Evaluation of Synchronous Metastatic Colonic Cancer Management; Single Center Experience; Short Term Outcome

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ABSTRACT:

BACKGROUND:

Colorectal cancer is the fourth most frequently diagnosed cancer after lung, breast and prostate cancer, and the second leading cause of cancer death after lung cancer globally. Sometimes, distant metastases can cause the initial clinical symptoms. Synchronous metastatic colon cancer define as initially presented metastatic disease.

OBJECTIVE:

To evaluate the clinical presentations of patients with synchronous metastatic colon cancer, the outcome of current chemotherapy protocols used and their toxicity in our center for those patients , and to correlate the different clinical and pathological parameters in patients with this disease .

PATIENTS AND METHODS:

This is a hospital based prospective study would hold in Oncology Teaching Hospital Medical City during the period from 1 July 2019 – 1 July 2020. 50 patients would be recruited, all have evaluated by histopathological and radiological parameters, all diagnosed as metastatic colon cancer who are treated with chemotherapy and biological agents. All involved cases would be re-assessed after at least 4 cycles of treatment by physical examination, Lab investigations and Survival curve then demonstrate to shows the relation between the outcome and prognostic factors.

RESULTS:

In this study a total of 50 patients were involved ; All of them were diagnosed and treated for synchronous metastatic colonic cancer. the median age of diagnosis was 55.30 years, males in this study were higher than females (56% versus 44%); of enrolled patients 74% were with negative family history.Our study shows that the left side of involvement was the predominant (54%), and the highest proportion of patients in both groups were with single metastasatic site (52%); and the liver was the most common single site of metastasis in (40.0%) of patients In both groups, the most frequent clinical features were altering bowel habit and abdominal pain which reported in (60.0%) the highest proportion of patients in our study were treated with both chemotherapy and target therapy, (78.0%) all of them were receive XELOX {xeloda tablet and oxaliplatin} as chemotherapy and Avastin as target one ; in both groups the commonest grade of differentiation is the grade two (82%); while adenocarcinoma was the commonest histopathological type (92%). The primary tumor was resected in (62%) of patients all due to intestinal obstruction. Reassessment of all patients in both groups was done by Lab investigation and radiological assessment, the median progression free survival was 24.7 months.

CONCLUSION:

In our study, the progression with statistical significance was seen among patients with right sided tumor, patients with multiple sites of metastases, those who treated by Chemotherapy only without target therapies, and in patients who had mucinous adenocarcinoma .

KEYWORDS: colon tumor, synchronous metastasis.

INTRODUCTION:

Colorectal cancer (CRC) is the fourth most diagnosed cancer after lung, breast and prostate cancer ,and the second leading cause of cancer death after lung cancer globally[1].

It approximately 25 percent higher in men than in women and is approximately 20 percent higher in African American than in whites [2].

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Age is a major risk factor for sporadic CRC; large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50 [3]. in the past decade, there has been a decrease in the incidence and mortality of colorectal cancer in the United States; findings from epidemiologic studies indicate that during the past 2 decades, the anatomic distribution of colorectal cancer may have shifted from the distal to the proximal colon, change in the anatomic distribution of CRC may be, in part, related to improvements in diagnosis and treatment, in addition to increase screening with removal of adenomatous polyps at the distal colon [4]. colonoscopy is more effective in preventing left-sided than right-sided CRC which could also contribute to a shift in distribution of cancers in the colon,It is likely that part of the difference is due to aspects of quality relating to the colonoscopy but the biology may also differ between CRC of the right and left colon[5]. Approximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases and 80% to 90% of these patients have unresectable metastatic liver disease [6]. Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver being the most common site of involvement, however 20% to 34% of patients with colorectal cancer present with synchronous liver metastases[7]. The 5-year survival rate of people with localized stage colorectal cancer is 90%. About 39% of patients are diagnosed at this early stage. If the cancer has spread to surrounding tissues or organs and/or the regional lymph nodes, the 5-year survival rate is 71%. If the cancer has spread to distant parts of the body, the 5-year survival rate is 14%[8]. In Iraq, colon cancer is the fourth common type of malignancy in both sex after Breast, lung and prostate cancers, accounting for approximately 6.12% of the registered patients cancers according to the latest Iraqi Cancer Registry/ Ministry of Health.

A total of 1963 colon cancer cases were registering among patients aged ≥20 years, representing 5.08 per 100.000 P ([9]).

Prognostic Factors in Synchronous Metastatic colon cancer [10]

Over the past 30 years, there has been a great interest in clinical and molecular prognostic factors in metastatic colorectal cancer [10].

The following prognostic factors have been associated with CRC:

Gender: Female sex has generally been considered a favorable prognostic factor, but data is limited and inconclusive, sex was not a predictive factor for treatment efficacy.

Age: Age impacts on CRC incidence greater than any other demographic factor.

Family History: Screening colonoscopy for high-risk patients with a family history of colorectal cancer in first-degree relatives but no clear evidence of FAP or HNPCC should begin at 40 years of age [10].

Histologic Grade: Histological grade significantly influences survival regardless of stage.

Histologic Type: Mucinous adenocarcinoma, signet ring cell carcinoma and small cell carcinoma have a poorer prognosis than other types of colorectal tumors[11].

Presentation: Patients who present with bowel obstruction or perforation have a worse prognosis than patients who present with neither of these problems.

Primary Tumor Location: the right-sided colon cancers carry a worse prognosis than left-sided ones [12].

Site and Number of metastasis: Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously [13].

Treatment of Synchronous metastatic colonic cancer [14]:

The prognosis for patients with stage IV disease without specific therapy is poor; the median survival was 5 to 6 months. However, a subset of patients with isolated sites of metastases is potentially curable with surgery. When treating a patient with metastatic colon cancer, the first determination is whether stage IV disease is potentially curable by a surgical resection of metastases either at the time of diagnosis or after downsizing initially un resectable metastases by neoadjuvant chemotherapy, If the patient's disease does not appear curable, the main goals of systemic chemotherapy are to extend the duration of a patient's life and to maintain quality of life for as long as possible . For decades standard first-line therapy consisted of fluorouracil/LV, with response rates of approximately 20% and a median survival of approximately 1 year.

The addition of oxaliplatin/irinotecan to the backbone of fluorouracil/LV resulted in an improvement in median survival to nearly 24 months when patients received active first-line and second-line therapy. The introduction of biologic agents, such as bevacizumab, cetuximab, and panitumumab, have further enhanced the efficacy of systemic medical therapy.

Surveillance for Metastatic Disease:[15]

The patients should have history and physical examination every 3 to 6 months for 2 years, then every 6 months for a total of 5 years, and should undergo contrast- enhanced CT scan of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment and then every 6 to 12 months for up to a total of 5 years. CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years, as in early-stage disease. Colonoscopy in one year except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 months If advanced adenoma, repeat in one year; if no advanced adenoma, repeat in 3 years then every 5 years[15].

AIM OF THE STUDY:

To evaluate the clinical presentations of patients with synchronous metastatic colonic cancer, to evaluate the outcome of current chemotherapy protocols used and their toxicity in our center for patients with this disease ,and to correlate the different clinical and pathological parameters in this patients .

PATIENT AND METHODS:

Study design

Hospital based prospective observational study was conducted to evaluate the management of synchronous metastatic colonic cancer in oncology teaching hospital.

Study population

This is prospective single center study, the patients with metastatic colonic cancer whom were diagnosed at Oncology Teaching Hospital/ Medical City, by colonoscopic biopsy, incisional biopsy, and/ or true cute biopsy; all have evaluation by histopathological and radiological parameters, all histopathological result reviewed by expert pathologist and diagnosed as metastatic colon cancer, patients were included in our study considered as synchronous metastatic colon cancer then their management evaluated from the period of 1 July 2019 – 1 July 2020; chemotherapy protocols were given with or without target agents every three weeks according to NCCN guidelines, physician choice and patients performance state; then evaluation were done every three months by getting a history; physical examination; laboratory investigation (completed blood count; renal and liver function tests , tumor marker; radiological images (CT chest and abdomen); and colonoscopy ,then Patients were divided according to their progression free survival to two groups; these with PFS of less than one year; and those group with PFS of more than one year according to progression free survival period; and the two groups were compared regarding their possible prognostic factors including age, sex, side of tumor, family history, presentation, stage, grade, number and site of metastasis, type of regimen used as first line treatment, use of biological agent, and if the primary or metastatic site resected; to detect the association of PFS with these factors.

Inclusion criteria: Patient with synchronous metastatic colonic cancer whom followed for at least 12 months.

Exclusion criteria: Patients with metachronous metastatic colonic cancer as well as those who lost their follow up visit.

Data collection

Primary patient's data were collected during their scheduled visits for their treatment or follow up at Oncology Teaching Hospital; the following demographic data at time of diagnosis about every patient were obtained including:

1. Age;
2. Family history of colonic cancer;
3. Sex;
4. Clinical features;
5. Side of primary disease;
6. 6 .number and site of spread;
7. First line treatment;
8. Resection status of tumor. Tumor histopathological study was performed in the hospital lab of histopathology.

Statistical analysis

The continuous data are expressed as mean ± SD (standard deviation) while the discrete data are expressed as numbers and percentages. The data are entered on Microsoft Excel sheet version 2013. The descriptive data were presented through a frequency distribution tables. The p value of less 0.05 was considered as statistically significant. We consider the date of diagnosis is the started time of evaluation.

The median evaluation period of our patients was 12 months.

Ethical consideration

The dissertation proposal was fully discussed and accepted by ethical and scientific committee in Iraqi board of medical specialties. a verbal consent was taken from all included patients after a full explanation of the aim of the study .

RESULTS:

In this study , 50 patients with synchronous metastatic colonic cancer were involved; the age ranged from 22 to 80 years with a mean of 55.30 years ± 12.94 years. More than half of patients (52%) were (40-55) years . males were more than females (56% versus 44%) with a male to female ratio of 1.27:1.

Concerning family history, 26% of enrolled patients had positive family history. primary tumor was right sided in 23(46%); (table1), metastatic was single detected in 26(52%) and liver being the site of metastasis in 22(44%). The most frequent clinical features were altering bowel habit and abdominal pain which reported in 30(60%), followed by anemia which recorded in 15 (30%)(table2), moderate differentiation is most common 42(84.0%) of patients, Mucinous adenocarcinoma was found in 4 (8 %) of patients while non-mucinous type 46 (92.0%), In regard to treatment modalities the most frequent one was chemotherapy(XELOX) and target therapy (Avastin) being used in 39(78%) of patients. The primary tumor was resected in 31(62%) of patients, However all were as emergency resection. reassessment of all patients 50 (100%) was done by Lab investigation (CBC and biochemistry) and radiological parameters(CT scan of chest and abdomen) while Colonoscopy was done for only 2 (4%) of patients .

Table 1: Demographical parameters of synchronous metastatic colon cancer

Age group (years)	**No. (%)**
<40	5 (10.0)
40-55	26 (52)
>55	19 (38.0)
Gender	**No. (%)**
Male	28(56.0)
Female	22(44.0)
Family history	**No. (%)**
Positive	13(26.0)
Negative	37(74.0)

Table 2: The clinical parameters in synchronous metastatic colon cancer.

Side of primary tumor	**No. (%)**
Right	23(46.0)
Left	27(54.0)
Number of metastasis	**No. (%)**
One	26(52.0)
Two	16(32.0)
Three or more	8(16.0)
Site of metastasis	**No. (%)**
Liver	22(44.0)
Lung and liver	17(34.0)
Others	13(22.0)
Clinical features	**No. (%)**
Alter bowl habits and abdominal pain	30(60.0)
SOB and abdominal pain	5(10.0)
Anemia and abdominal pain	15(30.0)

Table 3:The pathological parameters in synchronous metastatic colon cancer.

pathological subtype	**No. (%)**
Mucinous	4(8.0)
Non -mucinous (adenocarcinoma)	46(92.0)
Tumor grade	**No. (%)**
I	4(8.0)
II	42(84.0)
III	4(8.0)

Table 4: Treatment modalities in synchronous metastatic colon cancer.

Therapy guidelines	**No. (%)**
Chemotherapy only(XELOX)	11(22.0)
Chemotherapy and target therapy	39(78.0)
Surgical resection	**No. (%)**
Yes	31(62.0)
No	19(38.0)

Progression free survival {PFS} according to certain factors

After one year of evaluation , 18 (36%) patients exhibited disease progression within first year of fellow up , the remaining 32 (64%) patients showed no detectable progression within this year of follow up figure (1); Most of the progression events occur during the first 6 months post diagnosis.

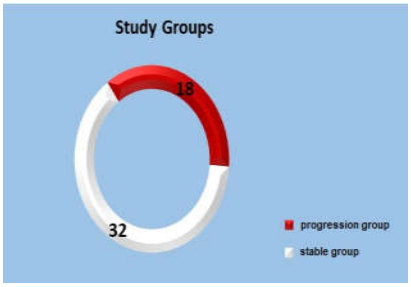

Figure no.1: PFS of both group

None of the studied demographic parameter {age, gender, family history} showed any influence on outcomes of the disease.

There was a statistically significant association between outcome of disease and side of tumor and number of metastasis, The proportion of progressive tumor was significantly higher among patients with right sided tumor (52.2%, P= 0.027), (table5) and multiple metastases (87.5%, P= 0.001).

No significant association was found with site of metastasis and clinical features.

Table 5: Distribution of study groups by outcome of disease and clinical parameters.

Clinical Parameters	Study Groups		Total (%) n= 50	P- Value
	Progression Group (%) n= 18	Stable Group (%) n= 32		
Side				
Right	12 (52.2)	11 (47.8)	23 (46.0)	0.027
Left	6 (22.2)	21 (77.8)	27 (54.0)	
Number of Metastasis				
One	9 (34.6)	17 (65.4)	26 (52.0)	0.001
Two	2 (12.5)	14 (87.5)	16 (32.0)	
Three	7 (87.5)	1 (12.5)	8 (16.0)	

this study In, all of the 4 patients who had mucinous adenocarcinoma were with progressive disease, with a statistically significant association between outcome of disease and type of histopathology . While grade of tumors were insignificantly associated with disease outcome (P= 0.009, and 0.667, respectively) table (6).

Table 6: Distribution of study groups by outcome of disease and histopathological findings.

Histopathological Findings	Study Groups		Total (%) n= 50	P- Value
	Progression Group (%) n= 18	Stable Group (%) n= 32		
Grade of Differentiation				
Mild	2 (50.0)	2 (50.0)	4 (8.0)	0.667
Moderate	14 (33.3)	28 (66.7)	42 (84.0)	
Poor	2 (50.0)	2 (50.0)	4 (8.0)	
Type of Adenocarcinoma				
Mucinous	4 (100.0)	0 (0)	4 (8.0)	0.009
Non Mucinous	14 (30.4)	32 (69.6)	46 (92)	

In regard to treatment modalities and outcome of the disease,chemotherapy(XELOX) and target therapy (Avastin) being used in 10 (55.6%) of progression patients, and 29 (90.6%) of stable patients table (7); there was a statistically significant association between outcome of disease and type of therapy (72.7%, P= 0.004), but the toxicity profile was not significant. The primary tumor was resected in 12 (66.7%) and 19 (59.4%) of patients in progression group and stable group, respectively, no significant association was found with surgical removal; however all were as emergency resection and the surgical margin was positive in progression group, reassessment of patients in both groups was done by Lab investigation and radiological parameters,colonoscopy was done for only 2 patients with stable disease and the result was normal .

Table 7: Distribution of study groups by outcome of disease and treatment modalities.

Treatment modalities	Study Groups		Total (%) n= 50	P- Value
	Progression Group (%) n= 18	Stable Group (%) n= 32		
Medical management				
Chemotherapy only	8(72.7)	3(27.0)	11	
Chemotherapy and target	10(25.6)	29(74.4)	39	0.004

DISCUSSION:

In present study all the clinical and pathological parameters showed no statistically significant risk factors for reduced PFS except for the tumor side ; number of metastasis, histopathological subtypes ,and target therapy availability , while the demographical parameter have no statistical significant with PFS.

We found there was a statically significant (p value <0.0027, Log Rank test) association between outcome of the disease and the side of primary disease ,the right side involvement will shorten the progression free survival; which was almost the same to Kwangmin Kim's et al [16], in terms of PFS and response to chemotherapy in favor the left side colonic cancer. According to the results of this study we found there was a statically significant (p value <0.001, Log Rank test) association between outcome of the disease and number metastases; patients who presented with multiple site of metastases had short PFS in comparison to those whom had single site of metastatic disease , while Jiwei Wang et al [17], stated that the site of distant

metastasis and number of metastasis site were independent prognostic factors for survival of patients with stage IV Colon cancer .

In this study we found all patients with mucinous adenocarcinoma were with shorter PFS than those with non mucinous type the association was statistically significant (p value <0.009, Log Rank test) ; which is almost similar to Roberto Maisano et al[18] ,which showed that the Mucinous adenocarcinoma is associated with poor prognosis and reduced activity of chemotherapy. During the follow up of 50 patients (stage four) we found those whom not received targeted therapy with there Chemotherapy had shorter PFS than those whom receive, with statistically significant association (p value <0.004, Log Rank test) between the outcome of the disease and this parameter, Suk-young Lee et al [19], stated that the application of biologic agents to patients extended median survival up to over 2 years, and the combination chemotherapy with conventional chemotherapeutic and targeted agents has been established as the standard therapy. However, resistance to the targeted agents has emerged as a new issue to overcome in recent years .Reassessment of patients in our study was done by Lab investigation (CBC and biochemistry) and radiological parameters (CT scan of chest and abdomen), every 4 cycles of chemotherapy in regard to treatment response and treatment related toxicity, however colonoscopy was not adequately performed, almost the same steps of follow up by Sibiani et al[20], with adequately performing colonoscopy.

CONCLUSION:

We are in Oncology teaching hospital/ Medical city follow the most significant facilitates as much as possible in order to provide the proper way of management according to universal guidelines .

We found the median age of diagnosis was 55.3 years old ; however the incidence increased in those of less than 50 years old , highest incidence of progression was among patients with right sided tumor, patients with multiple sites of metastases, those treated by chemotherapy only without target therapies, and in patients with mucinous adenocarcinoma type, tumor of moderately differentiated grade was the most common grade in our study as well as those with single site of metastases, the most of the events occur within the first 6 months of follow up, and visceral metastasis was the most common pattern.

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