Development of a prognostic nomogram for metastatic colorectal cancer patients: The study protocol of a multicenter, retrospective, observational, cohort study

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Abstract

Introduction: As patients with metastatic colorectal cancer (mCRC) have various clinical backgrounds and the treatment strategies that are applied in their management are diverse, it is difficult to accurately estimate their prognosis. We conducted this study to establish a prognostic nomogram for mCRC patients using a population-based database.

Materials and Methods: In this population-based, multicenter, retrospective, observational cohort study, we aimed to enroll 1,500 patients from all nine designated cancer hospitals across Fukushima prefecture from January 2008 to December 2015. Patients with a metastatic lesion according to the TNM classification (AJCC/TNM 8th) were eligible for inclusion. The primary outcome was overall survival. The last day of follow-up was December 31, 2017. We investigated the clinical significance of the following variables: age, sex, body mass index, Charlson comorbidity index, activities of daily living, location of colorectal cancer, degree of differentiation, TNM stage, number of distal metastatic organs, severity of each metastatic organ, symptoms from the primary lesion, laboratory markers, and method of treatment.

Discussion: This is the first prognostic nomogram of patients with mCRC created from a population-based cohort.

Trial registration: UMIN000033718 (registration date: 30/08/2018)

Keywords: prognostic nomogram, colorectal cancer, metastasis, overall survival

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Introduction

Metastatic colorectal cancer (mCRC) remains a lethal disease, even though the prognosis of patients with mCRC has been improving due to recent advances of multidisciplinary therapy including cytotoxic chemotherapy, molecular targeted agents, radiotherapy and surgical resection1. Systemic chemotherapy is becoming increasingly complex because of the development of new molecular targeted drugs and the diversity of administration routes. Newly identified biologic, genetic and other molecular information have increased the complexity of the therapeutic strategy2-5. Furthermore, immunotherapy—including immunity checkpoint inhibitor treatment—has been widely accepted in many countries6. The incidence of colorectal cancer in the elderly population is increasing7,8. Elderly patients have some physical problems, including reduced organ function and reduced functional reserves of the liver, kidneys, and bone marrow, a higher rate of cardiovascular risk factors, cognitive impairments, other comorbidities, and polypharmacy9,10. These factors may contribute to the frequency and severity of adverse events in elderly patients undergoing any type of therapy11,12. Because mCRC patients have various backgrounds and the treatment strategies for mCRC are also
diverse, the ability to accurately predict their survival would help patients and oncologists make better treatment decisions.

Unlike localized colorectal cancer, the prognosis of mCRC is quite difficult for physicians to predict. The outcomes from large-scale clinical trials are not always applicable in daily practice from the perspective of external validity. A prognostic nomogram is a clinically useful tool for predicting the survival outcome of patients and it has been widely applied in the field of medical oncology. Although several types of nomogram have previously been established for patients with mCRC, the focus of the studies was limited to patients receiving multidisciplinary therapy.

The primary goal of this study was to develop a useful prediction model for all mCRC patients using population-based clinical dataset. The nomogram will provide useful information for patients, their family and clinicians who treat colorectal cancer.

Materials and Methods

Study design

This multi-center, retrospective, observational, cohort study was performed with the aim of developing a prognostic nomogram for patients with mCRC, including those with unresectable cancer.

Participants

The study population included consecutive patients with histologically-confirmed colorectal adenocarcinoma who had been clinically or intraoperatively diagnosed with mCRC at one of nine designated cancer hospitals across Fukushima prefecture from January 2008 to December 2015.

Inclusion criteria

a) Patients diagnosed and treated in the nine designated cancer hospitals.
b) Patients registered in hospital-based cancer registries from January 2008 to December 2015.
c) Patients with histologically-confirmed colorectal adenocarcinoma.
d) Patients diagnosed with distant metastasis based on imaging or surgical findings before any treatments.

Exclusion criteria and missing data

Patients receiving treatment in hospitals other than the nine hospitals or whose data were lost were excluded. Patients with appendiceal carcinoma or anal carcinoma were excluded.

Potential prognostic variables were examined for individual and joint missingness and were considered for imputation. Missing covariate data were estimated using multiple-imputation methods.

Study assessments

All clinically important information was extracted from the hospital-based cancer registries or from the hospital medical records.

Outcome measures

The primary outcome was overall survival (OS). OS was defined as the period between the diagnosis of colorectal cancer and death from any cause. The final date of follow-up was December 31, 2017. The data of patients who had not experienced any events were censored at the date of the final observation.

Sample size

We aimed to construct a high-quality population-based cohort that reflected Fukushima prefecture as accurately as possible. The required sample size will be approximately 1,500 cases.

Ethical considerations

This study was approved by the Institutional Review Board of all nine cancer-specialized hospitals in Fukushima and was registered as UMIN000033718 (registration date: 30/08/2018).

Planned analysis

Descriptive analysis

Variables and outcomes will be summarized using a descriptive analysis. Categorical variables will be reported as frequencies and percentages. Continuous variables will be summarized as the median and interquartile (IQ) range. The percentage of values missing for each variable will also be presented. The survival times of patients will be summarized using the median and IQ range, and Kaplan Meier curves.

Model construction

After imputation and constructing the data set, we will examine the following variables for univariate associations with OS: age (per 10 years), sex, body mass index (BMI; continuous), Charlson comorbidity index (Low: 0, Medium: 1-2, High: 3-5, Very high: ≥5), activities of daily living (ADL) (Barthel index; ≥95, ≤95 or ≥90, ≤90 or ≥75, ≤75), location of colorectal cancer (right colon, left colon, rectum), degree of differentiation, depth of tumor invasion (T factor), lymph node metastasis (N factor), number of distal metastatic organs (1, 2, 3, 4, 5+), presence vs. absence of liver, lung, peritoneal, lymph node metastases, presence vs. absence of symptoms from primary lesion (melena, obstruction, or perforation), presence vs. absence of primary resection, palliative treatment, curative metastatic resection, and systemic chemotherapy, and laboratory markers, including hemoglobin, white blood cell (WBC) count, absolute neutrophil count,
The candidate variables will be ranked according to their frequency of selection in the bootstrap samples. If variable(s) are selected in >60% of bootstrap samples, we will include them as the final set of predictors in the model. Overfitting and exploring the reproducibility of the model will be evaluated based on the discrimination and calibration measurements. For the discrimination measurements of the survival model, we will use the c-statistic proposed by Pencina and D’agostino\(^2\). Kaplan-Meier curves will also be created for three risk groups according to the estimated risk score (low, medium, and high risk). The calibration plot and its slope were also studied.

The predictive performance of each prediction model will be evaluated based on the discrimination and calibration measurements. For the discrimination measurements of the survival model, we will use the c-statistic proposed by Pencina and D’agostino\(^2\). We will use a Cox regression model to develop a prognostic nomogram for OS. Backwards selection with P values of <0.05 will be used to select the variables for each prediction model. The main effects and the first order interaction terms for each possible variable will be considered as candidates for selection. Backward selection will be repeated using 1000 bootstrap samples to adjust the final model for overfitting and explore the reproducibility of the model\(^2\). We will use a Cox regression model to develop a prognostic nomogram for OS. Backwards selection with P values of <0.05 will be used to select the variables for each prediction model. The main effects and the first order interaction terms for each possible variable will be considered as candidates for selection. Backward selection will be repeated using 1000 bootstrap samples to adjust the final model for overfitting and explore the reproducibility of the model\(^2\). The candidate variables will be ranked according to their frequency of selection in the bootstrap samples. If variables are selected in >60% of bootstrap samples, we will include them as the final set of predictors in the model.

All statistical analyses will be performed using the STATA version 15.1 software program (STATA Corporation, College Station, TX).

Discussion

This prognostic nomogram has three strong points. Firstly, we will analyze a population-based cohort integrating hospital-based cancer registries from designated cancer hospitals. Secondly, the predictors selected in this study are based on information obtained from inquiry, laboratory data, and CT imaging examination, not genetic information. Finally, this study will be constructed using the data from patients with mCRC, which will include various characteristics, including comorbidities, ADL, tumor severity, and treatment strategy. In addition to the severity of the tumor itself, several factors influence the survival of patients with mCRC, including their physical potential and the treatment strategy. In this situation, nomograms for predicting the prognosis of all patients with mCRC is necessary for clinical practice. We therefore expect that this nomogram will be a useful prognostic prediction model for clinicians.

A systematic review of the prognostic tools for colorectal cancer reported that most studies did not follow TRIPOD guidelines for appropriate methodology\(^2\). This systematic review detected 35 nomograms focused on mCRC, of which the majority were developed specifically for patients with liver metastasis.

A recent report describes the development of a prognostic nomogram for mCRC using ARCAD database, which includes several randomized phase III control trials\(^2\). This study included not only the tumor severity and laboratory data but also genetic mutations (BRAF, KRAS) as candidate variables. However, because this study only included clinical trial populations, its generalizability is limited. In contrast, the present study is a population-based study; thus, the results are applicable to a wider range of patients with any advanced mCRC, any characteristics, and any treatment strategies.

The present study is associated with some limitations, including the retrospective design and lack of genetic information regarding MSI, BRAF, and RAS, which is an important factor for deciding treatment or predicting the prognosis. Furthermore, we could not validate this nomogram because of the insufficient sample size.

We expect our nomogram to be accepted as a useful tool for planning the treatment of mCRC patients and to be helpful clinical practice.

Conflicts of interest: Dr. Saji reports grants and personal fees from Eisai, grants and personal fees from Chugai, grants and personal fees from Astra Zeneca, grants and personal fees from Takeda, grants and personal fees from Novartis, grants and personal fees from Taiho, personal fees from Kyowa Kirin, personal fees from Pfizer, personal fees from Daiichi Sankyo, grants and personal fees from Nihon Kayaku, grants from Ono, outside the submitted work. The other authors declare no conflicts of interest in association with the present study.
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