

Tumor Depth Prediction of Gastric Cancer With a T4 Score

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Abstract. *Background/Aim:* Peritoneal metastases are often found at surgery of pT4 gastric cancers, preventing R0 resection. In the event of successful R0 resection, distant metastases still occur in a sizeable proportion of patients. Estimation of the depth of invasion has a relatively low accuracy (57%-86%) compared with pathological findings. This study sought to develop a clinical score to distinguish between pathological stage T4 (pT4) and pT1-3 gastric cancer. *Patients and Methods:* Reviewing the data of 2,771 patients who had undergone gastrectomy at our hospital from January 1996-December 2016, we assessed demographic factors plus tumor markers, diameter, location, histology, and macroscopic type according to the fifth edition (2019) of the WHO classification. Significant factors on multivariate analysis were used to develop a pT4 gastric cancer depth prediction score (T4 score). *Results:* Multivariate analysis revealed that the clinical factors associated with pT4 disease were CA19-9 elevation, tumor diameter ≥ 50 mm, poorly cohesive type adenocarcinoma, mucinous adenocarcinoma, and WHO macroscopic types 2-4. The T4 score was obtained by weighing these factors according to the β -coefficient. The optimum cutoff value of the T4 score was 4 points. A total of 79.4% of cases with a T4 score ≥ 4 points were stage pT4. A total of 93.9% of cases with a T4 score < 4 points were stage pT1-3, with 91.1% sensitivity, 85.3% specificity, 79.4% positive predictive value, and 93.9% negative predictive

value. *Conclusion:* T4 scoring can differentiate pT4 gastric cancer from pT1-3 gastric cancer.

According to the eighth edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumors, staging system (1), pT4 gastric cancer is categorized as tumor invasion that is contiguous with or extends beyond the serosa (pT4a), or invades adjacent structures (pT4b) (1). In the absence of metastatic disease, gastrectomy is performed. However, in pT4 disease, peritoneal metastases are often detected at laparotomy, preventing an R0 resection (2-4). Prognosis is guarded, as peritoneal (5) and distant (6) metastases often develop following surgery. Preoperative chemotherapy has been introduced to address this problem, and clinical studies from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) (7) and the Federation Nationale des Centres de Lutte contre le Cancer (FNCLCC) (8) have shown a survival advantage with NAC+ surgery vs. surgery alone. The 4-drug regimen of fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin (FLOT4) has been used to further improve prognosis (9). An accurate invasion depth measurement of pT4 gastric cancer is indispensable for therapy choice.

Different modalities, including endoscopic ultrasound (10-17) and computed tomography CT (18-22), have been employed for assessment of tumor depth invasion, with each method having its own strengths and weaknesses. Measurement of gastric cancer depth has not correlated closely with pathological findings (57%-86%) (17).

We conducted a retrospective analysis of factors used in the clinical diagnosis and developed a pT4 gastric cancer depth prediction score (T4 score), to investigate whether the T4 score could accurately distinguish pT4 disease from pT1-3 disease.

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Key Words: Gastric cancer, receiver operating characteristics analysis, prediction score, tumor depth.

Patients and Methods

We used the data of 2,771 cases of primary gastric cancer treated with gastrectomy between 1996 and 2016. These cases were previously analyzed in another study looking at the ability to distinguish between Stage III and IV disease using a clinical score (23). The need for

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informed consent was waived by the Institutional Review Board of our hospital as the study was retrospective. TNM categories were determined using the recent UICC classification of gastric carcinoma (Table I) (1).

We investigated multiple factors as potential predictors of pT4 disease, including demographics, and used receiver operating characteristics (ROC) analysis to set cutoffs for serum CEA ≤ 5.0 ng/ml vs. ≥ 5.1 ng/ml, serum CA19-9 ≤ 37 U/ml vs. ≥ 38 U/ml, and tumor diameter (≤ 49 mm vs. ≥ 50 mm). In order to assess the predictive values of anatomical location, the stomach was divided into the fundus, corpus, antrum, and pylorus. Investigation of the histological and macroscopic types (Types 0-4) was also performed. Both macroscopic and histological types were labeled according to the WHO classification of gastric carcinoma (24).

Statistical analysis. We initially investigated the association between pretreatment factors and pathologic stage (pT4 vs. pT1-3) by univariate logistic regression analysis, followed by multivariate logistic regression analysis of the factors identified as explanatory variables. Subsequently, factors predictive of pT4 disease were weighted, corresponding to the relative magnitude of the β -coefficient to obtain the T4 score. ROC analysis was then performed. The cutoff value of the T4 score was derived from the ROC curve by determination of the Youden index.

The accuracy of the T4 score for pathologic stage (pT4 vs. pT1-3) was evaluated in the case cohort using the chi-squared test. All analyses were performed using commercial software (JMP ver. 15, SAS Institute, Cary NC, USA).

Results

Univariate analysis. The associations between pT-category (pT4 vs. pT1-3) and factors derived from univariate analysis are shown in Table II.

A tumor diameter ≥ 50 mm, sex, serum CEA ≥ 5.1 ng/ml, and serum CA19-9 ≥ 38 U/m were significantly associated with pT4 disease. Regarding the influence of tumor anatomical subsites, histology of poorly differentiated adenocarcinoma, and mucinous carcinoma, and WHO macroscopic tumor types 2, 3, and 4 correlated positively with pT4 disease.

Multivariate analysis. A total of 22 factors that were significant according to univariate analysis were used as covariates for multivariate logistic regression analysis. The factors that remained significant for discriminating T-category (pT4 vs. pT1-3) by multivariate analysis were tumor marker CA19-9 level, tumor diameter ≥ 50 mm, WHO macroscopic type (type 0, type 2, type 3, and type 4), poorly differentiated adenocarcinoma, and mucinous histology. However, the other 14 factors, including macroscopic type 1, were not independent predictors (Table II).

Establishment of the T4 prediction score. The T4 score was generated by assigning points to each of the factors identified by multivariate analysis. The factors were weighted according to a non-standardized β -coefficient's relative magnitude. One

Table I. Patient characteristics.

Age	64.2 \pm 10.3
Sex	
M	1,881
F	890
T	
M	662
SM	595
MP	287
SS	180
SE	864
SI	183
N	
N0	1,528
N1	585
N2	423
N3	235
M	
M0	100
M1	2,671

M: Male; F: female. TNM categories according to the recent UICC classification of gastric carcinoma. The depth of tumor invasion is recorded in the T-category. The N-category denotes lymph node metastasis. Presence or absence and sites of distant metastasis as M-category (1).

point was assigned for poorly differentiated adenocarcinoma and mucinous histology. Two points were assigned for elevated CA19-9 and for macroscopic type 2. Three points were assigned for macroscopic type 3 or 4. A tumor diameter ≥ 50 mm was assigned 4 points due to the relative β -coefficient being approximately four times that for the mucinous histology, which was assigned one point (Table III).

ROC analysis was then performed to identify the optimal cut-off value for the T4 score, which, based on the Youden index, was set at 4 points (Figure 1). The accuracy of a T4 score ≥ 4 points for identifying pT4 disease was 87.5% [95% confidence interval (CI)=86.4-88.6%]. When we investigated the value of distinguishing pT4 gastric cancer from pT1-3 gastric cancer by the T4 score, its sensitivity was 91.1% (95%CI=89.6-92.5%), specificity was 85.3% (95%CI=84.4-86.2%), positive predictive value was 79.4% (95%CI=78.1-80.6%), and negative predictive value was 93.9% (95%CI=92.9-94.9%) (Table IV).

Discussion

We generated a new prediction score for pT4 gastric cancer (the T4 score) by analyzing preoperative factors in 2,771 cases. This score was effective in distinguishing between pT4 from pT1-3 disease prior to surgery.

Peritoneal metastases are often found with pT4 gastric cancer. If they are macroscopic, an R0 resection is impossible (2-5). Even if radical excision is performed in the absence of obvious peritoneal disease, metachronous peritoneal metastases

Table II. Analysis of preoperative factors.

	T4 n=1,047	%	T1-2 n=1,724	%	Total	Univariate analysis	Multivariate analysis
Age	67.3±11.8		65.4±11.5			<0.0001	0.8163
Sex	F336/M711		F546/M1178		F683/M1366	0.2276	
Tumor markers							
CA19_9	284	68.20	132	31.80	412	<0.0001	0.0008
CEA	253	60.64	161	39.36	404	<0.0001	0.4852
Tumor diameter							
<49	144	10.32	1251	89.68	1,395		
≥50	894	67.37	433	32.63	1,327	<0.0001	<0.0001
Anatomical subsites							
Fundus	270	49.27	278	50.73	548	<0.0001	0.1706
Corpus	416	33.99	808	66.01	1,224	<0.0001	0.1382
Antrum	352	37.05	598	62.95	950	0.3948	
Cardia	133	18.79	134	81.21	165	<0.0001	0.3409
Pylorus	132	76.74	40	23.26	172	<0.0001	0.1670

CEA: Carcinoembryonic antigen; F: female; M: male.

can occur and have a poor prognosis even with postoperative adjuvant chemotherapy (6). pT4 gastric cancer is categorized as a tumor invasion that is contiguous with the peritoneal cavity or that penetrates the serosa with exposure to the peritoneal cavity. Moreover, serosa-exposed subgroups of T4a gastric cancer have been identified as a significant risk factor for peritoneal recurrence in patients undergoing curative gastrectomy (25). Therefore, it takes expectation of the preoperative chemotherapy for treatment outcome improvement. Smyth *et al.* said that treatment with chemotherapy before surgery increases the chance for curative resection, eliminates early microscopic spread, and allows an *in vivo* response assessment of treatment (26). TNM categories T3-4 and N1.3 were selected as candidates for perioperative chemotherapy in a prospective cohort study to evaluate the validity of clinical staging in Stomach Cancer Study Group of Japan Clinical Oncology Group (JCOG)1302A (27). Above all, it is important to detect the pT4 disease association with metachronous peritoneal metastases.

The different modalities employed for measurement of tumor invasion depth all have strengths and weaknesses. Clinical staging of T category is relatively inaccurate (57%-89%) compared with pathological diagnosis. Because of the lack of objective criteria for assessing the depth of invasion, endoscopic staging is often based on clinical experience. Although endoscopic ultrasonography (EUS) is useful, it is difficult to assess the depth of ulcerated lesions, and its accuracy is not improved over that of standard endoscopy (17). It has been reported that narrow band imaging (NBI) achieves 92% accuracy for assessing the depth of invasion of early gastric cancer. However, NBI is only useful in early gastric cancer because it is limited to the mucosal surface (17).

Table III. Scores of factors for T4 disease prediction.

	Multivariate analysis		
	p-Value	β-Coefficient	Weighted score
Tumor marker			
CA19-9	0.0017	0.124	2
Tumor diameter, mm			
≥50	<0.0001	0.263	4
por	0.0087	0.071	1
MUC	0.0242	0.071	1
Macroscopic type			
Type 0	<0.0001	-0.324	-5
Type 2	<0.0001	0.119	2
Type 3	<0.0001	0.213	3
Type 4	<0.0001	0.208	3

MUC: Mucinous; por: poorly differentiated carcinoma.

In this study, we investigated preoperative factors related to depth of tumor invasion and generated the T4 score through weighting of each factor to obtain a useful predictor of the depth of invasion of gastric cancer.

Staging laparoscopy was performed in cases of suspected peritoneal spread, to spare the patient from an unnecessary resection (28, 29). However, it was difficult to detect tumor invasion beyond the serosa.

There are few reports of scores for pT staging. One scoring system for predicting metastases to regional lymph nodes has been reported to have a specificity and sensitivity of 65.7% and 83.5%, respectively (30). We have previously reported a score that can distinguish Stage III/IV from Stage I/II disease (23). Chemotherapy with or without surgery is the first-line treatment

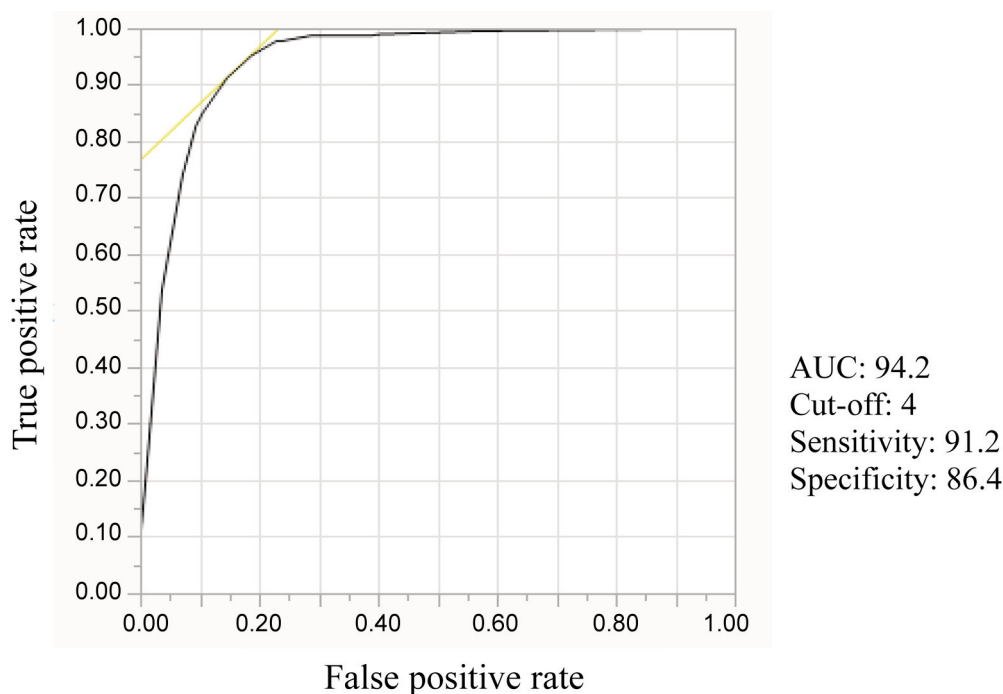


Figure 1. Receiver operating characteristics curve of the T4 score. ROC analysis was performed to identify the optimum cut-off value for the T4 score, which was 4 points based on the Youden index.

for stage III/IV gastric cancer, while surgery is the first-line treatment for stage I/II gastric cancer. When distinguishing between stage III/IV gastric cancer and stage I/II gastric cancer by the Clinical Stage Prediction score we found a sensitivity of 78.7%, specificity of 92.1%, positive predictive value of 86.0%, and negative predictive value of 87.5% (23). A depth-predicting score predicting intramucosal and minute submucosal (M-SM1; <500 μm in depth) and deeper submucosal invasion (SM2; ≥500 μm in depth) from characteristic endoscopic findings such as location of the tumor, its macroscopic type, its size, and the endoscopic findings has been reported to be an accurate predictor of the success of endoscopic treatment for early gastric cancer (31). However, to the best of our knowledge, there have been no other reports of an algorithm predicting pT4 gastric cancer. It has been reported that preoperative chemotherapy may improve outcomes for pT4 disease, suggesting that an accurate method of predicting the tumor depth invasion before planned surgery could be useful.

There are many reports of prognostic indicators for gastric cancer, including site of regional lymph node involvement (32), number of involved regional lymph nodes (33-35), regional lymph node involvement ratio (36, 37), distant metastases (32), cytodiagnosis by peritoneal lavage (38, 39), tumor size (40), macroscopic type (41, 42), location (43, 44), patient age (45, 46), patient sex (47), lymphatic invasion (48), venous invasion (49), histologic type (50), serosal

Table IV. T category and T4 score.

T4 score	T4	T1-3	Total
≥4 points	968 points	251 points	1,219 points
<4 points	94 points	1,458 points	1,552 points
Total	1,062 points	1,709 points	2,771 points

Accuracy 87.5% [95% confidence interval (CI)=86.4-88.6%]; Sensitivity 91.1% (95%CI=89.6-92.5%); Specificity 85.3% (95%CI=84.4-86.2%); Positive predictive value 79.4% (95%CI=78.1-80.6%); Negative predictive value 93.9% (95%CI=92.9-94.9%).

invasion on a macroscopic scale (51), CEA and CA19-9 (51, 52), and lymphadenectomy extent (53-55). Most of these factors are assessable before treatment initiation.

Pretreatment factors in the T4 score have prognostic value. The pretreatment factors in the T4 score are associated with prognosis, its objectivity and versatility. Moreover, there have been no previous reports of a score that can be used to decide whether a patient should receive a treatment which is the function of the T4 score. The sensitivity of the T4 score may be further improved by adding factors related to nutritional status, such as albumin or prealbumin, tumor markers, such as CA125 or AFP (56), or a biomarker such as DNA mismatch repair (MMR) deficiency (57).

Conclusion

The T4 score uses weighted factors to predict the depth of invasion of pT4 gastric cancer. This allows planning of the optimal treatment strategy.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

T.K. made substantial contributions to the conception, design, acquisition of data, and analysis and interpretation of data, and participated in drafting the article. O.M. made substantial contributions to the analysis and interpretation of data, and participated in revising it critically for important intellectual content. Y.T. made substantial contributions to the acquisition of data, and participated in drafting the article. S.A. made substantial contributions to the acquisition of data, and participated in drafting the article. K.S. made substantial contributions to the acquisition of data, and participated in drafting the article. I.S. made substantial contributions to the acquisition of data, and participated in drafting the article. S.K. made substantial contributions to the acquisition of data, and participated in drafting the article. Y.T. made substantial contributions to the analysis and interpretation of data, and participated in revising it critically for important intellectual content. All Authors gave final approval of the version to be published.

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