

Heterogeneity of Tumor Sizes in Multiple Pulmonary Metastases of Colorectal Cancer as a Prognostic Factor

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Background. The number of metastatic lesions is closely correlated with prognosis in most cancers. The aim of this study was to clarify the relationship between individual heterogeneity of metastatic tumor sizes and prognosis in patients with multiple pulmonary metastasis of colorectal cancer who received surgical treatment.

Methods. Clinical data for patients who had pulmonary metastasis from colorectal cancer and underwent curative resection at 46 Japanese institutions between January 2004 and December 2008 were collected. Among 898 patients eligible considering these inclusion criteria, 247 patients had multiple metastases and were analyzed. A difference between the maximum and minimum tumor diameters ($D_{\max-\min}$) on pathologic findings was used to evaluate size heterogeneity.

Results. The overall survival rate was 75% at 3 years and 58% at 5 years, with a median follow-up period of 65

months (range, 0 to 112). When $D_{\max-\min}$ of 5 mm was set as a cutoff value, overall survival was significantly different between small (≤ 5 mm, $n = 95$) and large (> 5 mm, $n = 152$) tumor groups (5-year survival rates, 66.5% and 53.3%, respectively; log rank test, $p = 0.025$). Multivariate analysis using a Cox proportional hazards model revealed that disease-free interval from resection of primary lesion, serum carcinoembryonic antigen level, number of pulmonary metastases, and $D_{\max-\min}$ were independent prognostic factors.

Conclusions. The heterogeneity of metastatic tumor sizes may be an indicator for prognosis in patients with multiple pulmonary metastases of colorectal cancer who underwent resection.

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Many studies have examined the resection of pulmonary metastases (PM) from colorectal cancer [1–13]. These studies have generally suggested that resection of PM can be beneficial to the patient's prognosis. In these studies, 5-year rates of overall survival have ranged from 38% to 68%. Some of these studies have used large multicenter retrospective designs [1, 3], and others have been systematic reviews [4]; however, few studies have focused specifically on multiple PM. It has been reported that multiple PM indicate a poorer prognosis than a solitary PM [1, 2, 4–7]. Recently, new drugs [14, 15] and targeted therapies [16, 17] have been developed for colorectal cancer. Consequently, the surgical criteria for multiple PM are broadening.

Multiple PM of similar and differing sizes can exist. Differences in tumor size may reveal features of tumor biology. Namely, the cancer cells of PM with narrow ranges of sizes may arrive at the lungs and grow for only one period. In contrast, the cancer cells of PM with wide ranges of sizes may arrive at the lungs and grow for various periods.

Here, we report the findings of a retrospective multicenter study of pulmonary metastasectomy for PM from colorectal cancer that was conducted after the

Dr Boku discloses a financial relationship with Taiho.

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introduction of new active chemotherapeutic regimens [14–17]. The immediate aim of this study was to clarify the relationship between the individual heterogeneity of metastatic tumor sizes and prognosis. The ultimate objective of this analysis was to gain new evidence that could be relevant to the surgical criteria for patients who have colorectal cancer with PM.

Patients and Methods

Patients

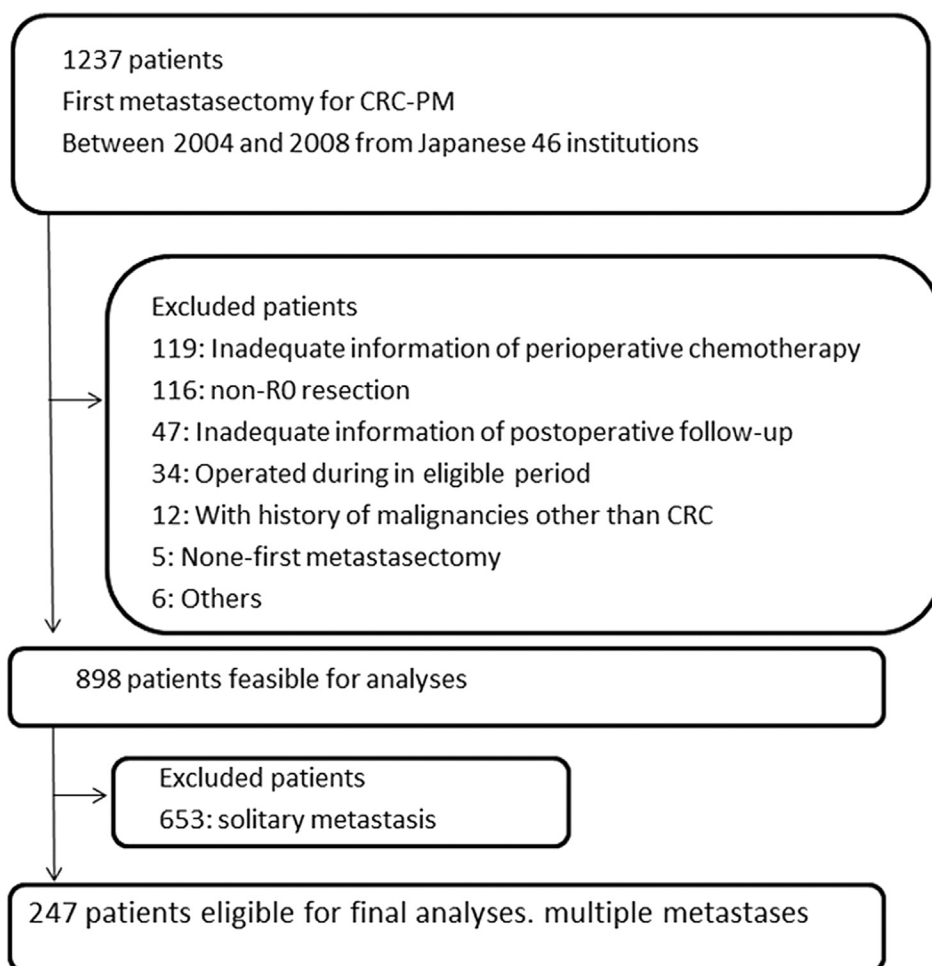
The study was a large cohort trial by the Tsukuba Cancer Clinical Group based in numerous institutions in Japan. The data in our analysis were originally obtained for all patients who had PM from colorectal cancer and underwent pulmonary resection between January 2004 and December 2008 at 46 institutions throughout Japan. The inclusion criteria for this study were (1) first metastasectomy for PM; (2) metastasectomy performed with curative intent; (3) pathologic diagnosis of the resected lesions as metastases from colorectal cancer; (4) metastasectomy with pathologically confirmed complete resection; and (5) curative resection of the primary cancer.

Patients with metastasis from cancer of the appendix or anal cancer were excluded.

This study was a multicenter retrospective study and operative indications for pulmonary metastasectomy, in detail, were referred to each institution. However, indications were based on the following: metastatic lesions are confined to the lungs; all lesions are resectable; there are no extrathoracic lesions except for liver metastasis or extralesions are clinically controlled by treatment; and the surgical procedure is tolerable for the patient. Whether pulmonary resection was performed through thoracotomy or video-assisted thoracic surgery was decided according to the situation of each case and the judgment of the physician of each institution. Lymph node dissection combined with pulmonary resection was not regulated, according to the judgment of the physician of each institution. Follow-up was not uniform in this study. However, most of the patients were treated according to the treatment guideline for colorectal cancer in Japan [18].

The study protocol was approved by the Institutional Review Board of all participating hospitals, including that of the Ethics Committee, Kyorin University Graduate School of Medicine (H24-051). We conducted a large-scale multiinstitutional retrospective cohort study to inform the

Fig 1. Study design and participants. (CONSORT = Consolidated Standards of Reporting Trials; CRC = colorectal cancer; PM = pulmonary metastases; R0 = resection for cure or complete remission.)



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