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ORIGINAL ARTICLE

# Pulmonary metastasis in newly diagnosed colon-rectal cancer: a population-based nomogram study

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## Abstract

**Background** Colorectal cancer (CRC) has a high worldwide incidence with a tendency to metastasize to the lungs. We aimed to identify clinical factors related to lung metastasis (LM) and analyze the prognosis of patients after LM.

**Methods** Multivariate logistic regression analysis was used to identify risk factors for LM from CRC. Univariate and multivariate Cox proportional hazard models were performed to identify potentially important prognostic factors for patients with LM.

**Results** Age ($p = 0.010$), tumor size ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), race ($p < 0.001$), tumor site ($p < 0.001$), liver metastasis ($p < 0.001$), brain metastasis ($p < 0.001$), bone metastasis ($p < 0.001$), serum levels of carcinoembryonic antigen (CEA) ($p < 0.001$), and circumferential resection margin (CRM) ($p < 0.001$) were associated with a risk of LM from CRC. All factors (all, $p < 0.001$) except tumor size ($p = 0.095$) and race ($p = 0.650$) were related to the overall survival of patients. Two nomograms were formulated to visually predict lung metastasis risk and 1-, 3-, and 5- year overall survivals for patients with LM. The concordance indices were 0.754 and 0.749, respectively.

**Conclusions** Age, tumor size, histological grade, serum levels of CEA, tumor site, surgery modalities of CRC, CRM, number of positive lymph nodes, and chemotherapy were independent risk factors for LM from CRC. The nomograms we developed can be effectively used to forecast the risk of LM and predict the survival for LM from CRC.

**Keywords** Colorectal cancer · Pulmonary metastasis · Risk factors · Prognosis · Nomogram

## Introduction

Colorectal cancer (CRC) is the most common cancer in the gastrointestinal system, with approximately 1.4 million new worldwide cases every year [1]. CRC has a tendency to metastasize to distant organs, and metastasis is the leading cause of cancer death in humans. The liver and lung are the most frequently affected organs in CRC. It has been reported that approximately 10–29% of CRC patients develop lung metastasis (LM) [2, 3]. A high accuracy of metastatic prediction is important for clinical decision making. As reported, the early detection and surgical treatment of lung metastases from CRC result in a 5-year survival > 50% in a selected patient population [4].

Most retrospective studies evaluated LM in patients with CRC and assessed prognostic factors for survival [5], including mediastinal lymph node involvement, size of the largest nodule, and preoperative carcinoembryonic antigen (CEA) levels [6]; whereas, there have been conflicting reports on certain prognostic factors. Population level studies to specifically identify relative risk factors for LM from CRC are also

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lacking. Thus, further research to identify predictors that could affect patient long-term survival is essential. Currently, the prognosis of CRC accompanied with LM is mainly determined by clinic experience. Constructing a quantitative prognostic model specific for pulmonary metastasis from CRC would be more beneficial in forecasting the prognosis for this patient population.

The major aim of this study was to examine the clinical pathological predictors of poorer survival for patients with CRC and LM, and to visually quantify survival estimates using a nomogram based on the Surveillance, Epidemiology, and End Results (SEER) database.

## Patients and methods

### Ethics statement

Because the data for this study came from the public SEER database and all patient data were anonymized, it was exempted by the Institutional Review Committee of Zhongshan Hospital, Fudan University (Shanghai, China).

### Patient inclusion and exclusion criteria

Patient data were downloaded from the SEER database using the SEER*stat software, version 8.4.4 (http://seer.cancer.gov/seerstat/). Since 1973, the SEER database has been collecting information about cancer management, which is estimated to involve approximately 28% of the population in the USA (https://seer.cancer.gov/about/overview.html). We performed a retrospective analysis of the SEER database for cases diagnosed from 2010 to 2015, because the collection of information on specific metastatic sites was initiated in 2010. The screening process was as follows (Fig. 1). Patients who had colorectal tumors (histological type ICD-O-3: 8140-8389, 8440-8499, 8010-8049, and 8050-8089) as their first primary tumor were identified. The baseline characteristics of all patients were collected, including race, sex, site, grade, the American Joint Committee on Cancer (AJCC) 8th Tumor Node Metastasis stage, age at diagnosis, surgical modalities, radiation, chemotherapy, tumor size, CEA, circumferential resection margin (CRM), liver metastasis, bone metastasis, and brain metastasis. Patients without clear diagnosis, active follow-up, or complete data of survival were not included in the cohort. Patients who were pathologically confirmed with a benign tumor or without pathological grade were also deleted. Patients with an unknown surgical approach, cause of death, T stage, N stage, or tumor size were also excluded. In this study, cancer-specific survival (CSS) and overall survival (OS) were adopted as the survival outcomes.

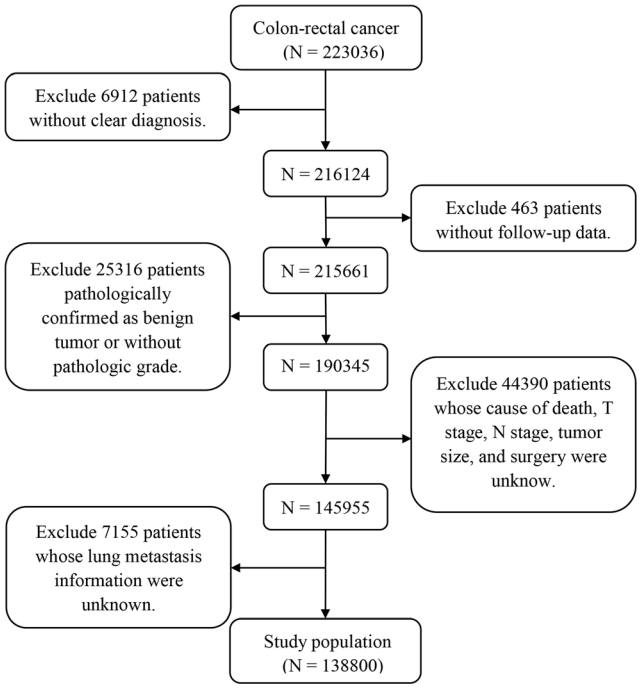


**Fig. 1** The flow diagram of the selection process for the study cohort

### Statistical analysis

We first analyzed the potential factors which may lead to LM by comparing the difference of clinical pathological features between patients with and without LM. Then, the prognoses of patients with LM were furtherly analyzed. All statistical analyses were conducted using R software, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS statistical software for Windows, version 24.0 (IBM, Armonk, NY, USA). The clinical pathological variables between patients with and without LM were analyzed by Pearson's $\chi^2$ test or Student's $t$ test. Multivariate logistic regression analysis was used to identify risk factors for LM from CRC. Univariate and multivariate Cox proportional hazard models were conducted to identify potentially important prognostic factors for patients with LM. The Kaplan-Meier method was used for plotting survival curves. Based on the results of the multivariate Cox proportional hazard model, a nomogram was developed and evaluated by the concordance index (C-index) and calibration curves. A two-tailed value of $p < 0.05$ was considered to be statistically significant.

## Results

According to the screening criteria, 138,800 patients from 2010 to 2015 were finally included in this study, with LM occurring in 3311 patients (2.4%). The average age of all patients with CRC was 66.00 ± 13.99 years (range 4–108). The 3-year and 5-year survival rates for patients with CRC

were 75.7% and 66.4%, respectively, while they were only 19.3% and 8.0%, respectively, in patients with combined pulmonary metastasis. The median OS for CRC and CRC accompanied with LM were 24.0 months (interquartile range 9.0–44.0 months) and 11.0 months (interquartile range 4.0–23.0 months), respectively. The results of survival analysis for patients with CRC and patients accompanied with lung metastases are shown in Supplementary Fig. 1, which reveals a distinctly lower survival in patients with LM ($p < 0.001$).

Multivariate logistic regression analysis was performed for all patients with CRC (Table 1). Patients of younger age ($p = 0.010$), greater tumor size ($p < 0.001$), and higher T and N stages suffered from a higher risk of LM. Patients of African descent were more prone to LM compared with Caucasians ($p < 0.001$). The LM often occurred when the primary CRC tumor was located in the rectum ($p < 0.001$) or sigmoid colon ($p < 0.001$). Patients were especially at a higher risk of LM when they suffered from liver metastasis ($p < 0.001$), brain metastasis ($p < 0.001$), or bone metastasis ($p < 0.001$), with hazard ratios of 10.91, 10.16, and 5.27, respectively. The higher CEA levels were also a significant factor associated with LM ($p < 0.001$). Using multivariable logistic regression analyses, neither sex ($p = 0.136$) nor pathological grade ($p = 0.065$) was associated with a risk of LM.

To more intuitively display the risk factors for LM in the CRCs, a nomogram was constructed (Fig. 2). The nomogram displayed a C-index of 0.754, which effectively predicted the risk of LM from CRC. Each of these variables was assigned a score using a point scale, and we could easily draw straight lines to determine the estimated LM probability by adding the total scores and positioning them on the total point scale.

Univariate analyses and multivariable Cox regression were conducted for patients with LM from CRC. Univariate analyses of CSS showed that the patient age ($p < 0.001$), tumor site ($p < 0.001$), grade ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), tumor size ($p < 0.001$), CEA ($p < 0.001$), liver metastasis ($p < 0.001$), brain metastasis ($p < 0.001$), bone metastasis ($p < 0.001$), surgical type ($p < 0.001$), CRM ($p < 0.001$), chemotherapy ($p < 0.001$), and radiation therapy ($p < 0.001$) were all significant predictors of the outcome for those patients accompanied with pulmonary metastasis, which was similar to the results of univariate analyses for OS (Supplementary Table 1). Using multivariable Cox regression for OS among patients with LM at diagnosis, age ($p < 0.001$), tumor site ($p < 0.001$), pathological grade ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), liver metastasis ($p < 0.001$), brain metastasis ($p < 0.001$), bone metastasis ($p < 0.001$), surgical type ($p < 0.001$), tumor size ($p < 0.001$), serum levels of CEA ($p < 0.001$), CRM ($p < 0.001$), and chemotherapy ($p < 0.001$) were identified as independent factors for prognosis, while a statistically significant difference was no longer shown for radiation therapy and tumor size. Multivariable Cox regression analyses for CSS also showed a consistent result. However, patients who received radiation showed a benefit from CSS ($p = 0.009$; Table 2).

The second nomogram was developed based on significant prognostic factors identified by multivariable COX regression analysis for predicting 1-, 3-, and 5- year OS (Fig. 3a). Interpretation of this nomogram was the same as the previously stated procedure. The nomogram illustrated pathological grade, surgical modalities, and chemotherapy as sharing the largest contribution to prognoses, followed by age, liver metastasis, brain metastasis, bone metastasis, and T stage. Tumor site, N stage, serum levels of CEA, and CRM showed a moderate effect on survival. Our nomogram was internally validated using the bootstrap validation method. The calibration curve of 1-, 3-, and 5- year survivals showed a relative satisfactory predictive accuracy of the nomogram, with a C-index of 0.749 (Fig. 3b, c, d).

We determined the cutoff values by dividing the patients into five subgroups based on their total score (score 0–208.5, 209–253, 254–288, 288.5–340, and ≥ 340.5); each group displayed a notably different 1-, 3-, and 5- year survival (Table 3). After grouping patients using the cutoff values in patients with LM, there was a significant distinction between Kaplan-Meier curves for OS outcomes because of stratification into different risk subgroups ($p < 0.001$; Fig. 4).

## Discussion

From both scientific and clinical points of view, effective and precise prognostic prediction of the long-term survival in CRC is essential. Identifying risk factors for LM from CRC may have significant implications for clinical decision making. The prognostic model could be applied to predict the long-term outcomes of CRC patients. As for high-risk CRC patients, the follow-up interval can be shortened appropriately in order to detect the recurrence or metastasis of tumors in the early stage. In recent years, various studies on survival factors for metastatic CRC have shown disparate results. These inconsistent results described differences in patient populations and research designs, which were therefore difficult to assess. Factors such as CEA, sex, surgical treatment, age, chemotherapy, and number of metastatic lesions were reported as significant predictors related to prognoses [7, 8]. In the current study, we identified age, race, tumor site, T stage, N stage, tumor size, CEA, liver metastasis, bone metastasis, as well as brain metastasis as associated with the risk of LM from CRC. All of these parameters except race and tumor size were also independent prognostic factors affecting the long-term survival of patients with LM from CRC.

There were some limitations in our study. This was a database-based retrospective analysis. Information of treatment measures such as surgery, chemotherapy, and radiotherapy after LM were not recorded in the database. In addition,

**Table 1** Multivariable logistic regression for the presence of lung metastases at diagnosis of colorectal cancer

| Variable | Total patients ($n = 138,800$) | Lung metastasis ($n = 3311$) | OR (95% CI) | $p$ value |
|---|---|---|---|---|
| Age | | | | 0.010 |
| < 45 | 8752 | 240 | 1 [Reference] | NA |
| 45–54 | 21,253 | 630 | 1.12 (0.95–1.31) | 0.183 |
| 55–64 | 31,977 | 888 | 1.12 (0.96–1.31) | 0.160 |
| 65–74 | 35,189 | 854 | 1.25 (1.07–1.46) | 0.005 |
| 75–84 | 28,842 | 522 | 1.11 (0.94–1.31) | 0.217 |
| ≥ 85 | 12,787 | 177 | 0.97 (0.79–1.20) | 0.779 |
| Sex | | | | 0.136 |
| Male | 113,322 | 1792 | 1 [Reference] | NA |
| Female | 25,478 | 1519 | 1.06 (0.98–1.14) | 0.136 |
| Race | | | | < 0.001 |
| White | 109,134 | 2439 | 1 [Reference] | |
| Black | 16,185 | 504 | 1.21 (1.09–1.34) | 0.001 |
| Other | 13,481 | 368 | 1.26 (1.12–1.42) | < 0.001 |
| Site | | | | < 0.001 |
| Ascending colon | 49,691 | 928 | 1 [Reference] | NA |
| Transverse colon | 18,461 | 341 | 1.02 (0.90–1.17) | 0.735 |
| Descending colon | 6361 | 139 | 1.17 (0.96–1.42) | 0.115 |
| Sigmoid colon | 36,979 | 1023 | 1.36 (1.23–1.50) | < 0.001 |
| Rectum | 25,478 | 812 | 2.30 (2.07–2.57) | < 0.001 |
| Other | 1830 | 68 | 1.53 (1.17–2.01) | 0.002 |
| Grade | | | | 0.065 |
| I | 15,100 | 168 | 1 [Reference] | NA |
| II | 97,974 | 2324 | 1.26 (1.06–1.49) | 0.081 |
| III | 21,199 | 675 | 1.15 (0.95–1.38) | 0.150 |
| IV | 4527 | 144 | 1.07 (0.83–1.36) | 0.617 |
| T stage | | | | < 0.001 |
| T0 | 1926 | 8 | 1 [Reference] | NA |
| T1 | 21,228 | 315 | 1.64 (0.80–3.36) | 0.173 |
| T2 | 20,871 | 107 | 0.57 (0.27–1.18) | 0.130 |
| T3 | 72,611 | 1690 | 1.11 (0.54–2.27) | 0.773 |
| T4 | 22,164 | 1191 | 1.64 (0.80–3.36) | 0.176 |
| N stage | | | | < 0.001 |
| N0 | 81,524 | 780 | 1 [Reference] | NA |
| N1 | 36,794 | 1376 | 1.90 (1.72–2.10) | < 0.001 |
| N2 | 20,482 | 1155 | 2.02 (1.81–2.26) | < 0.001 |
| Tumor size | | | | < 0.001 |
| ≤ 10 mm | 12,591 | 62 | 1 [Reference] | NA |
| 10–50 mm | 72,108 | 1301 | 2.11 (1.59–2.79) | < 0.001 |
| > 50 mm | 54,101 | 1948 | 2.71 (2.03–3.60) | < 0.001 |
| CEA | | | | < 0.001 |
| Negative | 45,858 | 402 | 1 [Reference] | NA |
| Positive | 33,959 | 1960 | 2.47 (2.20–2.78) | < 0.001 |
| Other | 58,983 | 949 | 1.51 (1.33–1.70) | < 0.001 |
| Mets at liver | | | | < 0.001 |
| No | 126,433 | 1189 | 1 [Reference] | NA |
| Yes | 12,367 | 2122 | 10.91 (10.03–11.86) | < 0.001 |
| Mets at brain | | | | < 0.001 |

**Table 1** (continued)

| Variable | Total patients ($n = 138,800$) | Lung metastasis ($n = 3311$) | OR (95% CI) | $p$ value |
|---|---|---|---|---|
| No | 138,630 | 3243 | 1 [Reference] | NA |
| Yes | 170 | 68 | 10.16 (6.90–14.98) | < 0.001 |
| Mets at bone | | | | < 0.001 |
| No | 138,201 | 3077 | 1 [Reference] | NA |
| Yes | 599 | 234 | 5.27 (4.33–6.41) | < 0.001 |

*CEA*, serum levels of carcinoembryonic antigen; *CI*, confidence interval; *NA*, not applicable

there might have been selection bias in the case screening, which may have led to slight differences between our results and previous findings. These findings deserve further randomized controlled trials and external validation in large-scale

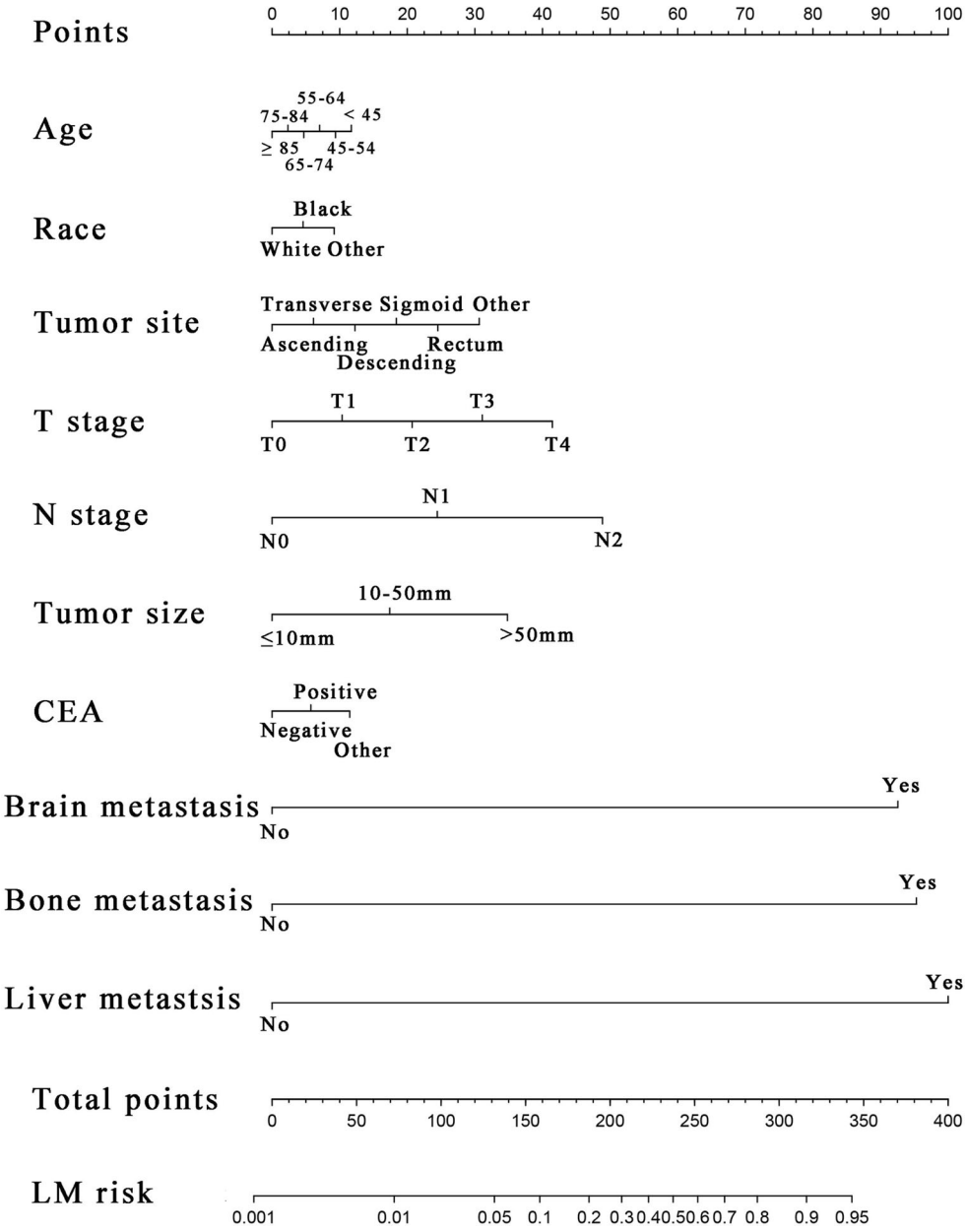


**Fig. 2** A nomogram for prediction of the risk of lung metastasis from colorectal cancer

**Table 2** Multivariable Cox regression for overall survival and colorectal cancer–specific survival among patients with lung metastases

| Characteristics | $N = 3747$ | Overall survival | | Cancer–specific survival | |
|---|---|---|---|---|---|
| | | HR (95%CI) | $p$ value | HR (95% CI) | $p$ value |
| Age | | | < 0.001 | | < 0.001 |
| < 45 | 240 | 1[Reference] | NA | 1[Reference] | NA |
| 45–54 | 630 | 1.12 (0.91–1.37) | 0.277 | 1.10 (0.89–1.35) | 0.378 |
| 55–64 | 888 | 1.13 (0.93–1.37) | 0.238 | 1.08 (0.88–1.31) | 0.476 |
| 65–74 | 854 | 1.20 (0.99–1.46) | 0.067 | 1.14 (0.94–1.39) | 0.196 |
| 75–84 | 522 | 1.79 (1.46–2.20) | < 0.001 | 1.69 (1.37–2.08) | < 0.001 |
| ≥ 85 | 177 | 1.85 (1.44–2.37) | < 0.001 | 1.76 (1.36–2.28) | < 0.001 |
| Site | | | < 0.001 | | < 0.001 |
| Ascending colon | 928 | 1[Reference] | NA | 1[Reference] | NA |
| Transverse colon | 341 | 1.18 (1.01–1.37) | 0.032 | 1.21 (1.04–1.41) | 0.015 |
| Descending colon | 139 | 0.95 (0.76–1.18) | 0.628 | 0.92 (0.72–1.16) | 0.459 |
| Sigmoid colon | 1023 | 0.77 (0.68–0.86) | < 0.001 | 0.77 (0.68–0.87) | < 0.001 |
| Rectum | 812 | 0.75 (0.65–0.86) | < 0.001 | 0.75 (0.65–0.87) | < 0.001 |
| Other | 68 | 1.04 (0.76–1.44) | 0.790 | 1.04 (0.75–1.45) | 0.816 |
| Grade | | | < 0.001 | | < 0.001 |
| I | 168 | 1[Reference] | NA | 1[Reference] | NA |
| II | 2324 | 1.00 (0.82–1.23) | 0.971 | 0.96 (0.78–1.18) | 0.706 |
| III | 675 | 1.61 (1.30–2.00) | < 0.001 | 1.57 (1.26–1.95) | < 0.001 |
| IV | 144 | 1.59 (1.20–2.10) | 0.001 | 1.55 (1.17–2.07) | 0.003 |
| T stage | | | < 0.001 | | < 0.001 |
| T0 | 8 | 1[Reference] | NA | 1[Reference] | NA |
| T1 | 315 | 1.14 (0.42–3.09) | 0.793 | 1.05 (0.39–2.85) | 0.919 |
| T2 | 107 | 0.97 (0.35–2.70) | 0.956 | 0.82 (0.30–2.30) | 0.711 |
| T3 | 1690 | 1.07 (0.40–2.89) | 0.893 | 0.94 (0.35–2.54) | 0.905 |
| T4 | 1191 | 1.40 (0.52–3.77) | 0.512 | 1.27 (0.47–3.43) | 0.640 |
| N stage | | | < 0.001 | | < 0.001 |
| N0 | 780 | 1[Reference] | NA | 1[Reference] | NA |
| N1 | 1376 | 1.14 (1.01–1.28) | 0.033 | 1.14 (1.01–1.29) | 0.038 |
| N2 | 1155 | 1.32 (1.16–1.50) | < 0.001 | 1.36 (1.19–1.56) | < 0.001 |
| Tumor size | | | 0.095 | | 0.126 |
| ≤ 10 mm | 62 | 1[Reference] | NA | 1[Reference] | NA |
| 10–50 mm | 1301 | 0.89 (0.59–1.34) | 0.572 | 0.95 (0.61–1.48) | 0.823 |
| > 50 mm | 1948 | 0.98 (0.65–1.48) | 0.927 | 1.05 (0.68–1.62) | 0.832 |
| CEA | | | < 0.001 | | < 0.001 |
| Negative | 402 | 1[Reference] | NA | 1[Reference] | NA |
| Positive | 1960 | 1.52 (1.30–1.77) | < 0.001 | 1.56 (1.32–1.83) | < 0.001 |
| Other | 949 | 1.40 (1.18–1.64) | <0.001 | 1.43 (1.20–1.69) | <0.001 |
| Mets at liver | | | < 0.001 | | < 0.001 |
| No | 1189 | 1[Reference] | NA | 1[Reference] | NA |
| Yes | 2122 | 1.94 (1.75–2.15) | < 0.001 | 2.02 (1.82–2.25) | < 0.001 |
| Mets at brain | | | < 0.001 | | < 0.001 |
| No | 3243 | 1[Reference] | NA | 1[Reference] | NA |
| Yes | 68 | 1.81 (1.36–2.40) | < 0.001 | 2.12 (1.57–2.87) | < 0.001 |
| Mets at bone | | | < 0.001 | | < 0.001 |
| No | 3077 | 1[Reference] | NA | 1[Reference] | NA |
| Yes | 234 | 1.50 (1.29–1.75) | < 0.001 | 1.55 (1.32–1.81) | < 0.001 |
| Surgery | | | < 0.001 | | < 0.001 |

**Table 2** (continued)

| Characteristics | *N* = 3747 | Overall survival | | Cancer–specific survival | |
|---|---|---|---|---|---|
| | | HR (95%CI) | *p* value | HR (95% CI) | *p* value |
| None | 842 | 1[Reference] | NA | 1[Reference] | NA |
| Local tumor excision | 36 | 0.42 (0.26–0.67) | < 0.001 | 0.43 (0.26–0.70) | 0.001 |
| Partial colectomy | 2297 | 0.55 (0.46–0.65) | < 0.001 | 0.57 (0.48–0.67) | < 0.001 |
| Total colectomy | 136 | 0.59 (0.45–0.78) | < 0.001 | 0.60 (0.45–0.80) | 0.001 |
| CRM | | | 0.001 | | 0.001 |
| > 5 mm | 547 | 1[Reference] | NA | 1[Reference] | NA |
| ≤ 5 mm | 904 | 1.07 (0.93–1.23) | 0.378 | 1.10 (0.95–1.28) | 0.196 |
| Positive | 460 | 1.36 (1.16–1.60) | < 0.001 | 1.39 (1.18–1.65) | < 0.001 |
| Other | 1400 | 1.18 (1.01–1.38) | 0.032 | 1.21 (1.03–1.42) | 0.019 |
| Radiation | | | 0.069 | | 0.009 |
| No | 2774 | 1[Reference] | NA | 1[Reference] | NA |
| Yes | 537 | 0.87 (0.76–1.01) | 0.069 | 0.83 (0.72–0.96) | 0.009 |
| Chemotherapy | | | < 0.001 | | < 0.001 |
| No | 976 | 1[Reference] | NA | 1[Reference] | NA |
| Yes | 2335 | 0.35 (0.32–0.39) | < 0.001 | 2.82 (2.54–3.12) | < 0.001 |

*CEA*, serum levels of carcinoembryonic antigen; *CRM*, circumferential resection margin; *CI*, confidence interval; *NA*, not applicable

studies. In addition, there are some potential predictive variables, such as targeted cancer therapy and KRAS mutations, which are not available in the database. Finally, the data of timeline of CEA levels in patients with LM were not available.

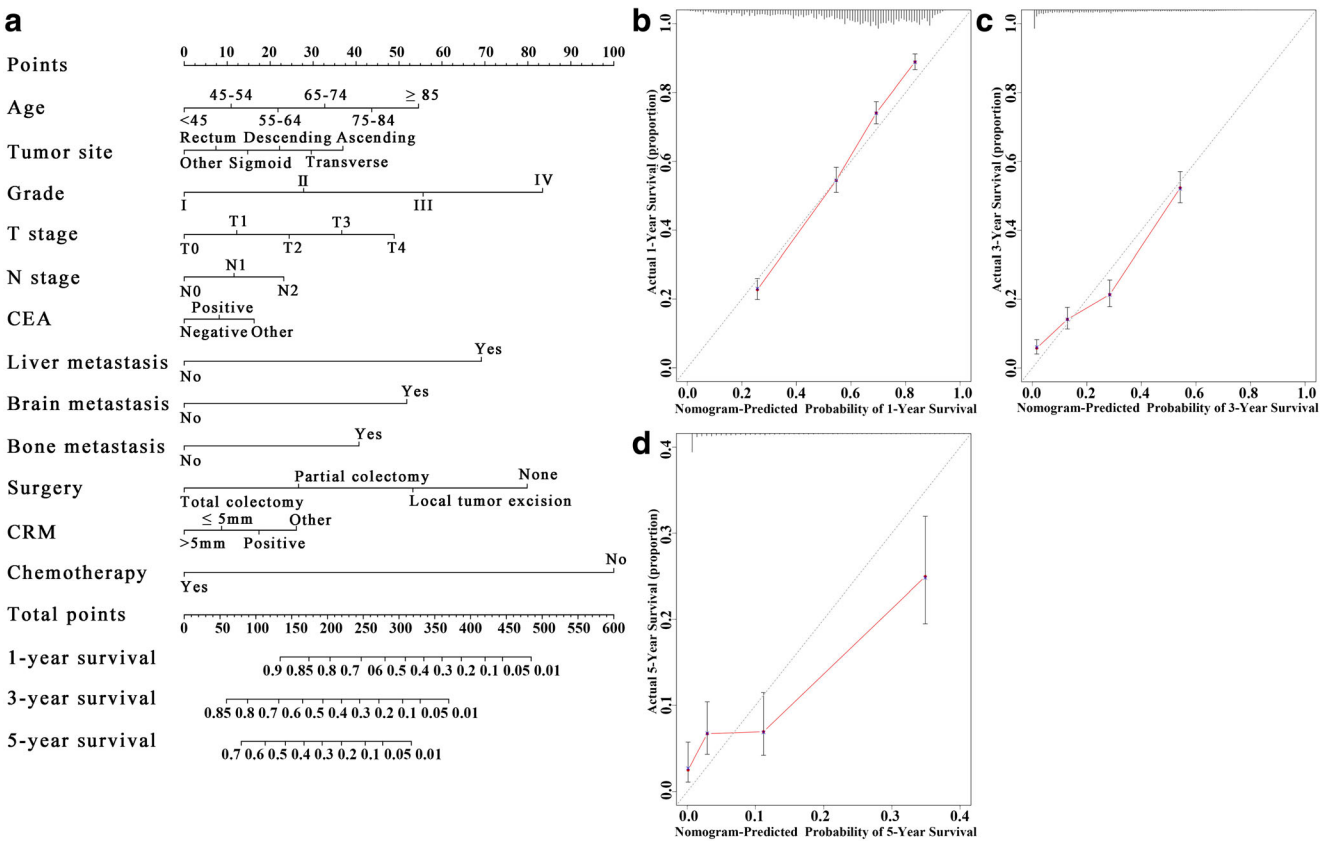


**Fig. 3** **a** A nomogram for prediction of 1-, 3-, and 5-year overall survival of patients with lung metastasis from colorectal cancer. Calibration curve of the nomogram predicting **b** 1-year, **c** 3-year, and **d** 5-year overall survival

**Table 3** Point assignment and prognostic score

| Variable and prognostic score | Score | Estimated 1-, 3-, and 5-year overall survival (%) |
|---|---|---|
| Age | | |
| < 45 | 0 | |
| 45–54 | 11 | |
| 55–64 | 22 | |
| 65–74 | 33.5 | |
| 75–84 | 44 | |
| ≥ 85 | 54.5 | |
| Site | | |
| Ascending colon | 37 | |
| Transverse colon | 30 | |
| Descending colon | 22.5 | |
| Sigmoid colon | 15 | |
| Rectum | 7.5 | |
| Other | 0 | |
| Grade | | |
| I | 0 | |
| II | 27.5 | |
| III | 55 | |
| IV | 83 | |
| T stage | | |
| T0 | 0 | |
| T1 | 12.5 | |
| T2 | 24 | |
| T3 | 37 | |
| T4 | 49 | |
| N stage | | |
| N0 | 0 | |
| N1 | 11.5 | |
| N2 | 23 | |
| CEA | | |
| Negative | 0 | |
| Positive | 7.5 | |
| Other | 16 | |
| Mets at liver | | |
| No | 0 | |
| Yes | 69 | |
| Mets at brain | | |
| No | 0 | |
| Yes | 52 | |
| Mets at bone | | |
| No | 0 | |
| Yes | 41 | |
| Surgery | | |
| None | 80 | |
| Local tumor excision | 53 | |
| Partial colectomy | 27 | |
| Total colectomy | 0 | |
| CRM | | |

**Table 3** (continued)

| Variable and prognostic score | Score | Estimated 1-, 3-, and 5-year overall survival (%) | | |
|---|---|---|---|---|
| > 5 mm | 0 | | | |
| ≤ 5 mm | 8 | | | |
| Positive | 17.5 | | | |
| Other | 25.5 | | | |
| Chemotherapy | | | | |
| No | 100 | | | |
| Yes | 0 | | | |
| Total prognostic score | | 1-year | 3-year | 5-year |
| 0–208.5 | | 90.9% | 56.0% | 30.2% |
| 209–253.5 | | 76.0% | 26.4% | 5.7% |
| 254–288 | | 64.3% | 17.7% | 8.8% |
| 288.5–340 | | 49.0% | 12.2% | 5.0% |
| ≥ 340.5 | | 19.6% | 4.8% | 2.3% |

*CEA*, serum levels of carcinoembryonic antigen; *CRM*, circumferential resection margin

The CEA levels at different timepoints may be better than levels of CEA in order to initiate timely diagnosis and surgery of potential metastasis.

It was clear that age was a prognostic factor in most tumors, but whether sex had an impact on the prognoses of patients with LM from CRC is still controversial. Blackmon et al. suggested that male sex predicts poorer survival [9]. However, a multicenter retrospective analysis performed in 2014 reported the opposite result. The majority of their cohorts were males, but they found there was no difference between the survival of the males and females [10]. Our study also showed that sex had no effect on long-term OS for patients with LM from CRC.

Liver metastasis is a useful independent parameter for predicting the survival of patients with stage IV CRC [11]. In clinical practice, metastasis of any site such as the brain or bone means a relatively poor prognosis [12]; however, many studies suggested it is not more sites of metastasis that worsen the prognosis [13, 14]. In our study, according to the nomogram we constructed, simultaneous metastases of the liver, brain, and bone meant that the higher the total score, the lower the long-term OS. The prognosis of primary CRC with liver metastasis was the worst. Liver metastasis from colon cancer was more common, while lung and bone metastasis presented relatively higher frequencies in patients with rectal cancer [15]. Compared with colon cancer, both metachronous and synchronous LM showed a higher risk in patients with rectal cancer [16]. Patients with rectal cancer may be associated with poorer survival [17]. Furthermore, previous studies have also shown a shorter disease-free survival in patients with rectal cancer [18], perhaps indicating disparate anatomical origins between colon and rectum. This is thought to be due to the direct spread of rectal cancer through the hemorrhoid vein into the systemic circulation [19]. Similarly, our study revealed that LM frequently occurred when the primary CRC tumor was located in the rectum or sigmoid colon, but they showed a better OS and CSS compared with those located in other sites of the colon. This contradictory conclusion may be due to bias in the screening process and further exploration is needed in the future.

Elevated serum levels of CEA are often reported as indicators associated with poor prognoses [20]. Elevated prethoracotomy serum levels of CEA are considered to be the most important independent prognostic factors for survival [7]. A multivariate analysis revealed that patients with normal CEA levels and adenocarcinoma, as well as without extrapulmonary disease and LM associated symptoms, had a higher OS [21]. High preoperative CEA levels are believed to be associated with an advanced stage, resulting in an increased recurrence rate and shortened survival [22]. Close monitoring of CEA levels after LM is therefore critical for the management of patients with metastatic CRC [23]. In the current study, we found that the CEA levels were associated with LM from CRC and long-term survival in patients with LM from CRC.

Surgery is still the best option for CRC patients who are able to undergo surgery. Even for patients with stage IV colorectal cancer, surgical resection is beneficial to the survival of patients compared to those who do not undergo surgical resection [24]. It was reported that patients with normal CEA levels but without lymph node involvement benefited most from surgery [25]. In this study, most of the patients (63.1%) were treated with resection for the primary CRC, including palliative resection and curative resection. After surgery, a positive CRM also had a significant effect on the occurrence of LM and long-term survival. The median survival of patients

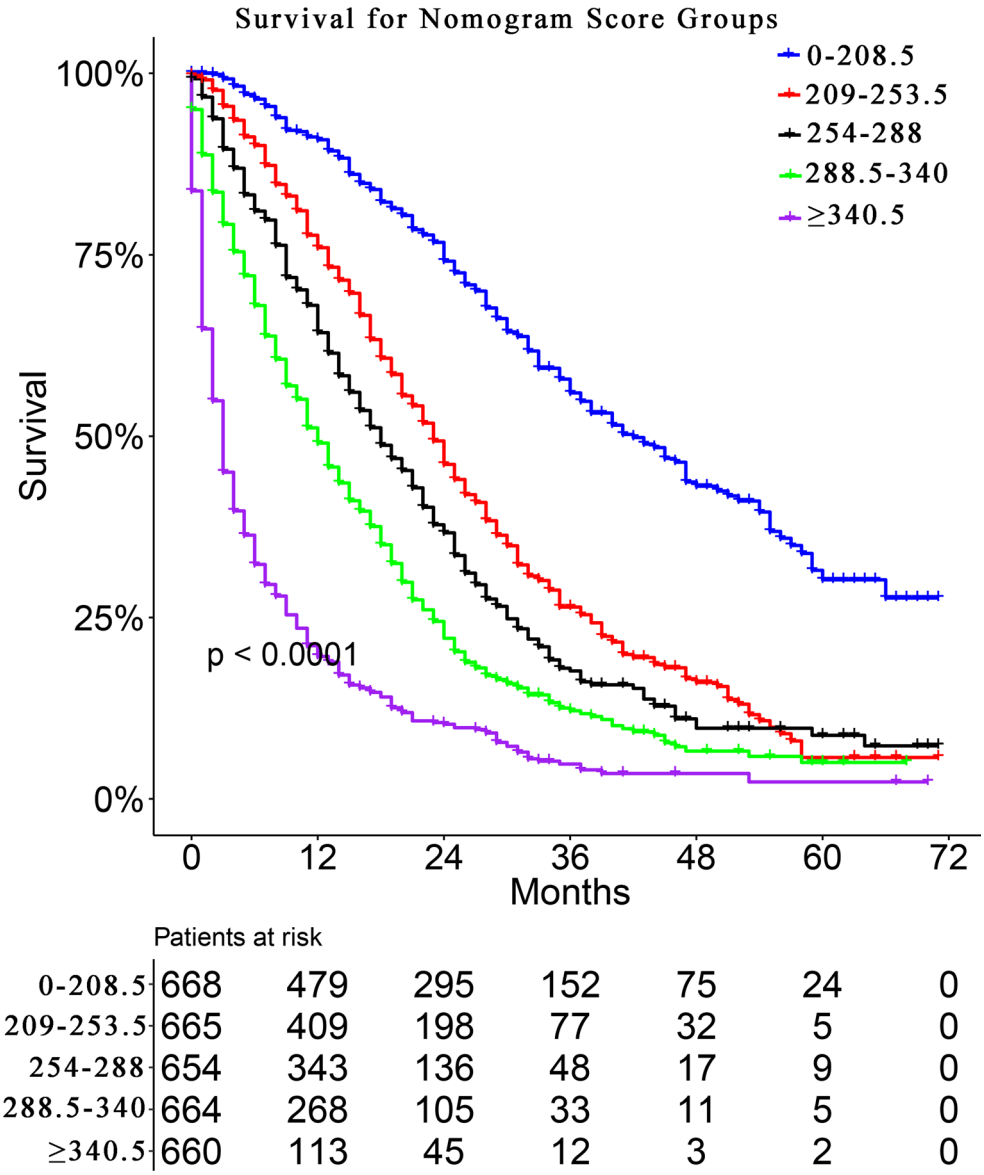


**Fig. 4** Survival analyses for patients of five subgroups based on their total score (total score 0–208.5, 209–253, 254–288, 288.5–340, and ≥ 340.5)

with R1 resection (1.4 years, 95% confidence interval (CI) 0.9–2.6) was significantly lower than that of patients with an R0 resection (4.4 years, 95% CI 4.0–6.0). The corresponding 5-year OS for patients with R1 and R0 resection were 14% (95% CI 0–29%) and 47% (95% CI 39–54%), respectively [26]. Our research obtained similar results that a positive CRM decreased the OS and CSS. The farther the CRM was from the tumor lesion, the better the long-term survival.

The current practice of CRC management utilizes all available technologies, including chemotherapy. Unfortunately, due to the lack of established guidelines, many different methods (preoperative chemotherapy, pre-chemotherapy surgery, and chemotherapy for the primary CRC) have been reported, which make it difficult to compare the various methods and clearly understand the contribution of each method [27]. A study by Kim et al. compared a group of patients receiving adjuvant chemotherapy after surgery with those who received palliative chemotherapy alone (for the same diagnosis). They reported that the former group had higher 3- and 5-year survivals, which was thought to demonstrate the benefit of chemotherapy in addition to surgery [28]. In our cohort, patients who received chemotherapy had a longer survival.

To facilitate clinical applications, we developed and validated two nomograms based on individual characteristics, so that clinicians can separately predict LM risk in each CRC patient and predict long-term survival. Both nomograms had good predictive efficiency, and they can be used to predict the possibility of LM from CRC and the 1-, 3-, and 5- year survivals for patients with LM from CRC, which may be a promising method to guide clinical management. We recommend close monitoring of follow-up computed tomography in patients with higher CEA; metastasis of the liver, brain, or bone;

higher histological grade; or who did not receive radical surgery and chemotherapy, to assess the progression of the disease. For those patients who have a higher risk of metastasis after calculating the total score, we recommend that they closely monitor the development of the tumor and receive surgical treatment if necessary.

## Conclusions

We showed nine independent risk factors associated with LM in CRC, including age, tumor size, histological grade, serum levels of CEA, T stage, N stage, surgery modalities of CRC, CRM, radiation, and chemotherapy; however, all these factors except radiotherapy could affect the OS. In addition, tumor site also affected the survival of patients. These risk factors provide clinicians and CRC patients with the opportunity to quantitatively assess the risk of LM and long-term survival after LM, which also reduce radiation exposure and unnecessary diagnostic investigations.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.



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