

# The Role of Staged Resection in Management of Hepatic Metastatic Nodules

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**Background:** Metastatic nodules are the most common malignancy affecting the liver. Colorectal cancer is the most common primary tumor sending metastases to liver, less commonly neuro-endocrine tumors and others.

**Aim:** To study the effect of staged resection (resecting the malignant primary site, neo-adjuvant chemotherapy for 1-3months, liver metastasectomy then chemotherapy completion).

**Patients and methods:** Eighteen patients were admitted to Zagazig University hospitals with hepatic metastases from different primary sites (mostly colorectal cancer) from June 2012 to September 2015. All patients were assessed clinically and radiologically. Neo-adjuvant chemotherapy was given to synchronous colorectal liver metastases.

**Results:** This study included 10 (55.5%) females and 8 (44.5%) males with mean age 43 years old. Thirteen patients had hepatic metastases from colorectal cancer. Classical approach was done in 16 patients. 14 patients had anatomical resection while the remaining 4 patients had non-anatomical resection. Postoperative complications occurred in nine patients while recurrence was only in 4 patients (two of them died during the follow-up period).

**Conclusion:** Liver resection for liver metastases from different primary sites improved the 5 years survival when used combination with neo-adjuvant chemotherapy.

**Key words:** Hepatic metastases, liver resection, neo-adjuvant, chemotherapy.

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## Introduction:

Although the liver is the most common site of metastasis from a variety of tumor types, isolated hepatic metastases mostly occur from colorectal cancer and, less frequently, from neuro-endocrine tumors, gastro-intestinal sarcoma, and others.<sup>1</sup> Complete evaluation of the extent of metastatic disease, both intra & extra-hepatically, is important before considering treatment options.<sup>2</sup>

Approximately 50% to 60% of diagnosed colorectal cancer patients develop colorectal metastases.<sup>3,4</sup> And unfortunately 80% to 90% of these patients have unresectable metastatic liver disease.<sup>5,6</sup> Metastatic disease mostly develops metachronously after treatment for loco- regional colorectal cancer, with the liver being the most common site of involvement.<sup>7</sup> However, 20% to 34% of colorectal cancer

patients present with synchronous liver metastases.<sup>8</sup> Some evidence postulated that synchronous metastatic colorectal liver disease is associated with more disseminated disease state and worse prognosis than metastatic colorectal liver disease that develops metachronously.<sup>9</sup>

Surgical treatment is considered the corner-stone of therapeutic approach to liver metastases, as curative resection of liver metastases increases survival, with 5-year survival rates of 30%-40%.<sup>10</sup> Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection.<sup>11</sup>

## Patients and methods:

Eighteen patients presenting with liver metastases from different primary sites as

colorectal cancer, neuro- endocrine GIT tumors; ovarian cancer and breast cancer were managed and followed-up at the advanced center of liver diseases, Zagazig University in the period from June 2012 to September 2015. All patients were assessed clinically by multidisciplinary team including (surgery, oncology, hepatology and radiology) doctors. All data regarding demographic data, radiology data, chemotherapy, operative data, postoperative complications and follow-up data were recorded.

Preoperative preparations: Assessment of the general performance of the patients was done to determine the ability of the patient to tolerate hepatic resection. Special attention was to cardiopulmonary status (pulmonary function tests and Echo). Assessment of the functional capacity of the liver was done by liver function tests and Child-Pugh classification. All patients were given prophylactic dose of low molecular weight heparin and preparation of pack RBCs (PRBCs) and fresh frozen plasma (FFP) if needed.

Assessment of site of the primary tumors was done by tumor markers (CEA, CA 125 and CA15-3), breast examination, rectal examination and colonoscopy (to eliminate anastomotic recurrence or new colic cancer). Also CT abdomen and pelvis was done to verify the absence of loco-regional spread in case of colorectal cancer, neuro-endocrine GIT tumors and ovarian cancer. Metastatic workup was completed by CT chest, brain and bone scans. Pre-operative assessment of hepatic involvement was done by triphasic CT and in some cases by triphasic MRI and PET scan in large metastatic nodules to detect small micro-metastases **Figure (1)**.

Our protocol of management of colorectal liver metastases was resection of the primary tumors first, followed by 4-6 cycles of chemotherapy for 2-3months, then hepatic resection and lastly completion of chemotherapy.

The protocols used for neo-adjuvant is (m FOLFOX 6):

- Oxaliplatin 85 mg/m<sup>2</sup> IV over 2 hours, day 1.

- Leucovorin 400 mg/m<sup>2</sup> IV over 2 hours, day 1.

- 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, then 1200 mg/m<sup>2</sup>/day for 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion. Repeat every 2 weeks 12.

Regarding staged resection cases, neo-adjuvant chemotherapy was for 3 months then completion chemotherapy for another 3 months. In the other cases where we discover liver metastases after primary resection in the follow up period, chemotherapy was for 6 months after resection.

Surgical procedures: J shaped incision was done for good exploration. First, intra-operative assessment of the primary tumor site was done to determine any recurrence. Then careful exploration of the abdominal cavity was performed to assess the presence of metastatic lymph nodes in the porta-hepatis, coeliac and para-aortic regions. Intra-operative ultra-sound (IOUS) was done in every case. It could provided data about the anatomical relations of the metastases to main vessels, also to detect small intra-parenchymatous lesions and thereby modify the extent of initially planned operation. Different types of liver resections were done (anatomical and non-anatomical) with safety margin more than 1cm. The specimens were sent for histopathology. Follow-up of the patients for 1year was done by liver triphasic CT to assess any recurrence.

Statistical analysis:

- The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 18.0.
- Qualitative data were represented as frequencies and relative percentages.
- Quantitative data were expressed as mean ±SD (Standard deviation).

I-Arithmetic Mean:

$$\bar{x} = \frac{\sum x}{n} \text{ Where:}$$

$\sum x$  = sum of individual data.

n = number of individual data.

II-Standard deviation (SD):

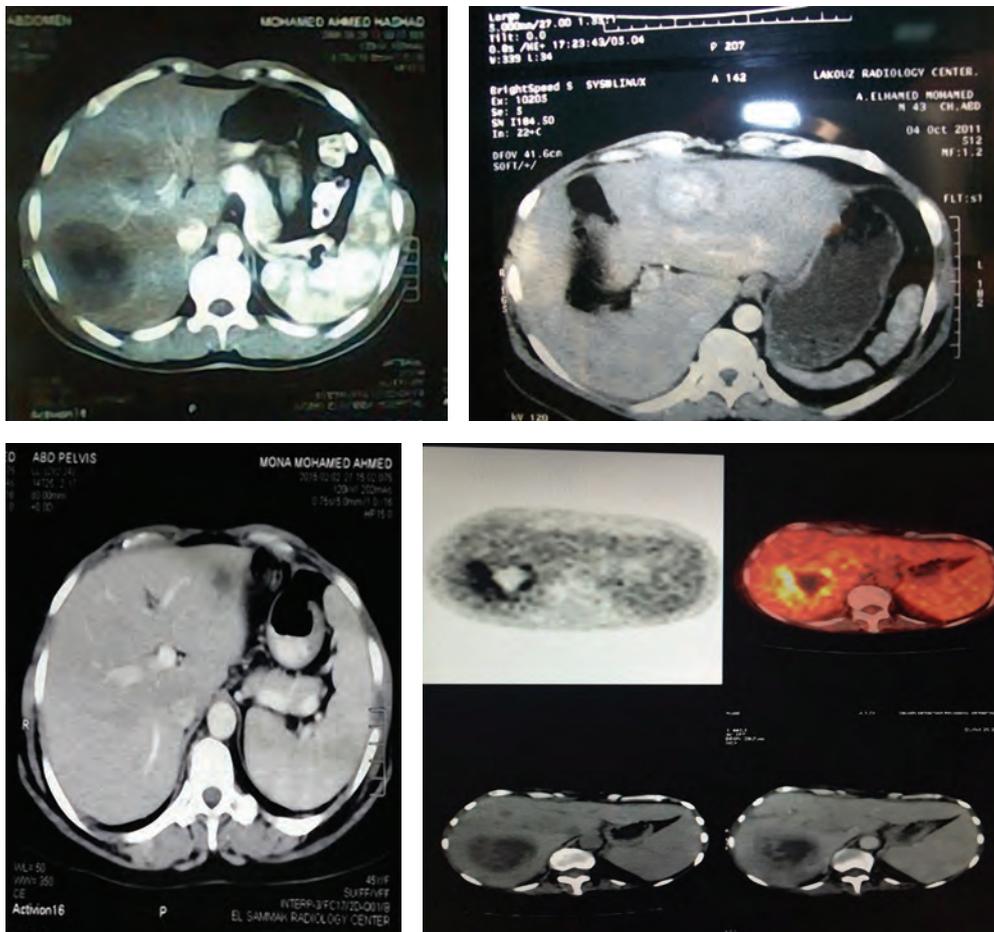


Figure (1): Laparoscopic hepatectomy: marking of tumor, excision of the tumor, homeostasis, liver after excision.

$$SD = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n - 1}} \text{ Where}$$

$\sum x$  = sum of data

$\sum x^2$  = sum of squares of data.

n = number of data.

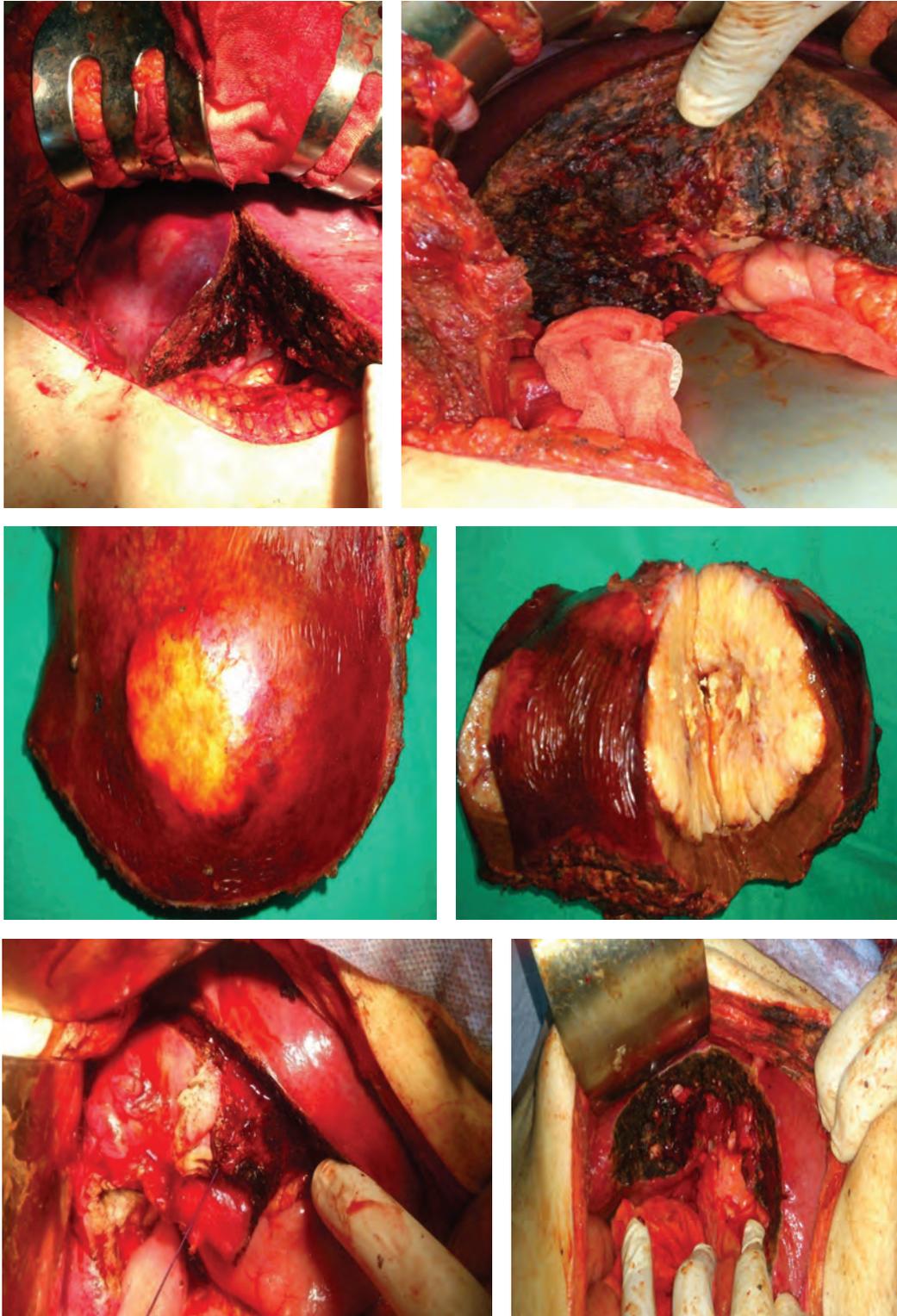
## Results:

In our work we found that, the most common primary tumors were colorectal tumors that presented in 13 patients. The most common pathology was adeno-carcinoma grade II. Patient's demographic data and site of primary tumor are shown in **Table (1)**.

The most common site of liver metastases was the right lobe presented in 14 patients (77.8%). 12 (66.7%) patients had synchronous metastatic nodules presented at the same time with the primary colo-rectal and carcinoid

tumors. While metachronous hepatic metastatic nodules occurred in six (33.3%) patients (two right lobe liver metastatic nodules after modified radical mastectomy for cancer breast, one left lobe after right hemi-colectomy for right sided cancer colon, one right lobe after pan-hysterectomy for cancer right ovary, bi-lobar liver metastatic nodules after abdomino-perineal operation for cancer lower rectum and one right lobe after abdomino-perineal operation for cancer lower rectum) **Figures (2,3)**. Characters of liver metastatic nodules regarding (site, size, number & time of presentation) are shown in **Table (2)**.

The operative time was 210 min., increased in patients with right hepatectomy with an estimated blood loss 800 ml. Blood transfusions using PRBCs occurred in 14 patients with 1-3 units and FFP in 12 patients with 2-4 units. ICU stay length was about two days for three patients with right hepatectomy.



*Figure (2): Right posterior sector metastasis & simultaneous primary colon cancer and liver metastases resection. A. Resection plane with the umbilicated appearance. B. Cut surface after resection. C. Mass after excision. D. Opening of the mass after excision. E. Site of liver metastases after primary colon cancer excision. F. Cut surface after liver metastases excision.*

Hospital length of stay for all patients was 9 days **Table (3)**.

Complications occurred in nine patients. Three patients suffered from pleural effusion,

in two of them ascites was found postoperative; all these patients were managed by diuretics and human albumin. Another three patients complained of wound infection that was

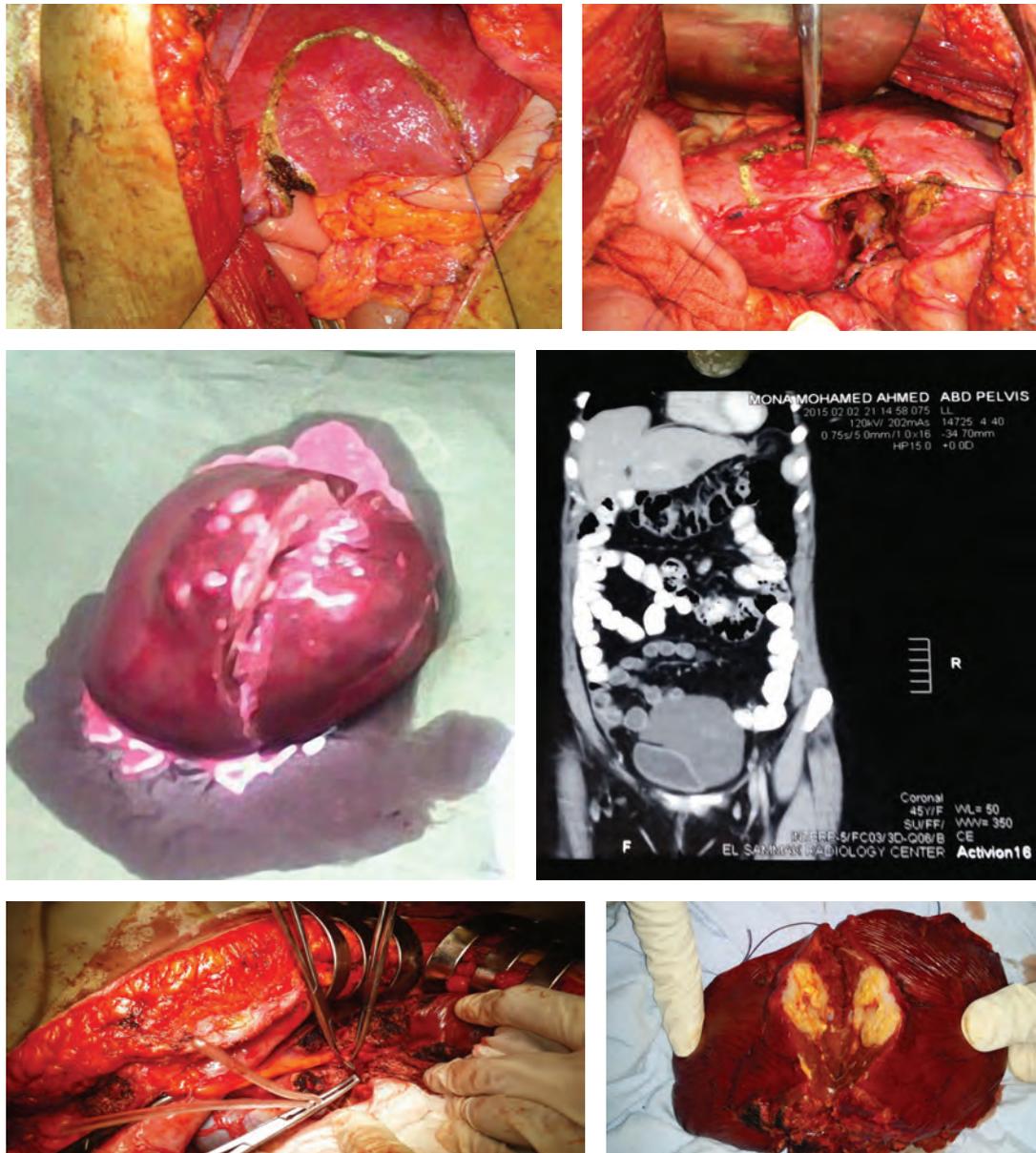


Figure (3): Bilobar liver metastases resection, right hepatectomy & left liver metastases. A. Demarcation of left liver metastases excision. B. Demarcation of right liver metastases excision. C. Right lobe hepatectomy. D. CT Abdomen showed left liver metastases. E. Left lateral segment hilum dissection. F. Opening of the liver metastases.

managed by drainage and strong antibiotics. Dyspnea and chest pain was the complaint from one patient diagnosed to have pulmonary embolism, and was managed by therapeutic doses of anticoagulant and stayed in ICU for two days. Last two patients complained of chest infection, which was managed by conservative measures.

Recurrence occurred in four patients during the follow-up period, two of them died. The first patient was male, 32 years old with past-history of low anterior resection then

right hepatectomy for right hepatic metastatic nodule. The pathology was mucinous adenocarcinoma grad III. He developed multiple liver and lung metastases after 9 months and died from respiratory failure after that by 6 months.

2<sup>nd</sup> patient was 40 years old male with bilobar colorectal metastatic nodules who underwent left lateral hepatectomy plus non anatomical resection of 3 right nodules. He developed multiple right nodules after one year. TACE by 5FU was done but the patient

**Table (1): Patient's demographic data.**

Type	Number
Sex:	
• Female	10 (55.5%)
• Male	8 (45.5%)
Age (in years):	
• Range	32-60 yrs.
• Mean $\pm$ SD	50.6 $\pm$ 8.2
Site Of Iry Tumor:	
• Cancer Ovary:	1case (5.5%)
• Cancer Breast:	2cases (11.1%)
• Colorectal Cancer:	13 cases (72.3%)
Lower Rectum	3
Recto-Sigmoid	3
Left Colon	3
Right Colon	3
Transverse Colon	1
• Carcinoid Tumor:	2 cases (1.1%)
Terminal Ileum	1
Jejunum	1

**Table (2):Characters of liver metastatic nodules.**

Type	Number
Site of Liver Mets:	
• Right Lobe	12 (66.7%)
• Left Lobe	4 (22.2%)
• Bi-lobar	2 (11.1%)
Size of Liver Mets (cm):	
• Range	4-8cm
• Mean $\pm$ SD	5.3 $\pm$ 1.5
Number of Liver Mets:	
• Solitary	14 (77.8%)
• Two	3 (16.7%)
• >two <sup>1</sup>	1(5.5%)
• Mean $\pm$ SD	1.33 $\pm$ 0.77
Time of Presentation:	
• Synchronous	12 (66.7%)
• Metachronuous	6 (33.3%)

<sup>1</sup> four nodules were presented in one case (male with past history of low anterior resection for colorectal mass.

died after that by one year from liver cell failure.

3<sup>rd</sup> patient was 35 years old female who

underwent right hepatectomy for metastatic carcinoid tumor after right hemicolectomy for terminal ileum mass. She developed recurrent

**Table (3): Patients' operative data.**

Type	Number	Range	Mean ± SD
Operative time :	18 (100%)	110 - 320	199.4± 65.1
Blood loss (ml):	18 (100%)	400-1300	805.5 ± 329.8
Blood transfusion :			
• PRBCs (1-3 units)	14 (77.7%)		
• FFP (2-4units)	12 (66.6%)		
Hospital stay (days):	18 (100%)	7 - 12	8.4 ± 1.6
ICU stay (days):	3 (16.6%)	1-2	
Time of operation:			
• Simultaneous	2 (33.3%)		
• Classic approach	16 (66.7%)		
Type of operations:			
• Right hepatectomy	1 (5.5%)		
• Left lateral hepatectomy	4 (22.2%)		
• Segment 6,7	2 (11.1%)		
• Segment 5,6	2 (11.1%)		
• Segment 6	2 (11.1%)		
• Segment 7	2 (11.1%)		
• Segment 8	1 (5.5%)		
• Non-anatomical	4 (22.2%)		

metastatic nodules in the liver and lung after one and half years, systemic chemotherapy was taken. She is still alive till now.

The last patient was 56 years old male who underwent simultaneous resection of transverse colon with non-anatomical liver resection and removal of coeliac LNs. After one year he developed two small liver nodules with para-aortic LNs and two small lung nodules. Repeated cycles of chemotherapy were taken. He is still alive till now.

### Discussion:

The liver is most commonly involved organ in metastatic colorectal cancer patients. About 20% of these patients have clinically recognizable liver metastases at the time of their primary diagnosis. After resection of a primary colorectal cancer in the absence of apparent metastatic disease, approximately 50% of the patients will subsequently manifest metastatic liver disease. In our study three patients (3/14) of colorectal cancer developed metachronous metastatic nodules.<sup>13</sup>

The potential for developing liver metastases from neuro-endocrine tumors depends on the tumor type. Appendiceal carcinoid tumors and insulinomas rarely develop liver metastases, while small bowel carcinoid tumors and other islet cell tumors (including gastrinoma and glucagonoma) develop hepatic metastatic disease in up to 40% of the cases.<sup>14</sup> Other tumor types including (renal cell carcinoma, Wilm's tumor and breast cancer), although, they do not metastasize principally to the liver, can occasionally develop isolated liver metastases.<sup>1</sup>

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that cannot be resected unless regression is done, chemotherapy is being considered in highly selected patients trying to downsize colorectal metastases and convert them to a resectable status.<sup>15</sup>

Surgical resection remains the only

treatment that can, ensure long-term survival and cure in some patients. However, only a minority of patients with liver metastases is able to surgery. Recent progress including (new chemotherapeutic regimens, ablative techniques and interventional radiology) may allow an increase in the number of patients that can be treated with curative intent.<sup>16</sup>

Patients with resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neo-adjuvant plus postoperative) chemotherapy can be used.<sup>17</sup> In our study we used the staged resection (resecting of the primary malignant site, neo-adjuvant chemotherapy then liver resection followed by postoperative chemotherapy).

Advantages of preoperative chemotherapy include: earlier treatment of micro-metastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in planning postoperative management), and avoidance of local therapy for those patients with early disease progression.<sup>18,19</sup> A recent meta-analysis of 27 studies including greater than 7200 patients found that patients with longer disease-free intervals; those, whose recurrences were solitary, smaller, or unilobular; and those lacking extra-hepatic disease derived more benefit from repeat hepatectomy.<sup>20</sup> An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steato-hepatitis and sinusoidal liver injury, respectively.<sup>21,22</sup>

To limit the development of hepatotoxicity in patients with initially unresectable disease when chemotherapy is planned, a surgical re-evaluation planned 2 months after initiation of chemotherapy, surgery performed as soon as possible after the patient becomes resectable, and that those patients who continue to receive chemotherapy, surgical re-evaluation every 2 months thereafter.<sup>23</sup>

In most recent studies, in-hospital mortality varies from 0–5% and is strongly affected by peri-operative blood loss, pre-operative liver function and extent of liver resection. Postoperative complications are observed

in 25% of patients. Morbidity is usually due to transient liver failure, hemorrhage, subphrenic abscesses or biliary fistula. The mean hospital stay after liver surgery averages 10–15 days in the absence of complications.<sup>24</sup> We had no major complications, only minor ones which occurred in 9 patients.

Liver resection of colorectal metastases is associated with 3- and 5-year survival rates close to 40% and 25%, respectively. After resection, recurrences are observed in two-thirds of the patients and involve the liver in 50% of the cases. In a large retrospective study, 5- year survival was 28% in 1588 patients who had a resection of isolated colorectal liver metastases and 15% in 250 patients who had resected liver and extra-hepatic metastases.<sup>25</sup>

To improve prognosis and provide a potential selection of the patients before surgery or for postoperative adjuvant treatment, many studies looked at factors affecting survival. The sex and the site of the primary tumor don't influence the outcome. Prognosis seems better in cases of metachronous metastases, small lesions, and less than 4 lesions, but the involvement of one or both lobes didn't influence the outcome. The CEA level is strongly correlated with recurrence-free survival. A free margin of at least 1 cm offers the best chance of avoiding recurrence.<sup>16</sup> We had recurrence in four patients (22.2%). We attributed them to, presence of extra-hepatic LNs, large size tumor in case of carcinoid and aggressive tumor (mucinous adenocarcinoma grade III in case of low anterior resection).

### **Conclusion:**

Surgery is the cornerstone of therapeutic approach to patients with hepatic metastases especially colorectal cancer. Liver resection for liver metastases from different primary sites improved 5 years survival when used with the combination with neo-adjuvant chemotherapy. However, with the progress in chemotherapy and local ablative treatments, we can expand the resectable definition in the treatment of liver metastatic disease.

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