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Impact of Neoadjuvant Chemotherapy with FOLFOX/FOLFIRI on Disease-free and Overall Survival of Patients with Colorectal Metastases

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Abstract

Study Aims—To determine if neoadjuvant FOLFOX/FOLFIRI is associated with improved disease free survival (DFS) or overall survival (OS) in patients with colorectal metastases (CRM) to the liver.

Methods—Ninety-nine patients (from 457 eligible) with CRM that underwent hepatic resection during 2000 to 2005 were included. Group 1 (n=44) patients received neoadjuvant FOLFOX/FOLFIRI, and Group 2 (n=55) did not receive neoadjuvant therapy.

Results—There were 58% men. The median age for Group 1 was 58 and Group 2, 64 (p=0.03). OS for Group 1 at 1-, 3-, and 5-years was 93%, 62%, and 51%, respectively, with a median OS of 5.8 years. In Group 2 survival at 1-, 3-, and 5-years was 90%, 63%, and 45%, respectively, with a median OS of 3.7 years (HR 1.06, p=0.87). The DFS for Group 1 at 1-, 3-, and 5-years was 51%, 20%, 20%, with a median DFS of 1.1 years and Group 2 at 1-, 3-, and 5-years was 58%, 32%, 32% (median DFS - 1.2 years) (HR=1.24, p=0.45).

Conclusions—Neoadjuvant FOLFOX/FOLFIRI was employed more frequently in younger patients with CRM, however, neoadjuvant chemotherapy for CRM was not significantly associated with an increase in OS or DFS, despite additional adjuvant therapy.

Keywords

neoadjuvant therapy; FOLFOX; hepatectomy; colorectal cancer metastases; survival

Introduction

Colorectal cancer is the third most common malignancy and is the second leading cause of cancer mortality, attributing to approximately 50,000 deaths in the United States in 2005 [1]. Metastatic colorectal cancer is associated with an even poorer prognosis with a five-year survival rate of 5–37% [2–4]. Approximately 25–30% of patients with colorectal carcinoma will initially present with metastatic disease, and the liver is the most common site of involvement [3,5,6]. Resection of isolated hepatic metastases is currently the most effective form of curative treatment offering a five-year survival rate ranging from 25–58% [7–11]. While 5-fluorouracil (5-FU) based chemotherapy was used in most patients with metastatic

colorectal cancer, during the past decade, combinations of 5-FU, leucovorin (LV), and the topoisomerase I inhibitor irinotecan (FOLFIRI) or the platinum analog oxaliplatin (FOLFOX) have proven more effective [2]. Moreover, the novel use of neoadjuvant FOLFOX initially reported in 1996 changed the surgical paradigm for patients with colorectal metastases to the liver converting 16% of patients with unresectable to resectable disease [5]. Expansion of the use of neoadjuvant therapy to include patients with resectable metastatic disease has occurred, but data for such patients is limited and whether outcomes are improved remains debatable. The objective of our study was to determine if neoadjuvant FOLFOX/FOLFIRI is associated with increased disease-free survival (DFS) or improved overall survival (OS) in patients with surgically resectable colorectal metastases (CRM) to the liver.

Material and Methods

A retrospective, institutional review board approved, review was performed on 457 consecutive patients who underwent hepatic resection for metastatic colorectal disease between January 1, 2000, and December 31, 2005, at Mayo Clinic, Rochester, Minnesota. Inclusion criteria included age greater than 18 years, pathologically documented metastatic colorectal cancer to the liver, resectability of hepatic metastases by surgical assessment prior to initiation of neoadjuvant therapy with FOLFOX/FOLFIRI, and patients who were not exposed to any prior neoadjuvant chemotherapy.

Exclusion criteria included a history of hepatic arterial infusion chemotherapy (n=82) or other any other neoadjuvant or adjuvant chemotherapeutic agents (n=126), documented presence of extra-hepatic metastases (n=60), upper abdominal/intraoperative radiation (n=25), history of hepatitis/cirrhosis (n=2), concomitant cancers (n=5) or a combination of the above (n=58). Data elements abstracted from the patient chart included demographics, symptomatic presentation, preoperative imaging, operative and pathologic findings, chemotherapy regimen, postoperative complications, date of death, and date of disease recurrence. Eligible patients were divided into two groups. Group 1 (n=44) consisted of patients who received neoadjuvant FOLFOX/FOLFIRI, and Group 2 (n=55) consisted of patients who did not receive neoadjuvant therapy.

We have reported descriptive statistics as number (percent) and as mean (SD) or median (range) where appropriate. Time of hepatic resection to death or last follow-up was used to calculate OS, while DFS assessment was from time of hepatic resection to either recurrence or last follow-up, censoring at patient death when not due to disease progression. Kaplan-Meier survival was used to calculate OS and DFS estimates with the median survival reported as the point in time when the survival estimate reaches 50%. Cox proportional hazard regression was used to assess the association between treatment group and overall, as well as DFS; the hazard ratio (HR) and 95% confidence interval are reported. Models included age and gender in addition to treatment group. The association between recurrence and patient death was assessed considering the date of recurrence as a time-dependent covariate in the Cox model. The study had 80% power to detect associations between neoadjuvant use and overall survival of $HR \geq 2.44$, and DFS of $HR \geq 2$. All missing data was excluded from analysis. The alpha-level was set at $p < 0.05$ for statistical significance.

Results

Demographics and presentation

Of the 457 eligible patients, 358 patients did not meet inclusion criteria, leaving a study group of 99 patients (22% of the hepatic resection patients), 58 males and 41 females. The median age of the overall study group at hepatic resection was 63 years (range 33–90). The median age of Group 1 and Group 2 was 58 and 64 years respectively ($p=0.03$), (Table 1). Overall,

patients were followed a median (range) of 3.9 years (0–6.6), to either death or last contact. There were 44 patients (20% of total) in Group 1 and 55 patients in Group 2 (12% of total). Hepatic metastases were evident at the initial colorectal operation in 48 patients of Groups 1 and 2 (49%). Twenty-one patients (21%) underwent simultaneous resection of the primary colorectal cancer and the hepatic metastases while 78 patients (79%) underwent staged resections of the primary tumor and hepatic metastases. Among the 61 patients for whom preoperative carcinoembryonic antigen (CEA) serum levels were available, only five patients had levels > 200 ng/mL and all of these patients were in Group 2.

Surgical Management

The average interval from initiation of chemotherapy to hepatic resection in Group 1 was seven months (3–26 months). The median interval from diagnosis of hepatic metastases to hepatic resection in Group 1 was 192 days (2–906 days) and in Group 2 was 38 days (0,804). The average smallest resection margin overall was 0.91 cm. The average closest resection margin in Group 1 and Group 2 was 0.81 cm and 0.97 cm, respectively ($p=0.08$), (Table 1). Metastases were described pathologically as poorly differentiated in 70 patients overall (81.4 %), moderately differentiated in 15 patients (17.4 %), dedifferentiated in one patient (1.2 %), and revealed post-chemotherapy fibrotic changes in six patients (6%), (Table 1).

There were no differences in the extent of resections between the two groups. Most patients underwent a major hepatic resection: right hepatectomy in 48% and left hepatectomy in 6%. The remaining patients underwent: left lateral sectorectomy in 4% , bisegmentectomy in 3% , segmentectomy in 19%, nonanatomic subsegmental resection in 39%, (Table 2). Of the patients who underwent a segmentectomy, the median number of segments removed was one, while the median number of nonanatomic subsegmental resections was two. The lymph node status of the primary colorectal cancer was pathologically positive in 57 patients, negative in 37 patients, and unknown in 5 patients. Of the patients with lymph nodes excised during the colorectal procedure, the average number of lymph nodes excised during resection of the primary colorectal cancer was 14 with an average number of 1 node positive in Group 1 and an average number of 2 nodes positive in Group 2 for metastatic cancer ($p=0.12$).

Chemotherapy treatment

Neoadjuvant chemotherapy prior to hepatic resection—Forty-four patients received neoadjuvant chemotherapy (Group 1) consisting of FOLFOX, FOLFIRI, or both. Fifty-five patients did not receive neoadjuvant chemotherapy (Group 2). All patients were deemed resectable by a hepatobiliary surgeon based on computed topography (CT) prior to the initiation of chemotherapy. Neoadjuvant FOLFOX/FOLFIRI was employed more frequently in younger patients: median age of 58 versus 64 years for Group1 and Group 2 respectively ($p=0.03$).

Adjuvant chemotherapy after hepatic resection

Forty-nine patients (58 %) received adjuvant chemotherapy after hepatic resection. Of these patients, 16 (33 %) received FOLFOX, 13 (27 %) received FOLFIRI, 12 (24 %) received both, three (6 %) received another form of chemotherapy, and the regimen was unknown in five (10 %) patients. Adjuvant chemotherapy was used in 68% of patients in Group1 and 49% of the patients in Group 2 ($p=0.08$). Eighteen patients in Group 1 and 23 patients in Group 2 received adjuvant FOLFOX, FOLFIRI or both.

Disease Free Survival Group 1 versus Group 2

Disease-free survival at 1, 3, and 5 years was 51%, 20%, and 20% in Group 1, with a median DFS of 1.1 years. The DFS for Group 2 at 1, 3, and 5 years was 58%, 32%, and 32% with a median DFS of 1.2 years (Figure 1). Adjusting for age and gender, use of neoadjuvant therapy

was not significantly associated with DFS ($p=0.45$), a patient receiving neoadjuvant therapy relative to a patient who did not receive neoadjuvant chemotherapy had a slightly increased risk of recurrent disease, HR=1.24 (95% CI 0.71–2.14).

In Group 1, 39 % of patients did not have any disease recurrence compared to 51% in Group 2. Group 1 had a recurrence pattern of primarily intrahepatic recurrence (36%), with 11% extrahepatic alone and 14% both intra and extrahepatic. In Group 2, the pattern of recurrence was similar with 50% intrahepatic alone, 15% extrahepatic alone and 18% with both intra and extrahepatic disease.

Overall survival Group 1 versus Group 2

There were three in-hospital deaths, two in Group 1 (post operative myocardial infarction and from multiorgan system failure from undetermined etiology) and one in Group 2 (hepatic failure). Overall survival for Group 1 at 1, 3 and 5 years was 93%, 62%, and 48%, respectively, with a median survival of 5.8 years. Overall survival at 1, 3, and 5 years for Group 2 was 90%, 63%, and 45%, respectively, with a median survival of 3.7 years (Figure 2). Adjusting for age and gender, use of neoadjuvant therapy was not associated with improved overall patient survival ($p=0.87$), in fact a patient receiving neoadjuvant therapy relative to a patient who did not had a slightly higher risk of death, HR=1.06 (95% CI 0.54–2.07).

Disease Free Survival Synchronous versus Metachronous

Of the total population of patients, DFS at 1, 3 and 5 years was 38%, 30%, and 30% in the patients undergoing synchronous resection. Disease-free survival at 1, 3 and 5 years was 58%, 26%, and 26% (Figure 3).

Overall survival Synchronous versus Metachronous

Overall survival rates at 1, 3 and 5 years were 94%, 64%, and 55% in those undergoing a synchronous resection and were 90%, 61%, and 46% in those undergoing a metachronous resection (Figure 4).

Discussion

The results of our study revealed that the use of neoadjuvant chemotherapy in patients with resectable metastatic disease does not offer a definite OS or DFS advantage over surgical resection alone with or without adjuvant chemotherapy. Our data also demonstrated no survival advantage of neoadjuvant chemotherapy with synchronous versus metachronous resection. These findings were in the setting of strict exclusion criteria, similar tumor burden and types of surgical resections performed. The only apparent significant difference amongst treatment groups was that the mean age of those treated with neoadjuvant chemotherapy was younger than those that went straight to operative resection.

The mean one-year OS was 93% in Group 1 and 90% in Group 2. At five years, the OS had decreased to 48% in Group 1 and 45% in Group 2. Lubezky, et al.[12] noted a similar one-year OS rate (91%) for patients receiving adjuvant chemotherapy when compared to patients receiving neoadjuvant therapy (95%). Lubezky also reported similar three-year OS of 84% for patients with adjuvant therapy compared to 70% OS for patients receiving neoadjuvant treatment (the OS was similar in both groups). Both Lubezky and we concluded that there is no OS advantage for neoadjuvant chemotherapy compared to adjuvant therapy except for those truly made resectable with neoadjuvant chemotherapy.

Our study demonstrated no difference in DFS at one-year (51% in Group 1 and 58% in Group 2). At 5 years, however, the DFS was only 20% in Group 1 and 32% in Group 2. Lubezky, et

al.[12] described a one-year DFS of 63% for patients having adjuvant therapy compared to a 94% one-year DFS in patients receiving neoadjuvant therapy. Although the neoadjuvant group appeared to have a DFS benefit in the first year (94% vs. 63%), the benefit disappeared by three years (50% vs 49%).

Another study by Adam, et al., [13] found similar results with respect to DFS in a series of 1104 unresectable patients who received neoadjuvant FOLFOX/FOLFIRI, of those patients 12.5% became eligible for curative resection. The DFS in the surgically resected patients was 30%, 22%, and 17% at three, five, and 10 years, respectively. The OS for this group was 52%, 33%, and 23% at three, five, and 10 years, respectively. By comparison, a control group that was primarily resected had a superior OS of 66%, 48%, and 30% at three, five, and 10 years, respectively. Unlike our study, Adam, et al., included patients with extra hepatic disease, preoperative portal vein embolization (PVE) and two-stage hepatectomy. In our study, we followed the methodology of the phase II North Central Cancer Treatment Group (NCCTG) Study [14] that excluded patients with extrahepatic disease and those who underwent PVE.

Allen, et al., [15], showed neoadjuvant treatment was an important prognostic factor for response to chemotherapy, however, neoadjuvant therapy failed to improve patient survival. Our results are commensurate with prior published survival rates for patients treated with neoadjuvant chemotherapy and surgical treatment alone.

Neoadjuvant chemotherapy does allow for resection of metastases initially considered unresectable, but the role of neoadjuvant chemotherapy in patients with resectable metastases is debatable. Disease –free survival and OS after resection of hepatic metastases following neoadjuvant chemotherapy does not appear to significantly differ after resection alone. The only trial to address this question in a controlled fashion was the recently published trial from the European Organization for Research and Treatment of Cancer (EORTC Intergroup 40983). This phase III trial and the data suggest that neoadjuvant chemotherapy followed by hepatic resection of metastases may improve OS, there was a trend toward improved OS following neoadjuvant chemotherapy, but statistical significance was not achieved [16].

Firm guidelines for initiating neoadjuvant chemotherapy in patients with colorectal metastases to the liver have yet to be established. Instead, factors reflective of aggressive disease such as synchronous presentation have been used as surrogate indicators. Such patients are thought to have biologically less favorable disease and, have a worse overall and disease-free interval compared to patients with metachronous disease [17,18]. Although the interval for defining synchronous metastases vary in the literature, most studies have shown that outcome after resection of synchronous metastases is worse than that for metachronous metastases. Scheele, et al., describes a five-year survival decrease from 43% to 30% in patients with synchronous metastases compared to those with metachronous disease [8], whereas Sugawara, et al., found that the only factor associated with survival in patients with synchronous disease was the resection margin status [19].

Simultaneous resection can be performed with minimal morbidity; however, the concern of survival after synchronous resection compared to delayed resection following neoadjuvant therapy has not been well-described [20–22]. In our series, patients undergoing synchronous resection, the one-, three-, and five-year DFS rates were 38%, 30%, and 30%; and OS rates were 94%, 64%, and 55%. In patients undergoing a metachronous resection, the DFS rate was much improved at one year, (58%) but the outcomes were similar to the patients with synchronous resection at three and five years (26%, and 26% respectively). The one-, three- and five-year OS rates of patients with metachronous resections were 90%, 61%, and 46% respectively, not significantly different than to those with synchronous disease. Our data

demonstrated the OS and DFS curves of the comparable groups were parallel, suggesting no survival advantage for neoadjuvant chemotherapy.

Today, hepatic resection is associated with morbidity and limited mortality. Most referral centers specializing in hepatobiliary procedures report mortality rates <5% after major liver surgery. However, with the advent of neoadjuvant chemotherapy, the morbidity of liver resection may be higher due to the hepatic parenchymal changes caused by the chemotherapy. Hepatic steatohepatitis has been associated with neoadjuvant therapy limiting the extent of liver resection and leading to increased operative morbidity and mortality [23]. The EORTC Intergroup Trial reported a 25% postoperative complication rate in the group receiving neoadjuvant chemotherapy [16]. Similarly, Aloia, et al., reported that the only significant contributing factor with multivariate analysis of patients requiring intraoperative blood transfusion and neoadjuvant chemotherapy. Surgical evaluation and histopathologic analysis also revealed an increase in liver fragility and an increased incidence of vascular hepatic lesions in the neoadjuvant patient population [24]. These concerns are valid and must be taken into consideration when deciding on a treatment plan that includes neoadjuvant chemotherapy for CRM to the liver.

Despite attempts to limit confounding factors in our study there are several obvious limitations. Primarily this is a retrospective study and patients did not undergo randomization. The second limitation is the small sample sizes with only 44 of the 99 patients receiving neoadjuvant chemotherapy due to the variable use of FOLFOX and FOLFIRI neoadjuvant chemotherapy during the period of study. Lastly, postoperative therapy was not standardized in either group adding to patient heterogeneity.

Conclusion

Hepatic resection for colorectal metastases is potentially curative. Neoadjuvant chemotherapy may downsize unresectable metastases allowing resection and improving OS in patients who are unresectable at presentation. The utility of neoadjuvant chemotherapy in patients with resectable metastatic disease does not offer a definite DFS or OS advantage over initial surgical resection; however, there may be a subset of patients, namely those younger than 60 years old that may benefit from neoadjuvant therapy. Further research is justified in this area in order to detect a true benefit.

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Figure 1.
Group 1 vs Group 2 - Disease-Free Survival

Figure 2.
Group 1 vs Group 2 - Overall Survival

Figure 3.
Synchronous vs Metachronous Disease-Free Survival

Figure 4.
Synchronous vs Metachronous - Overall Survival

Table 1

Group Characteristics

	Overall n=99 N (%)	Group 1* n = 44 N (%)	Group 2* n=55 N (%)	P-value
Gender				0.41
Male	58 (59)	28 (64)	30 (55)	
Female	41 (41)	16 (36)	25 (50)	
Median Age at liver Surgery (Years)	63	64	57.5	0.03
Primary Disease				
Synchronous Diagnosis	48 (48)	24 (55)	24 (44)	0.28
Positive Primary LN	57 (61)	28 (67)	29 (56)	0.28
Total # LN, median [min-max]	14 [3,77]	14 [3,77]	13.0 [5,36]	0.93
Total # LN Positive, median [min-max]	1.0 [0,19]	1.0 [0,19]	2.0 [0,19]	0.13
Metastatic Disease				
Synchronous Resection	21 (21)	7 (16)	14 (25)	0.25
Time CRM diagnosis to hepatic surgery, median days [min-max]	75 [0-903]	192 [2,903]	38 [0,804]	<0.001
Final Pathology, Differentiation				0.38
Well	0	0	0	
Moderately	15 (17.4)	5 (13.5)	10 (20.4)	
Poorly	70 (81.4)	31 (83.8)	39 (79.6)	
Dedifferentiated	1 (1.2)	1 (2.7)	0	
Largest tumor Size (cm)	3.9	3	4.7	0.001
Positive Margin	3	1	2	1.00
Mean Resection margin	0.91 cm	0.81 cm	0.97 cm	0.08

Group 1 = Neoadjuvant Chemotherapy, Group 2 = No neoadjuvant chemotherapy. Missing data excluded from analysis. Final pathology missing for n= 6 in Group 1 and n= 7 in Group 2.

Table 2

Operative Procedures

Type of Procedure	Overall %	Group 1* (n = 44) N (%)	Group 2* (n=55) N (%)
Right hepatectomy	47 (47.5)	22	25
Left hepatectomy	6 (6.1)	2	4
Left lateral Sectomy	4 (4.0)	4	0
Bisegmentectomy	3 (3.0)	1	2
Segmentectomy	19 (19.2)	9	10
Non-anatomic wedge	39 (39.4)	23	16

* Group 1 = Neoadjuvant Chemotherapy, Group 2 = No neoadjuvant chemotherapy