Original Study

Prognostic Factors for Patients With Advanced Colorectal Cancer and Symptomatic Brain Metastases

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Abstract

Patients with advanced colorectal cancer (CRC) have increased risks of brain metastases (BMs), which are associated with poor clinical outcomes. In a study of 25 patients with multiple brain lesions, we identified prognostic factors relevant to local treatment for BMs. After BMs onset, continued systemic chemotherapy might improve survival in cases of advanced CRC.

Background: Increased rates of long-term survival after CRC diagnosis are accompanied by increases in the incidence of BMs. Here, we retrospectively evaluated the outcomes of patients with BMs from CRC. **Materials and Methods:** We reviewed the records of 1364 patients with CRC treated between January 1999 and December 2010 at Kinki University Hospital in Japan. Twenty-five of these patients developed BMs. Log-rank tests and Cox regression analyses were used to assess potential prognostic factors for survival. **Results:** Among the patients with BMs, BMs developed a median of 25.3 (range, 11.4-111) months after primary CRC surgery. There was a median of 2 BMs per patient. Eleven patients had solitary BMs. Concomitant extracerebral metastases, particularly lung metastases, were found in 23 patients. Twenty-three patients were receiving systemic chemotherapy at the time of diagnosis with BMs. After the development of BMs, the median survival time (MST) was 2.8 months. The MST was 4.8 months among patients who underwent neurosurgical resection (n = 6) or stereotactic surgery (n = 9, including combined therapy in 2 patients) and 1.5 months among patients who underwent whole-brain radiotherapy only or best supportive care (n = 12). In multivariate analysis, single BMs and additional systemic chemotherapy after BMs diagnosis were significantly associated with overall survival ($P = .022$ and .023, respectively). **Conclusion:** Our results suggest that advancements in continuing systemic chemotherapy prolong survival among patients with BMs from CRC. Clinicians should be especially aware of BMs in patients with lung metastases.

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Introduction

Brain metastases (BMs) are the most common type of intracerebral neoplasms. BMs occur in 25% of all patients with systemic cancers,[1] reducing quality of life (QOL) and opportunities for treatment. In patients with colorectal cancer (CRC), recurrence most commonly occurs in the liver, the lungs, or locally.[2,3] CRC rarely metastasizes to the brain. Indeed, the reported incidence of BMs among patients with CRC is only 1% to 3%.[4-7] However, recent improvements in the management of advanced CRC have altered the natural history of this disease, indirectly increasing the incidence of metastasis at previously uncommon sites, such the brain and bone.[7-9]

A useful prognostic system for BMs has been developed using recursive partitioning analysis (RPA), based on a database of 3 Radiation Therapy Oncology Group trials.[10] This previous study analyzed BMs in patients with lung cancer, breast cancer, and melanoma. The median survival times (MSTs) among patients with RPA class I, II, and III were 7.1, 4.2, and 2.3 months, respectively; differences between these MSTs were statistically significant. Golden et al recently reported that prognostic factors for patients with BMs vary according to the primary cancer site.[11] Patients with BMs from CRC had a significantly worse prognosis than patients whose primary tumors were in the lungs, breast, or skin.[12,13]

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Patients with BMs from CRC frequently have extracerebral metastases; indeed, extracerebral metastases are found in 70% to 97% of patients with BMs from CRC.[1,14-17]

Most patients with BMs have neurological symptoms. BMs-related impairments with regard to cognition, memory, language, and adaptive skills worsen QOL, increase the need for supportive care, and result in considerable health care costs.[18] Therefore, QOL and the neurological condition are important considerations in cases of BMs, in addition to overall survival (OS).

In previous studies of patients with BMs from CRC, various potential prognostic factors have been identified, including the number of BMs,[17,19-21] extracerebral metastases,[19-21] the interval between diagnoses of CRC and BMs,[15,16,20] RPA class,[21,22] BMs curability,[17] treatment modalities used for BMs,[19] and carcinoembryonic antigen (CEA) levels.[17] However, in light of recent advances in chemotherapeutic regimens for CRC, including cytotoxic drugs and molecular-targeted agents, it might be necessary to reevaluate these previously identified prognostic factors. Accordingly, we performed the present study to analyze the clinicopathological characteristics and outcomes of patients with BMs from advanced CRC. We specifically sought to identify independent prognostic factors for OS.

Materials and Methods

Patients

Between January 1998 and December 2010, 1364 patients were treated for CRC at the Faculty of Medicine of Kinki University. Each of these patients underwent surgical resection. A retrospective review of these patients' medical records revealed 25 patients who had developed BMs, constituting a 1.8% incidence of BMs. Data on each of these 25 patients were retrospectively analyzed in the present study. All patients' BMs had been detected as a result of neurological symptoms. In each case, magnetic resonance imaging (MRI) or computed tomography (CT) scans of the brain were used to establish the number of BMs and their sizes. Information retrieved from the patients' medical records included the details of the primary tumor, the interval between treatment of the primary tumor and the occurrence of BMs, the extent of extracerebral metastases, neurological symptoms, the numbers of BMs, the size of BMs, and OS.

Twenty-three patients with extracerebral metastases were receiving concomitant systemic chemotherapy at the time of diagnosis with BMs. Nine patients received mFOLFOX6 (5-fluorouracil/leucovorin/oxaliplatin) or XELOX (capecitabine/oxaliplatin), 6 patients received UFT/UZEL (uracil/tegafur/leucovorin) with or without irinotecan, 4 patients received FOLFIRI (5-fluorouracil/leucovorin/irinotecan) with or without bevacizumab, 3 patients received cetuximab, and 1 patient received irinotecan only. In each of these cases, systemic chemotherapy was disrupted as a consequence of neurological symptoms caused by BMs. This study was approved by the Institutional Review Board of the Faculty of Medicine of Kinki University.

Patient Follow-Up and Eligibility Criteria for Systemic Chemotherapy

Follow-up for recurrence in patients diagnosed with stage I to III CRC was performed as follows: physical examination; evaluation of serum CEA levels; and chest, abdominal, and pelvic enhanced or plain CT scan performed every 6 months for the first 3 years and every 1 year for the next 2 years after surgery. With regard to BMs, we did not routinely perform brain CT scan or MRI.

The eligibility criteria for systemic chemotherapy were basically applied when unresectable distant metastases of CRC were detected. Furthermore, patients who only received primary tumor resection in stage IV were administered anticancer agents as soon as possible after primary surgery; they were followed-up with evaluation of serum CEA levels every 3 months and chest, abdominal, and pelvic enhanced CT scans performed every 3 to 6 months.

Treatments for BMs

All BMs treatments were performed by neurosurgeons and/or radiotherapists at our institute. The indications for neurosurgical resection were consistent with the requirements of Patchell et al.[23] Namely, the following patients with BMs were regarded as most likely to benefit from surgical resection: patients with a single surgically accessible lesion, either no remaining systemic disease or controlled systemic cancer limited to the primary site, and an expected survival time of at least 2 months.

Whole-brain radiotherapy (WBRT) is often considered the principal treatment for patients with multiple BMs and is directed at reversing neurological deficits and controlling progression in the brain. Stereotactic surgery (SRS) was considered in cases that included no more than 3 or 4 BMs, each having a maximum diameter of $\leq$ 3 cm. WBRT and SRS were performed with a 6-MV linear accelerator (CLINAC 21EX, Varian Medical Systems, Inc). Noninvasive fixation of the shell mask was performed for head fixation, and Eclipse irradiation planning software (Varian Medical Systems Inc) was used for WBRT. Irradiation doses were 3 Gy per 10 fractions or 2.5 Gy per 15 fractions with opposed lateral fields. For SRS planning and irradiation, treatment was planned using a dedicated CT scan for optimal tumor visualization with the treatment planning program BrainSCAN (BrainLAB AG). SRS involved a single high-dose fraction of 20 Gy.

Prognostic Factors

Overall survival was measured from the first diagnosis of BMs to death or the last date of follow-up. The following variables had been assessed for each patient and were reviewed in our analysis: locations of extracerebral metastases, Karnofsky performance status, serum CEA level, neurologic deficits and symptoms, and RPA class. Each assessment was made at the time of the patient's first BMs diagnosis.

Statistical Analysis

Statistical analyses were performed using the JMP10 software package (SAS Institute Inc, Cary, NC). OS curves were estimated using the Kaplan–Meier method and compared using the log-rank test. For each variable, hazard rates and confidence limits were estimated using the Cox proportional hazard model. Univariate and multivariate Cox regression analyses were used to evaluate each variable's ability to predict OS after BMs. The following variables were analyzed: tumor, node, metastases (TNM) stage of the primary CRC at the time of diagnosis, curability of the first surgery for CRC, number of BMs, RPA class, interval between the first surgery