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Brain Metastases from Colorectal Cancer: Risk Factors, Incidence, and the Possible Role of Chemokines

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Abstract

Background—Brain metastases from colorectal cancer (CRC) are uncommon. There has been relatively little published on the host and tumor factors that might lead to this clinical scenario. We reviewed all cases of brain metastases from CRC at Dartmouth-Hitchcock Medical Center over a more than 20-year period to establish incidence and to identify patient and cancer characteristics which were associated with their development.

Patients and Methods—We present a retrospective review of 39 confirmed cases of brain metastases from CRC diagnosed between 1984 and 2006. Immunohistochemical staining for CXCR4 was performed on all available brain metastasis biopsy specimens.

Results—The incidence of brain metastases from CRC was 2.3%. Left-sided primary colon tumors predominated. The majority of patients had pulmonary metastases at the time brain metastases were identified, and those with preexisting pulmonary metastases had progression of that disease. All patients were symptomatic from brain metastases, and the cerebellum was the most common area of brain involvement. Immunohistochemical analysis confirmed strong expression of CXCR4 in all brain metastases sampled.

Conclusion—The incidence of brain metastases from CRC is low. Primary tumor in the left colon, long-standing pulmonary metastases, especially those with recent progression, and CXCR4 expression by tumor cells are all associated with increased risk of brain metastases. Increased survival among patients with metastatic CRC will likely result in an increased incidence of brain metastases. Further characterization of the role of tumor and host factors might yield better insight into the development, and potentially the prevention, of this devastating situation.

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Keywords

Cerebellar metastasis; CXCR4; Gait disturbance; Pulmonary metastases

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the United States, with > 148,000 cases projected to have occurred in 2008.[1] Despite improvements in diagnosis and treatment, > 52,000 patients are estimated to have died of CRC at the end of 2007, and approximately 50% of all patients diagnosed with CRC will die of metastatic disease.[2] Common sites of metastases include the liver, lungs, and peritoneal cavity. Hepatic metastases are present in 30%-40% of patients with newly diagnosed disease and are the predominant cause of mortality.[3] In comparison, the incidence of pulmonary metastases is approximately 15%-20%.[4] Peritoneal metastases are present in ≤ 10% of patients at diagnosis (synchronous metastases) and in 20%-50% of patients with recurrence (metachronous metastases).[5] Brain metastases from CRC are rare in comparison to other common malignancies such as lung, breast, and renal carcinoma.[4] Previous studies have reported the incidence of brain metastases in CRC to range from 1% to 3%.[4,6] Patient survival from metastatic CRC (mCRC) has steadily improved in conjunction with advances in therapy. Median survival for patients with mCRC is now approximately 21-24 months.[7] As a result of prolonged survival with metastatic disease, the incidence of brain metastases might be expected to increase. We conducted a retrospective review to identify all patients with CRC treated at Dartmouth-Hitchcock Medical Center over a more than 20-year period. We attempted to identify incidence and clinical presentation as well as patient and tumor characteristics, including chemokine expression, that led to the development of brain metastases.

Patients and Methods

This study was approved by the Committee for the Protection of Human Subjects at Dartmouth College. The medical records of all patients with brain metastases from CRC treated at Dartmouth-Hitchcock Medical Center from 1984 to 2006 were identified using the tumor registry or a proprietary database. Information compiled for each patient included date of diagnosis, age, sex, stage of disease, location of primary tumor, treatment of primary tumor, carcinoembryonic antigen (CEA) level, date of confirmed brain metastases, location, number and clinical presentation of brain metastases, date of diagnosis of pulmonary metastases (if present), treatment of brain metastases, and outcome.

Surgical pathology reports and patient progress notes were reviewed to confirm the date of diagnosis and anatomic location of primary tumor, as well as tumor-node-metastasis stage, treatment, and outcome. Radiology reports and images, surgical pathology, and autopsy reports were reviewed to assess for the presence of pulmonary metastases. If present, the date of initial identification, number, and size of pulmonary metastases were recorded and used to calculate the interval to detection of brain metastases. The same electronic review was performed to discern the date, anatomic location, and number of brain metastases, as well as to determine whether systemic disease was controlled or progressing at the time of confirmed brain metastases. The diagnosis of brain metastases was made by computed tomography (CT), magnetic resonance imaging, and/or pathology reports. Treatment and outcome were obtained from hospital records.

All available pathologic specimens of brain metastases from colorectal adenocarcinoma (11 in all) and 10 random primary colorectal adenocarcinoma specimens with available paraffin

blocks were evaluated by immunohistochemistry. Immunostaining of the primary colorectal tumor was performed in 5 of the 11 patients in whom primary and brain metastases were available, to allow comparison of staining intensity between the primary and metastatic tumor.

Immunohistochemical staining by the avidin-biotin complex method was used to assess CXCR4. Primary antibody used CXCR4 (R&D Systems, Minneapolis, MN) at 1:500 dilution. Sections (4-5 mm) from one representative block of each case were deparaffinized, rehydrated in graded alcohols, and subjected to antigen retrieval by microwaving the slides in 10-mM citrate buffer at pH 6. After incubation with primary antibody, localization was performed via the standard streptavidin-biotin immunoperoxidase method, and diaminobenzidine was used as chromogen. Sections were counter-stained with Harris Modified Hematoxylin. The intensity, staining percentage, and pattern of staining (nuclear and cytoplasmic) were assessed for CXCR4. The nuclear and cytoplasmic pattern of staining was recorded as weak, moderate, or strong, compared with inflammatory cells in and around the tumor. The percentage of positive cells was estimated by calculating the ratio of the positively stained tumor cells to the total number of tumor cells.

Results

Of 1620 patients diagnosed with CRC, 39 (2.3 %) were diagnosed with brain metastases. A summary of patient demographics is shown in Table 1. Gait disturbance and altered mental status were the most common symptoms that prompted neurologic imaging. A summary of presenting symptoms is shown in Table 2. The median interval from diagnosis of CRC to the development of brain metastases was 25 months (range, 0-88 months). The longest interval from CRC diagnosis to brain metastases occurred in patients whose metastatic disease had been treated with previous surgical resection.

All 3 patients who presented with neurologic symptoms before diagnosis of CRC had extensive, synchronous pulmonary metastases at diagnosis. Of the 39 total confirmed cases, 78% had radiographic and/or pathologic confirmation of synchronous or antecedent pulmonary metastases at identification of brain metastases. Eight patients did not have pulmonary metastases at the time of brain metastases but had systemic disease at other sites including the liver, adrenals, bone, and, in women, reproductive organs.

The median interval from confirmation of pulmonary metastases to brain metastases was 8 months (range, 0-55 months). Chest CT scan in half of these patients was notable for an interval increase in size and/or number of pulmonary metastases before evidence of brain metastases. Seven of these patients had recurrence of previously resected pulmonary metastases before or synchronous with the diagnosis of brain metastases. Of note, no patient had stable systemic disease at the time that central nervous system (CNS) involvement was discovered. There did not appear to be a correlation between tumor grade and brain metastases, nor was CEA level predictive of brain metastases development.

The distribution of brain metastases is shown in Table 3. Forty-three percent of patients had cerebellar metastases, with isolated cerebellar metastases occurring in 23% of all patients. Twenty-seven percent of patients had frontal metastases, whereas the remainder were asymmetrically distributed among temporal, parietal, and occipital lobes. The majority of patients had multiple intracranial metastases, with 19% of patients having > 5 metastases dispersed throughout the brain.

A Kaplan-Meier curve according to treatment is shown in Figure 1. All patients received dexamethasone after diagnosis. Older patients were more likely to undergo single-modality therapy with whole-brain radiation therapy (WBRT). Fifteen patients (41%) were treated

with surgical resection and adjuvant radiation, delivered as WBRT or stereotactic radiosurgery. Patients with a single brain metastasis and younger patients seemed more likely to undergo surgical resection.

Immunohistochemical staining was performed on tumor specimens in 11 patients who underwent resection of brain metastases. All of the specimens (100%) were strongly positive for CXCR4, with a primarily nuclear location of CXCR4 expression. Furthermore, when tumor differentiation was poor, the nuclear intensity of CXCR4 became weak (Figures 2A-2C). The primary colorectal tumor was also stained in 5 patients in whom primary and brain metastases were available. The primary tumor in all of these patients stained equally strongly for CXCR4 as in the brain metastases. For comparison, we stained 10 random primary colon adenocarcinoma specimens for CXCR4 expression and found that 50% were positive for CXCR4 expression (Figure 2D). This corresponds with a Fisher exact 2-sided *P* value of .0124. The 50% CXCR4 positivity rate we found among 10 random primary CRCs is consistent with previous studies using larger numbers of CRC primary specimens to assess for CXCR4 expression.[8]

Discussion

Brain metastasis from CRC is a rare event, and risk factors are poorly understood. Our findings support those of previous studies in which longer survival with mCRC in general is associated with an increased risk of intracranial metastases.[9] The true incidence of brain metastases is likely underestimated because tumor registries emphasize coding of the primary tumor over subsequent metastases.[10] Because the incidence of brain metastases from CRC is likely to increase as median survival improves, understanding risk factors is important.

Although there have been a limited number of studies reviewing brain metastases from CRC, several findings have been previously observed. Our work confirms an incidence of pulmonary metastases among patients with brain metastases that is consistent with previous studies, which has ranged from 55% to 85%.[6,10-12] Left-sided primary tumors have predominated in nearly all reviews, and infratentorial metastases have been disproportionately observed.[10-13] The percentage of infratentorial brain metastases observed in CRC ranges from 22% to 55%, with the majority of studies citing approximately 35%.[10,12,14] Lastly, the outcome for patients remains poor, regardless of treatment.

Despite variation in the distribution of systemic disease among patients with mCRC, the end organs involved are fairly consistent. The nonrandom pattern of metastases observed in CRC supports the possibility of a “homing” mechanism in the pathophysiology of CRC metastases.[15] The high incidence of concurrent or antecedent pulmonary metastases supports a mechanical component, as originally postulated by Ewing,[16] in which pulmonary involvement would facilitate arterial seeding of the brain. The current study, along with nearly all previous investigations, identified a high incidence of pulmonary metastases among patients with brain metastases; however, the fact that some patients with pulmonary metastases develop brain metastases while others do not illustrates that mechanisms other than vascular drainage are likely involved. Specific characteristics of tumor and/or host tissue could account for these findings.

Infratentorial metastases appear to predominate not only in CRC but other abdominal and pelvic malignancies as well. In contrast, cumulative reviews of brain metastases among all patients have shown a predominance of frontal lobe involvement.[9,17,18] It has been hypothesized that the relative mass and regional blood flow to the frontal lobes are responsible for this observation. The distribution of brain metastases from all cancers is

approximately 80% to the cerebral hemispheres, 15% to the cerebellum, and 5% to the brain stem.[9] Our study, however, demonstrated a disproportionate number of brain metastases to the cerebellum, which cannot be explained on the basis of its relative mass or blood flow alone.

Batson's vertebral plexus, providing communication between the pelvic and vertebral veins, would permit metastatic emboli to reach the CNS during periods of transient increased intra-abdominal pressure. The internal vertebral venous plexus ultimately communicates with the intracranial venous system, and tumor emboli reaching the brain via this route would bypass the pulmonary circulation. The high incidence of pulmonary metastases observed in our study would not be anticipated using a retrograde venous route such as Batson's plexus.[17] Furthermore, no single mechanism of metastasis suffices to explain these long-observed findings, suggesting that concomitant local factors are likely involved in the development of successful metastases.

Several findings led us to further examine molecular determinants of metastases at work. First was the observation that nearly all patients had sigmoid or rectal primary tumors. Second, the incidence of preexisting pulmonary metastases among our patient population was 78% compared with an expected 20% among all patients with mCRC.[4] This finding suggests an association between antecedent pulmonary metastases and brain metastases. Additionally, only 18% of patients in our study had hepatic involvement before diagnosis of brain metastases. Nearly all similar reviews have observed a high incidence of pulmonary metastases, and several have also noted an inverse relationship between hepatic and brain metastases.[10,19] One of the largest cohort studies, consisting of 78 consecutive patients with CRC, found that 55% of the patients who developed brain metastases had isolated, concurrent pulmonary metastases.[19] Furthermore, the interval from primary diagnosis to pulmonary metastasis occurred 3 times earlier among patients who developed brain metastases.[19] The redundancy with which these findings have been observed led us to invoke mechanisms of tissue tropism.

The “Seed and Soil” hypothesis, originally postulated by Paget, has been employed for over a century to explain the non-random pattern of metastasis that many tumors exhibit.[20] Molecular determinants of tissue tropism, such as chemokine receptor expression, permit the integration of Paget's model with the mechanical model postulated by Ewing.[16]

The CXCR4/CXCL12 axis is an important and repeatedly observed chemokine/receptor pair expressed by numerous cancer cells.[21-23] In CRC, CXCR4 expression varies by anatomic location, with rectal primary tumors more strongly expressing CXCR4.[24] Its ligand, CXCL12, is highly expressed at common sites of CRC metastases, including the liver, lung, and lymph nodes.[22] CXCR4 expression by primary and metastatic tumors has been shown to correlate with distant metastases and overall survival.[3,15] Our study is the first that we know of to confirm an association between CXCR4 and brain metastases in CRC.

We cannot exclude that the apparent propensity for the posterior fossa we observed is artifactual, influenced by an ascertainment bias. Cerebellar metastases in particular, often produce earlier neurologic symptoms,[25] which along with our methods, could in part account for our findings. This might have resulted in a disproportionate number of cerebellar metastases being identified, resulting in our overestimation of the importance of high CXCR4 in its pathogenesis.

There are several facts, however, that lead us to believe that an association between CXCR4 and brain metastases is credible. First, nearly all published investigations over the past 25 years have similarly demonstrated a high incidence of pulmonary metastases among patients with brain metastases. This finding could reflect a molecular difference among these tumors,

which ultimately yields an altered distribution of metastases. Second, although the majority of the brain metastases we stained for CXCR4 were cerebellar, high CXCR4 expression was common to all brain metastases. The combination of high pulmonary and low hepatic metastases confirmed by numerous investigators might result from differential expression of CXCR4 by the primary tumor. High CXCR4 expression might not only promote pulmonary metastases but also provide an interaction that promotes growth when those cells reach the brain. The relatively long survival we identified among our patients is likely a combination of young age and a relatively low burden of hepatic involvement. This would allow sufficient survival to develop clinically significant brain metastases.

Regardless of the mechanism of dissemination, all patients with long-standing pulmonary metastases from CRC should be regarded as at risk for developing brain metastases. Because cerebellar metastases can produce subtle, early neurologic symptoms,[25] clinicians caring for these patients should pay particular attention to new complaints of clumsiness or unsteadiness. Because all patients were symptomatic in our study, we believe there is little use in neuroimaging of asymptomatic patients; however, all patients with pulmonary metastases and neurologic symptoms should undergo prompted radiologic evaluation. Because of the increasing median survival in mCRC, it can be anticipated that the number of patients with this clinical scenario will continue to increase.

Conclusion

In conclusion, our work supports the putative role of the CXCR4/CXCL12 interaction in the directed migration of CRC cells. It remains unknown whether the degree of CXCR4 expression in colorectal primary tumors independently predicts the pattern of metastases.

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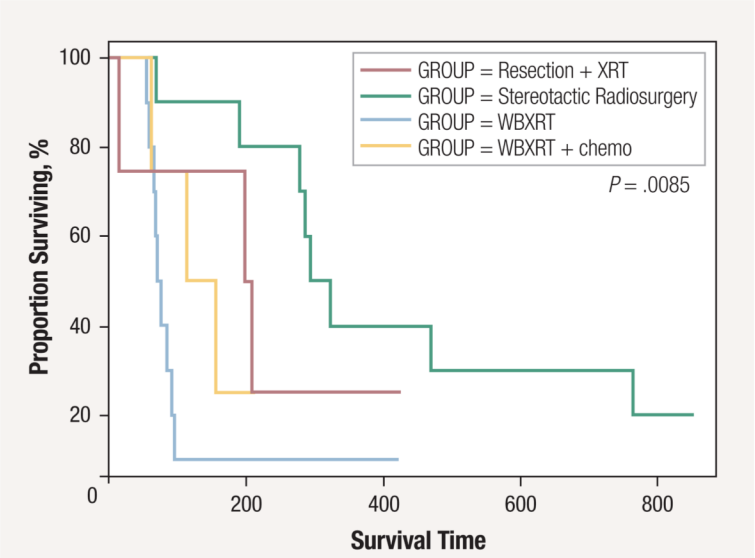

Figure 1. Survival Curve According to Treatment

Abbreviations: WBXRT = whole-brain external-beam radiation therapy; XRT = external beam radiation therapy

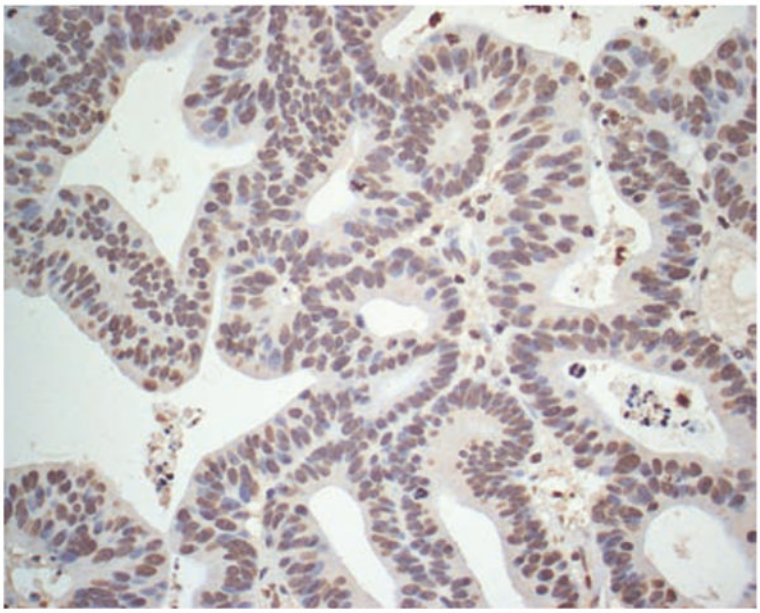

Figure 2A. CXCR4 in Brain Metastases

Metastatic moderately differentiated colorectal adenocarcinoma, positive for CXCR4 (moderate nuclear staining 80% of cells; weak cytoplasmic staining staining < 30% of cells). Magnification × 400.

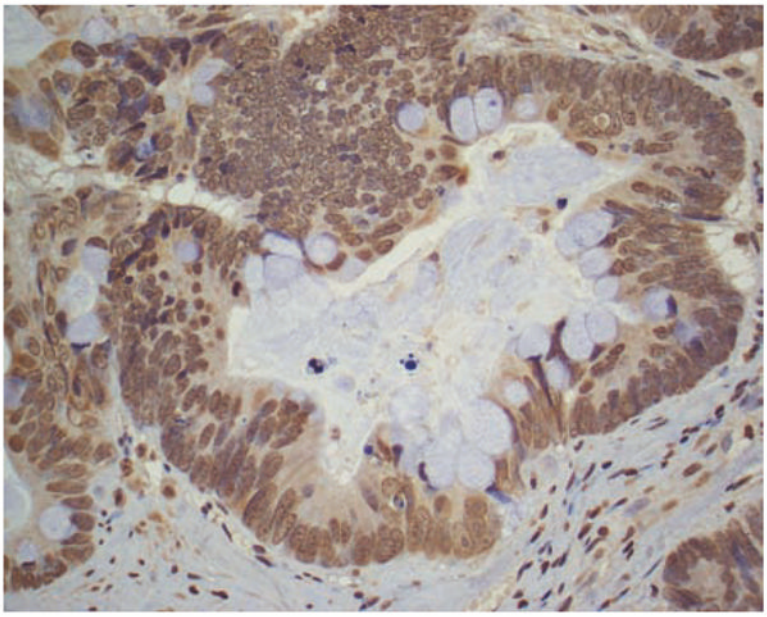

Figure 2B. CXCR4 in Brain Metastases

Metastatic poorly differentiated colorectal adenocarcinoma, positive for CXCR4 (strong nuclear staining > 80% of cells; weak cytoplasmic staining staining > 50% of cells). Magnification × 400.

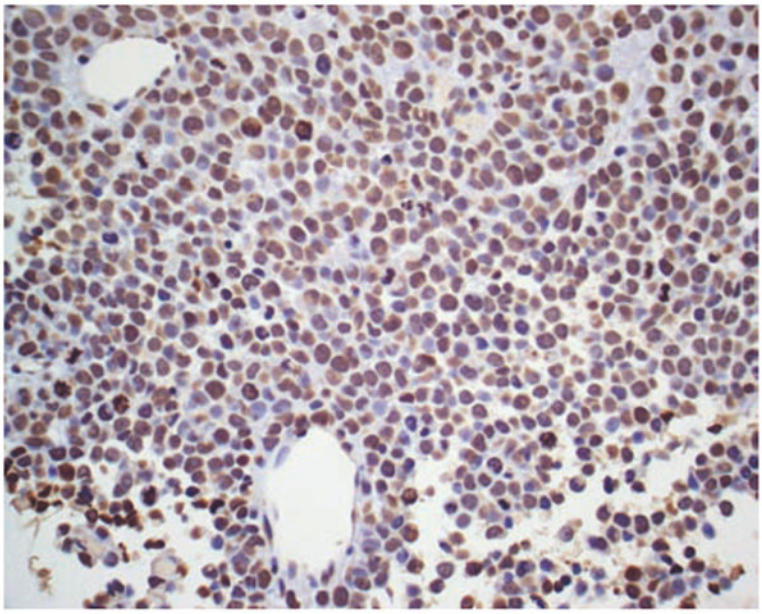

Figure 2C. CXCR4 in Brain Metastases

Metastatic moderately differentiated colorectal adenocarcinoma, positive for CXCR4 (strong nuclear staining > 80% of cells; moderate cytoplasmic staining staining > 50% of cells). Magnification × 400.

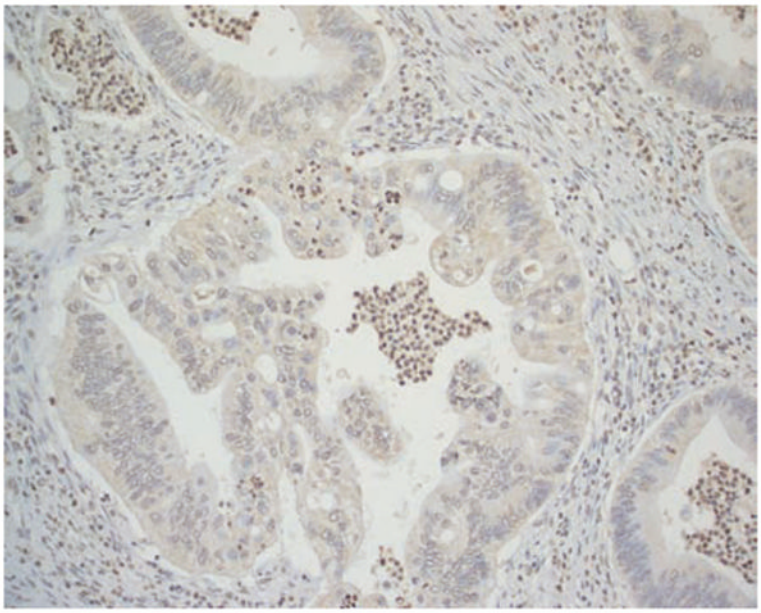

Figure 2D. CXCR4 in Primary Colorectal Cancer Specimen

Random primary well-differentiated colorectal adenocarcinoma, negative for CXCR4 (weak nuclear staining < 30% of cells, weak cytoplasmic staining > 80% of cells). Magnification × 400.

Table 1

Patient Demographics

Characteristic	Patients, n (%)
Sex	
Male	21 (54)
Female	18 (46)
Primary Tumor Site	
Ascending	4 (11)
Transverse	4 (11)
Descending	2 (5)
Sigmoid	6 (16)
Rectosigmoid	6 (16)
Rectum	17 (43)
Tumor Stage AJCC	
Stage II	5 (13)
Stage III	30 (77)
Stage IV	3 (8)
Unknown	1 (3)
Median Age at CRC Diagnosis, Years	59

Abbreviations: AJCC = American Joint Committee on Cancer; CRC = colorectal cancer

Table 2
Primary Neurologic Symptom at Diagnosis of Brain Metastases

Primary Sign or Symptom	Patients, %
Balance/Gait Difficulties	33
Altered Mental Status	14
Headache	13
Personality Change	12
Focal Neurologic Finding	10
Seizure	8
Visual Change	8
Speech Difficulty	2

Table 3
Anatomic Location of Brain Metastasis by Primary Tumor Site

Location of Brain Metastasis	Number of Patients	Primary Tumor Site, n
Cerebellum	17	Rectal, 11 Rectosigmoid, 2 Ascending colon, 2
Frontal Lobe	10	Rectal, 4 Rectosigmoid, 2 Sigmoid, 2 Transverse colon, 2
Temporal Lobe	4	Rectosigmoid, 2 Ascending colon, 1 Transverse colon, 1
Parietal Lobe	6	Rectal, 2 Rectosigmoid, 1 Transverse colon, 1 Descending, 1
Occipital Lobe	2	Sigmoid, 1 Ascending, 1