Clinical features of colorectal mucinous and poorly differentiated adenocarcinomas; study concept of a propensity score analysis in a pooled data of 5530 patients

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Abstract
The prognostic relevance of the mucinous subtype of colorectal cancer is still controversially discussed. We designed a large-scale cohort study with a propensity score matching to evaluate the impact of mucinous subtype on postoperative survival, recurrent patterns and chemo-sensitivity in patients with colorectal cancer using the integrated database of three phase III clinical trials. We introduce a study concept and present preliminary results of an overview of the total individual patients’ data here.

Key Words: Colorectal cancer, Mucinous adenocarcinoma, Poorly differentiated adenocarcinoma, Prognosis, Propensity score analysis.

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Introduction
Colorectal cancer (CRC) is the third most common cancer and a major cause of cancer mortality worldwide. CRC has been recognized as a heterogeneous disease in terms of progressive behavior and the histologic subtype represents an important phenotype of CRC. CRC comprise several histologic subtypes including signet ring cell carcinomas, mucinous, poorly differentiated and differentiated adenocarcinomas.

Mucinous CRC is defined as CRC in which extracellular mucin comprises >50% of the tumor volume and has been reported to account for 5–15% of CRC. The clinical signature of mucinous CRC were that it more often affected young and female patients, frequently located on the proximal colon and had more later-stage presentations. Although some studies have reported worse survival outcomes and poorer response to chemotherapy in mucinous CRC, the prognostic relevance of the mucinous subtype is still controversially discussed, mainly because of the relatively rare incidence of this disease.

Poorly differentiated adenocarcinomas of the colon and rectum have been reportedly accounted for 14–18% of all CRC and feature the poor prognosis compared to differentiated types. The objective of this study was to evaluate whether CRCs with mucinous histological type demonstrates any relevant specific feature with regard to postoperative survival, recurrences and chemo-sensitivity, by using a large cohort from the integrated database of large phase III studies. A propensity score weighting was employed to minimize the difference in the background between the three groups; mucinous, poorly differentiated and differentiated CRCs.
Materials and methods

Ethics

Study protocols conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects and has been reviewed and approved by an internal review board of each participating institution. Written informed consent for usage of clinical data was obtained from all the patients enrolled into these studies. Moreover, this integration analysis was approved by the Internal Review Board of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC).

Source of clinical data

Clinical data was obtained from the integrated database of three phase III trials conducted by the JFMC; JFMC-7, 15 and 33. In brief, JFMC-7 and 15 were large-scale clinical trials with more than 1000 patients for each to evaluate survival benefit of postoperative adjuvant 5-fluorouracil-based treatment in patients with macroscopic Dukes’ B and C CRC4). JFMC-33 was a randomized phase III trial compared overall and disease-free survivals between 6-month and 18-month adjuvant oral uracil and tegafur/leucovorin treatment in patients with stage IIB/III CRC5). In total, pooled data from 5530 patients were available for the current study.

Data analysis

Associations between different groups of histological type and baseline characteristics was determined using \( \chi^2 \) test for categorical variables and t-test for continuous variables. We used the propensity score weighting to balance more strictly in essential variables for the comparison analyses that followed6). Propensity scores were estimated using a multinomial logistic regression model including age, sex, tumor locations, extent of lymphadenectomy, and pathological disease stage. Other variables were also considered through a variable selection procedure based on the Akaike’s information criterion. Overall and disease-free survival rates were estimated using the weighted Kaplan-Meier method, and the overall differences between curves were compared using the weighted log-rank test. The weighted Cox proportional hazards model was used to evaluate the hazard ratio for survival relative to each variable. Statistical analysis was performed using the SAS version 9.4 (SAS Institute Inc., Cary, NC) and R ver 3.1.1. P < 0.05 indicates a statistically significant difference.

Completion of data analysis

Data collection, integration of data from the three clinical trials (JFMC 7, 15 and 33), propensity score weighting were already completed. Comparative analyses in clinical characteristics, prognosis between patients with mucinous, poorly differentiated and differentiated adenocarcinoma in the matched patient cohort also have been completed. Currently, the results are under interpretation and will be published elsewhere through an intense discussion with all contributors.

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Reference