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Young Patients with Synchronous Colorectal Metastases

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Abstract

Background—An increasing proportion of patients are presenting with colorectal cancer at an early age. A proportion of these occur with genetic syndromes; however the majority present as sporadic. The purpose of this study is to investigate the prognosis and treatment of young patients with sporadic metastatic colorectal cancer.

Methods—Following IRB approval, patients with sporadic metastatic colorectal cancer at 40 years or under were identified. Patient charts and pathology reports were analyzed retrospectively for clinical and pathological factors.

Results—302 patients were identified; 148 with liver metastases only and 154 with extra-hepatic disease. 5-year overall survival was 19%, 28% for liver only disease and 12% for extrahepatic disease. For patients with liver metastases only, factors associated with survival on univariable analysis included diagnosis in the 2000's, unilobular hepatic disease, smaller volume liver metastases, intrahepatic pump chemotherapy, resection of the primary and resection of liver metastases. On multivariable analysis factors associated with survival included resection of the primary, resection of liver metastases and diagnosis in the 2000's.

Conclusion—Sporadic metastatic colorectal cancer in young patients appears to have a similar prognosis to that in older patients. The most significant prognostic factor was the ability to resect all sites of disease.

Keywords

Colorectal; cancer; young; metastatic synchronous

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Introduction

An estimated 140,000 people will develop colorectal cancer in 2013 while 50,000 will die from the disease (generally due to metastatic spread). Approximately 20% of patients will have metastatic spread at the time of diagnosis with an estimated 5-year survival of 12.5% [1]. The incidence of colorectal cancer affecting young people is also increasing, from 9% of diagnosed cases aged under 50 in 1992 to 17% in 2010 [1, 2]. Approximately 6% of colorectal cancers arise in the setting of a genetic syndrome. [3] These typically affect patients of a younger age such as Familial Adenomatous Polyposis Syndrome (FAP) and Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC). There has been extensive investigation into the genetics, pathophysiology and treatment of these conditions [3–7], however they only represent about 20% of patients who develop colorectal cancer at a young age. [8] The purpose of this manuscript is to provide a review of metastatic colorectal cancer in young patients treated at our institution in an effort to better define the biology and treatment options for these challenging patients.

Methods

Patients

We obtained an IRB waiver of authorization to review electronic medical records and a prospective database selecting for patients diagnosed with adenocarcinoma of the colon or rectum who were treated at Memorial Sloan Kettering Cancer Center from January 1990 to December 2010. Patients were excluded if they had no pathological records, no metastatic disease on conventional imaging at initial presentation or if they were identified with a familial colorectal cancer syndrome (FAP, HNPCC etc). Recurrence was determined from the electronic medical records of all study patients including surgical and medical oncology clinic notes, endoscopy, radiology, operative, and pathology reports. Tumor progression was determined from electronic medical records of all study patients including surgical and medical oncology office notes. Eighty five of the 148 patients with liver only metastases had radiological imaging available and were analyzed separately for site, number and percentage volume of metastatic liver disease.

Statistical Analysis

Overall survival, measured from the diagnosis date to the time of death, was the principal endpoint of interest. Survival distributions were compared using the log rank test and illustrated with Kaplan-Meier curves. In addition, the 5-year outcomes were reported in tabular format with the log rank *P* value for the corresponding stratified survival distribution. Proportions of categorical variables were compared using the chi-squared test, unless expected cell counts were < 5, in which case the Fisher's Exact Test was used. A Cox proportional hazards model was constructed to measure overall survival for all patients and again for patients with metastatic liver disease only. Of the 302 patients identified, there were 254 deaths; therefore, adequate information for an analysis of up to 25 covariates existed. The following 6 potential predictor or confounder variables were included in our model based on *a priori* clinical knowledge and univariable analysis: the decade of tumor diagnosis, presence of extra-hepatic disease, resection of the primary tumor and liver

metastases, site of the primary tumor and the use of Hepatic artery infusion of chemotherapy (HAI). Analyses were conducted using SPSS version 22.0 (SPSS, Chicago, IL).

Results

Clinical and pathological factors

A total of 302 patients (148 patients with liver only metastases and 154 with extra-hepatic disease) were identified with a median follow up for survivors of 54 months (Table 1). The only pre-treatment factor associated with having extra-hepatic disease at presentation was the presence of a KRAS mutation (52% of patients with extra-hepatic disease vs. 16% of patients with liver only disease, $p=0.01$). Liver only disease was associated with patients who had resection of the primary tumor, resection of liver metastases and HAI.

Survival Analysis

The 5-year overall survival for the entire cohort was 19%; 28% for those with liver only disease, and 12% for those with extra-hepatic metastases ($p<0.001$)(Figure 1). On univariable analysis, factors associated with better survival include absence of extra-hepatic disease, diagnosis after 2000, KRAS wild type tumor, use of the HAI, resection of the primary tumor and resection of liver metastases. On multivariable analysis the only factors associated with survival were diagnosis after 2000, resection of the primary tumor and resection of liver metastases (Table 2).

For those patients with liver only disease, factors associated with survival on univariable analysis were the volume of liver metastases, the presence of bilobar disease, HAI therapy, resection of the primary tumor, resection of liver metastases and diagnosis after 2000 (Table 3). The results were similar when the extent of liver disease was measured on the available radiological images. On multivariable analysis, the factors associated with survival were the ability to resect liver disease, resect the primary and the era of diagnosis (Table 3).

Response to chemotherapy

There were 14 patients with documented tumor regression on pathology reports who received neo-adjuvant chemotherapy and resection of their primary tumor. The median treatment response in the primary tumor (tumor regression) was 55% (range 5–100%); 2 of the 14 patients (14%) had a pathological complete response in the primary tumor. There were 43 patients with documented treatment response in pathology reports of the resected liver metastases following neo-adjuvant chemotherapy. The median treatment response was 60% (range 5–100%), while 6 patients (14%) had a complete pathological response. Two patients had complete pathological response in both the primary tumor and the liver metastases following resection and are both alive and free of disease at 53 and 75 months.

Discussion

This study represents the largest comprehensive review of young patients with sporadic metastatic colorectal cancer. A 5 year survival rate of 19% compares favorably with the national survival figure for all patients with metastatic colorectal cancer of 12.5%[1]. Other

series have reported 5-year survival rates for young patients as low as 7% to 18% [9, 10]. Although this cohort of patients with sporadic synchronous colorectal metastases in patients less than 40 years of age is highly selected, it is a heterogeneous group with both liver only and extrahepatic metastases. It is therefore difficult to compare with young populations in other reports. However, for patients with extrahepatic disease, which represent a group of patients with mostly unresectable metastatic colorectal cancer, a median survival of 18 months is similar to prospective trials assessing treatment for unresectable metastatic colorectal cancer such as capecitabine, oxaliplatin and irinotecan (all synchronous tumors with median survival of 17 months)[11], 5 fluorouracil, oxaliplatin and bevacizumab (60% synchronous tumors with median survival of 21 months)[12]. In our analysis, for the 80 patients with liver only disease who underwent a liver resection, the median and 5 year survival were 57 months and 45% respectively. This is comparable to the entire cohort of patients at our institution who underwent liver resection, who had a median survival of 56 months and a 5 year overall survival of 46%. Of note, 53% of the patients in the larger cohort presented with synchronous metastases which has been shown to have worse outcomes when compared to resections for metachronous metastases.[13] These possibly superior outcomes for younger patients is not supported elsewhere in the literature with most reporting worse outcomes for patients with colorectal cancer on a stage to stage basis for young people comparing to older patients.[9] Possible explanations for these improved outcomes in this series include a selection bias; by virtue of this cohort being younger they are a more robust group of patients who are able to tolerate more aggressive and prolonged treatment.

There were better outcomes among patients diagnosed in the modern era on univariable analysis and multivariable analysis. This finding is not unusual and has been demonstrated elsewhere in the literature.[14–16] This may represent the improved chemotherapeutic agents which have become more available in recent times, which possibly leads to conversion of initially unresectable disease to resectability. In this series, the overwhelming factor associated with survival was the ability to resect the liver disease. Treatment strategies which convert patients from unresectable to resectable would therefore be desirable. The use of liver directed therapies such as HAI with or without systemic chemotherapy may prove useful in achieving this aim. The use of HAI treatment was associated with better survival on univariable analysis. Previous prospective studies at our institution have demonstrated that HAI can convert unresectable patients to liver resection. This was observed in 47% of patients following HAIP and systemic chemotherapy who were initially unresectable, which increased to 57% in patients who were naïve to chemotherapy [17].

Interestingly in this cohort of patients, there are people who have had durable cures with 10 patients surviving beyond 10 years. The majority of these patients have liver only disease but one patient had extra-hepatic disease (lung metastases) and had resection of all sites of disease. This finding is particularly heartening for those of us treating this aggressive disease in young patients.

In summary, sporadic metastatic colorectal cancer in young patients appears to have a similar prognosis to that in older patients. The most significant prognostic factor was the ability to resect all sites of disease.

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Synopsis

This paper reviews the treatment and outcomes for young patients presenting with sporadic synchronous metastatic colorectal cancer.

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Figure 1.
Kaplan Maier curve demonstrating survival differences between patients with and without extra-hepatic metastatic colorectal cancer

Table 1

Clinical and pathological variables

	Total	Liver only disease	Extrahepatic disease	P value
Number	302	148 (49%)	154 (51%)	
Gender: Male	131	71 (54%)	60 (46%)	0.11
Female	171	77 (45%)	94 (55%)	
Median Age (years)	36	37	35	0.04
Site of Primary: Rectum	66	38 (58%)	28 (42%)	0.28
Left colon	153	72 (47%)	81 (53%)	
Right colon	83	38 (56%)	45 (44%)	
Before 2000	123	61 (50%)	62 (50%)	0.86
After 2000	179	87 (49%)	92 (51%)	
Resection of primary tumor	247 (82%)	134 (91%)	113 (73%)	0.013
Node positive disease in the primary tumor	201 (85%)	107 (82%)	94 (88%)	0.24
Resection of liver metastases	103 (34%)	80 (55%)	23 (15%)	<0.001
Bilobar liver disease	147 (71%)	97 (70%)	50 (74%)	0.80
Median number of liver metastases (range)	4(1–20)	4(1–20)	3(1–7)	0.59
Median size of largest liver metastases (range)	4cm (1–18)	5cm (1–18)	4cm (1–17)	0.49
Median CEA at diagnosis (range)	68 (1–23,000)	67 (1–8,600)	70 (1–23,000)	0.30
HAIP chemotherapy	79 (26%)	66 (45%)	13 (8%)	<0.001
Pregnant	21 (7%)	10 (7%)	11 (7%)	0.89
Inflammatory bowel disease	14 (5%)	5 (3%)	9 (6%)	0.55
KRAS mutation	19 (34%)	6 (19%)	13 (52%)	0.01

Table 2

Univariable & Multivariable analysis of 302 patients with Sporadic Metastatic Colorectal Cancer.

Factor	Number	Univariable Analysis		Multivariable Analysis		
		5 year survival	P value	Hazard Ratio	95% Confidence Intervals	P value
Extrahepatic disease: Yes	154	12%	<0.001	1.00	0.73 – 1.39	0.96
No	148	28%				
Before 2000	123	7%	<0.001	1.55	1.19 – 2.01	0.001
After 2000	179	28%				
Gender: Male	131	14%	0.78			
Female	171	24%				
Site of primary tumor: Rectum	66	16%	0.12			
Left colon	153	24%		0.91	0.62 – 1.33	0.64
Right colon	82	15%		0.90	0.66 – 1.21	0.48
KRAS mutant: Yes	19	31%	0.02			
No	37	54%				
HAIP Chemotherapy: Yes	79	30%	<0.001	0.97	0.67 – 1.41	0.94
No	223	15%				
Liver resection: Yes	103	43%	<0.001	3.65	2.52 – 5.28	<0.001
No	197	7%				
Resection of primary tumor: Yes	249	23%	<0.001	2.01	1.40 – 2.88	<0.001
No	52	0%				
Nodal disease in primary tumor: Yes	201	22%				
No	36	34%				
Pregnant at Diagnosis: Yes	21	26%	0.42			
No	281	19%				
Inflammatory bowel disease: Yes	14	14%	0.10			
No	288	20%				

Table 3

Univariable & multivariable analysis of 148 patients with liver colorectal metastases only

Factor	Univariable Analysis			Multivariable Analysis		
	Number	5 year survival	P Value	Hazard Ratio	95% Confidence Intervals	P value
Before 2000	61	10%	<0.001	2.70	1.28 – 5.69	0.01
After 2000	87	40%				
Number of Liver Metastases: >4	57	25%	0.13	0.95	0.48 – 1.99	0.95
1–4	62	42%				
Volume of Liver Metastases: >30%	41	21%	0.007	1.24	0.60 – 2.51	0.43
<30%	52	44%				
Bilobar Liver Metastases: Yes	98	24%	0.01	0.69	0.27 – 1.74	0.43
No	41	42%				
CEA: >65	51	24%	0.27			
<64	49	41%				
Sex: Female	77	33%	0.49			
Male	71	23%				
HAIP Chemotherapy: Yes	66	34%	0.03	0.96	0.48 – 1.81	0.95
No	82	22%				
Liver Resection: Yes	80	46%	<0.001	6.23	2.99 – 12.97	<0.001
No	66	6%				
Resection of Primary: Yes	135	31%	<0.001	3.06	1.13 – 8.27	0.03
No	12	0%				
Node positive primary: Yes	107	29%	0.16			
No	23	42%				
Site of Primary Tumor: Rectum	38	25%	0.21			
Left Colon	72	34%		0.68	0.25 – 1.81	0.44
Right Colon	38	18%		0.80	0.37 – 1.70	0.56
Pregnant: Yes	10	30%	0.39			
No	138	28%				
Inflammatory bowel disease: Yes	5	20%	0.55			
No	143	28%				