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Original Research

Predictive factors of synchronous colorectal peritoneal metastases: Development of a nomogram and study of its utilities using decision curve analysis

Shaobo Mo[a,b,1], Weixing Dai[a,b,1], Wenqiang Xiang[a,b], Qingguo Li[a,b,***], Renjie Wang[a,b,**], Guoxiang Cai[a,b,*]

[a] Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, 200032, China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, China

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ABSTRACT

Background: The objective of this study was to summarize the clinicopathological and molecular features of synchronous colorectal peritoneal metastases (CPM). We then combined clinical and pathological variables associated with synchronous CPM into a nomogram and confirmed its utilities using decision curve analysis.

Materials and Methods: Synchronous metastatic colorectal cancer (mCRC) patients who received primary tumor resection and underwent KRAS, NRAS, and BRAF gene mutation detection at our center from January 2014 to September 2015 were included in this retrospective study. An analysis was performed to investigate the clinicopathological and molecular features for independent risk factors of synchronous CPM and to subsequently develop a nomogram for synchronous CPM based on multivariate logistic regression. Model performance was quantified in terms of calibration and discrimination. We studied the utility of the nomogram using decision curve analysis.

Results: In total, 226 patients were diagnosed with synchronous mCRC, of whom 50 patients (22.1%) presented with CPM. After uni- and multivariate analysis, a nomogram was built based on tumor site, histological type, age, and T4 status. The model had good discrimination with an area under the curve (AUC) at 0.777 (95% CI 0.703–0.850) and adequate calibration. By decision curve analysis, the model was shown to be relevant between thresholds of 0.10 and 0.66.

Conclusion: Synchronous CPM is more likely to happen to patients with age ≤60, right-sided primary lesions, signet ring cell cancer or T4 stage. This is the first nomogram to predict synchronous CPM. To ensure generalizability, this model needs to be externally validated.

1. Introduction

Colorectal cancer (CRC) is currently one of the most common malignancies worldwide, with a total of 50,260 deaths in America and 191,100 deaths in China [1,2]. Almost 5% of CRC patients are coupled with synchronous peritoneal metastases (PM) at the moment of diagnosis of the primary tumor [3,4]. In the process of its occurrence and growth, the onset of colorectal PM is traditionally perceived as a terminal condition, which is considered incurable and suitable for palliative chemotherapy at most [5]. However, with the advancement of multi-disciplinary treatment in recent years, the therapeutic strategies of colorectal peritoneal metastases (CPM) have regained interest of medical oncologists and gastrointestinal surgeons. Complete peritoneal cytoreduction surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic treatment have been widely applied in the treatment of PM from various origins such as CRC, which have remarkably improved the survival for highly selected CPM patients [6–8]. CRS involves five different peritonectomy procedures that are

* Corresponding author. Department of Colorectal Surgery, Fudan University Shanghai Cancer Center Department of Oncology, Shanghai Medical College, Fudan University, 270 Dong'an Road, Shanghai, 200032, China.
** Corresponding author. Department of Colorectal Surgery, Fudan University Shanghai Cancer Center Department of Oncology, Shanghai Medical College, Fudan University, 270 Dong'an Road, Shanghai, 200032, China.
*** Corresponding author. Department of Colorectal Surgery, Fudan University Shanghai Cancer Center Department of Oncology, Shanghai Medical College, Fudan University, 270 Dong'an Road, Shanghai, 200032, China.
E-mail addresses: oncosurgeonli@sohu.com (Q. Li), wangbladejay@sina.com (R. Wang), gxcaifuscc@163.com (G. Cai).
[1] Shaobo Mo and Weixing Dai contributed equally to this work.

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combined as needed with eight different visceral resections, with the purpose of making patients with PM visibly disease-free [9]. Immediately following the CRS, HIPEC is administered to eradicate the tiny and microscopic peritoneal diseases. Systemic chemotherapy is always significant since PM is often part of systemic metastasis. The combined application of these three aspects will probably improve the prognosis of CPM [8].

Although previous researches indicated prognostic factors for CPM, including the histologic type and the presence of lymph node metastasis [10,11], surprisingly few reports have reported the clinicopathological and molecular features of synchronous CPM. Furthermore, detecting synchronous PM preoperatively is currently difficult due to the absence of symptoms and the poor accuracy of imaging for diagnosis of PM [12]. In view of diverse treatment for CPM, further comprehensive understanding of its clinical and molecular features will be propitious to enhance the management of synchronous CPM and select appropriate individualized treatment strategy. In this study, synchronous metastatic colorectal cancer (mCRC) patients who underwent primary tumor resection were enrolled and divided into two groups: peritoneal metastatic colorectal cancer (pmCRC) and non-peritoneal metastatic colorectal cancer (non-pmCRC). We committed to figuring out the predictive factors of synchronous pmCRC compared to non-pmCRC. Then, we developed a nomogram and evaluated its performance with decision curve analysis (DCA).

2. Materials and methods

2.1. Patient selection

We extracted demographic and pathological data from CRC patients undergoing the detection of tumor KRAS, NRAS, and BRAF mutation between January 2014 and September 2015 from our center cancer dataset. We recruited patients meeting the following criteria: (1) mCRC patients with adenocarcinoma, mucinous adenocarcinoma or signet-ring cell carcinoma; (2) mCRC patients undergoing the primary tumor resection; (3) mCRC patients had a complete record of primary tumor invasion depth, lymph node status, lymphovascular invasion, and perineural invasion and distant metastatic site. Ovarian metastases were classified as peritoneal metastases. The synchronous peritoneal metastases were defined as peritoneal metastases diagnosed before, during, or within 6 months after the operation of primary tumor. The unique identifying number of the study is researchregistryXXX. The Ethical Committee and Institutional Review Board of our cancer center reviewed and approved this study protocol. All patients signed written informed consent.

2.2. Data collection

Records on the following clinicopathological and molecular variables were extracted from our center cancer dataset: gender; age at diagnosis; primary tumor site; histological type; grade of differentiation; number of metastatic lymph nodes; depth of intestinal wall invasion; lymphovascular invasion; perineural invasion; tumor deposits; distant metastatic site and KRAS, NRAS, and BRAF gene mutation detection. T stage and N stage were determined by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition).

2.3. Construction of the nomogram

To identify independent risk factors, variables achieving a significance of $p < 0.05$ were selected for multivariable analyses via the multivariate logistic regression model. Based on the results of the multivariable analyses, a nomogram, integrating the four clinicopathological risk factors, was formulated. The calibration plots graphically show the relationship between the predicted and observed risk for each outcome. Thus, the ideal nomogram would show a plot that perfectly fits the 45-degree reference line.

2.4. Receiver operating characteristic curve and decision curve analysis

The receiver operating characteristic (ROC) curve (AUC) was adopted to evaluate the predictive discrimination of the nomogram [13]. As is well known, the value of the AUC is the same as that yielded by the concordance index (c-index) in a logistic regression model. The maximum value of the AUC is 1.0, indicating a perfect discrimination, whereas 0.5 indicates a random chance to correctly discriminate outcome with the model. Decision curve analysis (DCA) was carried out to compare the potential net benefit of the predictive models [14]. The AUC value only means the discriminative accuracy of a predictive model [13]. However, DCA, which is recently proposed novel method for evaluating predictive model, visualizes the clinical consequences of a treatment strategy [14,15]. This represents a potential net benefit of each decision strategy at each threshold probability.

2.5. Statistical analysis

We compared the patient demographics, pathologic characteristics, and gene mutations between pmCRC and non-pmCRC patients using chi-squared tests and Fisher's exact tests. Multivariate logistic regression analysis was used to distinguish independent risk factors associated with the presence of synchronous peritoneal carcinomatosis. Nomogram development was carried out using the library “rms” in R for Windows. DCA analysis was performed using the code found at https://www.mskcc.org/departments/epidemiologybiostatistics/health-outcomes/decision-curve-analysis-01 according to its tutorials. All statistical analyses were performed using R (version 2.15.0, www.r-project.org). All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Furthermore, the work has been reported in line with the STROCSS criteria [16].

3. Results

3.1. Patient demographics

A total of 226 eligible synchronous mCRC patients from our center cancer database were enrolled in the analysis. The median age was 57 years (range, 22–81 years). Fifty patients (22.1%) patients were diagnosed with synchronous pmCRC. Patient demographics and pathologic characteristics based on pmCRC and non-pmCRC are summarized in Table 1 and Table 2.

3.2. The clinicopathological and molecular features of synchronous pmCRC compared with non-pmCRC

Compared to non-pmCRC patients, those with synchronous pmCRC presented with a higher proportion of females (62.0% vs. 38.6%, $p = 0.003$), age ≤60 (78.0% vs. 55.7%, $p = 0.004$), right-sided colon location (48.0% vs. 26.1%, $p = 0.002$), signet-ring cell carcinomas (10.0%vs. 0.6%, $p<0.001$), poor-differentiated tumors (62.0% vs. 35.2%, $p = 0.001$), and T4 cancers (48.0% vs. 29.0%, $p = 0.012$). There was no statistical difference in N stage, lymphovascular invasion, perineural invasion, or tumor deposits between these two groups (Table 1). The BRAF gene mutation was more frequent in pmCRC patients (10.0% vs. 2.8%, $p = 0.045$) while the rates of KRAS and NRAS gene mutation were not significantly different in these two groups (Table 2). Univariate logistic regression analyses of the entire sample indicated that sex ($p = 0.004$), age at diagnosis ($p = 0.005$), primary site ($p = 0.003$), histological type ($p = 0.001$), tumor differentiation ($p = 0.001$), T stage ($p = 0.013$), and BRAF status ($p = 0.041$) were risk factors for synchronous metastatic sites (peritoneal vs. non-peritoneal) (Table 3). Multivariate analyses identified age at diagnosis ($p = 0.014$), T4 stage ($p = 0.026$), primary tumor location ($p = 0.015$),