Int Surg 2017;**102:**102–108
DOI: 10.9738/INTSURG-D-16-00210.1

A Nomogram for Predicting Lymph Node Metastasis in Submucosal Colorectal Cancer

Shiki Fujino[1,2], Norikatsu Miyoshi[2], Masayuki Ohue[2], Masayoshi Yasui[2], Keijiro Sugimura[2], Hirofumi Akita[2], Hidenori Takahashi[2], Shogo Kobayashi[2], Yoshiyuki Fujiwara[2], Masahiko Yano[2], Masahiko Higashiyama[2], Masato Sakon[2]

[1]*Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan*

[2]*Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*

In colorectal cancer (CRC), the possibility of lymph node (LN) metastasis is an important consideration when deciding on treatment. We developed a nomogram for predicting lymph node metastasis of submucosal (SM) CRC. The medical records of 509 patients with SM CRC from 1984 to 2012 were retrospectively investigated. All the patients underwent curative surgical resection at the Osaka Medical Center for Cancer and Cardiovascular Diseases. A total 113 patients with inadequate data were excluded. Using a group of 293 patients who underwent surgery from 1984 to 2008, a logistic regression model was used to develop a prediction model for LN metastasis. The prediction model was validated in an additional group of 103 patients who underwent surgery from 2009 to 2012. Univariate analysis of pathologic factors showed the influence of low histologic grade (muc, por, sig; $P < 0.001$), positive lymphatic invasion ($P < 0.001$), positive vascular invasion ($P = 0.036$), and tumor SM invasion depth ($P = 0.098$) in LN metastasis. Using these variables, a nomogram predicting LN metastasis was constructed using a logistic regression model with an area under the curve (AUC) of 0.717. The prediction model was validated by an external dataset in an independent patient group with an AUC of 0.920. We developed a novel and reliable nomogram predicting LN metastasis through the integration of 4 pathologic factors. This prediction model may help clinicians to decide on personalized treatment following endoscopic resection.

Key words: Submucosal colorectal cancer – Lymph node metastases – Nomogram – Prediction model

Corresponding author: Norikatsu Miyoshi, MD, PhD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
Tel.: +81 6 6972 1181; Fax: +81 6 6981 8005; E-mail: miyosi-no@mc.pref.osaka.jp

Cancer is a leading cause of death worldwide, and colorectal cancer (CRC) is the primary cause of death among women and the third leading cause among men in Japan,[1] as well as in most Western countries.[2] According to the Japanese Society for Cancer of the Colon and Rectum guidelines for the treatment of colorectal cancer (JSCCR Guidelines), the treatment plan should be decided based on the tumor depth and the presence of lymph node (LN) and/or distant metastases, and a curative surgical resection of primary CRC with regional LNs is generally performed in stage I to III CRC.[3] In contrast, endoscopic resection can complete the treatment of intramucosal carcinoma because there is no LN metastasis. However, in submucosal (SM) carcinoma, the probability of LN metastasis is approximately 10%,[4] and surgical resection with LN dissection is generally recommended. In the guidelines, the additional surgical resection is determined by the pathologic findings of the primary tumor resected by endoscopic treatment.[3]

The additional surgical resection is required because retrospective analyses have determined that the following factors significantly relate to LN metastasis and tumor recurrence[5,6]: (1) depth of submucosal invasion greater than 1000 μm; (2) positive lymphovascular invasion; (3) positive endoscopic vertical margin; (4) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; and (5) grade 2/3 budding at the site of deepest invasion.

The rates of recurrence and 5-year disease-free survival were 0.8% and 95%, respectively, in the patients who had none of the risk factors listed above after endoscopic resection.[7] However, these rates were 6.6% and 89.3%, respectively, in the patients who had one or more of these risk factors and were treated by endoscopic resection alone. When these risk factors were combined, the probability of LN metastasis ranged from 7.4% to 46.9%,[8] and thus the importance of additional surgery is different in each patient.

Therefore, we examined the risk factors retrospectively and used them to develop a new prediction model. This is the first report of the prediction model for lymph node metastasis in SM CRC.

Materials and Methods

Patients and datasets

We retrospectively analyzed 509 consecutive patients with SM CRC that were surgically treated at the Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, from 1984 to 2012. We excluded 113 patients who lacked any of the required pathologic findings (Fig. 1). In a group of 293 patients who underwent surgery from 1984 to 2008, we assessed the clinicopathologic characteristics [sex, age, preoperative carcinoembryonic antigen (CEA), primary CRC location, macroscopic tumor type, tumor size, histologic grade, SM invasion depth, lymphatic invasion, vascular invasion, and LN metastasis] and recurrence-free survival. These patients were included in a training set (TS) aimed at developing a prediction model for LN metastasis using a logistic regression model. A total of 103 patients treated from 2009 to 2012 were included in a validation set (VS). The prediction model was validated in this independent group. This retrospective study was approved by the Osaka Medical Center for Cancer and Cardiovascular Diseases Ethics Committee, and written informed consent was obtained from all patients.

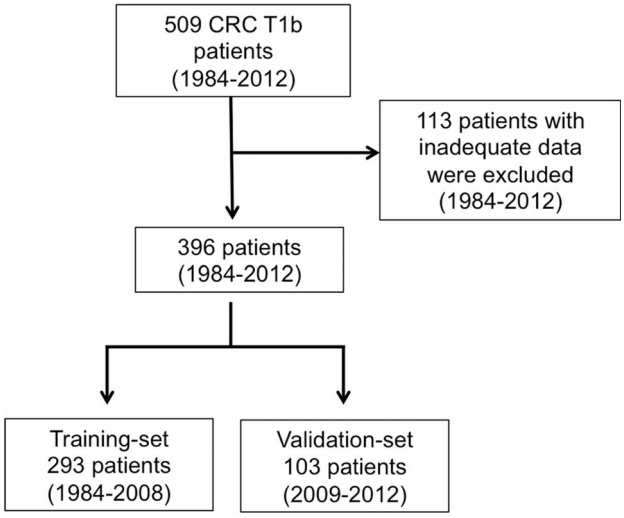

Fig. 1 The schema of this study. A total of 509 surgically treated SM CRC patients were enrolled in this study. One hundred thirteen patients were excluded because they lacked pathologic data. A total 396 patients were divided into 2 groups: 293 patients treated from 1984 to 2008 were included in the TS and 103 patients treated from 2009 to 2012 were included in the VS. The prediction model was developed in the TS and validated in the VS.

Pathologic examination

All of the resected specimens were fixed in 10% buffered formalin, processed through graded ethanol solutions, and embedded in paraffin blocks.

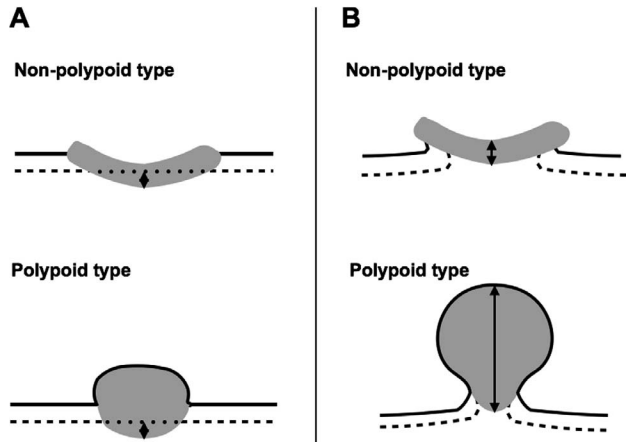

Fig. 2 SM invasion depth of CRC. (A) When the muscularis mucosae (dashed line) could be estimated (dotted line) in the location of the tumor, the vertical distance from the muscularis mucosae to the deepest level of invasion represented the "SM invasion depth" (arrow). (B) When the muscularis mucosae (dashed line) could not be estimated, the vertical distance from the superficial aspect of the tumor to the deepest level of invasion was determined as the "SM invasion depth" (arrow).

They were examined histologically using hematoxylin and eosin staining. The degree of histologic differentiation, SM invasion depth, lymphatic invasion, and venous invasion were assessed. The SM invasion depth was measured according to the Japanese Classification of Colorectal Carcinoma (8th edition).[9] When the muscularis mucosae could be identified, the vertical distance from the muscularis mucosae to the deepest level of invasion represented the SM invasion depth (Fig. 2A). When the muscularis mucosae could not be identified, the vertical distance from the superficial aspect of the tumor to the deepest level of invasion was determined (Fig. 2B). Fifty-five patients had only the relative (but not numeric) SM invasion depth data evaluated as sm1, sm2, and sm3, according to the previous Japanese Classification of Colorectal Carcinoma (6th edition).[10] We translated these classifications from our preliminary examination (data not shown) as follows: 1000 μm for sm1, 2000 μm for sm2, and 4000 μm for sm3.

Statistical model creation

We analyzed categorical variables using the χ^2 test and continuous variables using the Mann-Whitney test. The Kaplan-Meier method was used to estimate disease-free survival and cancer-specific survival. The log-rank test was used to analyze differences in survival between the groups, and significance was defined at $P < 0.05$. A nomogram as the prediction model for LN metastasis was structured by variables with the limit to enter a variable in the analysis being set at $P < 0.1$. All statistical analyses were performed using the JMP 11.0 statistical software program (SAS Institute, Cary, North Carolina). A nomogram was structured using R 3.1.3 (CRAN, the R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Clinicopathologic factors of all patients

Factors	Training set (n = 293)	Validation set (n = 103)
Sex		
Male	178	60
Female	115	43
Age,[a] year	60 (31–89)	65 (38–84)
CEA, ng/mL		
>5	13	9
<5	241	53
Primary CRC location (lower rectum and anus/others)	40/253	15/88
Tumor type		
Polypoid type[b]	206	68
Others[c]	87	35
Tumor size,[a] mm	16 (5–90)	17 (2–91)
Histologic grade		
Well-mod[d]	286	103
Others[e]	7	0
SM invasion depth,[a] μm	2500 (40–12,250)	2000 (50–8000)
Lymphatic invasion		
Present	89	21
Absent	204	82
Vascular invasion		
Present	64	24
Absent	229	79
Lymph node metastasis		
Present	37	7
Absent	256	96

[a]Continuous variables were evaluated.

[b]Polypoid type: type 0-I defined in the Japanese Classification of Colorectal Carcinoma.

[c]Others: type 0-II and 0-III in the Japanese Classification of Colorectal Carcinoma.

[d]Well-mod: well and moderately differentiated adenocarcinoma.

[e]Others: poorly differentiated, mucinous, and signet ring cell adenocarcinoma.

Results

The characteristics of all 396 CRC patients, including those of 293 TS patients and 103 VS patients, are shown in Table 1. LN metastasis was evident in 37 (12.6%) and 7 patients (6.5%), respectively, and the respective median tumor size was 16 (range, 5–90

Table 2 Univariate analyses of lymph node metastasis in TS

Factors	Lymph node metastasis		*P* value
	Present (37)	Absent (256)	
Sex (male/female)			0.594
Male	21	157	
Female	16	99	
Age,[a] year	59 (35–81)	61 (31–89)	0.467
CEA, ng/mL			0.863
>5	2	11	
<5	33	208	
Primary CRC location (and)			0.979
Lower rectum	5	35	
Anus/Others	32	221	
Tumor type			0.250
Polypoid type[b]	29	177	
Others[c]	8	79	
Tumor size,[a] mm	20 (6-35)	16 (5-90)	0.607
Histologic grade			<0.001
Well-mod[d]	33	253	
Others[e]	4	3	
SM invasion depth,[a] μm	3000 (200–10,000)	2500 (40–12,250)	0.098
Lymphatic invasion			<0.001
Present	21	68	
Absent	16	188	
Vascular invasion			0.036
Present	13	51	
Absent	24	205	

[a]Continuous variables were evaluated.

[b]Polypoid type: type 0-I defined in the Japanese Classification of Colorectal Carcinoma.

[c]Others: type 0-II and 0-III in the Japanese Classification of Colorectal Carcinoma.

[d]Well-mod: well and moderately differentiated adenocarcinoma.

[e]Others: poorly differentiated, mucinous, and signet ring cell adenocarcinoma.

mm) and 17 mm (range, 2–91 mm). Positive lymphatic invasion was observed in 89 (30.3%) and 21 patients (19.4%) and positive vascular invasion was observed in 64 (21.8%) and 24 patients (22.2%), respectively.

Univariate analysis of the clinicopathologic factors of LN metastasis in TS is shown in Table 2. It revealed the influence of low histologic grade (muc, por, sig; $P < 0.001$), positive lymphatic invasion ($P < 0.001$), positive vascular invasion ($P = 0.036$), and tumor SM invasion depth ($P = 0.098$). Tumor size and tumor type were not found to be significant. In the TS, the rate of 5-year disease-free survival was 96%, and the cancer-specific survival was 97% (Fig. 3). A nomogram for predicting LN metastasis in SM CRC was constructed using the 4 factors, histologic grade, SM invasion depth, lymphatic invasion, and

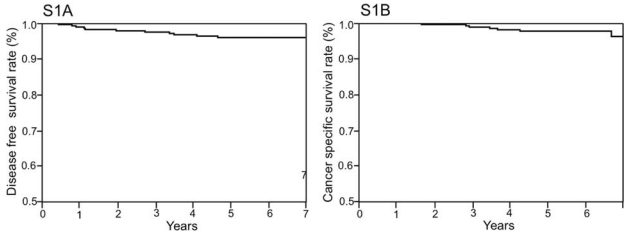

Fig. 3 (A) Disease-free survival of CRC patients in the TS. (B) Cancer-specific survival of CRC patients in the TS.

vascular invasion, through a logistic regression model (Fig. 4). The nomogram can assign the probability of LN metastasis by adding up the scores identified on the points scale for each factor. The total score projected to the bottom scale indicates the probability of LN metastasis. The area under the curve (AUC) in the TS was 0.717. The prediction model was validated by an external dataset in the VS, and the AUC was 0.920.

We performed a multivariate analysis of LN metastasis in the TS, as shown in Table 3. Low histologic grade (muc, por, sig; $P = 0.022$), SM invasion depth ($P = 0.033$), and positive lymphatic invasion ($P = 0.002$) were significant risk factors. However, vascular invasion was not a significant factor ($P = 0.525$). Another nomogram for predicting

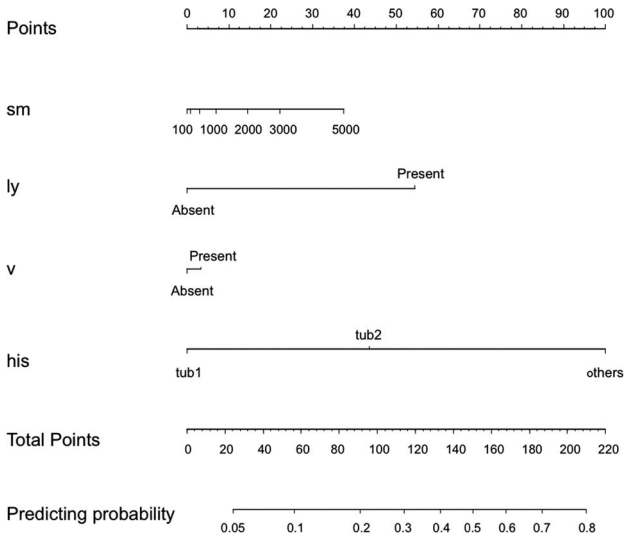

Fig. 4 The nomogram for predicting LN metastasis in SM CRC was developed using 4 factors: SM invasion depth (sm), lymphatic invasion (ly), vascular invasion (v), and histologic grade (his). The sum of these variable points was plotted on the total point axis, and the estimated LN metastasis rate was obtained by drawing a vertical line from the plotted total point axis straight down to the predicting probability axis.

Table 3 Multivariate analyses of lymph node metastasis in TS

Factors	HR	95% CI	*P* value
Histologic grade (Others[a]/Well-mod[b])	6.75	1.33–37.42	**0.022**
SM invasion depth,[c] μm	1.00	1.00–1.00	**0.033**
Lymphatic invasion (present/absent)	3.35	1.56–7.30	**0.002**
Vascular invasion (present/absent)	1.30	0.56–2.92	0.525

CI, confidence interval; HR, hazard ratio.

Bold entries indicate *P* value < 0.1.

[a]Others: poorly differentiated, mucinous, and signet ring cell adenocarcinoma.

[b]Well-mod: well and moderately differentiated adenocarcinoma.

[c]Continuous variables were evaluated.

LN metastasis in SM CRC was constructed using the 3 significant factors, namely, histologic grade, SM invasion depth, and lymphatic invasion, through a logistic regression model (Fig. 5). The AUC in the TS was 0.720 and 0.920 in the VS.

Discussion

Surgical resection is a standard treatment for CRC. Five-year disease-free survival and 5-year overall survival are 95% to 97% and 97% to 99%, respectively, in SM CRC after surgical resection.[7] This prognosis is good; however, intraoperative and perioperative complications may occur with surgical treatment,[11,12] and severe complications such as anastomotic leakage may be a major cause of death.[13] The mortality of the colorectal cancer operation has been reported to be approximately 5%.[11] Surgical resection including regional LNs is the standard treatment for colorectal cancer; however, the procedure can cause these complications or other functional problems. For example, local excision followed by chemoradiotherapy is preferred for low rectal cancer instead of surgery with total mesorectal excision, and this treatment results in good anal function.[14] Recent reports have suggested that older patients with certain risks could be overtreated, with the possibility of subsequent excess morbidity and mortality; the survival gain is smaller in older compared with younger patients.[15] Therefore, the need for surgical treatment must be evaluated in each individual case, and the tool for predicting LN metastasis in SM CRC is useful.

Recently, several predictive scores have been reported for predicting cancer prognosis, surgical complications, or genetic mutational status.[16–20] These scores can predict each individual patient's prognosis or complications.

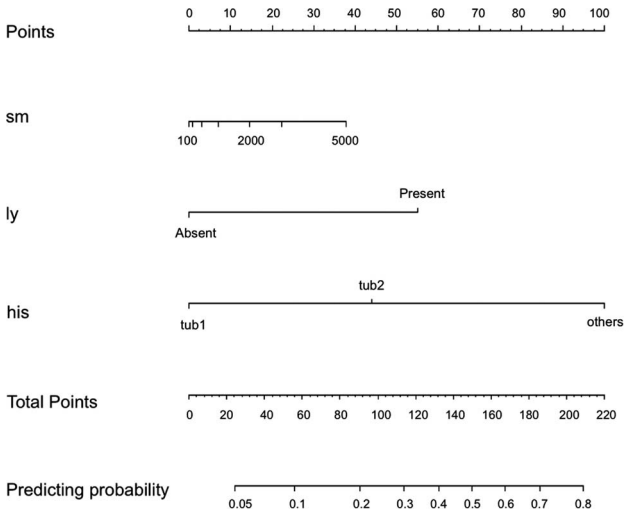

Fig. 5 The nomogram for predicting LN metastasis in SM CRC was developed using 3 factors: SM invasion depth (sm), lymphatic invasion (ly), and histologic grade (his). The sum of these variable points was plotted on the total point axis, and the estimated LN metastasis rate was obtained by drawing a vertical line from the plotted total point axis straight down to the predicting probability axis.

In previous reports, the probability of LN metastasis in SM CRC varied across a combination of risk factors. For example, the probability was 9.4% in patients with an SM depth >1000 μm and negative vascular invasion and was 46.9% in patients with an SM depth >1000 μm and low histologic grade.[8] However, it is recommended in the current Japanese guidelines that both patient groups undergo additional surgical resection.[3] In our study, we evaluated the risk factors for LN metastasis in SM CRC and developed a new nomogram for predicting LN metastasis in individual SM CRC cases. Recently, there has been an increasing number of surgeries for colorectal cancer with complications in elderly patients. Therefore, our nomogram may help to decide whether an additional surgical treatment is necessary after endoscopic resection.

The invasion depth is an important risk factor in this study, but the polypoid type (0-I) is difficult to evaluate. If the muscularis mucosae cannot be identified, the measure of the invasion depth will be wide; the tumor volume has greater effect in the polypoid type than the nonpolypoid type, as mentioned above. We also reevaluated the invasion depth according to the type of tumor, including polypoid type (0-I) and nonpolypoid type (0-II and 0-III).[9] Univariate analysis of the clinicopathologic

Table 4 Clinicopathologic factors of LN metastasis in polypoid type and nonpolypoid type (others)

	Polypoid type			Nonpolypoid type		
	LN metastasis			LN metastasis		
Factors	Present (29)	Absent (177)	*P* value	Present (8)	Absent (79)	*P* value
Sex			0.477			0.648
Male	15	104		6	53	
Female	14	73		2	26	
Age,[a] year	58 (35–76)	60 (34–89)	0.401	63 (42–81)	61 (31–84)	0.718
CEA, ng/mL	/	/	0.583			0.512
>5	2	7		0	4	
<5	26	143		7	65	
Primary CRC location			0.813			0.612
Lower rectum and anus	3	21		2	14	
Others	26	156		6	65	
Tumor size,[a] mm	20 (6–28)	18 (5–90)	0.541	21 (10–35)	15 (5–50)	**0.070**
Histologic grade			**0.091**			**< 0.001**
Well-mod[b]	27	174		6	79	
Others[c]	2	3		2	0	
SM invasion depth,[a] μm	2500 (200–10,000)	2700 (150–12,250)	0.557	4000 (1700–10,000)	2000 (40–7250)	**0.044**
Lymphatic invasion			**0.004**			**< 0.001**
Present	16	50		5	18	
Absent	13	127		3	61	
Vascular invasion			0.588			**< 0.001**
Present	7	35		6	16	
Absent	22	142		2	63	

Bold entries indicate *P* value < 0.1.

[a]Continuous variables were evaluated.

[b]Well-mod: well and moderately differentiated adenocarcinoma.

[c]Others: poorly differentiated, mucinous, and signet ring cell adenocarcinoma.

factors of LN metastasis in the polypoid type is shown in Supplementary Table 4A. There were influences of positive lymphatic invasion ($P = 0.004$) and low histologic grade (muc, por, sig; $P = 0.091$). Univariate analysis of the clinicopathologic factors involved in LN metastasis in the nonpolypoid type is shown in Supplementary Table 4B. There were influences of low histologic grade (muc, por, sig; $P < 0.001$), SM invasion depth ($P = 0.044$), positive lymphatic invasion ($P < 0.001$), positive vascular invasion ($P < 0.001$), and tumor size ($P = 0.070$). The SM invasion depth and tumor size were considered important factors to predict LN metastases in the nonpolypoid type; however, they were not significant factors in the polypoid type. In addition to the measure of the invasion depth in the polypoid type, the classification of the tumor types is various, because the type often contains some elements, such as "0-I + IIc." The type of tumor, such as polypoid or nonpolypoid type, should be evaluated to predict LN metastases relating to SM invasion depth with a large number of subjects.

This study has several limitations. The budding grade[9] was not evaluated in this study because there were so few data in the TS (collected from 1984 to 2008); the budding grade was added to the guidelines in 2009. SM invasion depth was evaluated as a relative invasion depth in 55 patients of the TS, and they were translated into numerical values. In addition, there were a small number of subjects in this study compared with previous studies,[16,18] and this may be related to the insignificant factor of SM invasion depth in univariate analysis and venous invasion in multivariate analysis. A multiple institutional study that enrolls many patients should be conducted. However, our new prediction model of LN metastasis in SM CRC is useful as a clinical tool because this model predicts the probability for the individual patient, resulting in more personalized medical care.

Conclusions

A nomogram predicting LN metastasis was successfully developed through the integration of 4 pathologic factors: invasion depth, lymphatic invasion, vascular invasion, and histologic grade. This tool could help physicians and patients decide on

the additional surgical treatments required after endoscopic resection.

References

1. Center for Cancer Control and Information Services. NCC, Japan Recent cancer statistics, 2014. Available at: http://ganjoho.jp/reg_stat/statistics/stat/summary.html. Accessed August 3, 2016
2. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J *et al*. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. *Eur J Cancer* 2015;**51**(9):1164–1187
3. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y *et al*. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. *Int J Clin Oncol* 2015;**20**(2):207–239
4. Japanese Society for Cancer of the Colon and Rectum. *Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer*. 1st ed. Tokyo, Japan: Kanehara, 2016.
5. Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K *et al*. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004;**127**(2):385–394
6. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H *et al*. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004;**39**(6):534–543
7. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N *et al*. Long-term outcomes after resection for submucosal invasive colorectal cancers. *Gastroenterology* 2013;**144**(3):551–559
8. Ueno H, Hase K, Hashiguchi Y, Shimazaki H, Yoshii S, Kudo SE *et al*. Novel risk factors for lymph node metastasis in early invasive colorectal cancer: a multi-institution pathology review. *J Gastroenterol* 2014;**49**(9):1314–1323
9. Japanese Society for Cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma*. 8th ed. Tokyo, Japan: Kanehara, 2013
10. Japanese Society for Cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma*. 6th ed. Tokyo, Japan: Kanehara, 1998
11. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM *et al*. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;**365**(9472):1718–1726
12. Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F *et al*. Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. *Ann Surg* 2014;**260**(1):23–30
13. Katsuno H, Shiomi A, Ito M, Koide Y, Maeda K, Yatsuoka T *et al*. Comparison of symptomatic anastomotic leakage following laparoscopic and open low anterior resection for rectal cancer: a propensity score matching analysis of 1014 consecutive patients. *Surg Endosc* 2016;**30**(7):2848–2856.
14. Glimelius B, Tiret E, Cervantes A, Arnold D, Group EGW. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24**(suppl 6):vi81–vi88
15. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D *et al*. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Ann Oncol* 2015;**26**(3):463–476
16. Han DS, Suh YS, Kong SH, Lee HJ, Choi Y, Aikou S *et al*. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. *J Clin Oncol* 2012;**30**(31):3834–3840
17. Pasic F, Salkic NN. Predictive score for anastomotic leakage after elective colorectal cancer surgery: a decision making tool for choice of protective measures. *Surg Endosc* 2013;**27**(10):3877–3882
18. Peng J, Ding Y, Tu S, Shi D, Sun L, Li X *et al*. Prognostic nomograms for predicting survival and distant metastases in locally advanced rectal cancers. *PLoS One* 2014;**9**(8):e106344
19. Eom BW, Joo J, Kim YW, Park B, Yoon HM, Ryu KW *et al*. Nomogram estimating the probability of intraabdominal abscesses after gastrectomy in patients with gastric cancer. *J Gastric Cancer* 2015;**15**(4):262–269
20. Loupakis F, Moretto R, Aprile G, Muntoni M, Cremolini C, Iacono D *et al*. Clinico-pathological nomogram for predicting BRAF mutational status of metastatic colorectal cancer. *Br J Cancer* 2016;**114**(1):30–36