Brain carcinoid metastases: outcomes and prognostic factors

Clinical article

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Object. Carcinoid tumors are rare and have generally been regarded as indolent neoplasms. Systemic disease is often incurable; however, patients may live years with this disease. Furthermore, metastatic brain lesions are extremely uncommon. As such, few series have examined outcomes and prognostic factors in those with brain involvement.

Methods. The authors performed a retrospective review of patients who underwent primary treatment at Mayo Clinic in Rochester, Minnesota, for metastatic carcinoid tumors to the brain between 1986 and 2011. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier statistics. Cox proportional hazards were used to determine predictors of survival.

Results. Fifteen patients underwent primary treatment for metastatic carcinoid tumors to the brain between 1986 and 2011. Their mean age was 58 ± 12 years. Eighty percent (n = 12) of patients underwent surgery, whereas 2 received stereotactic radiosurgery and 1 had whole-brain radiation therapy (WBRT) as the primary treatment. The median follow-up duration was 19 months (maximum 124 months). Systemic disease progression occurred in 73% and was the leading cause of death in known cases, while intracranial disease recurred in 40%. The median PFS and OS were 21 and 19 months, respectively. The use of adjuvant WBRT correlated with improved PFS (HR 0.15, CI 0.0074–0.95, p = 0.044). Those who underwent surgery as primary modalities trended toward longer progression-free intervals (p = 0.095), although this did not reach significance.

Conclusions. Metastatic carcinoid disease to the brain appears to have a worse prognosis than that of other extracranial metastases. Although there was a trend toward a survival advantage in patients who underwent surgery and WBRT, further study is needed to establish definitive treatment recommendations.

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Key Words • neuroendocrine tumor • carcinoid • central nervous system • metastasis • oncology

Carcinoid tumors are a rare, heterogeneous group of neoplasms thought to arise from endodermal precursor cells. They are a subtype of neuroendocrine tumors and are distinguished by their relative differentiation (low and intermediate grade) and by their capacity to produce and secrete neuropeptides and hormones such as prostaglandins, histamine, bradykinin, substance P, adrenocorticotropic hormone, catecholamines, and, notably, serotonin, which result in various hormonal syndromes. The term “carcinoïd” was originally coined by Oberndorfer to describe their seemingly indolent course and microscopic appearance similar to carcinomas. It has since been recognized that carcinoid tumors have malignant potential. They arise primarily from the gastrointestinal tract (54.5%) and bronchopulmonary system (30.1%); however, they also occur, albeit rarely, in other organs such as the liver, pancreas, thymus, ovary, uterus, testis, urinary bladder, and rectum. Unknown primaries occur in roughly 13%. Classification of these tumors has historically been based on embryonic origin. More recent classifications schemes encompass histological and pathological characteristics to further differentiate carcinoid subtypes by malignant potential, though there is still no unified classification system to date.

For unknown reasons, the incidence of carcinoids is increasing and is now estimated at 5.25 per 100,000 people per year in the US population according to a recent review of the Surveillance, Epidemiology, and End Results (SEER) database. The frequency of metastases in
patients with carcinoids has been reported to range from 15% to 40%, with the most common sites of metastases being the regional lymph nodes, liver, lung, and bones. Brain metastases are highly unusual, occurring in approximately 1.5% of patients. Little is known about patient outcomes and optimal management in this subset because of the lesion’s rarity. There exists an interesting dichotomy in patients with carcinoid tumors: while lesions in patients with systemic disease can follow a relatively indolent disease course, those in patients with metastatic brain lesions, it has been recognized, have a poor prognosis. We reviewed our series of carcinoid patients with brain involvement to better define treatment-related outcomes.

Methods

Selection Criteria

After receiving Mayo Clinic Institutional Review Board approval, our surgical log, pathology log, and the Mayo Clinic cancer registry were searched for the terms “neuroendocrine” and “carcinoid.” A total of 98 patients from the Mayo Cancer registry and 31 patients from the surgical and pathology logs were identified. Pathology reports were reviewed, and those patients with carcinoid tumors were included. The interval for the study based on inclusion criteria spanned from 1986 to 2011. Only patients with a brain metastasis and either intraaxial or extraaxial involvement were included. One hundred eleven patients were excluded on the basis of pathology, as they had high-grade, poorly differentiated, or large- or small-cell neuroendocrine variants that did not meet the criteria for carcinoid tumors. Three patients were excluded as they had only spinal disease (2 with epidural involvement and 1 with bony involvement), resulting in a total of 15 patients.

Baseline Demographics and Outcomes

A retrospective chart review was performed. Patients underwent a variety of treatment modalities such as surgery, WBRT, GKS, chemotherapy (somatostatin analogs in the majority, though some patients did receive cisplatin and etoposide). Both primary and adjuvant treatment types were recorded. The extent of surgery was defined as gross total (removal of all visible disease at the time of surgery with no evidence of residual tumor on postoperative imaging), subtotal (evidence of residual disease at the time of surgery or on postoperative imaging), and biopsy, or none. Treatment-related complications as a result of surgery or radiation were also recorded. Central nervous system recurrence was determined on the basis of follow-up imaging. Patients with residual disease and evidence of progression on follow-up imaging and those with recurrence of local or remote cranial disease were considered to have recurrent disease. Patients were also screened for progression of systemic disease following primary and adjuvant treatment for CNS disease. Progression-free survival intervals were measured from the time of primary treatment of CNS disease to the point of recurrence or progression in cases that occurred or until the point of last contact. Overall survival intervals were measured from the time of primary treatment of CNS disease to either death or last contact. The cause of death was sought in all cases and noted when evident in the medical record.

Statistical Analysis

Kaplan-Meier curves were used to estimate OS and PFS. Cox proportional hazards was used to determine the predictors of survival and recurrence. All statistical analysis was performed using JMP 9.0.1 software (SAS Institute Inc.).

Results

Demographic Data

Baseline characteristics are outlined in Table 1. The mean age of our cohort was 58 ± 12 years at the time of treatment, whereas it was 53 ± 14 years at the time of initial diagnosis. Median age was 60 years (range 38–78 years). The male to female ratio was 2:1 (10:5). Most patients had good performance status at presentation, with 10 having a KPS score greater than or equal to 70. Sensorimotor symptoms were the most common presentation (n = 6), followed by headache (n = 4), and then seizures and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
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<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>10 (67)</td>
</tr>
<tr>
<td>female</td>
<td>5 (33)</td>
</tr>
<tr>
<td>presenting symptom</td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>4 (27)</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>3 (20)</td>
</tr>
<tr>
<td>sensory or motor</td>
<td>6 (40)</td>
</tr>
<tr>
<td>seizure/spells</td>
<td>3 (20)</td>
</tr>
<tr>
<td>visual disturbance</td>
<td>2 (13)</td>
</tr>
<tr>
<td>carcinoid syndrome</td>
<td>3 (20)</td>
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<tr>
<td>KPS score</td>
<td></td>
</tr>
<tr>
<td>≤70</td>
<td>10 (67)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>5 (33)</td>
</tr>
<tr>
<td>site of primary tumors</td>
<td></td>
</tr>
<tr>
<td>pulmonary</td>
<td>7 (47)</td>
</tr>
<tr>
<td>stomach</td>
<td>4 (27)</td>
</tr>
<tr>
<td>pancreas</td>
<td>1 (6.6)</td>
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<tr>
<td>large intestine</td>
<td>2 (13)</td>
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<tr>
<td>thymus</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>renal</td>
<td>2 (13)</td>
</tr>
<tr>
<td>unknown</td>
<td>1 (6.6)</td>
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<tr>
<td>no. of CNS metastases</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (60)</td>
</tr>
<tr>
<td>2</td>
<td>2 (13)</td>
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<tr>
<td>≥3</td>
<td>4 (27)</td>
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</table>
Carcinoid metastasis to the brain

hydrocephalus. Only 3 patients (20%) had carcinoid syndrome. The mean duration of symptoms was 2.7 months. The mean time lapse between diagnosis and development of CNS disease was 53.4 months. Single brain metastases occurred in 9 patients. The maximum number of CNS metastases at presentation was 9. Supratentorial intraxial tumors were noted in 7 patients, whereas infratentorial tumors were documented in 3 patients. Extraxial involvement occurred in 6 patients. The majority of tumors had a pulmonary primary lesion (n = 7), followed by a gastrointestinal tract lesion (n = 4). The site of origin was not known in 1 patient. The liver was the most commonly involved organ in cases of systemic metastases, occurring in 11 of 15 patients. Four patients had lung metastases at presentation. On pathology review, 6 of the 15 tumors showed atypical features. The median follow-up was 19 months (maximum 124 months).

Treatment and Complications

Eighty percent (n = 12) of patients underwent resection, 2 underwent GKS, and 1 received WBRT as primary treatments. In the 12 patients (8 with a single metastasis) who underwent surgery, a gross-total resection was achieved in 7 patients. Resection was considered subtotal in 5 patients. Sixty percent of patients received adjuvant therapies, which included WBRT (n = 9), somatostatin analogs (n = 5), and cisplatin and etoposide (n = 2). Primary and adjuvant therapies are outlined in Table 2, and respective treatment algorithms are further delineated in Fig. 1. Surgical complications occurred in 3 patients (20%). There were 2 surgery-related deaths. One patient died of malignant cerebral edema following posterior fossa surgery, and the other died of pneumonia that progressed to sepsis and multisystem organ failure. Another patient suffered worsened hemiparesis due to postoperative stroke after resection of an insular metastasis (Fig. 2). Hospitalization and initiation of steroid therapy were required in another patient for cerebral edema from radiation effect, which occurred 2 months after completion of WBRT.

Outcomes and Predictors

Central nervous system recurrences were noted in 6 patients (40%) in whom the median recurrence time was 21 months (Fig. 3 upper). Seventy-three percent of patients experienced progression of systemic disease. The median OS for the cohort was 19 months (Fig. 3 lower). Only 2 patients were alive at last follow-up. The cause of death was not clear in the medical record in 6 patients. As previously mentioned, there were 2 treatment-related deaths. Only 1 patient died as result of CNS progression. Cox proportional hazards did not show age, treatment modality, duration of symptoms, tumor location, or number of CNS metastases to be predictive of survival. Complications were highly predictive of death (HR 11.4, CI 2.1–84.9, p = 0.005). A trend toward improved survival was noted in KPS status (p = 0.096) and female sex (p = 0.09). Using actuarial analysis, only WBRT was predictive of time to progression (HR 0.15, CI 0.0074–0.95, p = 0.044). Patients who underwent surgery trended toward longer PFS intervals (p = 0.095). Neither location nor use of adjuvant chemotherapy resulted in increased PFS intervals. Atypical histological features did not correlate with PFS or OS (p = 0.28 and p = 0.72).

Discussion

Although carcinoid tumors were traditionally thought to exhibit indolent behavior, their metastatic and malignant potential has been well established. Metastases to the brain from primary carcinoid tumors are highly unusual and likely occur only at advanced stages of metastatic disease. Existing series suggest that overall prognosis is worse in patients with brain metastases. The overall 5-year survival rate for patients with extracranial metastases is 40%. In comparison, series examining patients with intracranial metastases show a 1-year survival rate ranging from 33% to 42% and a median survival time of 7–10 months. The present series found a median survival of 19 months in patients with CNS involvement, a survival time that is similar to what has been observed in advanced cases of metastatic disease. The overall 5-year survival rate in our series was 10%. Not surprisingly, the most common cause of death was systemic disease progression (73%), further supporting the concept that brain metastases occur only after widespread dissemination. Therefore, it appears that patients with metastatic carcinoid brain lesions represent a distinct cohort of patients than is typical for those with metastatic carcinoid disease, and they succumb to their disease sooner.

Because intracranial carcinoid metastases are rare, there are no randomized or prospective data on which to base definitive treatment guidelines. Variable outcomes have been demonstrated in patients treated with surgery, stereotactic radiosurgery, WBRT, or chemotherapy as single therapies or in combination. The existing evidence favors surgery and WBRT Experience

<table>
<thead>
<tr>
<th>TABLE 2: Primary and adjuvant treatment modalities*</th>
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<tr>
<td><strong>Treatment</strong></td>
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<td>----------------</td>
</tr>
<tr>
<td>total</td>
</tr>
<tr>
<td>surgery</td>
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<tr>
<td>alone</td>
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<td>w/ WBRT</td>
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<tr>
<td>w/ chemo + WBRT</td>
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<tr>
<td>GKS</td>
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<tr>
<td>alone w/ chemo</td>
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<tr>
<td>WBRT</td>
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<td>alone w/ chemo</td>
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<td>w/ chemo</td>
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* chemo = chemotherapy.
with extracranial metastases supports a role for surgery because the extent of surgery has been shown to improve survival in patients with lung primary lesions and liver metastases.\(^5,7,10,15\) In this study, there was a trend on actuarial analysis toward improved survival with surgery as a primary treatment modality, which became significant when controlling for perioperative mortality. Our finding of a survival advantage with use of adjuvant WBRT is consistent with the findings of other series.\(^3,11,36\) Schupak and Wallner\(^36\) found that all 8 patients in their series treated with a median radiation dose of 3300 cGy had no further progression of intracranial disease after irradiation. All 12 intracranial metastasis patients in a study by Patchell and Posner\(^26\) also showed clinical improvement after WBRT. In a study of 24 patients by Hlatky and colleagues,\(^11\) the authors found the combination of surgery and WBRT correlated with improved survival compared with WBRT or surgery alone. The limited available evidence for treatment of intracranial carcinoid tumors, along with randomized evidence for other brain metastasis,\(^27,28,43\) suggests that surgery combined with WBRT should be considered in patients with good preoperative performance status and a single metastasis. However, further study is needed before treatment guidelines can be established.

Although chemotherapies have changed drastically during the time course of this study, there are still very few randomized trials to support the use of chemotherapy.\(^30\) The present study was underpowered to detect a difference in survival with the use of adjuvant chemotherapy and was further limited by a lack of homogeneity in chemotherapeutic agents used. Somatostatin analogs are frequently used because carcinoids have been found to express somatostatin receptors on their cell membranes.\(^40\)

![Fig. 1. Treatment algorithms in 15 patients with carcinoid brain metastases. Asterisk indicates chemotherapy (chemo) with cisplatin and etoposide. Otherwise chemotherapy consisted of somatostatin analogs. GK = Gamma Knife.](image1)

![Fig. 2. Preoperative (A [T1-weighted, Gd-enhanced] and B [T2-weighted]) and postoperative (C [T1-weighted, Gd-enhanced]) MR images in a 73-year-old man with a right-sided insular metastasis presenting with a mild left hemiparesis and homonymous hemianopia. The postoperative image (C) shows gross-total resection.](image2)
Carcinoid metastasis to the brain

Somatostatin is effective in controlling symptoms related to hormone production and has been shown to improve PFS in patients with extracranial disease. Its effectiveness solely for intracranial disease is likely limited due to poor penetration of the blood-brain barrier. A variety of other agents have been used including streptozotocin, 5-fluorouracil, doxorubicin, temozolomide, carboplatin, etoposide, sunitinib, everolimus, and radionuclide therapy. Current guidelines advocate for the use of platinum-based regimens to treat high-grade disease, and a streptozotocin combination to treat carcinoids of pancreatic origin, well-differentiated tumors of intermediate or high grade, or rapid progression. The high rate of systemic disease progression in the present series does suggest that patients with intracranial metastases should undergo surveillance for systemic disease. However, with sparse evidence and evolving chemotherapeutics, the role of adjuvant chemotherapy needs to be further explored.

An unusually high complication rate (13% mortality and 7% morbidity) was observed in our series in patients undergoing resection. There were 2 perioperative deaths, 1 due to malignant cerebellar edema postoperatively and 1 due to pneumonia and sepsis. There was 1 case of permanent morbidity secondary to an ischemic stroke in a patient undergoing resection of an insular metastasis. These are much higher rates of morbidity and mortality than we have seen in other cases of tumors resected at our institution. For example, in a recent series of elderly patients with glioblastoma (S. Tanaka et al., unpublished data [in press]), there was no mortality in 53 patients who underwent resection, and permanent neurological deficits were observed in only 3.8%. The mortality rate in all craniotomies for tumor resection at our institution between 2008 and 2012 (n = 2063) was 0.34%. While it is possible that, for unknown reasons, carcinoid brain metastases are associated with particularly high surgical risks, we suspect that this likely represents a combination of chance and a small sample size. Thus, we conjecture that the observed complication rate would substantially diminish with increasing numbers.

Limitations of our study include a small number of patients and a retrospective design. Thus, despite a trend toward improved survival with surgery and WBRT, no definitive treatment recommendations should be made on the basis of this small cohort. Additionally, the incomplete follow-up, particularly with cause of death, may underestimate the amount of CNS-related deaths and recurrences. However, this study does provide additional prognostic value with outcomes after surgery in a rarely encountered metastatic tumor.

Conclusions

With increasing incidence and improving therapies, tertiary referral centers are likely to see more cases of metastatic carcinoid disease with brain involvement. Compared with those who have other sites of involvement, those with intracranial spread may have a worse prognosis. The median survival duration and estimated 5-year survival rate were 19 months and 10%, respectively, which are lower than previously reported in the literature with extracranial metastases. No specific treatment recommendations can be made with current available evidence or on the basis of this small series. Further study is needed to better define the role of surgery and WBRT in this subset of patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Parney, Mallory, Van Gompel. Acquisition of data: Mallory, Fang, Giannini. Analysis and interpretation of data: Mallory. Drafting the article: Mallory, Fang, Van Gompel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Parney. Statistical analysis: Mallory. Administrative/technical/material support: Giannini. Study supervision: Parney, Van Gompel.

Fig. 3. Graphs showing PFS (upper) and OS (lower) in 15 patients who underwent treatment for intracranial neuroendocrine metastases. Recurrences were noted in 6 patients with a median recurrence time of 21 months (upper), and median overall survival for the cohort was 19 months.

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