperative data

Table 6: Surgical data

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Resection of the primary				0.42
No	140 / 192 (73%)	100 / 134 (75%)	40 / 58 (69%)	
Yes	52 / 192 (27%)	34 / 134 (25%)	18 / 58 (31%)	
Surgical Approach				0.33
Laparoscopic	132 / 192 (69%)	88 / 134 (66%)	44 / 58 (76%)	
Open	58 / 192 (30%)	44 / 134 (33%)	14 / 58 (24%)	
Percutaneous	2 / 192 (1.0%)	2 / 134 (1.5%)	0 / 58 (0%)	
Conversion to open				0.56
No	177 / 192 (92%)	122 / 134 (91%)	55 / 58 (95%)	
Yes	15 / 192 (7.8%)	12 / 134 (9.0%)	3 / 58 (5.2%)	
Operation type				0.15
Local treatment only	49 / 192 (26%)	35 / 134 (26%)	14 / 58 (24%)	
Resection MWA	77 / 192 (40%)	48 / 134 (36%)	29 / 58 (50%)	
Resection only	66 / 192 (34%)	51 / 134 (38%)	15 / 58 (26%)	
Previous PVE/PVL				0.63
No	175 / 192 (91%)	123 / 134 (92%)	52 / 58 (90%)	
Yes	17 / 192 (8.9%)	11 / 134 (8.2%)	6 / 58 (10%)	
Two stage procedure				0.62
No	172 / 192 (90%)	121 / 134 (90%)	51 / 58 (88%)	
Yes	20 / 192 (10%)	13 / 134 (9.7%)	7 / 58 (12%)	
Type				>0.99
ALPPS	8 / 20 (40%)	5 / 13 (38%)	3 / 7 (43%)	
LAPS	12 / 20 (60%)	8 / 13 (62%)	4 / 7 (57%)	
Surgical complexity				0.79
Major	41 / 143 (29%)	27 / 99 (27%)	14 / 44 (32%)	
Minor	84 / 143 (59%)	60 / 99 (61%)	24 / 44 (55%)	

Technically major	18 / 143 (13%)	12 / 99 (12%)	6 / 44 (14%)	
Pringle maneuver				0.70
No	149 / 192 (78%)	105 / 134 (78%)	44 / 58 (76%)	
Yes	43 / 192 (22%)	29 / 134 (22%)	14 / 58 (24%)	
Duration of clamping (min)	20.0 (14.5,36.5)	22.0 (15.0,36.0)	18.3 (14.3,38.3)	0.78
Concurrent procedure				0.82
No	87 / 192 (45%)	60 / 134 (45%)	27 / 58 (47%)	
Yes	105 / 192 (55%)	74 / 134 (55%)	31 / 58 (53%)	
Descriptive				0.71
Cholecystectomy	64 / 105 (61%)	47 / 74 (64%)	17 / 31 (55%)	
Other surgery	41 / 105 (39%)	27 / 74 (36%)	14 / 31 (45%)	
Hepatic hilar lymphadenectomy				0.21
No	147 / 192 (77%)	106 / 134 (79%)	41 / 58 (71%)	
Yes	45 / 192 (23%)	28 / 134 (21%)	17 / 58 (29%)	
Biliary reconstruction				0.64
No	187 / 192 (97%)	131 / 134 (98%)	56 / 58 (97%)	
Yes	5 / 192 (2.6%)	3 / 134 (2.2%)	2 / 58 (3.4%)	
Vascular reconstruction				0.37
No	186 / 192 (97%)	131 / 134 (98%)	55 / 58 (95%)	
Yes	6 / 192 (3.1%)	3 / 134 (2.2%)	3 / 58 (5.2%)	
Local treatment				0.092
No	63 / 192 (33%)	49 / 134 (37%)	14 / 58 (24%)	
Yes	129 / 192 (67%)	85 / 134 (63%)	44 / 58 (76%)	
Microwave MWA				0.092
No	63 / 192 (33%)	49 / 134 (37%)	14 / 58 (24%)	
Yes	129 / 192 (67%)	85 / 134 (63%)	44 / 58 (76%)	
Operation time (min)	330.0 (215.0,428.8)	312.5 (205.0,420.0)	365.0 (261.3,451.3)	0.10

Surgical data showed that nearly all examined parameters were independent of the choice of regimen. One of the two categories that showed borderline statistical significance was the use of local treatment

(p=0.092), which was slightly more common in patients treated with triplet therapy (76%) compared to those receiving doublet therapy (63%).

The other category was total surgery time, with a strong suggestion (p=0.06) of an association between the use of FOLFOXIRI and surgeries lasting more than 300 minutes (5 hours).

The kind of approach and the eventual conversion to open surgery (p>0.33), similarly to secondary surgical procedures and Pringle clamping, were evenly distributed between the cohorts.

All other categories, including surgical complexity (p=0.79) despite the greater efficacy of triplet therapy in nodule downsizing were not statistically related to the choice of therapy.

Duration of hospital stay

Table 8: Hospitalization time in surgical patients

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
ICU after surgery				0.33
No	99 / 192 (52%)	66 / 134 (49%)	33 / 58 (57%)	
Yes	93 / 192 (48%)	68 / 134 (51%)	25 / 58 (43%)	
ICU stay (days)				0.98
>1	20 / 192 (10%)	14 / 134 (10%)	6 / 58 (10%)	
0-1	172 / 192 (90%)	120 / 134 (90%)	52 / 58 (90%)	
Ward LOS	5.0 (3.0,7.0)	5.0 (3.0,7.0)	5.0 (3.3,7.0)	0.63
Ward+ICU LOS	6.0 (3.8,8.0)	6.0 (3.0,8.0)	5.0 (4.0,8.0)	0.43
Total inpatient days	7.0 (4.0,11.0)	7.0 (4.0,11.0)	6.0 (4.0,10.8)	0.41

Hospitalization, being closely related to the presence and severity of complications, also showed no particular asymmetry in the distribution of prolonged hospital stays or ICU admission. Regarding the ICU stay, specifically, the percentages of patients who had been kept for more than a day were exactly the same between the two groups.

Postoperative complications distribution

Table 7: Immediate postoperative complications in 192 patients affected by CRLM

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
Intra operative blood loss (ml)	400.0 (200.0,700.0)	400.0 (175.0,650.0)	550.0 (400.0,975.0)	0.10
Intra operative death				

No	192 / 192 (100%)	134 / 134 (100%)	58 / 58 (100%)	
Post operative complications				0.70
No	69 / 192 (36%)	47 / 134 (35%)	22 / 58 (38%)	
Yes	123 / 192 (64%)	87 / 134 (65%)	36 / 58 (62%)	
Infective complications				0.37
Fever over 38.5	39 / 90 (43%)	28 / 60 (47%)	11 / 30 (37%)	
Low fever	51 / 90 (57%)	32 / 60 (53%)	19 / 30 (63%)	
Bleeding				0.22
Anemia	14 / 21 (67%)	10 / 14 (71%)	4 / 7 (57%)	
Hemorrhage	2 / 21 (9.5%)	2 / 14 (14%)	0 / 7 (0%)	
Other	2 / 21 (9.5%)	0 / 14 (0%)	2 / 7 (29%)	
Rectal bleeding	3 / 21 (14%)	2 / 14 (14%)	1 / 7 (14%)	
Cardiovascular complications				0.077
Hypertension	9 / 16 (56%)	4 / 11 (36%)	5 / 5 (100%)	
Hypotension	3 / 16 (19%)	3 / 11 (27%)	0 / 5 (0%)	
Other	4 / 16 (25%)	4 / 11 (36%)	0 / 5 (0%)	
Pulmonary complications				0.52
Desaturation	6 / 23 (26%)	6 / 19 (32%)	0 / 4 (0%)	
Other	3 / 23 (13%)	2 / 19 (11%)	1 / 4 (25%)	
Pleural effusion	13 / 23 (57%)	10 / 19 (53%)	3 / 4 (75%)	
Pulmonary embolism	1 / 23 (4.3%)	1 / 19 (5.3%)	0 / 4 (0%)	
GI complications				>0.99
Abdominal pain	1 / 16 (6.3%)	1 / 13 (7.7%)	0 / 3 (0%)	
Intestinal disorders	3 / 16 (19%)	2 / 13 (15%)	1 / 3 (33%)	
Intestinal fistula	2 / 16 (13%)	2 / 13 (15%)	0 / 3 (0%)	
Other	1 / 16 (6.3%)	1 / 13 (7.7%)	0 / 3 (0%)	
Vomit	9 / 16 (56%)	7 / 13 (54%)	2 / 3 (67%)	
Liver complications				0.53
Bile leak	9 / 23 (39%)	7 / 16 (44%)	2 / 7 (29%)	

Hepatic hematoma	12 / 23 (52%)	7 / 16 (44%)	5 / 7 (71%)	
Hyperbilirubinemia	2 / 23 (8.7%)	2 / 16 (13%)	0 / 7 (0%)	
GU complications				>0.99
Difficult urination	7 / 8 (88%)	7 / 8 (88%)	0 / 0 (NA%)	
Other	1 / 8 (13%)	1 / 8 (13%)	0 / 0 (NA%)	
Other complications				0.34
Anastomotic failure	1 / 20 (5.0%)	0 / 15 (0%)	1 / 5 (20%)	
Ascites	6 / 20 (30%)	4 / 15 (27%)	2 / 5 (40%)	
Hypokalemia	2 / 20 (10%)	2 / 15 (13%)	0 / 5 (0%)	
Other	11 / 20 (55%)	9 / 15 (60%)	2 / 5 (40%)	
Clavien Dindo ≥ 3				0.45
No	142 / 192 (74%)	97 / 134 (72%)	45 / 58 (78%)	
Yes	50 / 192 (26%)	37 / 134 (28%)	13 / 58 (22%)	
N°of complications >2				0.95
No	166 / 192 (86%)	116 / 134 (87%)	50 / 58 (86%)	
Yes	26 / 192 (14%)	18 / 134 (13%)	8 / 58 (14%)	
Comprehensive Complication Index	20.9 (0.0,29.6)	20.9 (0.0,29.6)	20.9 (0.0,30.5)	0.73
CCI >30				0.68
No	146 / 192 (76%)	103 / 134 (77%)	43 / 58 (74%)	
Yes	46 / 192 (24%)	31 / 134 (23%)	15 / 58 (26%)	
Hepatic / Biliary complications				0.80
No	167 / 192 (87%)	116 / 134 (87%)	51 / 58 (88%)	
Yes	25 / 192 (13%)	18 / 134 (13%)	7 / 58 (12%)	
General complications				0.94
No	72 / 192 (38%)	50 / 134 (37%)	22 / 58 (38%)	
Yes	120 / 192 (63%)	84 / 134 (63%)	36 / 58 (62%)	
Portal vein thrombosis				

No	192 / 192 (100%)	134 / 134 (100%)	58 / 58 (100%)	
Post operative bile leak				0.78
No	176 / 192 (92%)	122 / 134 (91%)	54 / 58 (93%)	
Yes	16 / 192 (8.3%)	12 / 134 (9.0%)	4 / 58 (6.9%)	
Grade of bile leak				0.31
A	9 / 16 (56%)	8 / 12 (67%)	1 / 4 (25%)	
B	6 / 16 (38%)	3 / 12 (25%)	3 / 4 (75%)	
C	1 / 16 (6.3%)	1 / 12 (8.3%)	0 / 4 (0%)	
Post hepatectomy liver failure PHLF				
No	192 / 192 (100%)	134 / 134 (100%)	58 / 58 (100%)	
Post operative ascites				0.76
No	178 / 192 (93%)	125 / 134 (93%)	53 / 58 (91%)	
Yes	14 / 192 (7.3%)	9 / 134 (6.7%)	5 / 58 (8.6%)	
Re intervention				0.76
No	180 / 192 (94%)	126 / 134 (94%)	54 / 58 (93%)	
Yes	12 / 192 (6.3%)	8 / 134 (6.0%)	4 / 58 (6.9%)	
Percutaneous drainage				0.39
No	166 / 192 (86%)	114 / 134 (85%)	52 / 58 (90%)	
Yes	26 / 192 (14%)	20 / 134 (15%)	6 / 58 (10%)	
Post operative blood transfusion				0.41
No	168 / 192 (88%)	119 / 134 (89%)	49 / 58 (84%)	
Yes	24 / 192 (13%)	15 / 134 (11%)	9 / 58 (16%)	
RBCs transfusion units				0.26
>3	4 / 23 (17%)	4 / 15 (27%)	0 / 8 (0%)	
1-2	19 / 23 (83%)	11 / 15 (73%)	8 / 8 (100%)	

The postoperative complications were the true focus of the whole study.

Not only hepatic complications, but morbidity involving any apparatus was considered.

Intraoperative blood loss was borderline significant (p=0.1), with a higher chance of bleeding associated with FOLFOXIRI, while postoperative bleeding as well as every other different type of complication had a p value surpassing 0.1.

The Clavien Dindo classification also obtained similar results, with a non-significant p value of 0.45.

The analyses of specific complications regarding the liver, such as ascites, liver failure, biliary leak and portal vein thrombosis also yielded no significant results. The slightly higher prevalence of B-grade biliary leaks in the FOLFOXIRI group cannot be made into a correlation because of the low numerosity.

Other post-operative procedures, such as re-operation and blood transfusion were also comparable between the groups.

Follow-up data

Table 9: Survival and follow up

	ALL PATIENTS (192)	DOUBLET (134)	TRIPLET (58)	*p Value*
30 day readmission				0.36
No	178 / 192 (93%)	126 / 134 (94%)	52 / 58 (90%)	
Yes	14 / 192 (7.3%)	8 / 134 (6.0%)	6 / 58 (10%)	
Reason for readmission				0.046
Hepatic drainage	4 / 14 (29%)	0 / 8 (0%)	4 / 6 (67%)	
Hyperpyrexia	2 / 14 (14%)	2 / 8 (25%)	0 / 6 (0%)	
Jaundice	2 / 14 (14%)	2 / 8 (25%)	0 / 6 (0%)	
Other	6 / 14 (43%)	4 / 8 (50%)	2 / 6 (33%)	
90 day morbidity				0.16
No	154 / 192 (80%)	111 / 134 (83%)	43 / 58 (74%)	
Yes	38 / 192 (20%)	23 / 134 (17%)	15 / 58 (26%)	
Complications descriptive				0.94
Ascites	1 / 38 (2.6%)	1 / 23 (4.3%)	0 / 15 (0%)	
Bile leak	3 / 38 (7.9%)	2 / 23 (8.7%)	1 / 15 (6.7%)	
Hepatic drainage	2 / 38 (5.3%)	2 / 23 (8.7%)	0 / 15 (0%)	
Infection	11 / 38 (29%)	6 / 23 (26%)	5 / 15 (33%)	
Intestinal disorders	5 / 38 (13%)	2 / 23 (8.7%)	3 / 15 (20%)	

Other	13 / 38 (34%)	8 / 23 (35%)	5 / 15 (33%)	
Pleural effusion	3 / 38 (7.9%)	2 / 23 (8.7%)	1 / 15 (6.7%)	
30 day mortality				
90 day mortality				
Patient status				0.034
Alive	145 / 192 (76%)	107 / 134 (80%)	38 / 58 (66%)	
Deceased	47 / 192 (24%)	27 / 134 (20%)	20 / 58 (34%)	
Status if alive				0.53
AWD	69 / 143 (48%)	49 / 105 (47%)	20 / 38 (53%)	
NED	74 / 143 (52%)	56 / 105 (53%)	18 / 38 (47%)	
Survival/last follow up (days)	432.0 (101.8,857.0)	422.0 (63.0,777.3)	571.5 (237.3,908.3)	0.15
OS (months)	14.4 (3.4,28.6)	14.1 (2.1,25.9)	19.1 (7.9,30.3)	0.15

Finally, the analysis of patients' follow up period showed some differences between the pools of patients.

Although the rates of 30-day readmission were comparable, triplet-based therapies were linked to a higher probability (p=0.46) of the development of a fluid hepatic mass in need of drainage, be it caused by bleeding or bile leakage.

Instances of hyperpyrexia and jaundice were instead slightly more common in doublet therapy patients, while other, less specific complications, were evenly distributed between the groups.

The numbers showed that more patients in the "TRIPLET" group are deceased (34%) compared to the "DOUBLET" group (20%), with a statistically significant difference (p=0.034).
This could be attributed to a higher chance of post-hospitalization complications in the FOLFOXIRI pool, but many patients were also lost to follow up because of their different region of origin, which precluded the study from registering their eventual death. Therefore, this information should be further examined.

While the median OS is longer for the "TRIPLET" group, with a value of 19.1 months versus 14.1 months in the "DOUBLET" group, the p-value of 0.15 suggests this difference is not statistically significant.

COX model analysis

Various clinical and demographic characteristics were analyzed for their association with overall survival (OS).

The hazard ratio (HR) for males compared to females is 0.94 (p=0.8). This indicates that gender is not a significant predictor of survival in this analysis, as the HR is close to 1 and the p-value is well above 0.05.

Body metrics showed no significant association with survival either, with HRs of 0.77 for BMI >25 (p=0.5) and 0.97 for BMI as a continuous variable (p=0.5).

Smoking history has some impact on survival, with former smokers showing an HR of **0.41** (p=0.094) and never smokers an HR of **0.34** (p=0.011). This indicates a significant protective effect for those who never smoked, suggesting that non-smokers have better survival compared to current smokers.

As for comorbidities, their presence does not appear to significantly affect survival in this cohort.

Tumor location plays a significant role in survival:

- Right colon tumors have a higher hazard for worse outcomes, with an HR of **2.30** (p=0.020).
- Tumors located in the rectum and transversum suggest a trend toward worse outcomes, but not significantly.

Positive lymph nodes are a significant predictor of worse survival outcomes, with an HR of **2.40**.

Age at diagnosis and age at colectomy both have no significant impact on survival, as does adjuvant therapy.

The comparison between doublet (DOPP) and triplet (TRI) chemotherapy shows an HR of **1.45** (p=0.2), reconfirming no significant difference in overall survival between the two regimens. This could indicate that triplet therapy, while more aggressive, does not necessarily lead to better survival outcomes in this cohort.

Bevacizumab and panitumumab (targeted therapies) do not show significant associations with survival, with HRs of **1.20** and **0.54** respectively.

Post-operative complications (HR: 1.09, p=0.8) and specific complications such as **bile leak** or **reoperation** also show no significant effect on survival, suggesting an optimal management of postoperative morbidity.

Postoperative bile leak	192			
No		—	—	
Yes		0.85	0.26, 2.75	0.8
Grade of bile leak	16			
A		—	—	
B		2.16	0.20, 23.9	0.5
C				
Postoperative ascites	192			
No		—	—	
Yes		0.40	0.06, 2.91	0.4

Severe post-operative complications (Clavien-Dindo ≥3) show a non-significant HR of **1.03** (p>0.9), suggesting no strong effect on long-term survival despite their potential short-term impact.

The **FONG score**, which is used to predict outcomes in metastatic colorectal cancer, has a significant association with survival, with an HR of **1.53** (p=0.017). This indicates that a higher FONG score, reflecting more advanced disease, is associated with worse survival outcomes.

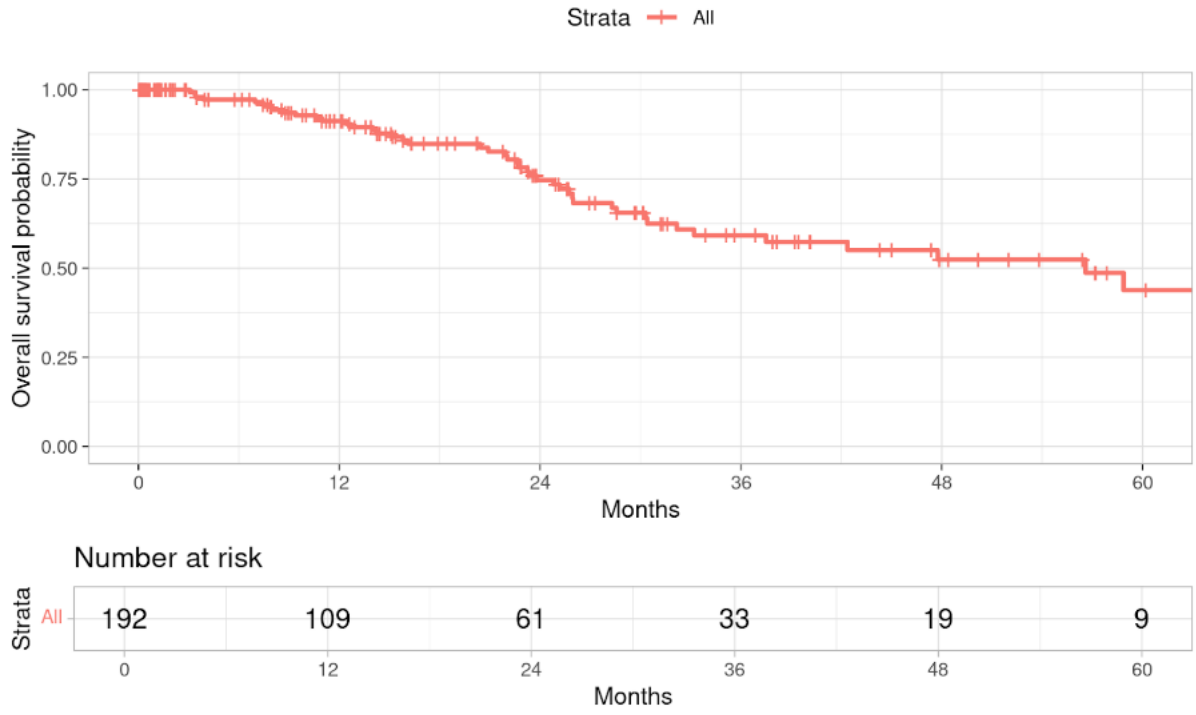
This univariate Cox analysis shows several key findings, coherent with literature:

- **Lymph node positivity** and **right-sided colon tumors** are strong negative predictors of survival.
- **Never smokers** have significantly better survival compared to current smokers.
- The **FONG score** is a significant predictor of poorer outcomes in metastatic disease.
- **Triplet therapy** does not seem to confer a significant survival advantage over doublet therapy, and other treatments like **bevacizumab** and **panitumumab** also do not show a strong survival benefit in this cohort.

Kaplan Meier Curves

Afterwards, a Kaplan Meier curve analysis was executed to better stratify patients based on preoperative characteristics.

KM OS

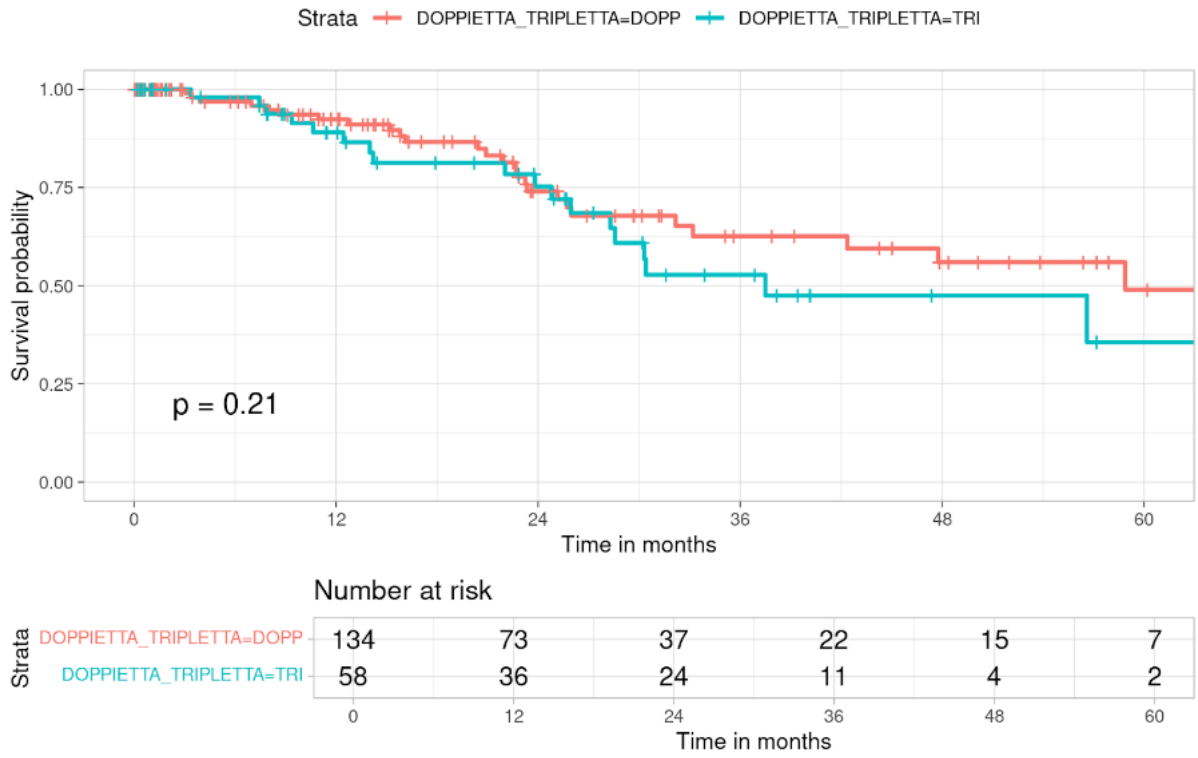


The Kaplan-Meier curves for overall survival across the entire cohort showed a decreasing trend in survival over time, with yearly checkpoints.
At 12 months, the survival rate was quite high, with a score of 91.2%, but it steadily declines to 75% at 24 months, and arrives at 43.8% at 60 months.

This decline in survival rates indicates that nearly half of the patients survive beyond 5 years, although a significant proportion does not, highlighting the aggressive nature of the disease being studied.

This graph alone does not give significant new data, but it's important as a starting base for comparison with the stratified data.

KM stratificata tripletta-doppietta



The survival data stratified by chemotherapy regimen showed distinct differences between the "DOPP" (doublet) and "TRI" (triplet) groups.

At the 12 months checkpoint, both groups showed relatively high survival rates: 92.36% for the doublet group and 89.06% for the triplet group, with no statistically significant differences.

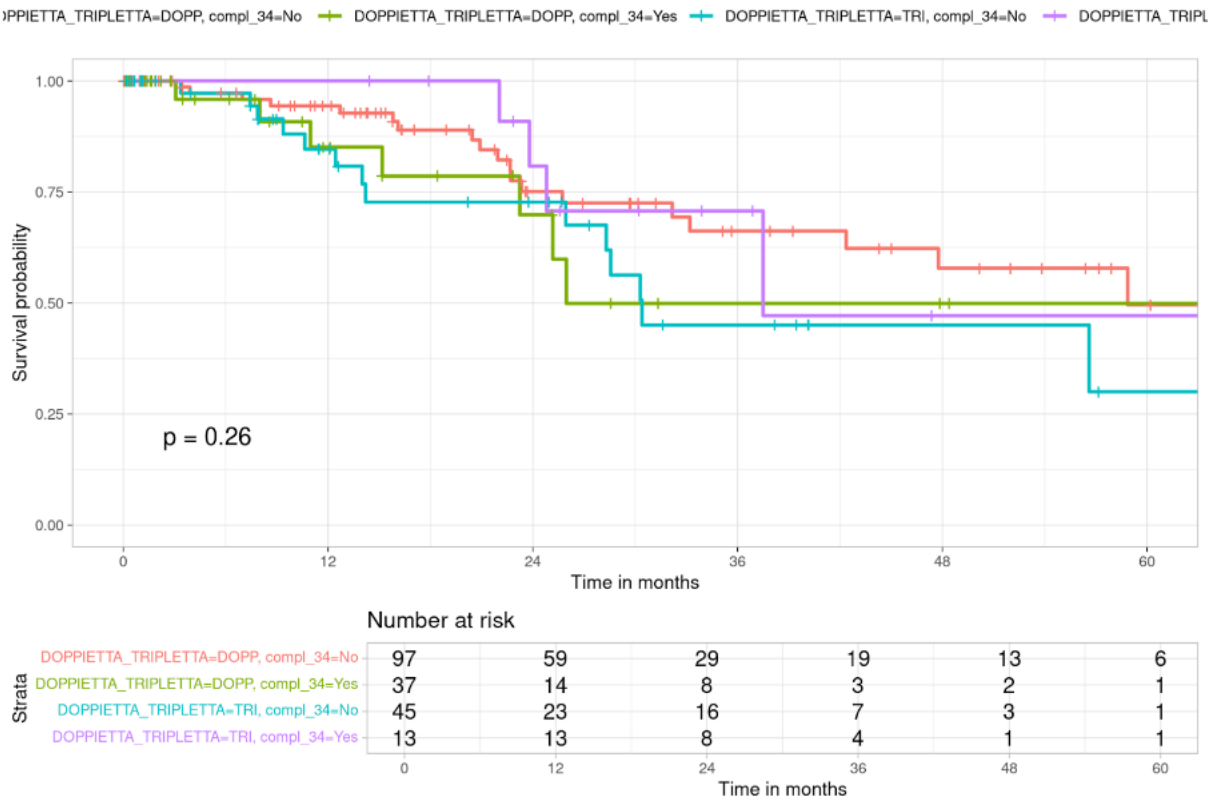
At the 24 months step the survival rates dropped to 74.0% for the doublet group and 75.23% for the triplet group, showing a brief convergence in the curves. Again, the survival was quite comparable between the two regimens at this point.

At the 36 months mark, a noticeable divergence started to appear, with the doublet group showing a survival rate of 62.62% compared to 52.76% for the triplet group.
This suggested that while triplet therapy was initially more aggressive and had no more postoperative complications than the doublet therapy option, long-term outcomes might show a difference between the two regimens.

After 60 months, survival in the doublet group was 48.99%, while the triplet group one dropped to 35.6%. These figures suggest that while triplet therapy may provide short-term advantages, the long-term benefits may be limited.

The next step was to analyze survival rates by stratifying patients based on their Clavien-Dindo maximum score.

This consented to visualize the impact of early complications on the overall survival rates.



The analysis distinguished patients by both treatment regimen and whether they had had complications with a Clavien-Dindo score of over 3 points (severe complications).

The rates at 12 months of patients without complications over II Clavien-Dindo grade in both the doublet and triplet groups were very high:

- Doublet: 94.38%
- Triplet: 94.64%

These figures suggested that for the first year, patients without complications fared well under both treatment regimens, although the doublet group had a slightly better survival rate.

In patients with Clavien Dindo complications exceeding the IIIa mark, the low numerosity rendered the analysis of survival rates less meaningful than hoped for.

- Doublet: 85.12%
- Triplet: 100%, an anomaly that was probably due to the very small sample size (13)

As time progressed, survival rates for both groups decreased significantly, particularly for patients with complications.

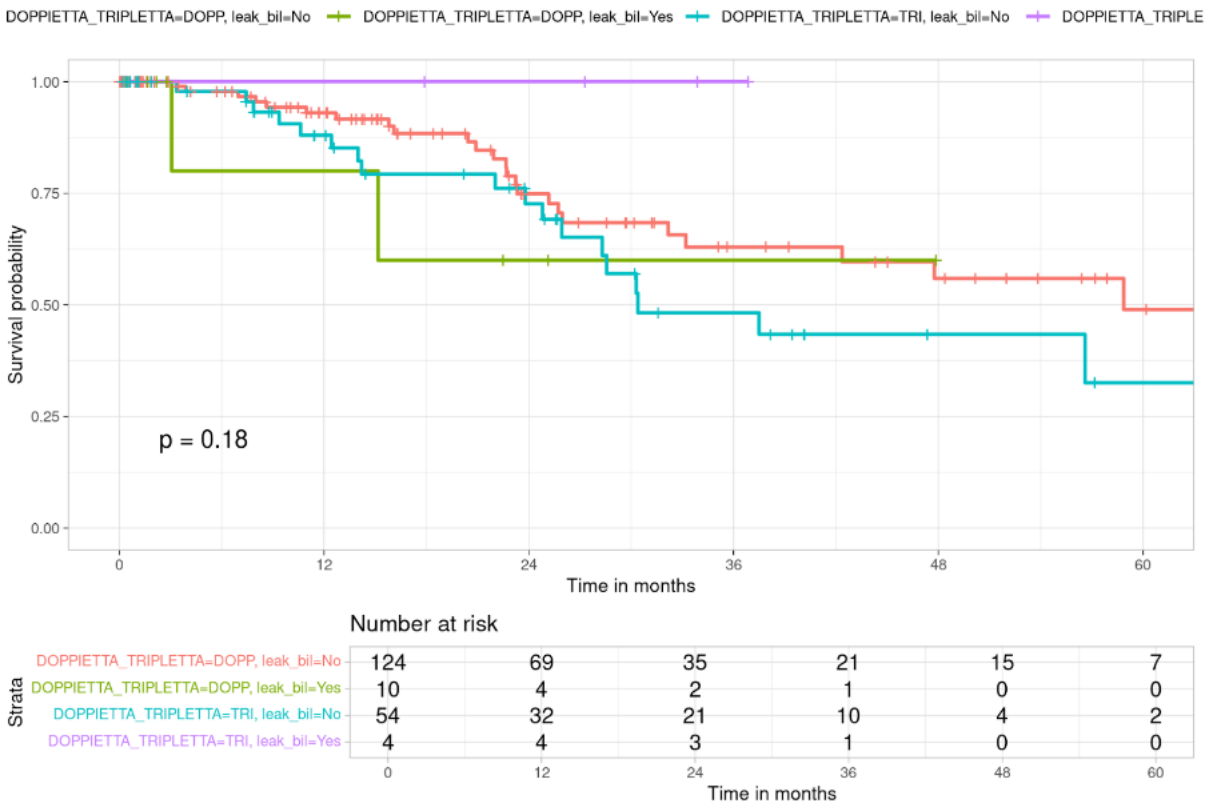
At 24 months, there still was no large difference in survival between complicated and uncomplicated patients, with the lowest rate being recorded in doublet therapy patients with Grade 3 complications (69.8%).

At 36 months, survival decreased sharply for patients with complications, although the lowest survival rate was registered in triplet patients with Clavien Dindo under 2 (45%).

Patients treated with triplet therapy and complications still showed relatively better survival compared to those in the doublet group, although the confidence intervals are wide, indicating less certainty due to fewer patients in this category.

Finally, by the 60 months mark, the "triplet with complications" survival rates fell in line with the rest of the groups' ones. This, though, demonstrated that no statistical significance was attributable to the presence and severity of early complications, as patients might initially have fared worse, but tended to stabilize over time.

KM stratificata tripletta-doppietta leak biliare



Biliary leak was another examined variable, as it is strongly associated with chemotherapy toxicity and thus might be more prevalent in triplet therapies.

The Kaplan-Meier (KM) analysis stratified by the presence or absence of biliary leakage provides specific insights into how this complication affects survival in patients treated with either doublet (DOPP) or triplet (TRI) chemotherapy regimens.

The presence of this complication is associated with lower survival rates compared to those without this complication. However, the trends differ slightly between the doublet and triplet treatment groups, and survival is particularly affected in patients with biliary leakage over the longer term.

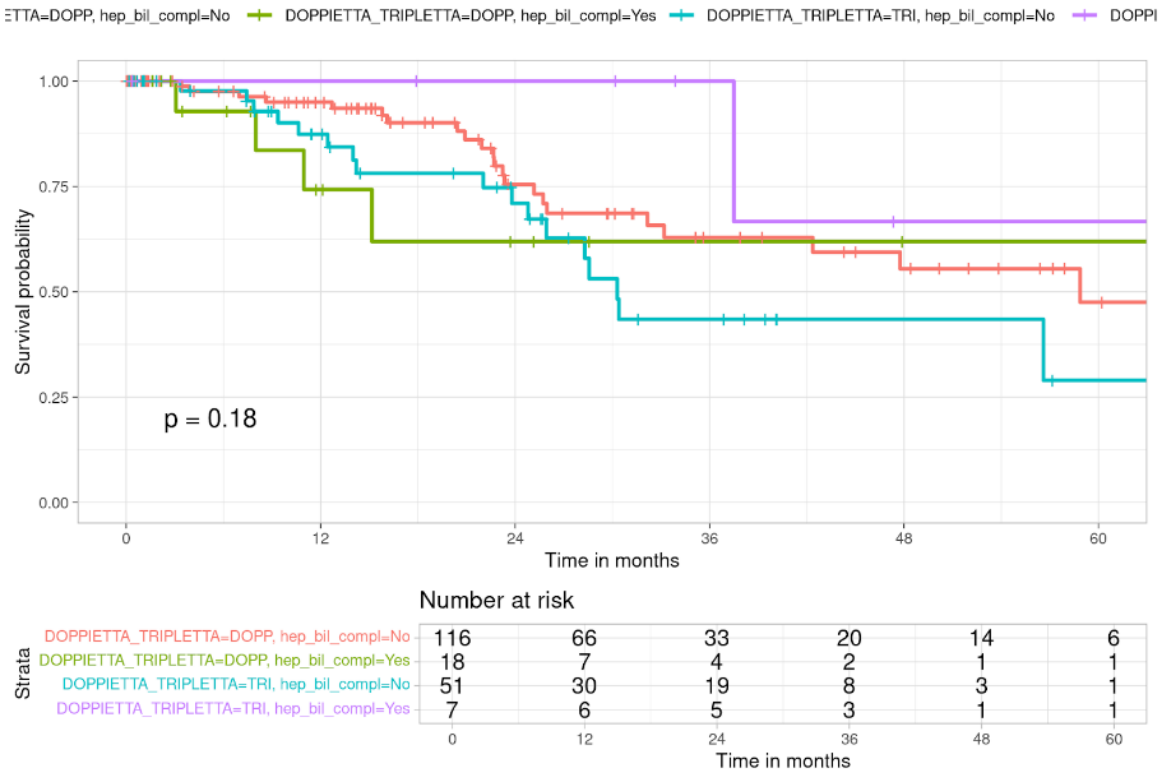
Patients with no biliary leakage show better overall survival across both treatment regimens.

There are clear declines in survival for those who experienced biliary leakage, and this subgroup tends to show poorer outcomes over time.

Early on, patients without biliary leakage fare better in both treatment groups. Notably, the triplet group with biliary leakage shows no events at the 12-month mark, but this may be due to small sample size, which can lead to less reliable estimates.

At 24 months, the impact of biliary leakage becomes even more apparent, particularly in the doublet group, where survival drops to 60%, but then tends to remain steady.

The overall lack of statistical significance suggests that while biliary leakage negatively affects survival trends, particularly in the doublet group, the sample sizes may be too small to draw definitive conclusions.



Besides biliary leak, the Kaplan Meier curve of survival stratified by any kind of hepato-biliary complication was also studied.

Patients with hepato-biliary complications tended to have poorer survival outcomes compared to those without complications, reflecting the significant impact of these complications on overall survival (OS).

Patients without complications:

- Doublet: 95.02% survival rate
- Triplet: 87.4% survival rate

Here, the doublet group shows slightly better survival, but both groups perform well.

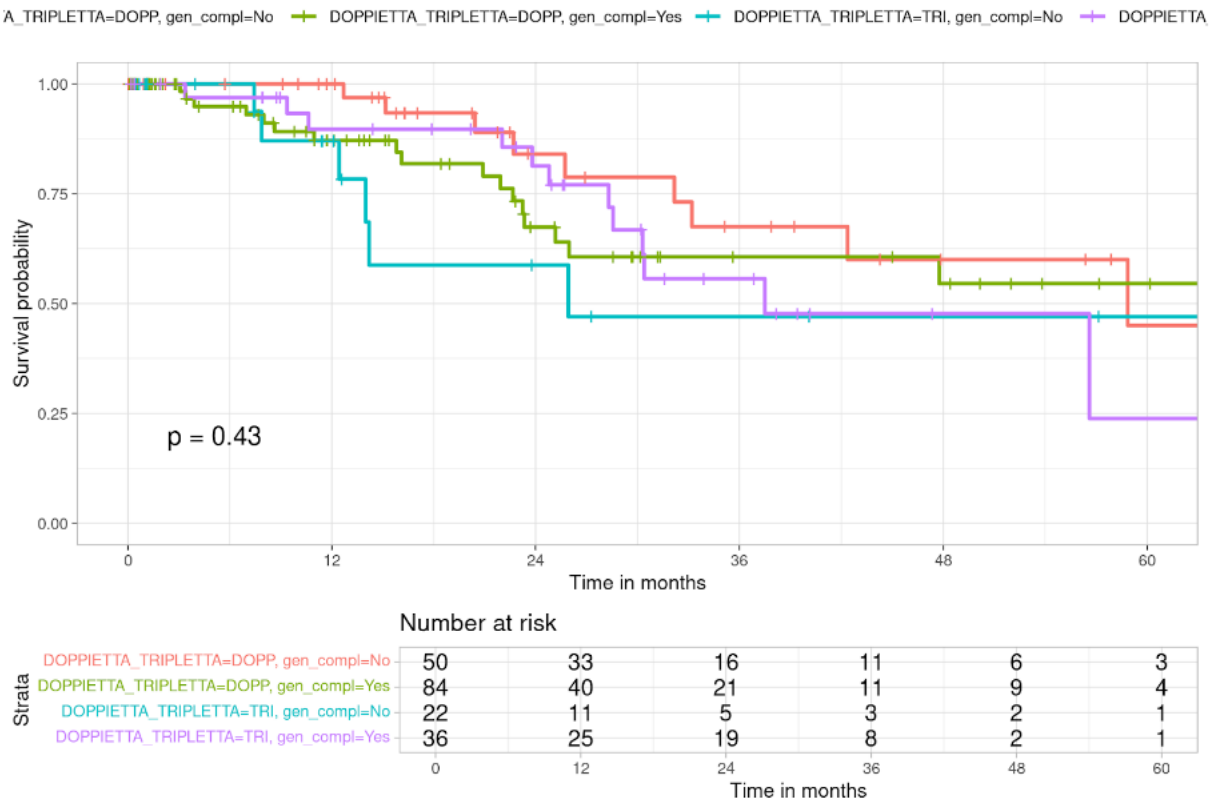
Patients with Hepato-Biliary Complications:

- Doublet: 74.3% survival rate
- Triplet: 100% (no events)

In patients with hepato-biliary complications, survival is significantly lower in the doublet group, dropping to 74.3%, compared to no recorded events (100% survival) in the triplet group. However, like in the previous KM curves, the lack of events in the triplet group could be due to a small sample size, so this should be interpreted with caution.

As with biliary leak, in the following months survival declines in each group. While doublet therapy shows a similar decrease in both populations, triplet therapy OS vastly varies between those with and without hepatobiliary complications.

Finally, at 60 months, the triplet and doublet therapy groups with complications converge to a similar percentage of survival, while the lowest registered survival is in triplet patients without complications (29%).



This last analysis investigated how general complications, which cover a broad range of issues beyond hepato-biliary complications, influenced overall survival (OS) in patients receiving either doublet or triplet regimens.

Like in other stratifications, patients without general complications fared better overall than those who experienced complications, regardless of the chemotherapy regimen. The presence of general complications resulted in a clear drop in survival over time, beginning as early as the first 12 months.

At 12 months, the population had tendentially similar survival rates across all groups, apart from the "Doublet without complications" category, which had not registered any death.

At 24 months, the gap between triplet and doublet groups had become more evident in both categories:

- Doublet without complications: 84.02% survival rate
- Triplet without complications: 58.8% survival rate
- Doublet with complications: 67.39% survival rate
- Triplet with complications: 81.34% survival rate

Patients with complications in the triplet group maintained better survival at 24 months than those in the doublet group. This could be reflective of a more aggressive management of complications or the initial benefits of triplet therapy.

36 months after surgery, survival rates continued to decline for both groups, but with an inversion in the trends of the category characterized by the presence of complications. Therefore, both "Doublet-associated" populations showed an advantage in survival in comparison to triplet ones.

This trend remained stable in the following months, with the early advantage seen in the triplet group diminished, as the survival curves converged:

- Doublet without complications: 60%
- Doublet with complications: 54.58%
- Triplet without complications: 47%
- Triplet with complications: 47.7%

At 60 months, instead, the survival rates of most categories showed nearly identical values, indicating that long-term outcomes for patients without general complications had become similar for both regimens, while doublet and triplet groups with general complications showed a significant difference. The lowest score is seen in the "Triplet with complications" category, with a 23.85% survival rate.

While there are observable differences in survival trends, they are not robust enough to achieve statistical significance, likely due to the variability and potential small sample sizes in the subgroups.

General complications clearly worsened survival outcomes, particularly in the long term. While triplet therapy offered some early advantages for patients with complications, it did not sustain these benefits after 24 months, with survival dropping sharply by the 60-month mark.

DISCUSSION

Colorectal cancer is a very common disease, with a high incidence and mortality. The most frequent site of metastasis is the liver, which in almost 20% of cases can present resectable disease.

In resectable patients, margin negative surgery represents the only potentially curative option, and it's often preceded by chemotherapy to improve the chance of radicality. While neoadjuvant treatments' efficacy is closely tied to the number of different drugs in the combination, there are also downsides to combining many cytotoxic agents. Chemotherapy regimens can have significant side effects, and therefore must be carefully tailored to the patient to avoid additional toxicity in those who may not withstand it.

Through this study, we analyzed the postoperative complications and mortality associated with the administration of a doublet rather than a triplet regimen. A similar analysis (45) had already been conducted, in a multi institutional database.

EP01A-057 - Table 1 Patient and tumor characteristics of patients undergoing FOLFOXIRI vs. doublet preoperative chemotherapy for CLM.

	FOLFOXIRI (n = 160)	Doublet regimen (n = 1556)	p value
Demographic factors			
Age, median (IQR), yr	55 (45.5-64)	59 (50-67)	<0.001
Male sex, n (%)	92 (57.5)	948 (60.9)	0.393
BMI, median (IQR)	24.9 (22-27.6)	26.7 (23.7-30.7)	0.743
CLM factors			
Synchronous, n (%)	148 (92.5)	1192 (78.8) [a]	<0.001
Bilateral, n (%)	108 (67.5)	511 (64.1) [b]	0.414
Number of CLM, median (IQR) [c]	4 (2-7)	2 (1-4)	<0.001
Largest CLM diameter, median (IQR), cm [d]	2.7 (1.5-4.8)	2.4 (1.5-3.8)	0.010
Chemotherapy factors			
Number of cycles, median (IQR) [e]	6 (5-9)	6 (4-8)	0.520
Targeted therapies, n (%)	95 (59.4)	1124 (72.4)	0.001
Major hepatectomy, n (%)	67 (41.9)	548 (35.2)	0.096
Early outcomes			
Intraoperative transfusion, n (%)	11 (6.9)	36 (6.4) [f]	0.840
90-day mortality, n (%)	2 (1.2)	9 (0.6)	0.311
90-day major complications, n (%)	21 (13.3)	155 (10.0)	0.198

Figure 11: Table from Panettieri.E et.al.

Similarly to that study, the median age of the two analyzed groups here was significantly different across cohorts, underlining the tendency to administrate FOLFOXIRI to younger patients: only 12% of patients over 65 were considered "fit" for triplet therapy, compared to 30% for doublet therapy.

Demographically, patients in this study were comparable in terms of sex and BMI, as was true for the aforementioned article.

A significant factor that was not previously considered and that we analyzed, was the difference in comorbidities across cohorts. It was found that the presence of comorbidities strongly influenced treatment choice, with doublet therapy being more common (p=0.001), likely due to the higher toxicity of triplet therapy. The most significant comorbidities were hypercholesterolemia (p=0.056) and arterial hypertension (p<0.001), both more prevalent in the doublet therapy group. Diabetes mellitus (p=0.083) and peripheral vascular disease (p=0.11) also showed some trends toward

influencing treatment choice. Conversely, liver disease and a history of extra-hepatic abdominal surgery had no effect on therapy selection.

Another significant correlation was also observed between higher Charlson Comorbidity Index (CCI) scores and the use of doublet therapy ($p<0.001$), indicating that both the presence and number of comorbidities influence the decision to prescribe less toxic doublet treatments.

Tumor localization, another additional factor included in this study, also showed borderline significance ($p=0.056$), with right-sided and transversum-located tumors pushing towards triplet therapy, while left-sided tumors were more common in the doublet group. Lymph node positivity was evenly distributed between the two groups and did not influence treatment choice.

CLRM data was then analyzed, similarly to the previously mentioned study. Here, the strongest association between its characteristics and the choice of neoadjuvant regimen was found in the categorization of synchronous versus metachronous CRLM nodules, although with a slightly less significant p value than the one shown in Figure 11.

Some factors that were instead found to be not significant, possibly because of the smaller numerosity in comparison to the other study, were the number of metastases, their maximum size and their unilateral or bilateral distribution. Preoperative data such as CEA levels and ASA score were also equalized between groups.

The gathered surgical data included the type of approach, the choice of a resective or ablative surgery, surgical complexity and the duration and blood loss registered intraoperatively.

The analysis showed that nearly all examined parameters were independent of the choice of regimen. One of the two categories that showed borderline statistical significance was the use of local treatment ($p=0.092$), which was slightly more common in patients treated with triplet therapy (76%) compared to those receiving doublet therapy (63%).

The other category was total surgery time, with a strong suggestion ($p=0.06$) of an association between the use of FOLFOXIRI and surgeries lasting more than 300 minutes (5 hours). This parameter was chosen based on a similar study (30), which found a borderline but significant correlation between this parameter and the incidence of postoperative liver failure.

Other significant factors in the development of complications highlighted by that article were ASA score, male gender and the performance of a major resection, neither of which had any significant difference between groups in the present study.

Notably though, in this case no liver failure instances were registered, contrarily to the aforementioned study, possibly because of the lower numerosity, but also thanks to an apt selection and preparation of resectable patients.

The analyzed complications included both an overview of any possible type of morbidity, and a focus on the complications highlighted as most important by Neef et al., specifically wound infection, abscesses, liver failure, postoperative bleeding and in-hospital mortality.

Similarly to that study, though, none of those categories showed a particularly marked incidence in one of the two groups. The only notable exception was a borderline significant association between triplet therapy and hypertensive peaks (p=0.077). This result, while not fully conclusive, suggests that hypertensive complications may warrant further investigation, particularly given the small sample size of the study. It's possible that the study's limited data either exaggerated or underestimated the true frequency of this complication, which means additional research with a larger cohort could clarify whether this finding is clinically relevant.

Mortality at 30 days was also null, which is an indicator of a well-structured patient management and follow-up. 90-day mortality, although characterized by more missing data because of patients from other regions, also showed impressive results, with an even lower mortality rate than the one detected in the Panettieri et al. study.

The lack of statistically significant differences suggests that factors such as comorbidities, mortality, and surgical risks were well-managed and balanced in both therapy groups. The similar Clavien-Dindo complication grades and nearly identical Comprehensive Comorbidity Index (CCI) scores further reinforce this conclusion, indicating that both groups had comparable postoperative outcomes.

In conclusion, triplet chemotherapy did not significantly increase the risk of surgery-related adverse events compared to doublet therapy. The study suggests that the therapeutic algorithm for assigning patients to doublet or triplet therapy is effective in optimizing treatment benefits while minimizing postoperative risks. The careful selection of "fit" patients for triplet therapy (FOLFOXIRI) may have played a role in achieving these balanced outcomes, ensuring that only those able to tolerate the higher toxicity levels were included.

As for the secondary aim of the study, the median survival was characterized by a higher value in the triplet therapy group, with and advantage of 5 months over the doublet one, and although this wasn't considered statistically significant because of its p value=0,15, it should be examined further.

The Kaplan-Meier curve analysis focused instead on overall survival across different chemotherapy regimens and preoperative characteristics. The overall survival rates for the entire cohort steadily declined from 91.2% at 12 months to 43.8% at 60 months, indicating that while a significant proportion survived beyond five years, the disease remains aggressive. This initial analysis set the stage for further stratification based on treatment regimens and complications.

When considering complications, patients without severe complications had higher survival rates initially, but the difference between the doublet and triplet groups lessened over time. Severe complications (such as those with Clavien-Dindo scores over IIIa) led to worse outcomes in both groups, but long-term survival rates became similar by the five-year mark. Biliary leaks and hepato-biliary complications were associated with poorer survival, particularly in the doublet group, but results were less conclusive in the triplet group, likely due to small sample sizes.

Therefore, the use FOLFOXIRI rather than a doublet had no significant negative impact on mortality both in the early postoperative stages and over the course of the following years, with some results even suggesting a slightly better outcome.

CONCLUSIONS

This study aimed to evaluate the impact of different neoadjuvant chemotherapy regimens, specifically the doublet therapies (FOLFOX, FOLFIRI) and the triplet regimen (FOLFOXIRI) on morbidity, mortality, and overall surgical outcomes in patients undergoing resection or ablation for colorectal liver metastases (CRLM).

Given the aggressive nature of triplet therapy and its potential for increased hepatotoxicity, this research explored whether these effects translate into poorer post-surgical outcomes compared to the less toxic doublet regimens.

The analysis highlights several areas of statistically significant differences between the "DOPP" and "TRI" groups, particularly concerning comorbidities, age at diagnosis, arterial hypertension, and some association treatments.

This aspect is coherent with the general consensus that triplet therapy should only be administered in fit patients, therefore the population was correctly divided between suited subjects for the more aggressive treatment and excluded patients.

Our findings indicate that triplet therapy (FOLFOXIRI) does not significantly increase the rate of postoperative complications compared to doublet therapies. This suggests that concerns regarding hepatotoxicity leading to worsened surgical outcomes may be overstated, at least in the context of high-volume centers with advanced surgical expertise.

However, patients treated with FOLFOXIRI did show a slightly increased incidence of certain complications, particularly in liver parenchyma-related injuries, though these did not translate into statistically significant differences in overall survival or morbidity rates.

In patients with CRLM, especially those with high tumor burden or requiring aggressive downsizing for resection, triplet therapy remains a valuable option. The fear of increased postoperative complications should not preclude its use, provided careful patient selection and close monitoring. For patients with significant comorbidities or liver dysfunction, doublet therapy remains a safer and effective alternative.

This study has several limitations, including its retrospective nature and the single-center design, which may limit the accuracy of the findings. Additionally, longer follow-up is needed to fully assess the long-term survival outcomes in these patients.

Future research should therefore focus on prospective, multicenter trials that further investigate the role of FOLFOXIRI in relation to specific complication profiles, particularly liver toxicity and its management.

In conclusion, while triplet chemotherapy regimens pose a slightly higher risk of liver-related complications in the general population, their potential for enhanced oncological benefit should not be overlooked in the treatment of CRLM. This study provides evidence supporting the safe and effective use of both doublet and triplet regimens, allowing for a more personalized approach in managing patients with colorectal liver metastases.

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