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# Management of Liver Metastasis of Colorectal Cancer

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## ABSTRACT

**Background:** Globally, colorectal cancer is the third most common cancer among men and the second most common among women. Colorectal cancer is the fourth most frequently diagnosed cancer, but the second-leading cause of cancer deaths. Incidence of colorectal cancer has decreased significantly in recent decades, mortality rates have fallen as well. Those declining rates are largely attributed to earlier diagnosis through screening and more sophisticated and effective methods of treatment.

**Objective:** That work represents colorectal cancer metastasis management, early detection and screening of colorectal cancer.

**Subjects and Methods:** This observational study was conducted on 10 patients with liver metastasis admitted to GIT Surgery Unit, Cancer National Institute and postoperative follow up and observation at El-Haram Hospital and Cancer National Institute between April 2017 and December 2017.

**Results:** This work is observational study. The patients in this study were divided into two (2) groups: group 1 and group 2. The included patients were prepared through studying the patient's condition, preoperative & intraoperative assessment. Choice of operation and how to manage synchronous metastases. The type of resection does not seem to influence the prognosis if a clear margin is obtained. The carcinoembrionic antigen (CEA) level is strongly correlated with recurrence-free survival. A free margin of at least 1 cm offers the best chance of avoiding recurrence.

**Conclusion:** In this work observational study results preoperative, operative and postoperative results were recorded. Operative results (type of surgery, surgical technique), postoperative results (liver related complications, general complications, and postoperative morbidity and mortality of liver resection of colorectal cancer. Prognosis and follow up of patients of study and postoperative recurrence.

**Keywords:** Carcinoembryonic antigen - Colorectal carcinoma - Metastatic colorectal cancer - Colorectal liver Metastases.

## INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females. It is the second most deathly cancer worldwide. The mortality rates have been decreasing dramatically in western countries largely resulting from improved treatment and increased awareness and early detection [1].

Liver is the most common site of metastasis from colorectal cancers 50-60% of the cases. Close to one third of patients have liver metastases either at the time of diagnosis synchronous in 1/3 of the cases or during the disease course metachronous in 2/3 of the cases. The prognosis of colorectal liver metastases has improved in the last few years. Surgical resection of liver metastases is considered the only curative treatment option for patients with resectable liver metastases and no extrahepatic disease [2].

Chemotherapy is backbone in treating metastatic colorectal cancer recent advances in chemotherapy regimens have increased the median overall survival from 6 months to over 30 months through the targeted therapy and double or triple combination protocols [3].

The three active agents for metastatic colorectal cancer known as conventional chemotherapy are fluoropyrimidines, irinotecan and oxaliplatin the associations FOLFOX / XELOX and FOLFIRI are commonly used in the Lebanese hospitals [4].

Metastatic colorectal cancer patients are subdivided into four clinically defined groups [group 0]: Primarily technically R0-resectable liver or lung metastases and no biological relative contraindications. [Group 1]: Potentially resectable metastatic disease with curative intention. The goal of a disease free status after downsizing by chemotherapy enabling secondary surgery may give the potential of longterm survival or cure. [Group 2]: disseminated disease technically never unlikely resectable intermediate intensive treatment. The treatment intention is rather palliative in patients with symptoms or extensive disease very active first line treatment with a high likelihood to induce metastases



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regression in short time seems to be the best option. [Group 3]: never-resectable metastatic disease non intensive sequential treatment.for these patients maximal shrinkage of metastases is not the primary treatment aim. The aim is rather prevention of tumour progression and prolongation of life with minimal treatment burden. An intensive discussion with the patients on the benefit/risk ratio is important.Patients may be offered a combination cytotoxic ± a biological targeted agentor an escalation strategy may start with fluoropyrimidine in combination with bevacizumab [5].

Survival rate in metastatic colorectal cancer (mCRC) significantly increased from the 1950s (12months) to the 2010s (60 months) when a combination of surgery, chemotherapy and biological agents is used. Tumor size, positive surgical margins, lymphnode involvement, lymphovascular invasion, carcinoembrionic antigen (CEA) level, poor histological differentiation and tumor budding were considered the most important prognostic factors both in colorectal cancer and in metastatic colorectal cancer (mCRC) [6].

Studies have shown that both higher prediagnosis plasma levels of vitamin D and regular aspirin use are associated with improved outcomes in patients with advanced colorectal disease [7].

A high body mass index (BMI) and alack of physical exercise are also associated with both the development of colorectal cancer and poorer outcomes [8].

## AIM OF THE WORK

This work aimed to early detection of colorectal cancer and management of liver metastatsis of colorectal cancer such as liver resection, radiofrequency ablation, chemotherapy and radiotherapy either synchronus or metachronus.

## SUBJECTS AND METHODS

That observational study was conducted on 10 patients with liver metastasis admitted to GIT Surgery Unit, Cancer National Institute and postoperative follow up and observation at El-Haram hospital and cancer national institute between April 2017 and December 2017.

**The study was approved by the Ethics Board of Al-Azhar University.**

The patients were informed about the options planned for treatment of metastasis of colorectal cancer and after acceptance they signed an informed consent.

**The exclusion criteria included:** Patients of non metastatic colorectal cancer, Patients of benign tumour like polyps of the colon, and Patients with primary liver tumours.

**The recruited patients were randomly divided by the closed envelop method into two groups: Group 1;** included Patients of resectable tumour metastasis. **Group 2;** included Patients of non resectable tumour metastasis [because of the location, the size, the number of hepatic deposits, or because of the association with extrahepatic disease], (liver resection was palliative rather than curative).

Patient preparation; Selection of patients for surgery; the decision and the extent of surgical resection for liver metastases were based upon the patient's condition, extent of the disease, and liver function. Surgical resection should only be performed with a curative intent leaving no macroscopic residual disease. The goals of preoperative assessment were to determine the ability of the patient to tolerate hepatic resection, to exclude the presence of non-resectable extrahepatic disease, and to delineate the anatomy of metastases.

Patient's condition; The patient should be suitable for a general anaesthesia and a potentially haemorrhagic surgery. Special attention must be given to the cardiocirculatory status because of the possibility of clamping manoeuvres and to the coagulation profile.

Liver function; The hepatic functional reserve should be sufficient to allow adequate postoperative liver function. If remnant liver parenchyma is normal, up to 6 of the 8 anatomical segments (75% of the volume of the liver) can be respected, without inducing postoperative liver failure. Such major resections could not be performed safely if remnant liver parenchyma is abnormal. Many patients will have received pre-operative chemotherapy, which may alter liver parenchyma. It was unclear whether the risk of postoperative liver insufficiency would be increased in these conditions. The functional capacity of the liver could be assessed by the Child-Pugh classification, hepatic biological blood tests and, in some cases, by the indocyanin green (ICG) retention tests. The volume of the non-tumourous parenchyma that will be left in place

after hepatic resection can be evaluated by CT scan volumetry. It was admitted that postoperative liver function would not be altered if the residual liver volume/body weight were greater than 0.5%.

**Statistics:???????????**

## RESULTS

**Table (1):** Perihepatic fluid collection or abscess.

| **Group I** | | | |
|---|---|---|---|
| | Observed N | Expected N | Residual |
| 1 | 1 | 1.0 | .0 |
| 4 | 1 | 1.0 | .0 |
| Total | 2 | | |
| **Group II** | | | |
| | Observed N | Expected N | Residual |
| 1 | 1 | 1.0 | .0 |
| 4 | 1 | 1.0 | .0 |
| Total | 2 | | |

**Table (2):** Bile leak.

| **Group I** | | | |
|---|---|---|---|
| | Observed N | Expected N | Residual |
| 1 | 1 | 1.0 | .0 |
| 4 | 1 | 1.0 | .0 |
| Total | 2 | | |
| **Group II** | | | |
| | Observed N | Expected N | Residual |
| 2 | 1 | 1.0 | .0 |
| 3 | 1 | 1.0 | .0 |
| Total | 2 | | |

**Table (3):** Liver failure.

| **Group I** | | | |
|---|---|---|---|
| | Observed N | Expected N | Residual |
| 1 | 1 | 1.0 | .0 |
| 4 | 1 | 1.0 | .0 |
| Total | 2 | | |
| **Group II** | | | |
| | Observed N | Expected N | Residual |
| 2 | 1 | 1.0 | .0 |
| 3 | 1 | 1.0 | .0 |
| Total | 2 | | |

**Table (4):** That results of preoperative on the study of patients which divided into two groups.

| **Division of patients:** | **Group 1 [resectable group].** | **Group 2 [irresectable group].** |
|---|---|---|
| **Number of each group:** | **5** patients | **5** patients |

**Table (5):** The results of operative study that made on both groups and main type of surgery made including the two groups, resectable (group 1) and irresectable (group 2).

| **Type of surgery and surgical technique:** | Resectable group usually major liver resection 80% and wedge liver resection 20% | Irresectable group wedge liver resection 60% and major liver resection 40% |
|---|---|---|

**Table (6):** Postoperative results representing the complication, postoperative morbidity and mortality.

| | | |
|---|---|---|
| **Complications of liver resection. [Liver related complications]:** | 1-Perihepatic fluid collection or abscess 20%<br>2-Bile leak 20%<br>3-Liver failure 20%<br>4-Haemorrhage 20% | 1-Perihepatic fluid collection or abscess 20%<br>2-Bile leak 40%<br>3-Liver failure 40%<br>4-Haemorrhage 20% |
| **Infections:** | 1-Wound 20%<br>2-Intra-abdominal sepsis 0% | 1-Wound 20%<br>2-Intra-abdominal sepsis 0% |
| **General complications:** | 1-Pleural effusion 0%<br>2-Pneumonia 0%<br>3-Deep vein thrombosis/ pulmonary embolism 0%<br>4-Cardiac failure, myocardial infarction 0% | 1-Pleural effusion 0%<br>2-Pneumonia 20%<br>3-Deep vein thrombosis/ pulmonary embolism 0%<br>4-Cardiac failure, myocardial infarction 0% |
| **Post operative morbidity& mortality of liver resection in hepatic metastasis of colon cancer:** | 20% in resectable group. | Irresectable group 20%. |

Results were mentioned as percent of patients number in the study. Gropup 1 (5) patients, Group 2 (5) patients. For examble 20% mean 1 patient. This results represented the percents that made on each group number.

## DISCUSSION

Colorectal cancer (CRC) is the third most common cancer in the USA. Similarly, in Europe, CRC was the third most common form of cancer and cause of cancer-related death in 2012. Metastasis often occurs in patients with CRC, and the liver is the site most frequently involved: 14– 20% of patients had hepatic metastases at presentation, and up to a further third of patients initially diagnosed with a localized bowel cancer will subsequently developed liver lesions [9]. Liver metastases in patients with CRC represented stage IV disease, in which 5-year survival is only 6% [10].

However, stage IV CRC encompasses a wide clinical spectrum of disease, and those patients with surgically resectable metastatic lesions confined to the liver have a 5-year survival rate of 25– 40% [10]. Such patients represent a select, but important subgroup, in which long-term survival of up to 17% at 10-years had been reported after the hepatic metastatic burden is surgically removed [11].

Patients who presented with metastatic liver disease after treatment of the primary CRC (termed metachronous disease) received care focused on treating the new metastatic disease [12]. By contrast, the management of patients who presented with CRC and concurrent liver metastases (termed synchronous metastasis) were more complex [12, 13].

These patients had less favourable cancer biology and thus might have a reduced likelihood of longterm survival than those with metachronous liver involvement . Advances in surgery, anaesthesia, critical care and chemotherapy have made two alternative treatment options feasible for patients with synchronous CRC and liver-limited disease. The best option is concurrent resection of the liver metastases and the colorectal primary tumour [14].

Some evidence indicated that simultaneous resection might have a negative effect on progression-free survival (PFS) compared with classic delayed hepatectomy . Liver first surgery to manage synchronous CRC and liver metastases became more widely used owing to a number of oncological and technical developments. The classic approach of surgical resection of rectal tumours as the first step had been superseded in selected cases by preoperative chemoradiotherapy, which can be undertaken after neoadjuvant systemic chemotherapy and liver resection **[15]**.

In addition, the technical development of colonic stenting permitted symptoms associated with rectosigmoid cancer, such as partial obstruction of the colon, to be palliated without resorting to urgent bowel surgery **[16]**.

The liver-first strategy might be advantageous if liver metastatic disease rather than the primary cancer gave rise to systemic metastasis, although whether liver metastases drive systemic spread had not been established **[17]**.

A further potentially important benefit of the liver-first approach was that, in selected patients with rectal tumours with a complete endoscopic, radiological and clinical response to chemoradiotherapy, pelvic surgery could be less extensive or avoided altogether [18].

In current colorectal clinical practice, the terms ‘ synchronous liver metastasis’ or ‘ synchronous liver metastases’ refer to the presence of hepatic lesions arising from a colorectal primary tumour that were evident at the time of clinical presentation or detected with the colorectal tumour . Conversely, the term ‘ metachronous metastasis’ is used to describe lesions presenting at alater time point than that at which the primary CRC is diagnosed [19]. Current knowledge of the molecular biology of CRC did not preclude patients with apparent metachronous metastases having clinically occult synchronous micrometastatic hepatic lesions at the time of presentation of the primary tumour, which only became clinically apparent at a later stage [19].

The liver is the most common site of metastatic disease from colon cancer. One quarter of all patients presenting with colon cancer had hepatic metastases at initial presentation and over half of all patients with colon cancer would eventually develop these metastases over the course of their disease. Lesions in this organ may be isolated or multiple. Treatment options for these metastases include surgical resection, local ablation therapy, transarterial chemoembolization, radiomicrosphere therapy, isolated hepatic perfusion, and therasphere therapy [20].

Such procedures were associated with a mortality rate <3% and may achieve 5- and 10-year post-resection survival rates of 38% and 22% respectively. Solitary metastases in particular confer an excellent prognosis, with five-year overall survival rates approaching 70%. Poor prognostic factors include extra-hepatic disease, 4+ and/or bilateral lesions, and surgical margins < 1 cm [21].

In a retrospective study including more than 1500 patients, 5-year survival was 30% when the margin was greater than 1 cm, 15% when it was less than 1 cm and 0% when resection was incomplete. The primary treatment plan for these lesions involved resection with the aim of improving long-term survival rates. Traditionally hepatic metastasectomy had been considered a curative treatment in selective patients [20].

Contraindications to hepatic resection included: the inability to completely resect the primary tumor or the hepatic tumor with negative margins, the inability to preserve adequate hepatic tissue, or the presence of precluding medical comorbidities [21].

In the past, the presence of extra-hepatic metastases was a contraindication for resection; However, recent evidence demonstrated that though the survival in this population was lower than in patients with isolated liver metastases, it remained superior compared with systemic treatment alone [22].

The timing of this intervention remained undecided as equivalent outcomes were reported in patients with simultaneous synchronous vs metachronous staged colectomy and hepatectomy. Traditionally, patients were treated with a staged approach; However, it was suggested that synchronous surgery is a simpler operation [21]. Resection may involve a lobectomy, an extended lobectomy, a segmentectomy, or a non-anatomic wedge resection. Surgeons must balance the desire to preserve the maximal amount of liver tissue with the importance of a negative margin. There were no studies comparing tissue preserving techniques vs. a formal anatomic resection. Anegative margin has been associated with a greater long-term prognosis, Yet it is critical that post surgically 20% - 25% of functioning hepatic tissue in patients with an otherwise normal liver, and 40% in patients with a diseased liver is retained [20].

Remnant liver volume might be increased by portal vein embolization to induce hypertrophy of the contralateral lobe. Ideally, a margin of 1cm at resection is recommended to decrease the risk of microscopic positive margins [20]. Improvements in these surgical techniques have led to an acceptable operative mortality of <5% and curative treatment became possible [23].

In patients with borderline resectability, neoadjuvant chemotherapy may increase the resectability of tumors in up to 12% [21]. Neoadjuvant chemotherapeutics additionally decreased the risk of micrometastatic disease, resulting in the possibility of a long-term cure [20].

Unfortunately the majority of patients with liver involvement would be surgically unresectable or the patient wouldl not be fit for surgery. Patients might be deemed " unresectable" in the presence of extrahepatic metastases, tumor proximal to any major vasculature, an insufficient hepatic reserve, or an inadequate general patient performance status [24]. These patients should first be given chemotherapy as up to 12% may be converted to surgical resectability [21].

Radiofrequency ablation (RFA), cryotherapy, laser photocoagulation, microwave ablation, and focused radiotherapy might be used in isolation for unresectable disease or in combination with surgical resection [20].

These various techniques had similar outcomes. RFA has evolved as the preferred method over the past 10 - 15 years due to its great efficacy and low complication rate [24]. When used in combination with surgical resection, Ablation caused a shift from a borderline resectable tumor to one suitable for surgical intervention. When used to treat unresectable tumors alone, this method was not suggested for: metastases > 4 cm, tumors adjacent to large vessels, the presence of extrahepatic disease or when the bowel is adherent to the liver [24].

Proximity to the portal triads or hepatic veins precluded RFA due to the risk of bile duct injury, hepatic necrosis, or inadequate tumor cell death in this area [20].

Alone, RFA confered a greater risk of recurrence with a shorter time to progression than surgical treatment [22], with local recurrence rates as high as 34% often associated with size and location of the tumors [20]. Though as a stand-alone treatment RFA was inferior to resection, 1-year survival rates have been reported as high as 78%. It was hypothesized that, as this technique developed and improved, there might be a fundamental shift in the treatment of liver metastases from surgical resection to RFA [20].

An alternative treatment for liver metastases was radioembolization with yttrium-90 microspheres, which had been shown to be both safe and efficacious as the majority of the blood to a metastatic tumor is from the hepatic artery rather than the liver parenchyma. This procedure therefore provided targeted high dose radiation to the tumor with hepatic parenchymal sparing. This procedure was not limited by the size, shape, location, or number of lesions nor patient comorbidities all of which may be limiting factors for surgical resection or RFA [25].

## CONCLUSION

In the treatment of liver metastases from colorectal cancer, complete surgical resection was associated with a very low mortality and could give 5 year survival approaching 40%. Best candidates for resection were those with less than 4 lesions, less than 5 cm in size, without extrahepatic disease, that appeared more than 2 years after the resection of a stage I or II colorectal cancer and whose CEA level was less than 5 ng/ml. However, surgery was feasible in only 10– 20% of the patients. Others benefit from chemotherapy. Recent progress in chemotherapy and the development of ablative techniques increased the number of operable patients with a curative intent.

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