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RESEARCH ARTICLE

CAN RESECTION OF LIVER METASTASIS IMPROVE SURVIVAL AFTER RESECTABILITY CONVERSION CHEMOTHERAPY IN PATIENTS WITH METASTATIC COLO-RECTAL CANCER?

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Abstract

Background: Colon-rectal cancer is the fourth most frequent cancer worldwide, unfortunately 35%-50% develop metastasis, 60%- 80% of them have unresectable liver metastasis, 20% to 34% present with synchronous liver metastasis, while the others are metachronous, only 15%-20% will be candidate for hepatectomy, While chemotherapy can convert around 10% to resectability, R0 surgical resection leads to improvement in median 5-years survival in patients with resected liver metastasis.

Aim: To study the efficacy of **FOLFOX6** in resectability conversion of unresectable Colo-rectal cancer with liver limited disease. Neo-adjuvant chemotherapy was given to synchronous colorectal liver Mets unfit for upfront resection. **Patients and methods:** 167 patients presented to the advanced center of liver diseases, Zagazig University hospitals with metastatic Colo-rectal cancer to the liver from June 2012 to September 2015, all patients were assessed clinically, laboratory, pathologically. Only 90 patients were eligible, with liver limited disease and adequate organ function and laboratory results, resection the malignant primary site, neo-adjuvant chemotherapy for 1-3months, liver metastasectomy then chemotherapy±radiotherapy completion.

Results: our study included 51(56.7%) females and 39 (43.3%) males with mean age 47.7 years' old. 68 patient were colon cancer while 22 was rectal, 18 patients were converted to resectable. Classical approach for resection was done, 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 12 patients (two of them died during the follow-up period). CEA level at presentation and before surgery was statistically significant different in the resectable group with p-value 0.001, but this was not the case in the unresectable group with p-value 0.067.

The median OS was not reached in the resected group. The estimated mean OS for the unresectable group was 15.7 ± 0.96 (95% CI 13.8-17.6) compared to 20.1 ± 1.24 (95% CI 17.7-22.6) in the resected group that is statistically significant different with p-value 0.015.

Conclusion: chemotherapy can help in resectability conversion of unresectable liver metastasis. Resection for liver Metastasis in cases with Colo-rectal cancer improve survival.

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Introduction:-

Colon cancer is the fourth most common diagnosed cancer and the second cause of cancer related death in the united states (1), 50% to 60% of colorectal cancer patients develop metastases,(2). 80% to 90% of them have unresectable liver metastasis(3). most frequently Metastasis develops metachronously after locoregional treatment for colorectal cancer, liver is the most common involved site , while 20% to 34% ofpatients present with synchronous liver metastases.(4). Before considering treatment options, it is important to evaluate the extent of metastatic disease, both intra& extra hepatically. (5).

Surgical treatment is the corner-stone of therapeutic approach to liver Mets, as curative resection of liver Metastasis increases survival, with 5-year survival rates of 30%-40 %(6).selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.(2) Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,(7) andChemotherapy can be used for resectability conversion of unresectable liver limited metastatic Colo-rectal cancer,Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection (8).

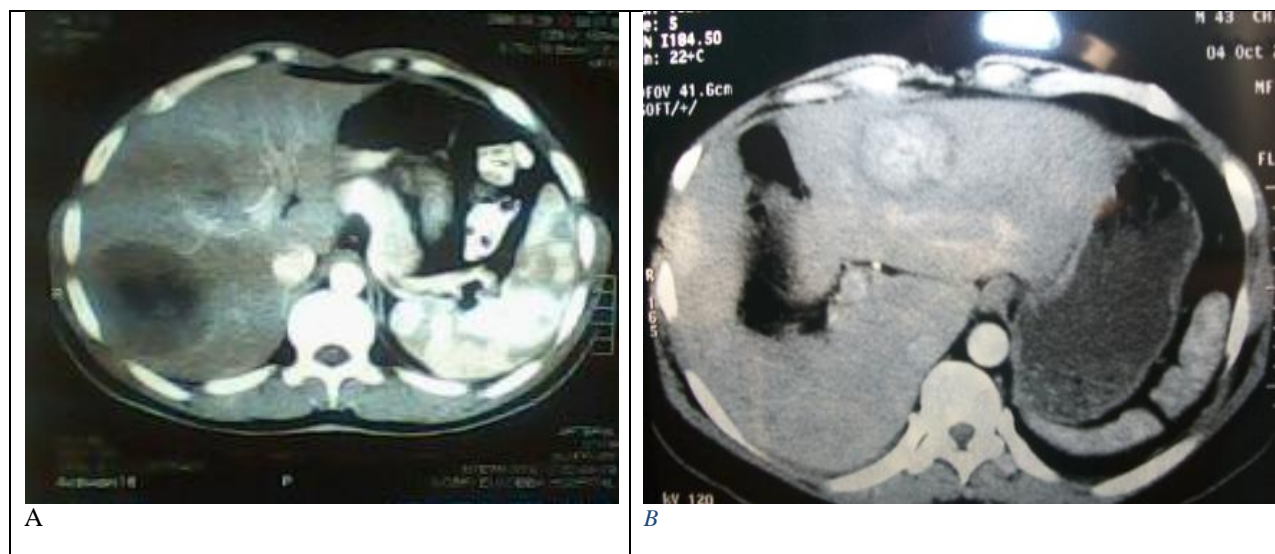
Patients and methods:-

167 patients with liver limited unresectable metastatic Colo-rectal cancer were presented to the advanced center of liver diseases, Zagazig Universityhospitals in the period from June 2012 to September 2015. All patients were assessed by multidisciplinary team including (surgery,medical oncology,radiation oncology, hepatology and radiology) doctors to confirm that the patient had liver limited metastasis and eligible for hepatic resection regarding general condition and future hepatic reserve.90 patients out of 167 were included in our study. All data regarding demographic data,laboratory results, 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 to cardiopulmonary status (pulmonary function tests and Echo).Laboratory evaluation including CBC, liver and kidney function test, tumor marker CEA initially and before each cyclethereafter, if progression was suspected because of increasing CEA, assessment by CT or MRI was done. Assessment of the functional capacity of the liver was done by liver function tests and Child-Pugh classification, patients with child A were included. All patients were given prophylactic dose of low molecular weight heparin and preparation of pack RBCs (PRBCs) and fresh frozen plasma (FFP) if needed.

Metastatic workup completed by CT chest, brain and bone scans. Pre-operative assessment of hepatic involvement 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).



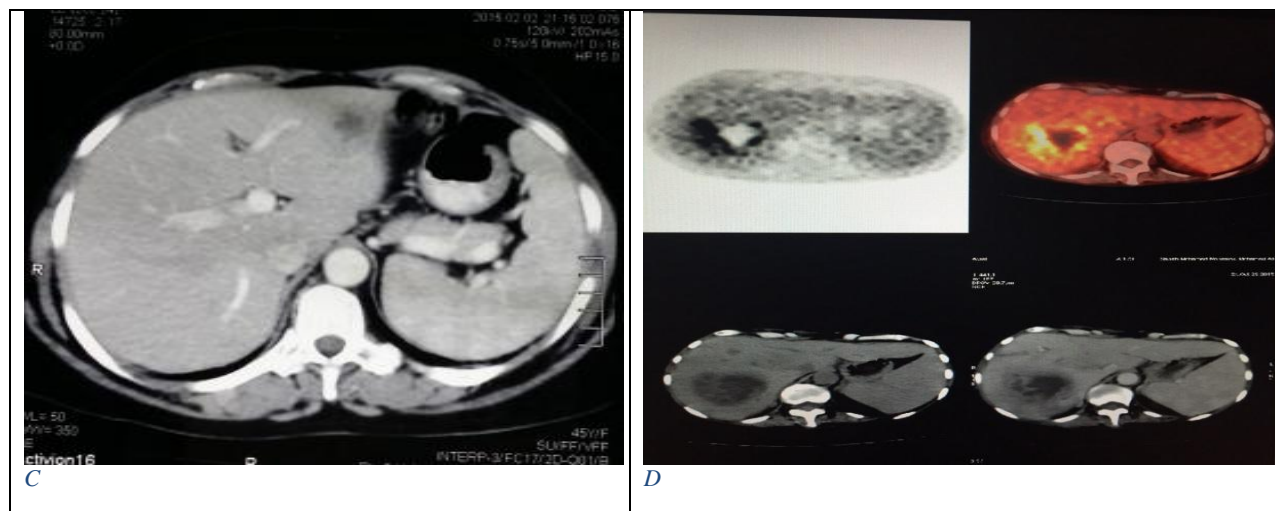


Figure (1) diagnostic imaging for liver Mets. A. Right lobe liver mets. B. Bi-lobar liver Mets. C. Left lobe liver Mets. D. PET-CT for right lobe liver Mets.

Our protocol of management of colorectal liver metastases was resection of the primary tumors first, followed by 4-6 cycles of chemotherapy, laboratory evaluation was done before each cycle, then re-evaluated by the same multidisciplinary team to assess resectability after 2-3 months, if patient was considered resectable then hepatic resection and lastly completion of chemotherapy, if not chemotherapy is continued.

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

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1.
- Leucovorin 400 mg/m² IV over 2 hours, day 1.
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day for 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks (9).

Regarding staged resection cases, neo-adjuvant chemotherapy was for 3 months then completion chemotherapy for another 3 months.

Surgical procedures:-

J shaped incision done for good exploration. First, intra-operative assessment of the primary tumor site done to determine any recurrence. Then careful exploration of the abdominal cavity 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 as it provides 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 sent for histopathology. Follow-up of the patients for 1 year 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 \pm SD (Standard deviation).

I-Arithmetic Mean:

$$\bar{X} = \frac{\sum X}{n}$$

Where:

$\sum X$ = sum of individual data.

n = number of individual data.

II-Standard deviation (SD):

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

Where : $\sum x$ = sum of data

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

n = number of data.

Results:

Patient's demographic data and site of primary tumor, Characters of liver metastatic nodules regarding (site, size, and number) showed in (table 1, 2).

Table 1: patient's demographic data.

Type	Number (%)
Site Of Iry Tumor:	
▪ Colorectal Cancer:	
○ Rectum	22
○ Recto-Sigmoid	24
○ Left Colon	20
○ Right Colon	17
○ Transverse Colon	7
Size of Liver Mets (cm):	
▪ Range	4 - 8
▪ Mean \pm SD	5.3 \pm 1.5

Table 2: Characters of liver metastatic nodules

	Male	Female	Total	p-value
Primary site:				
• Colon	37 (72.5%)	31 (79.5%)	68 (75.6%)	0.265
• Rectal	14 (27.5%)	8 (19.5%)	22 (24.4%)	
Number:				0.537
• Solitary	2	2	4(4.4%)	0.80
• \leq three	8	10	18(20%)	
• > three	40	28	68(75.6%)	
Age	49.5 \pm 10.6 (21-62)56.7%	45.4 \pm 11.4 (24-65)43.3%	47.7 \pm 11.1 (21-65)100%	0.475
▪ Colon			48.1 \pm 10.8 (24-62)75.6%	
▪ Rectal			46.2 \pm 14 (21-65)24.4%	

Table 3: patient characteristics in unresectable and conversion group:

variable	All (n=90)	Unresectable group (n=72)	Conversion group (n=18)	P value
Age	47.7 \pm 11.1 (21-65)	47.1 \pm 11.2	50.1 \pm 10.6	0.31
Sex:				0.56
Male	51(56.7%)	41 (56.9%)	10 (55.6%)	
Female	39(43.3%)	31(43.1%)	8 (44.4%)	0.037
Location:				
Rectal	22(24.4%)	21(29.2%)	1(5.6%)	
Colon	68(75.6)	51(70.8%)	17(94.4%)	0.61
Lobe				
Right	59(65.6%)	46(63.9%)	13(72.2%)	
Left	11(12.2%)	8(11.1%)	3(16.7%)	0.85
Bilobar	20(22.2%)	18(25%)	2(11.1%)	
Size	6.7 \pm 1.2(3-9)	6.6 \pm 0.9(4.5-8)	6.7 \pm 1.2(3-9)	

The most common site of liver Mets was the right lobe presented in 59 patients (65.6%), 20 patients (22.2%) had bi-lobe liver metastasis, while 11 patients (12.2%) had isolated left lobe metastasis. (Figure 2&3).

4 cases have single metastasis, while 18 patients had 2-3 metastatic site, while 68 patients had more than 3 focal lesions in the liver.

There was no significant association between the mean size of liver metastasis in both the resectable and the unresectable group pre-chemotherapy with p-value 0.85.

CEA level at presentation and before each cycle, there was statistically significant difference between the level of CEA at presentation and its level before surgery in the resectable group with p-value 0.001, but this was not the case in the unresectable group with p-value 0.067 as shown in table 4.

Table 4: CEA level before and after conversion chemotherapy:

CEA	Before			After			P value
	mean	St deviation	Range	mean	St deviation	Range	
TOTAL	235.5	157.5	1.9-637	42.3	36	1.5-152	
Resectable	150.7	105.7	11-321	7.9	3.6	2-14	0.001
unresectable	256.7	161.6	1.9-637	50.9	35.8	1.5-152	0.067

Conversion Chemotherapy related adverse events \geq grade 2 were noticed in 7 patients (2 cases with diarrhea, 3 with neutropenia, 2 with peripheral neuropathy) in the unresection group compared to 4 cases in the resection group (2 with diarrhea and the other 2 with neutropenia), no grade 4 adverse events were noticed.

Surgery was conducted 25 days (range 21-45) after the last chemotherapy administered.

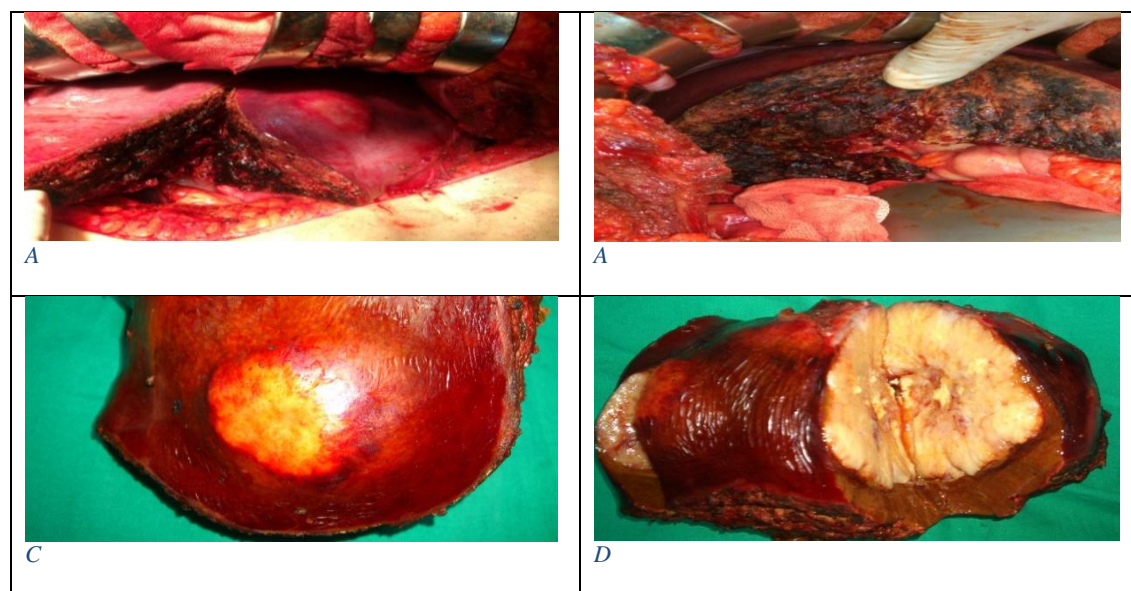
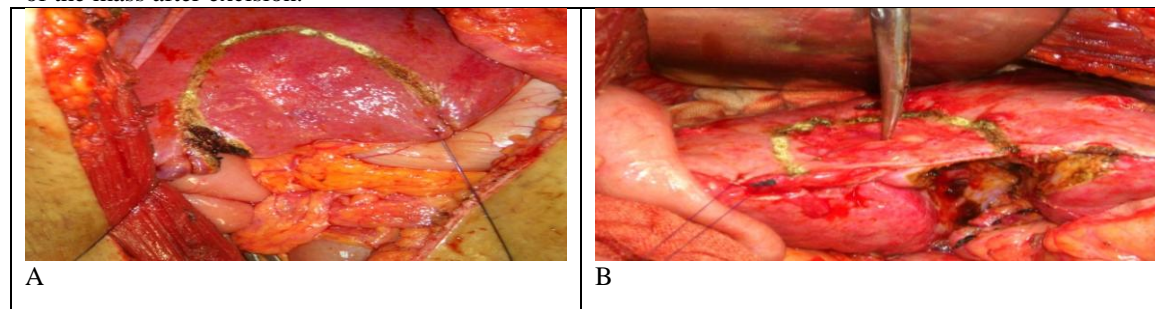


Figure (2) Right posterior sector metastasis & simultaneous primary colon cancer and liver Mets resection. A. Resection plane with the umbilicated appearance. B. Cut surface after resection. C. Mass after excision. D. Opening of the mass after excision.



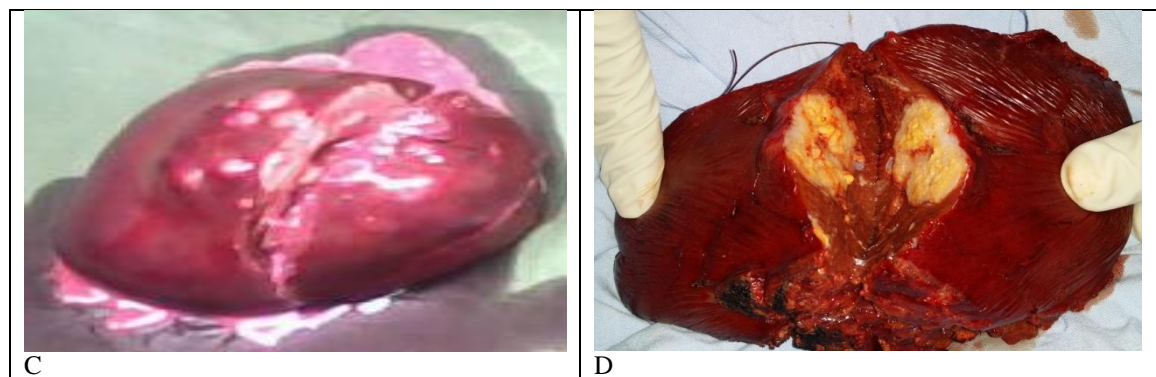


Figure (3): bilobar liver Mets resection, right hepatectomy & left liver Mets. A. Demarcation of left liver Mets excision. B. Demarcation of right liver Mets excision. C. Right lobe hepatectomy. D. Opening of the liver Mets.

The operative time was 210min., increased in patients with right hepatectomy with an estimated blood loss 800 ml. Blood transfusions using PRBCs occurred in 70 patients with 1-3 units and FFP in 60 patients with 2-4 units. ICU stay length was about two days in four patients (for three patients with right hepatectomy and for one patient with left lateral hepatectomy developed postoperative pulmonary embolism. And hospital length of stay for all patients was 9 days (table 5).

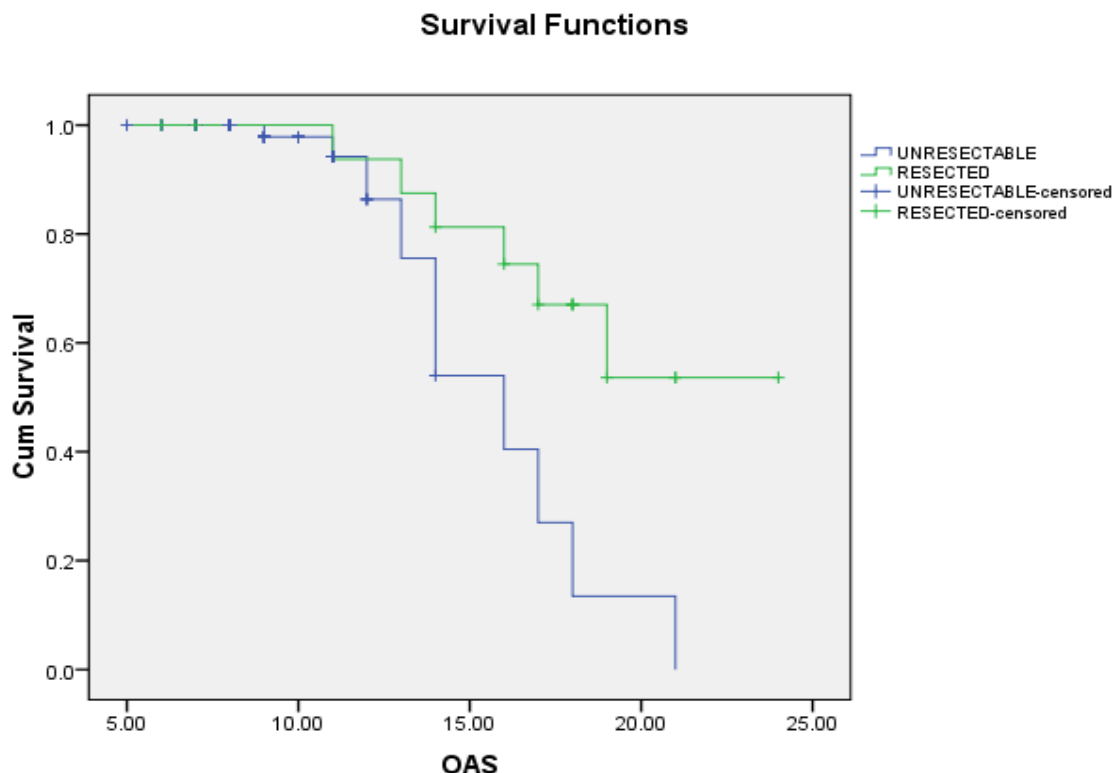
Table 5: Patients' operative data.

operative data	Number (%)	Range	Mean \pm SD
Operative time :	18 (100%)	110 - 320	199.4 \pm 65.1
Blood loss (ml):	18 (100%)	400-1300	805.5 \pm 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 \pm 1.6
ICU stay (days):	3(16.6%)	1 – 4	
Type of operations:			
Right hepatectomy	3 (16.7%)		
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	1 (5.5%)		
Segment 8	1 (5.5%)		
Non-anatomical ¹	4 (22.2%)		
Surgical margins:			
RO	16 (88.9%)		
R1	2(11.1%)		
1 non -anatomical+ left lateral hepatectomy in male patient that has mass in the left lobe + 3 nodules in the right lobe.			

Complications occurred in nine patients. Three patients (16.7%) 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 (16.7%) complaint with wound infection that managed by drainage and strong antibiotics. Dyspnea and chest pain was the complaint from one patient diagnosed as pulmonary embolism, managed by therapeutic doses of anticoagulant and stayed in ICU for 4 days. Last two patients complaint from chest infection, managed by conservative measures.

Recurrence was occurred in 12 patients during the follow-up period, two of them died.10 recurrence was to the liver, while two recurrence was in both liver and lung.

Figure 4:



The median OS was not reached in the resected group the estimated mean OS in the resected group mean is statistically significant higher than the unresectable group as shown in table 6.

Table 6: OAS

	Mean \pm std. error	95% confidence interval	p-value
Resected	20.1 \pm 1.24	(17.7-22.6)	0.015
Unresected	15.7 \pm 0.96	(13.8-17.6)	
Total	18.3 \pm 0.92	(16.5-20.1)	

There was statistically significant improvement in OAS in the resected group.

Discussion:-

The liver is most commonly involved organ in metastatic colorectal cancer patients, liver metastasis is one of the main causes of death in patients with Colo-rectal cancer. About 20% of these patients have clinically recognizable liver Mets 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 (10).

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. The major improvement in treating for those with liver-limited unresectable disease in the past decade has been the development and the use chemotherapy is being considered in highly selected patients trying to downsize colorectal Mets and convert them to a resectable status as surgical resection remains the only treatment that can, ensure long-term survival and cure in some patients (11).

Patients with resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neo-adjuvant plus postoperative) chemotherapy can be used (12).

In our study we used the staged resection (resection 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 (13). A 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 get more benefit from repeat hepatectomy (14). 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 (15).

In patients with initially unresectable disease when chemotherapy is planned, a surgical re-evaluation planned 2 months after initiation of chemotherapy to limit the development of hepatotoxicity, surgery should be performed as soon as possible after the patient becomes resectable (16).

In a study including 1104 patients with initially unresectable colorectal liver metastases were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection. (17) In another randomized controlled trial 13% of patients with unresectable colorectal cancer metastatic to the liver received (mFOLFOX6 or FOLFIRI) converted to be resectable (18). In our study conversion to resectability was in 20% of the patients, that is similar to that shown by Coskun et al (19).

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, sub-phrenic abscesses or biliary fistula. The mean hospital stay after liver surgery averages 10–15 days in the absence of complications (20). We had no major complications, only minor ones which occurred in 9 patients.

Liver resection of colorectal Mets 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 resected patients and involve the liver in all of the cases.

Selection of the patients before surgery or for postoperative adjuvant treatment can help in improving prognosis and outcome, many studies looked at factors affecting survival. The sex and the site of the primary tumor don't influence the outcome as shown in our study. The CEA level is significantly negatively influence OS (21).

Conclusion:-

Surgery is the potentially curative option for patients' with colorectal cancer with liver limited metastasis as it improved median survival when used with the combination with neo-adjuvant chemotherapy. Conversion chemotherapy improve survival in those patients as it increased the portion of patients legalized for resection. With the progress in chemotherapy and local ablative treatments, we can expand the resectable definition in the treatment of colorectal cancer with liver metastasis.

References:-

1. **Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65:5-29
2. **Van Cutsem E, Nordlinger B, Adam R, et al.** Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006; 42:2212-2221.
3. **Dawood O, Mahadevan A, Goodman KA.** Stereotactic body radiation therapy for liver metastases. *Eur J Cancer* 2009; 45:2947-2959.
4. **Hayashi M, Inoue Y, Komeda K, et al.** Clinic-pathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. *BMC Surg* 2010; 10:27.
5. **Tosulfas G, Georgios M, Kanellos I.** Surgical treatment of hepatic metastases from colorectal cancer. *World J Gastrointest Oncol* 2011; 3(1):1-9.
6. **Kemeny N, Kemeny MM, Lawrence TS.** Liver Metastases. In: Abelloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. *Clinical Oncology*. 3rd ed. Elsevier Philadelphia, 2004: 1141-1178.
7. **Pawlik TM, Scoggins CR, Zorzi D, et al.** Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; 241:715-722.
8. **Abdalla EK.** Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. *Am J Surg* 2009; 197:737- 739.

9. **Andre T, Boni C, Mounedji-Boudiaf L, et al.** Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350:2343-2351.
10. **Landis SH, Murray T, Bolden S, Wihgo PA.** Cancer statistics, 1998. *CA Cancer J Clin* 48:6-29, 1998.
11. **Christophe Penna and Bernard Nordlinger.** Surgery of liver metastases from colorectal cancer: new promises. *British Medical Bulletin* 2002; 64:127-140
12. **Araujo R, Gonen M, Allen P, et al.** Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. *Ann Surg Oncol* 2013; 20:4312-4321.
13. **Bischof DA, Clary BM, Maithel SK, Pawl, et al.** Surgical management of disappearing colorectal liver metastases. *Br J Surg* 2013; 100:1414-1420.
14. **Luo LX, Yu ZY, Huang JW, Wu H.** Selecting patients for a second hepatectomy for colorectal metastases: An systemic review and meta-analysis. *Eur J Surg Oncol* 2014; 40:1036-1048
15. **Kishi Y, Zorzi D, Contreras CM, et al.** Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 2010; 17:2870-2876
16. **Ciliberto D, Prati U, Roveda L, et al.** Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. *Oncol Rep* 2012; 27:1849-1856
17. **Adam R, Delvart V, Pascal G, et al.** Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; 240:644-657; discussion 657-648.
18. **Ye LC, Liu TS, Ren L, et al.** Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013; 31:1931-1938
19. **Coskun U, Buyukberber S, Yaman E, et al.** Xelox (capecitabine plus oxaliplatin) as neoadjuvant chemotherapy of unresectable liver metastases in colorectal cancer patients. *neoplasma*. 2008;55:65-70.
20. **Scheele J, Stang R, Altendorf-Hofmann A, et al.** Resection of colorectal liver metastases. *World J Surg* 1995; 19: 59–71.
21. **Kataoka K, Kanazawa A, Iwamoto S, et al.** Does “conversion chemotherapy” really improve survival in metastatic colorectal cancer patients with Liver-limited Disease?, *World j surg* 2014;38;936-946.