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ORIGINAL ARTICLE

Nomogram for predicting recurrence in stage II colorectal cancer

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ABSTRACT

Background: There have been no established criteria to distinguish patients at high and low risk of recurrence in stage II colorectal cancer. Several risk factors have been identified but recurrence could not be fully predicted by each factor alone. This retrospective study sought to develop a nomogram for accurate prediction of recurrence in stage II colorectal cancer.

Material and methods: We reviewed the data for 4167 patients with stage II colorectal cancer who underwent surgery between January 1997 and December 2006. The risk factors for recurrence were identified, and a nomogram for recurrence was created using the factors. The performance of the nomogram was assessed with a bootstrapped-concordance index and calibration plots.

Results: Sex, carcinoembryonic antigen, tumor location, tumor depth, lymphatic invasion, venous invasion and number of lymph nodes studied were significantly associated with recurrence. A nomogram for five-year freedom from recurrence was created with these factors. The bootstrapped-concordance index of the nomogram was 0.64, and it was well calibrated.

Conclusions: Our nomogram can be a useful tool for accurate prediction of recurrence in stage II colorectal cancer.

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Colorectal cancer is a common neoplasm worldwide, and both its incidence and mortality rate are increasing in many countries [1]. In Japan, more than 47 000 people per year died of colorectal cancer, and it was the third leading cause of cancer death in men and the leading cause in women according to national surveillance data from 2013 [2]. Prognostication and therapeutic strategies are mainly based on TNM staging [3] and use of adjuvant chemotherapy is recommended in stage III disease. However, the prognosis of stage II colorectal cancer varies, and current clinical guidelines recommend adjuvant chemotherapy only for patients with risk factors, but it remains debatable how to identify those who are at high risk of recurrence [4].

The nomogram is a graphical prediction model that combines several prognostic factors, and it has been created for many types of cancer including colorectal cancer [5–12]. Some nomograms have been considered to be more useful than the traditional staging system in prognostic prediction [13]. We considered that we could make use of a nomogram for identifying high-risk stage II colorectal cancer patients, who are not fully covered by TNM staging [3]. There has been no nomogram for the prediction of recurrence in stage II colorectal cancer [14]. Therefore, the aim of this study was to create a nomogram, which could accurately predict the probability of recurrence in stage II colorectal cancer, using common clinicopathological factors.

Material and methods

Patients

The Japanese Study Group for Postoperative Follow-up of Colorectal Cancer (JFUP-CRC) retrospectively collected data for 18 993 colorectal cancer patients without distant metastases who underwent surgery with curative intent at 22 hospitals from January 1997 to December 2006 in Japan. From this database, we extracted the patients with stage II colorectal cancer who underwent sufficient (D2 or D3) lymph nodes dissection (i.e. the removal of pericolic, intermediate, and/or main lymph nodes around the root of the regional artery). Classification of lymph node dissection was based on the General Rule of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [15]. Eligible age was restricted to ages between 40 and 80 years to minimize patient heterogeneity because young patients might have genetic differences and older patients have many prognostic factors other than colorectal cancer. We excluded patients with cancer in other organs regardless of the severity of carcinoma. Also, we excluded those receiving preoperative chemotherapy/radiotherapy which was performed based on the therapeutic strategy of each hospital.

Statistical analysis

Survival or recurrence rate was estimated with Kaplan-Meier methods. Overall survival (OS) was defined as the time

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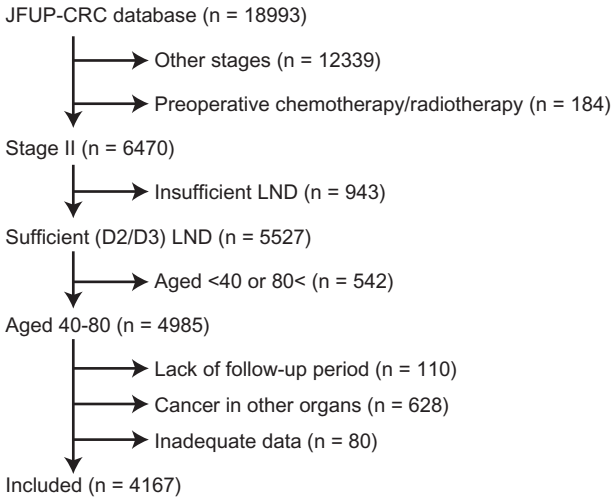

Figure 1. Consort diagram of patient selection. JFUP-CRC: the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer; LND: lymph node dissection.

between date of surgery and date of death, and relapse-free survival (RFS) was defined as the time between date of surgery and date of recurrence or death, whichever came first. Cox proportional hazard model was used to detect independent risk factors for time to recurrence (TTR) in univariate and multivariate analyses. TTR was defined as the time between date of surgery and date of recurrence. A nomogram was developed using multivariate Cox proportional hazard model for TTR. All risk factors were dealt as continuous variables in the analyses for linear prediction in nomograms. All p-values were two-sided, and p-values less than 0.05 were considered significant. The performance of the nomogram was assessed using a concordance index and calibration plots with bootstrap samples. A concordance index is a numeric measure of discrimination ability, and calibration plots are graphical assessment of predictive ability, which compares the nomogram-predicted probabilities with observed probabilities. All statistical analyses were performed using R [16] and the nomogram was made using 'rms' package [17].

Results

Patient background characteristics

A total of 4167 patients in the JFUP-CRC database were included in the analyses (Figure 1). Clinicopathological characteristics of all patients are shown in Table 1. We identified 538 patients (13.2%) with cancer recurrence and 3534 patients (86.8%) with no recurrence. Median follow-up period of surviving patients was 83 months (interquartile range 61–105). Five-year OS, RFS and recurrence rate were 91.1%, 83.0% and 13.5%, respectively.

Nomogram for five-year freedom from recurrence

We evaluated the association between clinicopathological factors and recurrence in univariate and multivariate analyses. Sex, preoperative carcinoembryonic antigen (CEA), tumor location, tumor depth, lymphatic invasion, venous invasion and number of lymph nodes studied (NLNS) were significantly associated with recurrence, whereas age and differentiation were not. Moreover, adjuvant chemotherapy did not influence the prognosis of patients (Table 2). We created a nomogram for five-year freedom from recurrence using these factors (Figure 2). CEA was used with restricted cubic spline to fit clinical experience. The nomogram had a bootstrapped-concordance index of 0.64 and was well calibrated (Figure 3).

Table 1. Patient background characteristics.

Factor	Category	n	%
Age (years)	40–49	267	6.4
	50–59	1019	24.5
	60–69	1520	36.5
	70–80	1361	32.7
Sex	Male	2494	59.9
	Female	1672	40.1
CEA (ng/ml)	<5.0	2593	67.2
	5.0–9.9	652	16.9
	10.0–14.9	203	5.3
	15.0–19.9	103	2.7
	20.0–24.9	69	1.8
	25.0–29.9	39	1.0
	30.0–34.9	29	0.8
	35.0–39.9	31	0.8
	40.0–44.9	19	0.5
	45.0–49.9	9	0.2
	≥50.0	110	2.9
Tumor location	Right colon	1172	28.1
	Left colon	2008	48.2
	Rectum	986	23.7
Lymph node dissection	D2	1002	24.1
	D3	3165	76.0
Differentiation	Well, Moderate	3923	94.5
	Low	227	5.5
Tumor depth	T3	3351	80.4
	T4	816	19.6
Lymphatic invasion	0	1715	41.4
	+	2429	58.6
Venous invasion	0	1570	37.9
	+	2569	62.1
Number of lymph nodes studied	0–11	715	17.6
	12–23	1560	38.3
	24–35	967	23.8
	36–47	443	10.9
	≥48	387	9.5
Adjuvant chemotherapy	–	2620	74.9
	+	878	25.1

CEA: carcinoembryonic antigen.

Discussion

The main purpose of using a nomogram is to predict the prognosis of the patients with a high accuracy. It is beneficial to know the risk of recurrence in terms of postoperative surveillance and indication for adjuvant chemotherapy. In the recommendations of American Society of Clinical Oncology (ASCO) [18] or European Society for Medical Oncology (ESMO) [19], several risk factors for recurrence in stage II colon cancer have been suggested, including a small number of lymph nodes examined, T4 lesion, intestinal occlusion or perforation, poorly differentiated pathology, vascular, lymphatic or perineural invasion and CEA >5 ng/dl. The current guidelines consider patients who have at least one of these factors at high risk of recurrence. Recently, Böckelman et al. [20] reported that the prognostic impact of tumor depth, differentiation, NLNS, mismatch repair status and emergency surgery were confirmed. In our study, preoperative CEA elevation, tumor depth, lymphatic invasion, venous invasion and small NLNS were identified as risk factors. In terms of

Table 2. Analyses of time to recurrence.

	Univariate analysis			Multivariate analysis		
Factor	HR	95% CI	p-Value	HR	95% CI	p-Value
Age (by 10 years)	0.99	0.90–1.09	.843			
Sex (female/male)	0.74	0.62–0.88	<.001	0.77	0.64–0.93	.006
CEA (by 5 ng/ml)	1.08	1.05–1.12	<.001	1.07	1.04–1.11	<.001
Tumor location (rectum/left colon/right colon)	1.56	1.39–1.76	<.001	1.56	1.38–1.78	<.001
Lymph node dissection (D3/D2)	1.11	0.90–1.37	.319			
Differentiation (low/well, moderate)	0.91	0.62–1.34	.629			
Tumor depth (T4/T3)	1.71	1.41–2.06	<.001	1.63	1.33–1.99	<.001
Lymphatic invasion (+/0)	1.39	1.17–1.66	<.001	1.22	1.01–1.48	.035
Venous invasion (+/0)	1.47	1.22–1.77	<.001	1.30	1.07–1.58	.009
Number of lymph nodes studied (by 12)	0.92	0.86–1.00	.037	0.89	0.82–0.96	.002
Adjuvant chemotherapy (+/−)	1.46	1.20–1.77	<.001			

CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio.

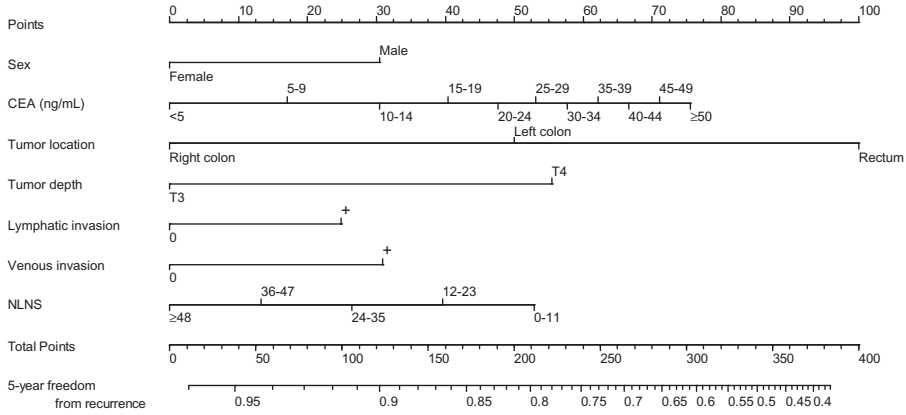

Figure 2. Nomogram for 5-year freedom from recurrence. To estimate the probability of 5-year freedom of recurrence, locate patient values at each axis, draw a straight line upward to the point axis, and sum the points of all variables. Then, locate the sum on the total point axis, and trace a straight line downward to the probability axis. CEA: carcinoembryonic antigen; NLNS: number of lymph nodes studied.

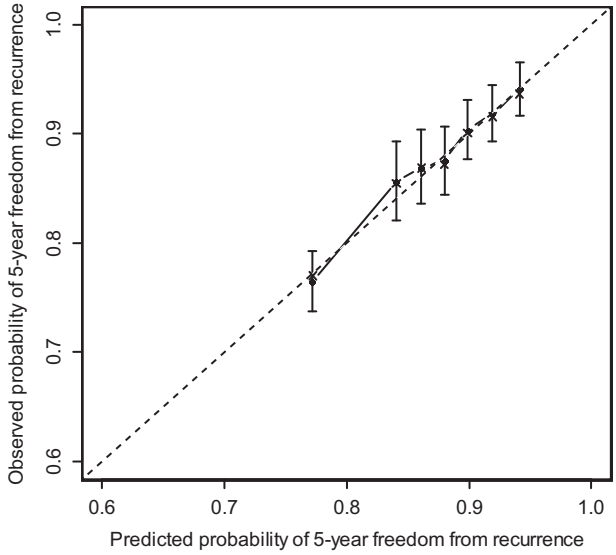

Figure 3. Calibration of the nomogram for 5-year freedom from recurrence. The x-axis shows the predicted probability of 5-year freedom of recurrence, and the y-axis shows the observed probability of 5-year freedom of recurrence and 95% confidence intervals.

prediction performance, when we used each factor individually for the prediction of recurrence, the boot-strapped concordance indices were 0.55, 0.54, 0.54, 0.54 and 0.53, respectively, which were consistent with those in a previous report [14]. However, prediction by the nomogram developed is more precise (concordance index =0.64).

One of the main purposes of precise prediction of recurrence is to determine the indication for adjuvant chemotherapy. The efficacy of adjuvant chemotherapy in stage II patients has been discussed for a long time. Many randomized controlled trials and meta-analyses have been performed [21–24] but a conclusion has not been reached. The best explanation for this discrepancy is the prognostic diversity of stage II patients [23]. In stage II disease, patients at low risk of recurrence might gain little survival benefit from adjuvant chemotherapy, whereas patients at high risk could benefit. Moreover, Påhlman et al. [25] reported that fewer patients might need adjuvant chemotherapy according to the recent improvement of diagnostic and therapeutic modalities. Excessive use of adjuvant chemotherapy would make a harmful impact on patients. Therefore, it is important to detect high-risk patients with accuracy. The nomogram developed in this study would be useful for the appropriate selection of candidates for adjuvant chemotherapy.

The strength of our study was the use of data from a large sample and common clinicopathological factors only, which permits high generalizability. Although the usefulness of the genetic signature of cancer has been reported recently such as ColoPrint or Oncotype DX, the high cost of genetic testing is an important problem [26,27]. Also, we assessed only stage II colorectal cancer patients so the heterogeneity of the cancer stage is not an issue, especially the influence of nodal status. However, this study has some limitations. No

information about patient performance status and comorbidity was available. These factors might affect prognosis, but we made an effort to minimize the effects by excluding the patients with insufficient lymph node dissection, which was often performed in patients with poor performance status or severe comorbidities. Also, we could not obtain data about emergency surgery, mismatch repair status and intestinal occlusion or perforation, which are potential factors that influence the prognosis of the patients [20]. In addition, this study used not-so-new data (1997–2006), and the diagnostic/therapeutic modalities today might be different from present ones [25]. Despite these limitations, we believe that our nomogram can help with the detection of patients at high risk of recurrence and in determining the need for adjuvant therapy in stage II colorectal cancer.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2016. [Epub ahead of print].
2. Cancer Information Service, National Cancer Center, Japan (2013) CANCER STATISTICS IN JAPAN-2013. http://ganjoho.jp/en/professional/statistics/brochure/2013_en.html Accessed 9 May 2016
3. Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
4. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyzes of the multicenter international study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. J Clin Oncol 2012;30:3353–60.
5. Matsuda N, Hayashi N, Ohde S, et al. A nomogram for predicting locoregional recurrence in primary breast cancer patients who received breast-conserving surgery after neoadjuvant chemotherapy. J Surg Oncol 2014;109:764–9.
6. Li J, Liu Y, Yan Z, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy. Br J Cancer 2014;110:1110–17.
7. Rose PG, Java J, Whitney CW, et al. Nomograms predicting progression-free survival, overall survival, and pelvic recurrence in locally advanced cervical cancer developed from an analysis of identifiable prognostic factors in patients from NRG oncology/gynecologic oncology group randomized trials of chemoradiotherapy. J Clin Oncol 2015;33:2136–42.
8. Weiser MR, Landmann RG, Kattan MW, et al. Individualized prediction of colon cancer recurrence using a nomogram. J Clin Oncol 2008;26:380–5.
9. Kattan MW, Gonen M, Jarnagin WR, et al. A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. Ann Surg 2008;247:282–7.
10. Massacesi C, Norman A, Price T, et al. A clinical nomogram for predicting long-term survival in advanced colorectal cancer. Eur J Cancer 2000;36:2044–52.
11. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a project study for hepatic surgery of the Japanese society of hepato-biliary-pancreatic surgery. J Hepatobiliary Pancreat Sci 2012;19:72–84.
12. Kawai K, Ishihara S, Yamaguchi H, et al. Nomograms for predicting the prognosis of stage IV colorectal cancer after curative resection: a multicenter retrospective study. Eur J Surg Oncol 2015;41:457–65.
13. Han DS, Suh YS, Kong SH, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. J Clin Oncol 2012;30:3834–40.
14. Tsikitis VL, Larson DW, Huebner M, et al. Predictors of recurrence free survival for patients with stage II and III colon cancer. BMC Cancer 2014;14:336.
15. Watanabe T, Itabashi M, Shimada Y, et al. Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 2012;17:1–29.
16. http://r-project.org/Accessed 6 January 2016
17. https://cran.r-project.org/web/packages/rms/Accessed 6 January 2016
18. Benson AB, 3rd, Schrag D, Somerfield MR, et al. American society of clinical oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–19.
19. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23:2479–516.
20. Böckelman C, Engelmann BE, Kaprio T, et al. Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature. Acta Oncol 2015;54:5–16.
21. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from national surgical adjuvant breast and bowel project C-04. J Clin Oncol 1999;17:3553–9.
22. Gray R, Barnwell J, McConkey C, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020–9.
23. Mamounas EP. Adjuvant chemotherapy for stage II colon cancer: the time has come. Eur J Surg Oncol 2000;26:725–9.
24. Wilkinson NW, Yothers G, Lopa S, et al. Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. Ann Surg Oncol 2010;17:959–66.
25. Pahlman LA, Hohenberger WM, Matzel K, et al. Should the Benefit of Adjuvant Chemotherapy in Colon Cancer Be Re-Evaluated? J Clin Oncol 2016;34:1297–9.
26. Maak M, Simon I, Nitsche U, et al. Independent validation of a prognostic genomic signature (ColoPrint) for patients with stage II colon cancer. Ann Surg 2013;257:1053–8.
27. Ward S, Scope A, Rafia R, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1–302.