Clinical Features of Precocious, Synchronous, and Metachronous Brain Metastases and the Role of Tumor Resection

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■ OBJECTIVE: **The purpose of this study was to clarify clinical features, outcomes, and the role of tumor resection in precocious, synchronous, and metachronous brain metastases.**

■ METHODS: **Brain metastases were found before primary cancer detection in the precocious group, within 2 months after primary cancer detection in the synchronous group, and 2 months or later after primary cancer detection in the metachronous group.**

■ RESULTS: **Of 471 patients with brain metastases, 93 (20%) were included in the precocious group, 76 (16%) in the synchronous group, and 302 (64%) in the metachronous group. The precocious group tended to be symptomatic, show a low Karnofsky Performance Status, and have a large single tumor, infrequent extracranial metastases, and frequent tumor resection compared with the other 2 groups. There were no differences in overall survival from the detection of brain metastases among the 3 groups in univariate and multivariate analyses. Of 471 cases, 97 (21%) underwent surgeries. Among this surgical cohort, overall survival from surgery was significantly shorter in the precocious group than in the metachronous group ($P = 0.039$). After adjustment for age, sex, tumor size, primary cancer, and the Graded Prognostic Assessment score, the hazard ratio for metachronous metastases was 0.52 (confidence interval, 0.29–0.95; $P = 0.035$).**

■ CONCLUSIONS: **The timing of brain metastasis diagnosis is not a modifiable factor but affects patient demographics and treatment strategies. In particular, the precocious group is a unique subset of brain metastases that require special consideration during clinical decision making.**

INTRODUCTION

Brain metastases are common brain tumors that occur in approximately 8.5%–9.6% of patients with cancer.[1-4] Over the last 3 decades, the number of brain metastases has been increasing[3,5] because of population aging and advancements in neuroimaging and systematic therapy.[2,6] Most patients develop brain metastases during or after treatment for primary cancers, and these are called metachronous metastases.[2,7] Some patients are diagnosed before the diagnosis of primary cancers or simultaneously with the diagnosis of primary cancers, and these are called precocious and synchronous metastases, respectively.[2] In terms of the general patient condition and brain lesions, diverse factors affect the outcomes of these 3 groups. For example, most precocious brain metastases have neurologic symptoms at diagnosis, whereas many synchronous and metachronous brain metastases do not show neurologic symptoms. The difference between precocious and synchronous groups is only the timing of diagnosis and not the timing of metastasis, but

Key words
- Brain metastasis
- Metachronous
- Precocious
- Surgery
- Synchronous

Abbreviations and Acronyms
GPA: Graded Prognostic Assessment
HR: Hazard ratio
KPS: Karnofsky Performance Status
OS: Overall survival

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neurosurgeons must deal differently with these 2 groups, because the former needs surgical intervention to resolve neurologic emergency. Generally, the metachronous group receives various types of treatment for the primary cancer before brain lesion development, whereas precocious and synchronous groups are mostly naive. Overall, the precocious group is considered to be unique compared with the other 2 groups,[8] and in this group, the time for clinical evaluation and decision making is limited at the time of treatment. To our knowledge, no report has analyzed the differences between the precocious, synchronous, and metachronous groups together.

The present study aimed to clarify the clinical characteristics and treatment outcomes of precocious, metachronous, and synchronous brain metastases and compare the findings of precocious metastases with those of synchronous and metachronous metastases in an attempt to provide information that helps in clinical decision making when precocious brain metastases are encountered.

METHODS

Patients and Analyzed Parameters

This retrospective study included consecutive patients with brain metastases identified between October 2003 and March 2014, at Sendai Medical Center. We reviewed the medical records of all patients diagnosed with brain metastases during that period. Patients with brain metastases were divided into precocious, synchronous, and metachronous groups according to the timing of metastasis identification. Precocious metastases were defined as brain metastases found before the detection of the primary cancer.[2] Synchronous metastases were defined as brain metastases found within 2 months after the detection of the primary cancer[7,9] Metachronous metastases were defined as brain metastases found 2 months or more after the detection of the primary cancer.[2,7] Data on age, sex, symptoms, the Karnofsky Performance Status (KPS), tumor size (the largest diameter), the number of brain tumors (1, 2, 3, or more), the primary tumor, the presence of extracranial metastasis, the location of tumors, treatment for brain metastases, and treatment for the primary tumor were collected. Overall survival (OS) was defined as the interval between the day of brain metastasis detection and the day of death or the last follow-up examination.

We first investigated all patients (the entire cohort) to clarify the clinical features of each group and then focused on surgical cases (the surgical cohort) to assess the features of each group. This study conformed to the protocols approved by the ethics committee of Sendai Medical Center.

Prognostic Index for Brain Metastases

The Graded Prognostic Assessment (GPA)[10] was used for classifying the patients with brain metastases. The GPA score is calculated by adding the scores (0, 0.5, and 1) of the following 4 factors: age (>60 years, score 0; 50–59 years, score 0.5; <50 years, score 1); KPS (<70, score 0; 70–80, score 0.5; 90–100, score 1); number of brain metastases (>3, score 0; 2–3, score 0.5; 1, score 1); and extracranial metastases (present, score 0; absent, score 1). The GPA score ranges from 0 (the worst condition) to 4 (the best condition).

Indications for Tumor Resection

We performed tumor resection when the patient had a good general condition with controlled systemic disease, when the tumor was >30 mm,[7,11] and when surgical removal was believed to improve or stabilize neurologic symptoms. We also performed resection for smaller lesions with strong brain edema and impending neurologic symptoms. In the precocious group, we also performed tumor resection for histologic diagnosis to facilitate systemic treatment under limited information of the primary cancer and general conditions.

Treatment for Primary Cancers

Any treatments for primary cancers, including surgery, chemotherapy, and radiation therapy, were decided by each specialist of oncology following the standard guideline.

Statistical Analysis

Differences in baseline characteristics among the precocious, metachronous, and synchronous groups were statistically tested using nonparametric methods, the Kruskal-Wallis test for continuous variables, and Fisher exact test for categorical variables. Survival was calculated using the Kaplan-Meier method. To control potential confounders, we constructed 3 adjustment models as previously reported.[12] We first conducted univariate analysis, with brain metastasis detection status as the only independent variable. Next, we conducted analysis after in addition adjusting for age (categorized as <50/50–59/60–69/70–79/≥80 years) and sex. In the final model, we in addition adjusted for tumor size, primary cancer, and the GPA score (as a continuous variable) to eliminate the effect of the prognostic index. A Cox proportional hazard model was used for estimating hazard ratios (HRs) and the 95% confidence intervals. All calculations were performed using Prism (GraphPad Software [GraphPad Software Inc., San Diego, California, USA]) or Stata 13.1 (StataCorp, College Station, Texas, USA). A P value of < 0.05 was considered statistically significant.

RESULTS

Patient Demographics in the Precocious, Synchronous, and Metachronous Groups

We reviewed the records of 471 consecutive patients with brain metastases (the entire cohort) during the study period. **Table 1** summarizes the baseline characteristics of the 3 groups. The precocious group tended to be symptomatic, show a low KPS, have a large single tumor, and have infrequent extracranial metastases compared with the other 2 groups. The distribution of the GPA score differed in the 3 groups, and the condition tended to be worse in the precocious group than in the other 2 groups (**Table 1**). Location of the tumor is summarized in **Supplementary Table 1**.

Table 2 summarizes the origin of the primary cancer. In the entire cohort, the primary sites were the lungs in 288 patients (61%), gastrointestinal tract in 59 (13%), and breasts in 54 (11%). In each group, the lungs were the leading primary site. The proportion of patients with lung cancer was higher and the proportion with breast cancer was lower in the precocious and synchronous groups than in the metachronous group (**Table 2**). We experienced only 1 case of brain metastasis from malignant melanoma.