European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Risk prediction model of peritoneal seeding in advanced gastric cancer: A decision tool for diagnostic laparoscopy

Norihito Kubo [a, e, 1], Hyunsoon Cho [b, 1], Dahhay Lee [b], Hannah Yang [a, h], Youngsook Kim [a], Harbi Khalayleh [a, f, g], Hong Man Yoon [a], Keun Won Ryu [a], George B. Hanna [c], Daniel G. Coit [d], Kenichi Hakamada [e], Young-Woo Kim Professor, MD,PhD [a, b, *]

[a] Center for Gastric Cancer, National Cancer Center, Korea
[b] Department of Cancer Control and Population Science, Graduate School of Cancer Science and Policy, National Cancer Center, Korea
[c] Department of Surgery and Cancer, Imperial College of London, United Kingdom
[d] Gastric and Mixed Tumor Service, Memorial Sloan Kettering Cancer Center, USA
[e] Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Japan
[f] Faculty of Medicine, Hebrew University of Jerusalem, Israel
[g] The Department of Surgery, Kaplan Medical Center, Israel
[h] Division of Biology and Biological Engineering, California Institute of Technology Pasadena, California, 91125, USA

ARTICLE INFO

Article history:
Received 12 September 2022
Received in revised form
7 December 2022
Accepted 23 December 2022
Available online xxx

Keywords:
Peritoneal seeding
Gastric cancer
Diagnostic laparoscopy
Nomogram

ABSTRACT

Background: Selective diagnostic laparoscopy in gastric cancer patients at high risk of peritoneal metastasis is essential for optimal treatment planning.
In this study available clinicopathologic factors predictive of peritoneal seeding in advanced gastric cancer (AGC) were identified, and this information was translated into a clinically useful tool.
Methods: Totally 2833 patients underwent surgery for AGC between 2003 and 2013. The study identified clinicopathologic factors associated with the risk of peritoneal seeding for constructing nomograms using a multivariate logistic regression model with backward elimination. A nomogram was constructed to generate a numerical value indicating risk. Accuracy was validated using bootstrapping and cross-validation.
Results: The proportion of seeding positive was 12.7% in females and 9.6% in males. Of 2833 patients who underwent surgery for AGC, 300 (10.6%) were intraoperatively identified with peritoneal seeding. Multivariate analysis revealed the following factors associated with peritoneal seeding: high American Society of Anesthesiologists score, fibrinogen, Borrmann type 3 or 4 tumors, the involvement of the middle, anterior, and greater curvature, cT3 or cT4cN1 or cN2 or cN3, cM1, and the presence of ascites or peritoneal thickening or plaque or a nodule on the peritoneal wall on computed tomography. The bootstrap analysis revealed a robust concordance between mean and final parameter estimates. The area under the ROC curve for the final model was 0.856 (95% CI, 0.835–0.877), which implies good performance.
Conclusions: This nomogram provides effective risk estimates of peritoneal seeding from gastric cancer and can facilitate individualized decision-making regarding the selective use of diagnostic laparoscopy.

1. Introduction

Out of the nearly one million people diagnosed with gastric cancer annually, approximately two-thirds present with advanced forms of gastric cancer [1], and the peritoneum is the most common site of metastasis [2]. Peritoneal seeding renders curative resections unfeasible; therefore, the precise detection of this metastatic condition is critical for the avoidance of unnecessary

* Corresponding author. Department of Cancer Control and Population Science, Graduate School of Cancer Science and policy & Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, Ilsan-ro 323, Ilsandong-gu, Goyang-si, 10408, Korea.
E-mail addresses: youngwookim@ncc.re.kr, gskim@ncc.re.kr (Y.-W. Kim).
[1] Norihito Kubo and Hyunsoon Cho contributed equally to this work.

https://doi.org/10.1016/j.ejso.2022.12.013

laparotomies [3]. Diagnostic laparoscopy is an accurate and reliable method of detecting intra-abdominal metastases [3,4], including occult and micro-peritoneal deposits that can develop unnoticed by non-invasive radiologic modalities[5]. However, countries such as Korea and Japan selectively administer diagnostic laparoscopy for four main reasons: a high proportion of early-stage patients due to nationwide screenings for gastric cancer, avoidance of a procedure that may be associated with some morbidity especially in older comorbid patients [6], an intent to minimize the clinical response time for candidates of curative resections, and the reduction of costs associated with unnecessary testing [7,8]. Traditionally, computed tomography scans (CT) readings have facilitated decisions to pursue diagnostic laparoscopy, but this modality fails to consistently deliver accurate readings of peritoneal seeding [9]. These countries, therefore, experience higher rates of types I and II errors, resulting in significant deviations from the appropriate treatment pla [10]. However, combining CT findings, independently associated with P+, with other independent clinical risk factors may augment the clinician's ability to assess the peritoneum for seeding from primary gastric cancer. On the other side of the spectrum, routine diagnostic laparoscopy – as recommended in Western countries – can lead to similar issues. However, when done on hurry or by non-experienced surgeon may lead to false negatives results that lead to unnecessary laparotomies, can delay definitive treatment, increase costs, and introduce adverse oncologic effects. In the past 15 years, several retrospective studies that recognized this issue have found several clinicopathologic factors associated with increased rates of peritoneal seeding, such as regional lymph node spread, signet ring cell status, and tumor size, depth, and location [11–14]. However, a lack of integrative models bridging these results to a clinically useable form perpetuates the gap between knowledge and practice.

In this study, a large cohort was analyzed to develop a risk assessment tool comprised of routinely measured and validated parameters. This decision-making aid will allow clinicians and advanced gastric cancer patients to generate a personalized score regarding the risk of metastasis to the peritoneum, and a more effective role can be defined for the use of diagnostic laparoscopy in the management of gastric cancer.

2. Methods

2.1. Patient selection

The institutional review board approved the study (IRB No. NCC2016-0079) and waived the need for patients' informed consent.

Using information provided by the National Cancer Center, Korea, 7354 patients who received surgical intervention for primary gastric adenocarcinoma from 1 January 2003 to 31 December 2013 were retrospectively identified. The exclusion criteria were as follows: history of malignant diseases, existence of other malignant diseases, history of gastrectomy, preoperative chemotherapy or radiotherapy for gastric cancer, and diagnosis of clinical T1 or grossly early gastric cancer type tumor. Of the original 7354 patients, 2833 met all the above criteria and were included in our analysis (Fig. 1). Data analyses were performed from 5 April 2016 to 30 September 2019.

We defined the peritoneal seeding as any macroscopic dissemination that found during the surgery. We excluded cytology-positive cases from the analysis because cytology results were unavailable for immediate analysis in the operating room.

2.2. Preoperative clinicopathologic predictors of peritoneal seeding

All factors were examined and obtained preoperatively within a ten-year analysis period. Tumor type and TNM were classified according to the Japanese Gastric Cancer Classification (JGCC) 4th edition. Tumor type and size were determined by esophagogastroduodenoscopy. Tumor location and wall involvement were classified as an upper third (U), middle third (M), lower third (L), anterior wall (Ant), posterior wall (Post), lesser curvature (Less), or greater curvature (Gre) based on the JGCC classification.

Classified factors also included sex, age, American Society of Anesthesiologists (ASA) score (1–2/more than 3), cT (2/3/4), cN (0/1/2/3), cM (0/1), cH (0/1), cP (0/1), histopathologic classification from biopsy specimen (well-differentiated; WD/moderately differentiated; MD/poorly differentiated; PD/Signet Ring Cell; SRC/Others), tumor type (2/3/4), tumor size, multiplicity of cancer (single/multiple), tumor location in the stomach (U/M/L), involvement of gastric wall (Ant/Post/Less/Gre), complete blood count, platelet lymphocytes ratio (PLR), serum fibrinogen, tumor markers (CEA, AFP, CA19-9), and CT findings.

CEA, AFP, and CA19-9 were categorized by each value based on the reference value of the institution. All tumor markers were divided into four categories: 1) within reference value, 2) more than but less than double that of the reference value, 3) more than double but less than triple, and 4) more than triple.

For the staging, the 8th edition TNM classification for gastric carcinoma of the American Joint Committee on Cancer (AJCC) was used. The clinical TNM staging were based on preoperative CT reports. CT findings were extracted from preoperative CT reports, which were read and described by experienced radiologists. The CTs were categorized by the presence of each finding as follows: ascites, omental cake, thickening of the peritoneal wall, plaques or nodules in the peritoneal cavity, or infiltration or stranding in abdominal fatty tissue.

2.3. Statistical analysis

Patients were divided into two groups according to the status of peritoneal seeding: seeding positive (+) or seeding negative (−). We excluded cytology-positive cases in the analysis because we cannot discriminate with bear eyes and cytology results were unavailable for immediate analysis in the operating room. The distribution of age, blood examination results, and tumor size in the two seeding groups were compared using the Wilcoxon Mann-Whitney *U* test. Associations between the existence of peritoneal seeding and ASA score, tumor markers, CT imaging, and TNM stage were evaluated by the chi-square test and the Mantel-Haenszel chi-square test. See Table 1 for details. To model the probability of peritoneal seeding, univariate and multivariate logistic regression analyses were conducted on associative factors. In the final model, all covariates included were selected using backward elimination.

To evaluate the performance of the final model, receiver operating characteristic (ROC) curve analysis was done. The area under the curve (AUC) was calculated, and diagnostic cut-off values were derived. Youden's index [15] was used to select an optimal cut-off. For internal validation, 10-fold cross-validation and the bootstrapping technique with 1000 resamples from the study data were used. Based on the final model, a nomogram was developed to predict the individual risk of peritoneal seeding occurrence. Statistical results were considered significant if the p-value was less than 0.05. All statistical analyses were performed with SAS (9.4; SAS Institute Inc., Cary, North Carolina) and R software (3.2.2; www.R-project.org).

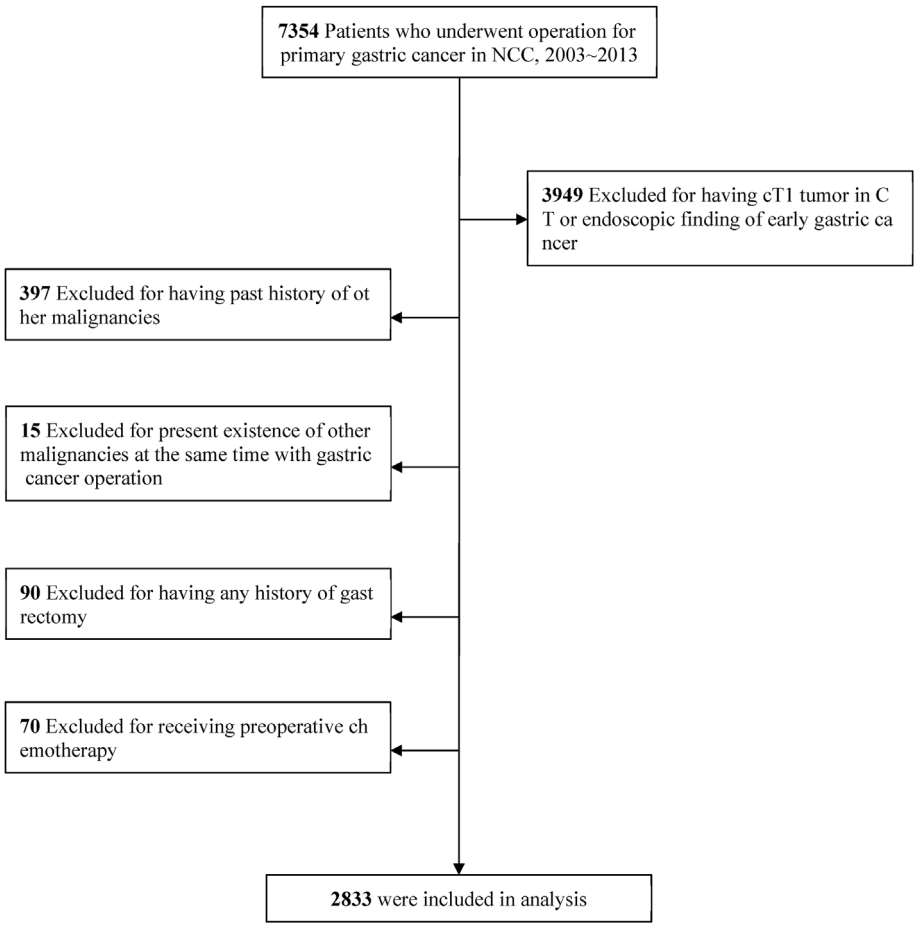


Fig. 1. Selection of the patients for the study cohort.

3. Results

Of the 2833 patients with advanced gastric cancer in our study cohort, 300 (10.6%) were intraoperatively identified with peritoneal seeding.

3.1. Factors predictive of peritoneal seeding in patients with gastric cancer

Baseline and distribution of clinical patient information, blood and imaging results, tumor markers, biopsy histology, and TNM stage can be found in Table 1. The study population consisted of 69.1% male and 30.9% female patients, and the proportion of seeding positive was 12.7% in females and 9.6% in males ($p = 0.01$). The median age of all patients was 60 (interquartile range; IQR 49–68).

Table 2 lists the results of the logistic regression analyses. In multivariate logistic regression, covariates selected via backward elimination were as follows: decrease in age (OR = 0.99, 95% CI 0.98–1.00, $p = 0.02$), high ASA score (OR = 2.13, 95% CI 1.21–3.73, $p = 0.01$), increase in fibrinogen (OR = 1.20, 95% CI 1.05–1.38, $p = 0.01$), tumor type 3 (OR = 2.69, 95% CI 1.62–4.47, $p < 0.001$) or 4 (OR = 8.71, 95% CI 4.61–16.42, $p < 0.001$) rather than type 2, involvement of middle (OR = 1.95, 95% CI 1.45–2.64, $p < 0.001$), anterior (OR = 0.60, 95% CI 0.43–0.83, $p = 0.002$), greater curvature (OR = 1.88, 95% CI 1.39–2.55, $p < 0.001$), CT finding of ascites (OR = 3.51, 95% CI 2.54–4.86, $p < 0.001$), peritoneal thickening (OR = 2.30, 95% CI 1.20–4.41, $p = 0.01$), plaques or nodules (OR = 7.03, 95% CI 4.14–11.93, $p < 0.001$), clinical T stage cT3 (OR = 3.22, 95% CI 1.94–5.32, $p < 0.001$) or cT4 (OR = 3.44, 95% CI 1.91–6.18, $p < 0.001$) rather than cT2, clinical N stage cN1 (OR = 4.21, 95% CI 2.35–7.54, $p < 0.001$), cN2 (OR = 3.76, 95% CI 2.06–6.84, $p < 0.001$), cN3 (OR = 3.35, 95% CI 1.66–6.78, $p < 0.001$) rather than cN0, and cM1 (OR = 2.29, 95% CI 1.38–3.82, $p = 0.002$) rather than cM0. No significant difference was found in other covariates.

3.2. Internal validation of performance and accuracy

The AUC under the ROC curve was 0.86, which implies a good performance of the developed nomogram in predicting seeding occurrence (Fig. 2). Sensitivity and 1-specificity, which represent the performance of a logistic model in different values of diagnostic cut-offs, were derived and summarized in **eTable 2**. An optimal cut-off probability level maximizes Youden's index, which was 7.5% with 84.6% sensitivity and 67.5% specificity. A fitted multivariate logistic regression model from each of the 1000 bootstrap resamples was also drawn. Mean parameter estimates obtained from the bootstrap samples were very close to the estimates in the final model, as biases for all selected covariates were less than 0.005 (eTable 1). Average AUC from 10-fold cross-validation was 0.85 (eFig. 1).

3.3. Resulting nomogram

A nomogram consisting of 13 variables was constructed (Fig. 3A) based on the multivariate logistic analysis results. As compared to

Table 1
Demographic information, blood test and imaging characteristics, tumor markers, TNM Stage and histology distribution of the study cohort.

Characteristics	No. (%[a])	No. (%[b])		*P* Value[c]
	All Patients	Seeding (−)	Seeding (+)	
	(n = 2833)	(n = 2533)	(n = 300)	
Age, median (IQR)	60 (49–68)	60 (50–69)	56 (45–66)	<.001[d]
Sex				
Men	1959 (69)	1770 (90)	189 (10)	0.01
Women	874 (31)	763 (87)	111 (13)	
ASA score[e]				
Low	2687 (95)	2409 (90)	278 (10)	0.07
High	146 (5)	124 (85)	22 (15)	
White blood cells[f], median (IQR), $10^3/\mu l$	6 (5–8)	6 (5–8)	6 (5–8)	0.28
Hemoglobin[f], median (IQR), $10^3/\mu l$	13 (11–15)	13 (12–15)	13 (11–14)	<.001[d]
Fibrinogen[f], median (IQR), $10^3/\mu l$	352 (296–420)	350 (293–418)	363 (308–445)	0.005[d]
Plt/Lymph[f], median (IQR)	134 (104–179)	131 (103–175)	164 (126–212)	<.001[d]
AFP, ng/mL				0.20[g]
0–20.0	2686 (97)	2402 (89)	284 (11)	
≥20.1	81 (3)	76 (94)	5 (6)	
CEA, ng/mL				0.59[g]
0–5.0	2259 (81)	2016 (89)	243 (11)	
5.1–10.0	542 (19)	488 (90)	54 (10)	
CA19–9, U/mL				<.001[g]
0–37.0	2088 (88)	1889 (90)	199 (10)	
37.1–74.0	290 (12)	240 (83)	50 (17)	
EGD type				<.001
2 (Ulcerated tumors with raised margins surrounded by a thickened gastric wall with clear margins)	514 (18)	495 (96)	19 (4)	
3 (Ulcerated tumors with raised margins, surrounded by a thickened gastric wall without clear margins)	2133 (75)	1919 (90)	214 (10)	
4 (Tumors without marked ulceration or raised margins, the gastric wall is thickened and indurated and the margin is unclear)	186 (7)	119 (64)	67 (36)	
Tumor size, median (IQR), cm	6 (4–8)	6 (4–8)	6 (5–13)	<.001*
Multiplicity				0.07
Single region	2704 (96)	2413 (89)	291 (11)	
Multiple region	124 (4)	117 (94)	7 (6)	
Tumor location				
Upper	774 (27)	632 (92)	142 (8)	<.001
Middle	657 (23)	513 (78)	144 (22)	<.001
Lower	2302 (81)	2058 (89)	244 (11)	0.97
Circumferential tumor location				
Anterior	880 (31)	794 (90)	86 (10)	0.34
Posterior	1121 (40)	1003 (89)	118 (11)	0.93
Lessor curvature	1646 (58)	1471 (89)	175 (11)	0.93
Greater curvature	888 (31)	757 (85)	131 (15)	<.001
Abdominal CT finding				
Ascites	357 (13)	242 (68)	115 (32)	<.001
Omental Cake	–	–	–	<.001
Peritoneal Thickening	64 (2)	38 (59)	26 (41)	<.001
Plaque or Nodule	89 (3)	39 (44)	50 (56)	<.001
Stranding or Infiltration	270 (10)	188 (70)	82 (30)	<.001
cT (primary tumor)				<.001
2 (Tumor invades the muscularis propria)	889 (31)	868 (98)	21 (2)	
3 (Tumor invades the subserosa)	1452 (51)	1260 (87)	192 (13)	
4 (Tumor invasion is contiguous to or exposed beyond the serosa or tumor invades adjacent structures)	492 (17)	405 (82)	87 (18)	
cN (regional metastasis)				<.001
0 (No regional lymph node metastasis)	716 (25)	701 (98)	15 (2)	
1 (Metastasis in 1–2 regional lymph nodes)	1029 (36)	907 (88)	122 (12)	
2 (Metastasis in 3–6 regional lymph nodes)	838 (30)	720 (86)	118 (14)	
3 (Metastasis in 7 or more regional lymph nodes)	250 (9)	205 (82)	45 (18)	
cM (distant metastasis)	112 (4)	74 (66)	38 (34)	<.001
cH (liver metastasis)	15 (1)	14 (93)	–	0.62
cP (peritoneal metastasis)	138 (5)	89 (64)	49 (36)	<.001
otherM (other distant metastasis)	41 (1)	38 (93)	–	0.49
Histological Differentiation				<.001
Well differentiated	310 (11)	297 (96)	13 (4)	
Moderately differentiated	856 (30)	807 (94)	49 (6)	
Poorly differentiated	1063 (38)	927 (87)	136 (13)	
Signet ring cell carcinoma	516 (18)	427 (83)	89 (17)	
Other	88 (3)	75 (85)	13 (15)	

Abbreviation: ASA, American Society of Anesthesiologist; EGD, Esophagogastroduodenoscopy.
[c] P value without any mark is from Chi-Square test.
[d] P value from Wilcoxon Mann-Whitney *U* test.
-: Less than 10 cases.
[a] Percentage of total patients (n = 2833). For some variables sample size is smaller than 2833 due to missing observations (AFP, n = 2767; CEA, n = 2801; CA19-9, n = 2378; Fibrinogen, n = 2799; Plt/Lymph, n = 2828; Abdominal CT finding, n = 2831; Tumor size, n = 2751; Multiplicity, n = 2828).

[b] Row percentage of each characteristic.
[e] Low, ASA Physiological Status category 1 and 2; High, ASA Physiological Status category 3.
[f] Standardized variable.
[g] P value from Mantel-Haenszel chi-square test.

the current standard of radiologic examination, this nomogram outperformed CT scans in the ability to identify peritoneal seeding. False-positive readings of peritoneal seeding using CT scans were high, even with interpretation by highly experienced radiologists (ascites: 67.8%, peritoneal thickening: 59.4%, plaque or nodule: 43.8%, stranding or infiltration of fat: 69.6%), whereas the nomogram produced an overall sensitivity rate of 84.6%. Fig. 3B juxtaposes two cases to demonstrate this nomogram's superior diagnostic capabilities compared to CT scans. Both patients were diagnosed with advanced gastric cancer without suspicion of seeding upon review of CT scans, and peritoneal deposits were subsequently discovered during exploratory laparotomy. However, risk estimates derived from the nomogram retrospectively predicted the presence of peritoneal seeding.

4. Discussion

In this large, single-institution study, a nomogram was generated after the investigation of clinicopathologic factors predictive of peritoneal seeding in advanced gastric cancer. Due to the highly heterogeneous nature of gastric cancer, personalized medicine tailored to the unique indexes of each patient is a necessary but unmet need in this oncologic field [16]. Nomograms, which can be understood as an individualized and non-invasive diagnostic medium, have shown superior prognostic abilities compared to traditional staging systems in gastric cancer as well as other cancer types [17–19], and comparison to other decision aids (including risk groups, artificial neural networks, probability tables, and classification and regression tree analyses) demonstrated its superior ability to assess risk [20].

The inability to accurately identify peritoneal deposits in the preoperative setting may reveal unexpected and unresectable tumors during exploratory laparotomy – resulting in longer hospital stay, increased risk of postoperative complications, increased medical costs, and decreased likelihood of receiving systemic therapy in unresectable cases [21]. Diagnostic laparoscopy is, therefore, critical in the staging of gastric cancer patients. However, overutilization of this resource to detect seeding leads to several disadvantages. While there is a slight increase in morbidity associated with diagnostic laparoscopy, this does not necessarily outweigh its benefits, diagnostic laparoscopy has the potential to differentiate between localized and widespread peritoneal metastasis. Also in the localized type, documentation of the metastatic area before neoadjuvant chemotherapy is essential to include it in the resection specimen at the time of gastric resection, especially if the metastasis have disappeared after chemotherapy. However, only a small proportion of patients eventually gain clinically useful information [6,9]. Additionally, experts state that even minimally invasive procedures introduce surgical trauma and should be wielded with an abundance of caution [22], as complications of this procedure include hemodynamic instability, posterior penetrating trauma with highly potential bowel injury, and intraabdominal injury. Second, routine diagnostic laparoscopy results in inefficient economics when done in cases whose risk of peritoneal seeding is low. But this procedure still has important role in staging and decision making in the selective cases. In a study of Korea's healthcare delivery system, 85% of patients received unnecessary outpatient hospital services [23]. A consequence of Korea's fee-for-service payment system without restrictive gate-keeping regulations results in the overutilization of specialist care [24]. Selective diagnostic laparoscopy ameliorates the disadvantages found with its over- and underutilization, and this nomogram can be used to identify candidates who can benefit from this procedure.

To construct the nomogram, routinely tested, preoperative factors were identified in a comprehensive manner, and aggressive statistical analysis of specific variables was performed on these wide-ranging categories (patient characteristics; blood examinations; tumor biomarkers, type, size, and location; patterns of stomach wall involvement; CT scans; and histopathologic and TNM classifications).

Concerning elevated levels of fibrinogen, there are two theories to explain this event. The first is that fibrinogen is directly involved with the pathogenesis of peritoneal seeding, where its increased interaction with fibroblast growth factor-2 (FGF-2) promotes cell growth and angiogenesis [25]. To note, previous studies theorized that fibroblasts at peritoneal metastatic sites stimulate tumor progression by promoting adhesion of tumor cells to the submesothelium, which is a critical step in peritoneal dissemination [26]. Second, increased fibrinogen levels may simply be a response to solid tumor growth and spread, considering that fibrinogen plays a role as an extracellular matrix protein [27]. Fibrinogen serves as a scaffold for the binding of growth factors to promote the actions of metastasis, such as adhesion and migration during cell growth and proliferation [28,29].

As for stomach wall involvement, the results indicated that localized invasion of the greater curvature increased the probability of peritoneal metastasis. It might be due to lack of obstructive symptoms which allow tumors to grow large until diagnosis. A previous study found similar results, implicating the anterior wall as a site correlated with increased peritoneal metastasis [12]. These results were also validated by a study that associated the upper-third of the stomach with increased rates of peritoneal seeding [11], which generally falls in line with results associating peritoneal seeding with the upper and middle portions of the stomach.

CT indicators of peritoneal seeding – involving ascites, peritoneal thickening, and plaque/nodule in peritoneal cavity – have also been associated with peritoneal metastasis. However, accurate staging of peritoneal metastasis with traditional radiologic modalities is challenging because microscopic malignancies can develop unnoticed [30]. In a recent study assessing the role of CTs in identifying peritoneal disease in 52 patients with potentially curable gastric cancer, the overall sensitivity was found to be 25%, with one false positive and six false negative patients whose seeding was identified during laparoscopy, and nine patients whose seeding was identified during surgery [31]. However, it also frequently produces false negatives, and its sensitivity and diagnostic performance compared with CT readings is controversial among various studies [32–34]. Even after a multimodal radiologic approach using CTs, ultrasound, and PET scans, unexpected and unresectable tumors were found during exploratory laparotomy.

Poorly differentiated and SRC histological classifications also showed an independent association with peritoneal metastasis in advanced gastric cancer patients. A study of 662 patients with advanced SRC gastric adenocarcinoma showed a trend toward deeper tumor invasion of the gastric wall, greater lymph node spread, and peritoneal metastasis compared to the non-SRC group [35].

Internal validation of this nomogram revealed robust performance in terms of accuracy and the balance between specificity and sensitivity. A 1000-sample bootstrapping method designed to

Table 2
Result of logistic regression analysis for the probability of peritoneal seeding.

	Univariate		Multivariate[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.98 (0.97–0.99)	<.001	0.99 (0.98–1.00)	0.02
Sex				
Male	1 [Reference]			
Female	1.45 (1.10–1.91)	0.01		
ASA score[b]				
Low	1 [Reference]		1 [Reference]	
High	1.67 (0.99–2.80)	0.05	2.13 (1.21–3.73)	0.01
White blood cells[c], $10^3/\mu l$	0.97 (0.84–1.11)	0.66		
Hemoglobin[c], $10^3/\mu l$	0.78 (0.69–0.89)	<.001		
Fibrinogen[c], $10^3/\mu l$	1.23 (1.08–1.39)	0.001	1.20 (1.05–1.38)	0.01
Plt/Lymph[c]	1.33 (1.19–1.50)	<.001		
AFP, ng/mL				
0–20.0	1 [Reference]			
≥20.1	0.67 (0.28–1.62)	0.38		
CEA, ng/mL				
0–5.0	1 [Reference]			
≥5.1	0.82 (0.58–1.17)	0.28		
CA19–9, U/mL				
0–37.0	1 [Reference]			
≥37.1	1.96 (1.38–2.76)	<.001		
EGD type[d]				
2	1 [Reference]			
3	2.62 (1.56–4.39)	<.001	2.69 (1.62–4.47)	<.001
4	11.75 (6.45–21.40)	<.001	8.71 (4.61–16.42)	<.001
Tumor size	1.17 (1.13–1.21)	<.001		
Multiplicity				
Single region	1 [Reference]			
Multiple region	0.40 (0.15–1.04)	0.06		
Tumor location				
Upper				
Absent	1 [Reference]			
Present	2.77 (2.12–3.64)	<.001		
Middle				
Absent	1 [Reference]			
Present	3.61 (2.75–4.75)	<.001	1.95 (1.45–2.64)	<.001
Lower				
Absent	1 [Reference]			
Present	0.99 (0.71–1.40)	0.97		
Anterior				
Absent	1 [Reference]			
Present	0.9 (0.67–1.20)	0.47	0.60 (0.43–0.83)	0.002
Posterior				
Absent	1 [Reference]			
Present	1.03 (0.78–1.35)	0.86		
Lessor curvature				
Absent	1 [Reference]			
Present	1.01 (0.77–1.32)	0.94		
Greater curvature				
Absent	1 [Reference]		1 [Reference]	
Present	1.85 (1.41–2.42)	<.001	1.88 (1.39–2.55)	<.001
Abdominal CT finding				
Ascites				
Absent	1 [Reference]		1 [Reference]	
Present	5.75 (4.27–7.73)	<.001	3.51 (2.54–4.86)	<.001
Omental Cake				
Absent	1 [Reference]			
Present	79.66 (3.03->999.99)	<.001		
Peritoneal Thickening				
Absent	1 [Reference]		1 [Reference]	
Present	4.67 (2.57–8.49)	<.001	2.30 (1.20–4.41)	0.01
Plaque or Nodule				
Absent	1 [Reference]		1 [Reference]	
Present	12.41 (7.74–19.88)	<.001	7.03 (4.14–11.93)	<.001
Stranding or Infiltration				
Absent	1 [Reference]			
Present	4.62 (3.33–6.41)	<.001		
cT[e]				
2	1 [Reference]		1 [Reference]	
3	5.12 (3.16–8.29)	<.001	3.22 (1.94–5.32)	<.001
4	7.04 (4.20–11.81)	<.001	3.44 (1.91–6.18)	<.001
cN[f]				
0	1 [Reference]		1 [Reference]	
1	6.16 (3.30–11.48)	<.001	4.21 (2.35–7.54)	<.001

Table 2 (*continued*)

	Univariate		Multivariate[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
2	8.08 (4.35–15.03)	<.001	3.76 (2.06–6.84)	<.001
3	10.17 (5.13–20.16)	<.001	3.35 (1.66–6.78)	<.001
cM				
0	1 [Reference]		1 [Reference]	
1	4.15 (2.61–6.6)	<.001	2.29 (1.38–3.82)	0.002
cH				
0	1 [Reference]			
1	0.35 (0.02–6.59)	0.48		
cP				
0	1 [Reference]			
1	5.8 (3.85–8.73)	<.001		
other M				
0	1 [Reference]			
1	0.86 (0.28–2.62)	0.78		
Histological Differentiation				
Well differentiated	1 [Reference]			
Moderately differentiated	1.65 (0.80–3.39)	0.17		
Poorly differentiated	3.78 (1.92–7.45)	<.001		
Signet ring cell carcinoma	4.77 (2.37–9.63)	<.001		
Other	4.11 (1.63–10.34)	0.003		

Abbreviation: OR, Odds ratio; CI, Confidence interval, ASA, American Society of Anesthesiologist; EGD, Esophagogastroduodenoscopy.

[a] Covariates are from the best fitting multivariate logistic regression model.

[b] Low, ASA Physiological Status category 1 and 2; High, ASA Physiological Status category 3.

[c] Standardized variable.

[d] 2, Ulcerated tumors with raised margins surrounded by a thickened gastric wall with clear margins; 3, Ulcerated tumors with raised margins, surrounded by a thickened gastric wall without clear margins; 4, Tumors without marked ulceration or raised margins, the gastric wall is thickened and indurated and the margin is unclear.

[e] 2, tumor invades the muscularis propria; 3, tumor invades the subserosa; 4, Tumor invasion is contiguous to or exposed beyond the serosa or tumor invades adjacent structures.

[f] 0, No regional lymph node metastasis; 1, Metastasis in 1–2 regional lymph nodes; 2, Metastasis in 3–6 regional lymph nodes; 3, Metastasis in 7 or more regional lymph nodes.

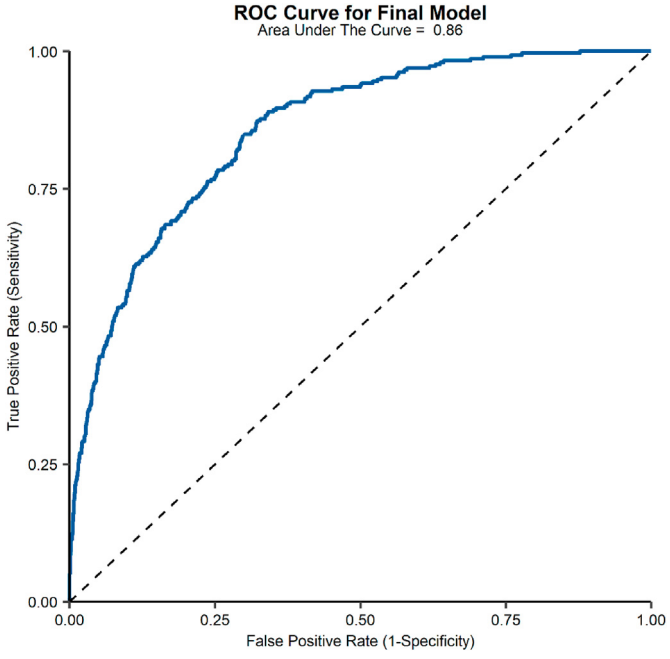


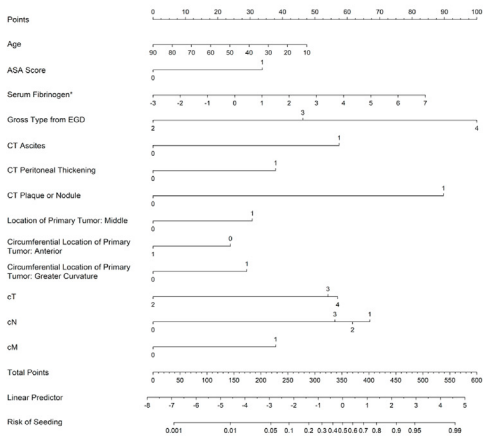
Fig. 2. Receiver operating characteristic curve illustrating the performance of the final multivariate logistic regression model using selected covariates. After comparing for sensitivity (true positive rate) and 1-specificity (false positive rate), the area under curve indicates the accurate ability of the final model to classify peritoneal seeding (+) and (−) cases of gastric cancer.

estimate the sensitivity of each factor showed a bias of less than 0.005 between parameter estimates derived from the final multivariate logistic model and mean model parameter estimates obtained from random sampling; this means there was hardly any deviation between observed and sampled pools. Testing of the selected covariates using a ROC curve revealed an AUC indicative of a statistically good correlation between specificity (84.6%) and sensitivity (67.5%) with a cut-off probability of 7.5%. Future studies from external sources will provide further validation.

This study has several limitations. The use of retrospective data can potentially incorporate selection bias into the results despite efforts to adjust for confounding variables. Also, patients with advanced stage gastric cancer who received neoadjuvant chemotherapy were excluded, so the role of staging laparoscopy nomogram in those group of patients should be further evaluated. Despite the robust results of this nomogram, solely relying on this prognostic methodology will produce incidences of false positive and negative cases and therefore this tool should serve as an adjunct to judicious, multimodal clinical decision-making. However, deciding cut off value in nomogram depends on different situations like the neoadjuvant treatment setting or the upfront surgery setting, and therefore should be adjusted according to varying purposes.

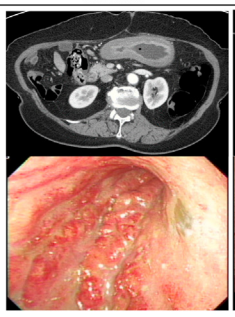
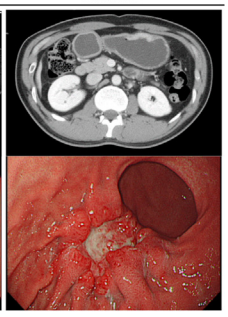
Nomograms would be useful to assist clinicians in planning diagnostic laparoscopy in different situations. This nomogram may be used to minimize unnecessary laparotomies by detecting patients unqualified for surgery due to peritoneal seeding, whose diagnostic laparoscopy did not indicate otherwise. This, in turn, may reduce the large volume of patients who receive upfront surgery in Korea and Japan. In this case, cut-off criteria with higher sensitivity would be preferred. Considering the aforementioned purposes, we evaluated the performance of the nomogram. Among 2560 patients who did not receive diagnostic laparoscopy, 215 had peritoneal seeding. Among them, our nomogram correctly predicted 179 patients (83.3%) to be seeding positive with and optimal cut-off probability at 7.5%. If diagnostic laparoscopy was conducted after nomogram prediction, this means one could identify

A



Note. Serum fibrinogen is standardized variable

B

	Patient A			Patient B		
CT Image						
Endoscopic Images						
Histologic Diagnosis	Signet Ring Cell Adenocarcinoma			Poorly Differentiated Adenocarcinoma		
CT Stage	T2N1M0			T4aN3M0		
Selected Covariates	**Value**	**Points**	**Note(s)**	**Value**	**Points**	**Note(s)**
Age	74	9.6		31	35.4	
ASA Score[a]	Low	0		Low	0	
Serum Fibrinogen[b] ($10^{-1}/\mu l$)	0.07	25.9		-0.07	24.2	
CT Findings						
Ascites	0	0		0	0	
Peritoneal thickening	0	0		0	0	
Plaque or nodule	0	0		0	0	
Gross Type from EGD	4	100		3	46	
Tumor Location						
Middle	1	31		0	0	
Anterior	1	0		0	24	
Greater curvature	1	29		1	29	
cT	2	0		4	57	
cN	1	67	Lesser curvature	3	56	Multiple enlarger LN at greater and lesser curvature
cM	0	0		0	0	
Total Points		262.5			271.6	
Estimated Probability (%) [95% CI]	12.5 [6.6-22.3]			15.0 [8.9-24.1]		
Status of peritoneal seeding after diagnostic laparoscopy	+			+		

Abbreviation: CT, computed tomography; ASA, American Society of Anesthesiologist; EGD, Esophagogastroduodenoscopy
[a] Low, ASA Physiological Status category 1 and 2; High, ASA Physiological Status category 3.
[b] Standardized variable.

Fig. 3. (A) Nomogram with selected variables from the multivariate logistic regression model to assess the probability of peritoneal seeding. (B) Two cases demonstrated to compare performance between CT scans and our nomogram to detect peritoneal seeding in patients with gastric cancer. To generate a numerical value depicting probability, first draw an upward, vertical line from the determined value for each clinicopathologic factor, ending at the Points axis. Calculate the total points of all 14 factors. After pinpointing the appropriate location in the Total Points axis, draw a downward, vertical line to determine the probability of seeding. The optimal cut-off probability was determined to be at 7.5%, and a higher total score indicates a larger probability of peritoneal seeding.
Note. Serum fibrinogen is standardized variable.

peritoneal seeding approximately 83% correctly and avoid unnecessary laparotomy.

On the other hand, in the situation in which neoadjuvant chemotherapy is popular, like in many western countries, our nomogram can be utilized to select the patients who can get chemotherapy without diagnostic laparoscopy to minimize treatment delay, medical cost, and morbidity. Thus, in this case, cut-off criteria with higher specificity would be preferred. In real the nomogram had better ability to detect the peritoneal metastasis if compared to the computer tomography. Finally, we believe that there is no magic procedure or imaging, or nomogram and all the mentioned evaluation methods should be discussed and used as needed dependent on the circumstance of the cases.

5. Conclusion

In conclusion, this study demonstrated the independent association of various factors with peritoneal seeding. This nomogram could have different clinical utilities in different treatment strategies and finally contribute to patient-centered decision-making in any situation.

Source of funding

There are no declared conflicts of interest that could lead to bias for any of the authors of this manuscript. This work was supported by grant NCC-1410130, 1710120, 2010090, and 2310210 from the National Cancer Center, Korea.

Ethical approval

This study was approved by the Institutional Review Board of the National Cancer Center (IRB No. NCC2016-0079).

Consent to participate

The IRB waived the need for informed consent for this retrospective study.

Data availability

Data available on request due to privacy/ethical restrictions: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CRediT authorship contribution statement

Norihito Kubo: Data accrual, Design of the study, manuscript writing, critical review. **Hyunsoon Cho:** Statistical, Formal analysis, manuscript writing, critical revie. **Dahhay Lee:** Statistical analysis, manuscript writing, critical review. **Hannah Yang:** manuscript writing, critical review. **Youngsook Kim:** Data acquisition, critical review. **Harbi Khalayleh:** manuscript writing, critical review and

revision. **Hong Man Yoon:** Data acquisition, critical review. **Keun Won Ryu:** Data acquisition, critical review. **George B. Hanna:** Critical Review, approval of the study. **Daniel G. Coit:** Critical Review, approval of the study. **Kenichi Hakamada:** Critical Review, approval of the study. **Young-Woo Kim:** design of the study, Data acquisition, Formal analysis, manuscript writing, critical review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work was supported by grant NCC-1410130, 1710120, 2010090, 2310210 from the National Cancer Center, Korea. There are no declared conflicts of interest that could lead to bias for any of the authors of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.12.013.

References

[1] Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003;56(1):1–9.
[2] Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. Br J Surg 2000;87(2):236–42.
[3] Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. Gastric Cancer 2012;15(Suppl 1):S38–47.
[4] Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 1996;223(2):134–40.
[5] Yoon H, Lee DH. New approaches to gastric cancer staging: beyond endoscopic ultrasound, computed tomography and positron emission tomography. World J Gastroenterol 2014;20(38):13783–90.
[6] Richardson JR, Khan OA. In patients with radiologically-staged resectable oesophago-gastric junctional tumours, is diagnostic laparoscopy useful as an additional staging procedure? Int J Surg 2012;10(4):198–202.
[7] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24(14):2137–50.
[8] Sandler G. Costs of unnecessary tests. Br Med J 1979;2(6181):21–4.
[9] Lehnert T, Rudek B, Kienle P, Buhl K, Herfarth C. Impact of diagnostic laparoscopy on the management of gastric cancer: prospective study of 120 consecutive patients with primary gastric adenocarcinoma. Br J Surg 2002;89(4):471–5.
[10] Giger U, Schafer M, Krahenbuhl L. Technique and value of staging laparoscopy. Dig Surg 2002;19(6):473–8.
[11] Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. Am J Surg 2006;191(1):134–8.
[12] Hur H, Lee HH, Jung H, Song KY, Jeon HM, Park CH. Predicting factors of unexpected peritoneal seeding in locally advanced gastric cancer: indications for staging laparoscopy. J Surg Oncol 2010;102(7):753–7.
[13] Hosogi H, Shinohara H, Tsunoda S, Hisamori S, Sumida H, Hida K, et al. Staging laparoscopy for advanced gastric cancer: significance of preoperative clinicopathological factors. Langenbeck's Arch Surg 2017;402(1):33–9.
[14] Irino T, Sano T, Hiki N, Ohashi M, Nunobe S, Kumagai K, et al. Diagnostic staging laparoscopy in gastric cancer: a prospective cohort at a cancer institute in Japan. Surg Endosc 2018;32(1):268–75.
[15] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3(1):32–5.
[16] Lordick F, Allum W, Carneiro F, et al. Unmet needs and challenges in gastric cancer: the way forward. Cancer Treat Rev 2014;40(6):692–700.
[17] Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol 2003;21(19):3647–50.
[18] Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29(23):3163–72.
[19] Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 2003;10(10):1140–51.
[20] Shariat SF, Capitanio U, Jeldres C, Karakiewicz PI. Can nomograms be superior to other prediction tools? BJU Int 2009;103(4):492–5. ; discussion 495-497.
[21] Velanovich V, Wollner I, Ajlouni M. Staging laparoscopy promotes increased utilization of postoperative therapy for unresectable intra-abdominal malignancies. J Gastrointest Surg 2000;4(5):542–6.
[22] Siewert JR. Invited commentary: are the staging systems for lymphatic spread important in gastric cancer? Surgery 2000;127(2):127–8.
[23] Lee JY, Jo MW, Yoo WS, Kim HJ, Eun SJ. Evidence of a broken healthcare delivery system in korea: unnecessary hospital outpatient utilization among patients with a single chronic disease without complications. J Kor Med Sci 2014;29(12):1590–6.
[24] Chun CB, Kim SY, Lee JY, et al. World health organization. Regional office for E, European observatory on health S, policies. *Republic of Korea: health system review*. Copenhagen: World Health Organization. Regional Office for Europe; 2009. available at: https://apps.who.int/iris/handle/10665/330337.
[25] Sahni A, Simpson-Haidaris PJ, Sahni SK, Vaday GG, Francis CW. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemostasis 2008;6(1):176–83.
[26] Koyama T, Yashiro M, Inoue T, Nishimura S, Hirakawa YSCK. TGF-beta1 secreted by gastric fibroblasts up-regulates CD44H expression and stimulates the peritoneal metastatic ability of scirrhous gastric cancer cells. Int J Oncol 2000;16(2):355–62.
[27] Simpson-Haidaris PJ, Rybarczyk B. Tumors and fibrinogen. The role of fibrinogen as an extracellular matrix protein. Ann N Y Acad Sci 2001;936:406–25.
[28] Yu X, Hu F, Yao Q, Li C, Zhang H, Xue Y. Serum fibrinogen levels are positively correlated with advanced tumor stage and poor survival in patients with gastric cancer undergoing gastrectomy: a large cohort retrospective study. BMC Cancer 2016;16:480.
[29] Repetto O, De RV. Coagulation and fibrinolysis in gastric cancer. Ann N Y Acad Sci 2017;1404(1):27–48.
[30] Turlakow A, Yeung HW, Salmon AS, Macapinlac HA, Larson SM. Peritoneal carcinomatosis: role of (18)F-FDG PET. J Nucl Med 2003;44(9):1407–12.
[31] Burbidge S, Mahady K, Naik K. The role of CT and staging laparoscopy in the staging of gastric cancer. Clin Radiol 2013;68(3):251–5.
[32] Tanaka T, Kawai Y, Kanai M, Taki Y, Nakamoto Y, Takabayashi A. Usefulness of FDG-positron emission tomography in diagnosing peritoneal recurrence of colorectal cancer. Am J Surg 2002;184(5):433–6.
[33] Lim JS, Kim MJ, Yun MJ, Oh YT, Kim JH, Hwang HS, et al. Comparison of CT and 18F-FDG PET for detecting peritoneal metastasis on the preoperative evaluation for gastric carcinoma. Korean J Radiol 2006;7(4):249–56.
[34] Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JFM, Bosscha K. FDG-PET has no definite role in preoperative imaging in gastric cancer. Eur J Surg Oncol 2009;35(5):449–55.
[35] Li C, Kim S, Lai JF, et al. Advanced gastric carcinoma with signet ring cell histology. Oncology 2007;72(1–2):64–8.