



Clinical Manifestations of Late Isolated Metachronous Brain Metastases after Colorectal Cancer Hepatic Metastectomy

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Abstract

Isolated brain metastases in patients in remission after successful colorectal cancer hepatic metastectomy are rare and not well characterized. Generally, the central nervous system is an uncommon site for metastasis in patients with stage IV colorectal cancer. Herein, we present a case series of patients diagnosed with isolated, metachronous brain metastases that arose in patients who had been disease-free for more than five years after resection of liver metastases. The incidence of this metastatic pattern is very low and the time to presentation is late, being an average of almost 10 years after hepatic metastectomy. Notably, all nine patients presented with onset of new neurologic symptoms leading to axial brain imaging studies which demonstrated metastatic disease. Hence, new neurologic symptoms in long-term stage IV colorectal cancer survivors warrants immediate notification of treating physicians for evaluation, as late metachronous brain metastasis is a potential diagnosis.

Keywords: Colorectal cancer; Stage IV; Liver metastases; Brain metastases

Introduction

Colorectal cancer metastases appearing in the liver or lungs are common. Approximately 20-34% of patients with colorectal cancer present with synchronous hepatic metastases and furthermore, 25-30% of patients with colorectal cancer will develop metachronous metastases during the disease course [1-3]. Validated treatment strategies with intent to cure exist for localized and metastatic colorectal cancer. Currently, following resection of hepatic colorectal cancer metastases the median 5-year disease-free survival rate is 38%, and 5-year overall-survival rate is 71% [4,5]. Similarly, surgical treatment for selected subsets of patients with colorectal cancer lung metastases yields 5-year overall and progression-free survival rates of 53% and 33%, respectively [6]. Multidisciplinary treatment strategies must be individualized based on disease stage at presentation and include resection of the primary colorectal tumor, staged or simultaneous hepatic and pulmonary metastectomy, liver-directed therapies, and neoadjuvant and adjuvant cytotoxic and targeted chemotherapy.

Isolated metachronous brain metastases after curative therapy for colorectal cancer occurs rarely, with a 0.3% incidence in a case series from Ireland [7]. These authors noted the development of central nervous system metastasis portends a poor clinical prognosis. We report the clinical outcomes of patients with isolated brain metastases previously in remission from colorectal cancer after hepatic metastectomy.

Methods

Patients with isolated colorectal cancer brain metastases who previously underwent colorectal hepatic metastectomy were retrospectively identified from a prospective hepatobiliary cancer database between the years 1995 and 2015. During this time frame, over 2,500 hepatic metastectomies for colorectal cancer were performed. All patients had undergone resection of their primary colorectal cancer prior to the hepatic metastectomy. Clinical parameters evaluated included age at colorectal cancer diagnosis, location of the primary colorectal tumor, hepatic resection performed, chemotherapy regimen, interval time between colorectal cancer diagnosis and brain metastasis, symptoms at presentation of brain metastasis, interval time between onset of symptoms and brain metastasis diagnosis, location of brain metastases, treatment of brain metastases, and survival time.

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Table 1: Characteristics of patients with isolated metachronous brain metastases after colorectal cancer hepatic metastectomies.

Patient	Sex	Age at CRC Diagnosis	Stage at CRC Diagnosis	Primary CRC Location	Adjuvant Chemotherapy	Time to hepatic metastases (in months)	Number of hepatic metastases	Partial Hepatectomy
1	F	58	3	right	FOLFOX	18	3	Right
2	M	61	3	sigmoid	FOLFOX/BEV	24	2	Left
3	M	49	4	left	FOLFOX	0	1	Segmentectomy 2/3
4	M	71	4	rectum	ChemoXRT	0	8	Right, left RFA
5	F	62	3	rectum	ChemoXRT	32	3	Left, right wedge
6	F	54	4	right	FOLFOX	0	5	Extended Right
7	F	68	4	transverse	FOLFIRI	0	4	Right
8	M	66	2	rectum	NONE	39	2	Right, left wedge
9	M	63	3	right	FOLFOX/BEV	9	4	Left, right RFA

CRC: Colorectal Cancer; RFA: Radiofrequency Ablation; FOLFOX: 5-Fluorouracil, Leucovorin, Oxaliplatin; BEV: Bevacizumab; FOLFIRI: 5-Fluorouracil, Leucovorin, Irinotecan.

Results

Of the over 2,500 patients who underwent hepatic metastectomy for colorectal cancer, 9 patients were identified with isolated, metachronous brain metastases.

Patient characteristics

The brain metastasis cohort (Table 1) consisted of five men and four women. Median age at the time of initial diagnosis of colorectal cancer was 62 years, range 49-71 years. The majority (8 of 9 patients, 89%) were diagnosed with stage III or stage IV colorectal cancer, with equal distribution of the colorectal primary tumor location (3 right colon, 1 transverse colon, 2 left colon, 3 rectum). Four of 9 patients (44%) presented with synchronous hepatic metastases and five (56%) developed metachronous hepatic metastases within 24.4 ± 11.7 months, range 9-39 months, of initial colorectal cancer diagnosis. The median number of hepatic metastases was 3 (range 1-8). The majority (8 of 9 patients, 89%) received adjuvant chemotherapy (3 FOLFOX, 2 FOLFOX/ bevacizumab, 2 neoadjuvant chemo-radiation to a rectal primary followed by adjuvant FOLFOX, 1 FOLFIRI). All patients required a partial hepatectomy (5 right or extended right hepatectomy, 3 left hepatectomy, 1 bisegmentectomy of segments 2 and 3) and 4 of 9 patients (44%) required contralateral lobe wedge resection or radiofrequency ablation of additional hepatic metastases.

Disease progression

All 9 patients in remission from metastatic colorectal cancer developed new neurologic symptoms leading to computed tomography or magnetic resonance imaging studies (Table 2). The

interval time between colorectal cancer hepatic metastectomy and diagnosis of brain metastases was 9.7 ± 2.1 years, range 6-13 years (or 115.9 ± 24.4 months, range 81-157 months). Presenting neurologic symptoms included headache (6 patients), seizures (2), vision changes (1), unsteady gait (1), and dysphasia (1). Median number of brain metastases was 1 (range 1-3), with frontal lobe (4 patients), temporal lobe (4), occipital lobe (1) or cerebellum (1) involved.

Clinical outcomes

Only two of nine (22%) patients with new neurologic symptoms were quickly diagnosed with brain metastases (Table 3). The interval time between new neurologic symptoms to diagnosis of brain metastases was a median of 2 months, range 0-8 months.

Most (6 of 9 patients) underwent neurosurgical metastectomy followed by chemotherapy and external beam irradiation, while 3 of 9 patients received external beam irradiation followed by chemotherapy. Unfortunately, all 9 patients succumbed to recurrent brain metastases with a median survival of 13 months, range 5-28 months.

Discussion

Isolated, metachronous brain metastases occur as a late manifestation in a small minority of patients after colorectal hepatic metastectomy. In our series, metachronous brain metastases occurred an average of approximately 10 years after hepatic metastectomy.

Clinical experience in colorectal cancer patients with brain metastases has been evaluated in Japan [8]. In their series of 113

Table 2: Disease progression and development of isolated, metachronous brain metastases in patients surviving long-term after colorectal cancer hepatic metastectomy.

Patient	Time to CNSM diagnosis (in months)	Presenting Symptoms	Number of CNSM	Location of CNSM (lobe)
1	99	Headache	1	Frontal
2	114	Headache	1	Temporal
3	132	Seizure	1	Temporal
4	81	Headache, unsteady gait	1	Cerebellum
5	125	Vision change	3	Frontal, temporal
6	102	Headache	2	Occipital
7	139	Headache	1	Frontal
8	157	Headache, seizure	2	Frontal
9	94	Dysphasia	1	Temporal

CNSM: Central Nervous System (Brain) Metastases.

Table 3: Clinical outcomes in patients with isolated brain metastases after colorectal hepatic metastectomy. All patients received systemic chemotherapy after surgery or radiation therapy.

Patient	Time from Symptoms to CNSM Diagnosis (in months)	Treatment of CNSM	Survival with CNSM (in months)
1	5	Surgery, XRT	16
2	8	Surgery, XRT	14
3	0	Surgery, XRT	11
4	1	XRT	7
5	2	Surgery, XRT	5
6	4	XRT	13
7	1	Surgery, XRT	19
8	6	Surgery, XRT	28
9	0	XRT	12

CNSM: Central Nervous System (Brain) Metastases; XRT: External Beam Radiation Therapy.

patients, isolated brain metastases portend a cautiously favorable prognosis in patients undergoing neurosurgical resection, with 21 month overall survival in patients with isolated brain metastases versus 11.1 month overall survival with other, extracranial metastases.

There may be a predisposition for brain metastases in a subgroup of patients, as molecular studies have suggested brain metastases occur most frequently in patients with mutant K-Ras colorectal cancer [9,10]. K-Ras mutant status in colorectal cancer is an independent predictor of metastasis to lung, bone, and brain (HR 1.5, 1.6, and 3.7, respectively) [9]. These findings imply the K-Ras mutation subgroup of colorectal cancer patients may need to be monitored with additional long-term surveillance and follow-up. However, the incidence of central nervous system metastasis is not sufficiently high to justify routine axial imaging of the brain.

Better selection of patients combined with improved surgical outcomes following resection of hepatic or pulmonary metastases from colorectal cancer have produced higher long-term survival rates [4-6]. Part of this improved survival may be related to combining active chemotherapy regimens as a component of multidisciplinary cancer care [11]. Our report of 9 patients with late clinical presentation of brain metastasis, while a fractionally small proportion of all patients undergoing hepatic metastectomy for colorectal cancer, serves to emphasize the importance of long-term survivorship and follow up programs for patients throughout the duration of their lives after active cancer treatment. The onset of new symptoms should not be ignored or minimized, and mandate a thorough diagnostic evaluation.

Conclusion

While the incidence of brain metastases is low in colorectal cancer patients in remission after hepatic metastectomy, patients and treating physicians alike should be counseled on the importance of seeking evaluation for the onset of any new or unusual neurologic symptoms. Metachronous brain metastases are included in the differential diagnosis in the presence of new neurologic symptoms. Therefore, new neurologic symptoms warrant immediate notification of treating physicians. Neurosurgical intervention may be indicated and may improve survival marginally despite the seemingly poor long-term prognosis. Further clinical and scientific studies are needed to predict patients with molecular profiles suggesting a higher risk to develop central nervous system metastasis, and to delineate optimal treatment strategies for colorectal cancer patients with metachronous brain metastases.

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