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European validation of the Yonsei Gastric Cancer Prognosis Prediction Model after gastrectomy: Validation with the Netherlands Cancer Registry

Hylke J.F. Brenkman [a, b, 1], Minah Cho [c, d, 1], Jelle P. Ruurda [a], Kijun Song [e], Taeil Son [c, d], Hyoung-Il Kim [c, d], Sung Hoon Noh [c, d], Richard van Hillegersberg [a], Woo Jin Hyung [c, d, *]

[a] Department of Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Surgery, Diakonessenhuis, Utrecht, the Netherlands
[c] Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Gastric Cancer Center, Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea
[e] Department of Biostatistics, Yonsei University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Recently, a novel model predicting 5-year survival after gastrectomy was developed, the Yonsei Gastric Cancer Prognosis Prediction Model, to overcome limitations of the tumor-node-metastases (TNM) staging system. This study aimed to validate this model in a European cohort.
Methods: All patients who underwent gastrectomy for gastric cancer were selected from the Netherlands Cancer Registry (2005–2015). Patients with 30-day mortality, co-existing cancer, neoadjuvant therapy, or missing data were excluded. The prediction model included gender, age, resection type, pT-stage, pM-stage, number of retrieved lymph nodes, number of metastatic lymph nodes, and tumor histology. The model was validated and compared to the 7th TNM staging system using calibration plots and the concordance index (c-statistic with 95% confidence interval (CI)).
Results: From the 5748 patients who underwent gastrectomy, 2253 were included in this study. Mean age was 72.1 years, most patients had advanced gastric cancer (88%), and in 1102 patients (49%) no proper TNM staging could be performed since <16 lymph nodes were retrieved. Median overall survival was 24.6 months, and the 5-year overall survival was 30%, respectively. Model calibration was accurate in predicting 5-year overall survival, and the degree of discrimination was high (c-statistic = 0.807, 95% CI (0.787–0.826)). The model was superior to the TNM staging system in patients who could be properly staged: c-statistic = 0.861, 95% CI (0.838–0.885) vs. 0.711, 95% CI (0.692–0.729), $p < 0.0001$.
Conclusion: The Yonsei Gastric Cancer Prognosis Prediction Model was superior over the TNM staging system in predicting prognosis after gastrectomy in a European cohort, although it is not applicable to patients treated by neoadjuvant therapy.

Introduction

For gastric cancer, accurate assessment of a patient's prognosis is essential for clinical decision-making and informing patients. The tumor-node-metastasis (TNM) staging system has historically been the preferred method of classifying gastric cancer, but has several limitations, such as the lack of including essential patient- and surgery-related factors that affect prognosis, and as a minimum number of 16 lymph nodes is required for proper staging [1].

To overcome these limitations of the TNM staging system, a novel model for predicting 5-year overall survival after gastrectomy was recently developed [2]. The model is applicable to patients who underwent primary gastrectomy and includes age, gender, resection type, and tumor histology. Furthermore, the model replaces pN-stage of the TNM staging system by the number of retrieved and metastatic lymph nodes. During validation of the prediction model

* Corresponding author. Department of Surgery, Yonsei University, College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul, 120-752, Republic of Korea.
E-mail address: wjhyung@yuhs.ac (W.J. Hyung).
[1] These authors contributed equally.

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in datasets from different Asian hospitals and the American Surveillance, Epidemiology, and End Results (SEER) database, the prediction model was found statistically more accurate than the TNM staging system [2,3].

As the patients, the treatment, and the prognosis of gastric cancer differs worldwide, external validation in a European cohort is required for further clinical implementation of the prediction model [4,5]. The aim of this study was therefore to validate this predication model in a European cohort of patients who underwent gastrectomy for gastric cancer.

Methods

Study design

European validation of the prediction model was performed with data from the Netherlands Cancer Registry (NCR). Working procedures of the NCR have been described in previous studies [6,7]. The Privacy Review Board of the NCR and the Dutch Upper GI Cancer Group (DUCG) approved this study.

Patients, staging and treatment

All patients who underwent gastrectomy for gastric cancer between 2005 and 2015 were selected from the NCR. Patients who experienced 30-day postoperative mortality, who underwent neoadjuvant treatment, with co-existing cancer (<5 years prior to the diagnosis of gastric cancer), or with incomplete data were excluded as the model was not developed for these patients [2]. Tumor staging was based on the 7th edition of the American Joint Committee on Cancer TNM staging system, and consisted of gastroscopy and computed tomography in all patients [1,8]. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3), since the prediction model was generated by testing WHO classification only [9]. Patients with gastro-eosophageal junction tumors were included as long as they underwent gastrectomy. Surgical treatment of patients was performed according to Dutch national guidelines, which are based on the Japanese Gastric Cancer Treatment guidelines [10,11]. Baseline characteristics of patients in the dataset were compared to patients in whom the prediction model were previously developed and validated, the Yonsei dataset and SEER dataset, using the Chi-square and One-way ANOVA tests [2,3].

Prediction model

Development and validation of the prediction model was described in a previous study [2]. In short, in a dataset containing 11,851 patients from the Yonsei Gastric Cancer Center, variables prediction 5-year overall survival were identified by multivariable regression analysis. After validation in 4 external Asian datasets, the model included the following variables: age, gender, resection type, pT-stage, pM-stage, number of retrieved lymph nodes, number of metastatic lymph nodes, and tumor histology. The 5-year overall survival probability is estimated as follows: $P = P_0^A$, in which P is the 5-year survival probability, and P_0 is the baseline survival probability. A is calculated as follows:

$A = \text{Exp}[(0.024 * \text{age}) + (0.038 * \text{men}) - (0.014 * \text{AMD}) + (0.079 * \text{APD}) - (0.161 * \text{MUC}) + (0.009 * \text{SRC}) + (0.051 * \text{other}) + (0.412 * \text{T1b}) + (0.790 * \text{T2}) + (1.464 * \text{T3}) + (1.706 * \text{T4a}) + (2.169 * \text{T4b}) + (0.050 * \text{metastatic LNs}) - (0.014 * \text{total number of retrieved LNs}) + (0.806 * \text{M1}) + (0.366 * \text{TG})]$

In this equation, the abbreviations are defined as follows: AMD = adenocarcinoma moderately differentiated; APD = adenocarcinoma poorly differentiated; MUC = mucinous adenocarcinoma; SRC = signet ring cell carcinoma; LNs = lymph nodes; TG = total gastrectomy.

Validation process

Validation of the model comprised 2 components. Firstly, discrimination was assessed using the concordance index (Harrel's c-statistic with 95% confidence interval (CI)) using the bootstrap method. Secondly, the model was calibrated by plotting the mean predicted survival probabilities against the observed Kaplan-Meier survival estimate. To determine the additive value of the prediction model, the model's c-statistic was compared with the 7th edition of the TNM staging system. Data were analyzed with SPSS software, version 23 (IBM Corp, Armonk, NY) and SAS software, version 9.2 (SAS institute, Cary, NC).

Results

Dataset

A total of 5748 patients who underwent gastrectomy for gastric cancer were selected from the NCR. Among them, 3495 patients were excluded due to 30-day postoperative mortality (n = 346), co-existing cancer (n = 375), neoadjuvant therapy (n = 2041), or incomplete data (n = 773) (Fig. 1). Incomplete data mostly included tumor differentiation grade and pT-stage, the latter due to the inability to translate the pT-stage of the 6th edition to the 7th edition of the TNM staging system. For instance, pT1 tumors (tumors invading the lamina propria, muscularis mucosae, or

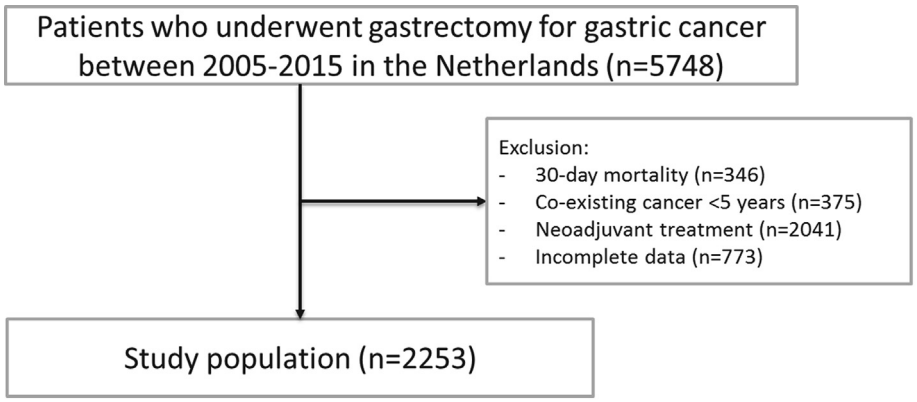

Fig. 1. Study flow chart.

Table 1
Baseline characteristics.

	NCR dataset		Yonsei dataset		SEER dataset		p-value
	No.	(%)	No.	(%)	No.	(%)	
N	2253		11,851		15,483		
Age (mean)	72.2		55.9		65.5		<0.001
Sex							<0.001
Male	1357	(60.2)	7844	(66.2)	9443	(60.9)	
Female	896	(39.8)	4007	(33.8)	6040	(39.1)	
Resection							<0.001
DG	1517	(67.3)	8648	(73.0)	11,424	(73.8)	
TG	736	(32.7)	3203	(27.0)	4059	(26.2)	
No. LN retrieved (median, IQR)	14.1		40.0		16.6		<0.001
Histology							<0.001
AWD	68	(3.0)	1564	(13.2)	0	(0.0)	
AMD	539	(23.9)	3270	(28.2)	3501	(22.1)	
APD	952	(42.3)	4118	(35.6)	6835	(43.1)	
MUC	107	(4.7)	366	(3.1)	447	(2.8)	
SRC	539	(23.9)	2278	(19.2)	2111	(13.3)	
Other	48	(2.1)	255	(2.2)	2589	(16.3)	
T category							<0.001
T1a	79	(3.5)	2627	(22.2)	552	(3.6)	
T1b	131	(5.8)	2295	(19.4)	2126	(13.7)	
T2	300	(13.3)	1522	(12.8)	1977	(12.8)	
T3	902	(40.0)	1707	(14.4)	3311	(21.4)	
T4a	697	(30.9)	3329	(28.1)	6051	(39.1)	
T4b	144	(6.4)	371	(3.2)	1466	(9.5)	
N category							<0.001
N0	250	(11.1)	6453	(54.5)	5443	(35.2)	
N1	125	(5.5)	1427	(12.0)	898	(5.8)	
N2	126	(5.6)	1141	(9.6)	1012	(6.3)	
N3	525	(23.3)	2451	(20.7)	2301	(14.9	
Nx	1227	(54.5)	379	(3.2)	4279	(27.6)	
No. metastastic LN (mean)	4.1		4.4		4.8		<0.001
AJCC staging							<0.001
IA	77	(3.4)	4404	(37.2)	747	(4.8)	
IB	68	(3.0)	1168	(9.9)	530	(3.4)	
IIA	95	(4.2)	978	(8.3)	712	(4.6)	
IIB	69	(3.1)	1149	(9.7)	891	(5.8)	
IIIA	139	(6.2)	887	(7.5)	830	(5.4)	
IIIB	227	(10.1)	1133	(9.6)	1177	(7.6)	
IIIC	284	(12.6)	1586	(13.4)	1789	(11.6)	
IV	192	(8.5)	497	(4.1)	1551	(10.0)	
ND	1102	(48.9)	60	(0.5)	7256	(46.8)	

DG: distal gastrectomy; TG: total gastrectomy; LN: lymph nodes; IQR: interquartile range; AWD: adenocarcinoma well differentiated; AMW: adenocarcinoma moderately differentiated; APW: adenocarcinoma poorly differentiated; MUC: mucinous adenocarcinoma; SRC: signet ring cell tumor; AJCC: American Joint Committee on Cancer; ND: unable to stage.

submucosa) staged in the TNM 6th edition cannot be translated to the pT1a and pT1b stages of the TNM 7th edition, which are necessary for the prediction model. For such translation, the original pathology reports or resection specimens are warranted, which were unavailable.

Patients

The 2253 included patients were predominantly males (60%), and the mean age was 72.1 (±11.2) years (Table 1). Most patients underwent a distal gastrectomy (67%) and had advanced tumors (stage II and higher in 88%). The median number of lymph nodes retrieved was 12 (IQR 7–19), and in 49% of patients no proper TNM staging could be performed since <16 lymph nodes were retrieved. Only a minority (7%) of patients underwent adjuvant therapy after gastrectomy.

Comparing the patients to the Korean Yonsei dataset demonstrates differences in all baseline characteristics (Table 1) [2]. Comparison to patients from the American Surveillance, Epidemiology, and End Results (SEER) database show differences mostly on age, gastrectomy type, histology, and pT-stage (Table 1) [3].

The median survival of the total patient cohort was 24.6 months, and the 1-, 3-, and 5-year survival were 70%, 40%, and 30%, respectively. Kaplan-Meier curves stratified according to TNM stages are demonstrated in Fig. 2.

Validation

For predicting 5-year overall survival after gastrectomy, the model demonstrated a high degree of discrimination, with a C-statistic (95%CI) of 0.807 (0.787–0.826). After excluding patients that could not be accurately staged according to the 7th TNM staging system since <16 lymph nodes were retrieved (n = 1141), the c-statistic (95%CI) of the prediction model demonstrated superiority over the 7th TNM staging system: 0.861 (0.838–0.885) vs. 0.711 (0.692–0.729), $p < 0.0001$ (Table 2). The calibration plot demonstrated accurate and useful 5-year survival predictions of the model (Fig. 3).

Discussion

In order to support the worldwide application of prediction models, external validation with various international gastric cancer populations is necessary. The present study demonstrated that

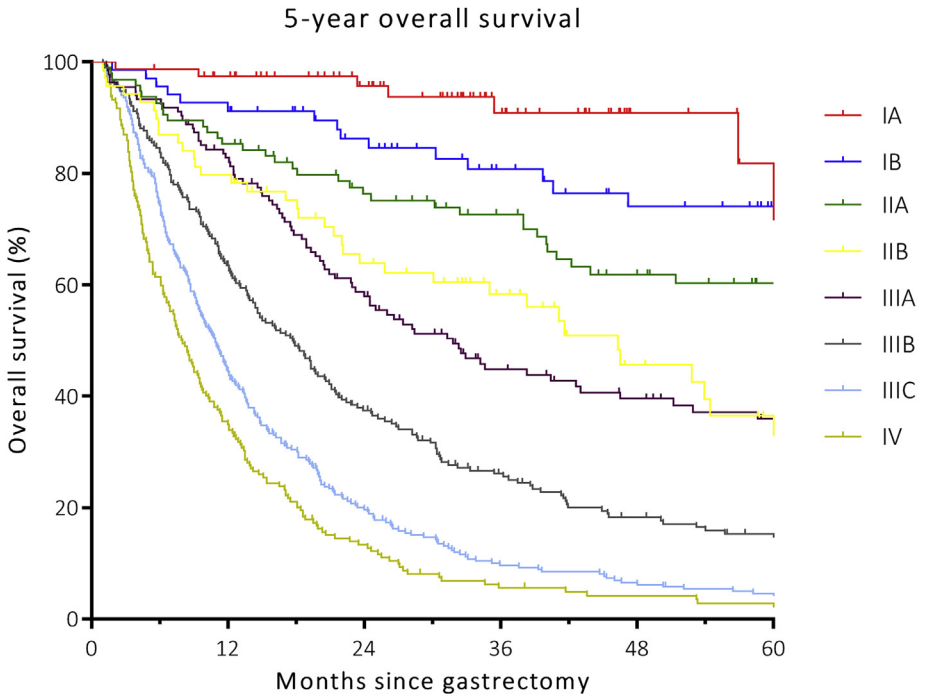

Fig. 2. Kaplan-Meier curves of the study population according to TNM-stage.

Table 2
C-statistics of the TNM-classification and Yonsei Gastric Cancer Prediction Model.

	n	TNM	Yonsei model	*p-value*
		c-statistic (95% CI)	*c-statistic (95% CI)*	
Yonsei data	11.851	0.788 (0.782–0.795)	0.824 (0.818–0.830)	<0.0001
SEER data	15.483	0.704 (0.697–0.712)	0.762 (0.754–0.769)	<0.001
NCR data	2.253	0.711 (0.692–0.729)	0.861 (0.838–0.885)	<0.0001

Data from the Yonsei Center, American Surveillance Epidemiology and End Results (SEER) and the Netherlands Cancer Registry (NCR).

the Yonsei Gastric Cancer Prognosis Prediction Model after gastrectomy for gastric cancer recently developed in Asia and validated in the United States had a high degree of discrimination in a European population [2,3]. The model was superior over the 7th TNM staging system in predicting prognosis after gastrectomy in a European gastric cancer cohort, from the Netherlands Cancer Registry [2].

The importance of European validation of the prediction model is demonstrated by the differences in baseline characteristics of the datasets used in the current study and the previous development and validation studies [2,3]. In comparison to most patients of the Asian centers used in one previous study, in the present study patients were relatively older, tumors were more advanced, and a lower number of lymph nodes was retrieved. These results reflect differences in treatment, patient-, and tumor characteristics between the East and West that were described before [4,5,12]. Patients in the present study also differed from patients from the SEER dataset used in the American validation study [3]. The differences in histology may reflect differences in tumor biology. The differences in pT-stage and resection type or probably related to each other by tumor size, and could reflect differences in the organization of cancer care and tumor diagnosis. Last, the difference in age between the populations is probably due to the fact that in the Netherlands, younger patient undergo neoadjuvant chemotherapy and are therefore not included in the present study. Since the concordance index (c-statistic) of the prediction model demonstrated a comparable degree of discrimination in the previous studies and the current study, the model is valid in all evaluated populations and may be applied worldwide.

The prediction model has several advantages over the 7th TNM staging system. Firstly, the prediction model includes several patient- and surgery-related factors that affect prognosis and are lacking in the TNM staging system, such as patients' age, gender, extent of surgery, and lymph node yield [13]. Including these factors has probably resulted in the superior performance of the model over the TNM staging system. Secondly, unlike the TNM staging system, the prediction model is accurate in patients in whom an inadequate number of lymph nodes are resected, which occurred in approximately half of the patients in this study. Interestingly, the prediction model performed better after excluding patients in whom an inadequate lymph node yield was retrieved. These results demonstrate the importance of an adequate lymph node yield for this prediction model as well.

This prediction model was developed in Korea, and validated in several Asian centers and the SEER database from the United States. In contrary to the Asian centers, but in line with the SEER dataset, the proportion of patients in whom an inadequate number of lymph nodes were retrieved was high in this study from the Netherlands [2,3]. Although this may reflect poorer surgical quality in Western countries compared to Asian countries, other factors may have played an important role as well. Firstly, in more patients a palliative resection for stage IV disease was performed, in whom an extensive lymphadenectomy can be omitted. Secondly, in the Netherlands specimens are generally submitted *en-bloc* instead of in separate containers [14]. Last, pathologists may have had a low awareness of the importance of a high lymph node yield [15]. Nowadays in the Netherlands, the proportion of patients in whom an inadequate number of lymph nodes is retrieved is lower (14%) and is still decreasing, which may be a result of centralization and national auditing [16,17].

Although several other prediction models for overall survival

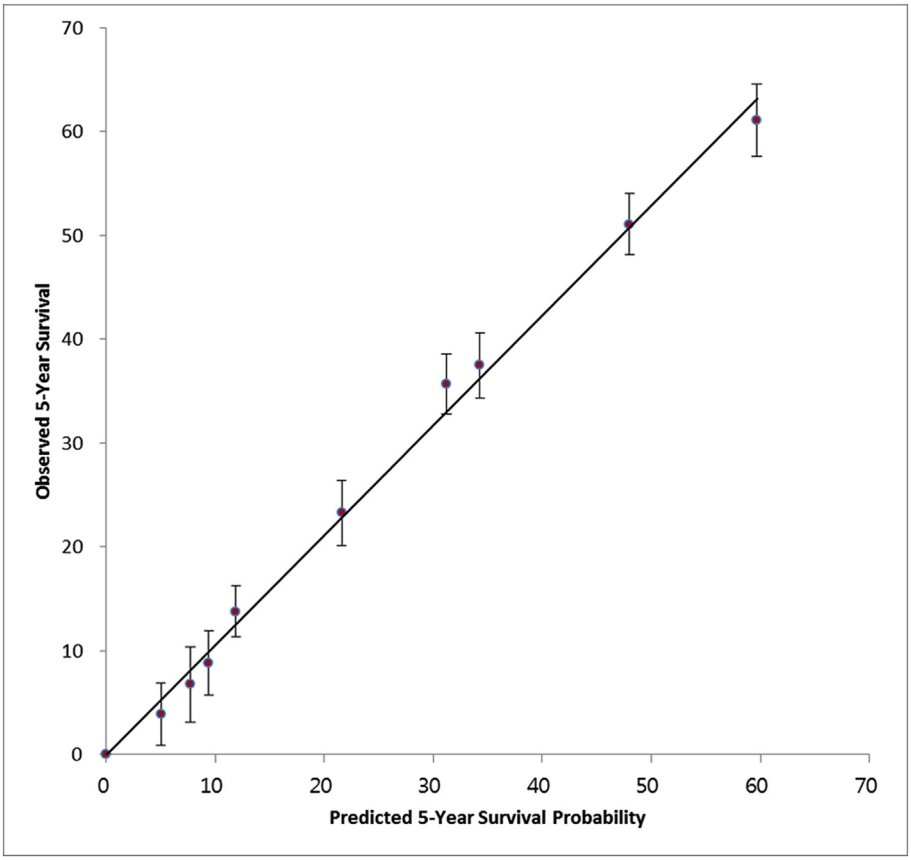

Fig. 3. Calibration plot of the prediction model.

after gastrectomy have been developed in the past [18,19], the present model may have the highest potential. Previously, a Korean model developed in 2012 also demonstrated a better degree of discrimination than the TNM staging system [18]. Recently, this model was successfully validated in an Italian cohort [20]. Although the concordance index of this previous and the current model are somewhat comparable between 0.80 and 0.86, the current model can also be applied to patients who underwent a palliative (M1) or non-radical (non-R0: R1 or R2) resection and may therefore be more suitable for future use. For instance, the model may be used as a valuable tool involving patients in clinical decision-making whether adjuvant therapy is warranted.

Despite the promising potential of this prediction model, some limitations should be mentioned. Firstly, the present model does not account for patients who underwent neoadjuvant therapy, which is the preferred treatment strategy for patients with advanced gastric cancer in most European countries [21]. Although we tried to develop a slightly adjusted prediction model in the data of the NCR, insufficient data on specific chemotherapy regimens and treatment response hindered the development of an adequate model. Future studies may try to develop a novel model for patients who underwent neoadjuvant treatment using more extensive datasets. Secondly, since perioperative chemotherapy is the standard of care in the Netherlands, this study represents a selected population of patient staged with early gastric cancer and patients that were deemed unfit for perioperative chemotherapy. However, especially in unfit patients, the current prediction model may be beneficial over the TNM staging system as not only tumor-related factors are included. Thirdly, as mentioned earlier, a majority of cases in this study could not be adequately staged due to a low lymph node yield. However, also among adequately staged patients the prediction model performed better than the TNM staging system. Lastly, according to the study period in which the study was conducted, the prediction model was compared to the 7th TNM staging system. Recently, however, the 8th edition of the TNM staging system has shown higher accuracy than the 7th edition. Besides comparing the prediction model to the 8th edition, future steps to further apply this prediction model may be by updating it with other relevant factors, such as (neo)adjuvant therapy, biochemical and/or genetic variables. Furthermore, its clinical impact should be evaluated in a prospective study. Development of an online scoring tool would contribute to easy and wide application of the model.

In conclusion, this study presented the external European validation of the Yonsei Gastric Cancer Prognosis Prediction Model after Gastrectomy. The model demonstrated an excellent degree of discrimination, and superiority over the TNM staging system due to the addition of several relevant patient- and surgery related factors. The model has benefits over other staging systems and can be used worldwide to accurately predict patients' prognosis after gastrectomy.

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References

[1] Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging

manual. seventh ed. ed. New York: Springer; 2010.
[2] Woo Y, Son T, Song K, Okumura N, Hu Y, Cho GS, et al. A novel prediction model of prognosis after gastrectomy for gastric carcinoma: development and validation using Asian databases. Ann Surg 2016;264:114–20.
[3] Woo Y, Goldner B, Son T, Song K, Noh SH, Fong Y, et al. Western validation of a novel gastric cancer prognosis prediction model in US gastric cancer patients. J Am Coll Surg 2018;226:252–8.
[4] Griffin SM. Gastric cancer in the East: same disease, different patient. Br J Surg 2005;92:1055–6.
[5] Brenkman HJ, Haverkamp L, Ruurda JP, van Hillegersberg R. Worldwide practice in gastric cancer surgery. World J Gastroenterol 2016;22:4041–8.
[6] Brenkman HJ, Ruurda JP, Verhoeven RH, van Hillegersberg R. Safety and feasibility of minimally invasive gastrectomy during the early introduction in The Netherlands: short-term oncological outcomes comparable to open gastrectomy. Gastric Cancer 2017;20. 853-0.
[7] Brenkman HJ, Visser E, van Rossum PS, Siesling S, van Hillegersberg R, Ruurda JP. Association between waiting time from diagnosis to treatment and survival in patients with curable gastric cancer: a population-based study in The Netherlands. Ann Surg Oncol 2017;24:1761–9.
[8] Landelijke werkgroep gastro-intestinale tumoren. Richtlijn maagcarcinoom; 2016. 2016.
[9] Fritz A, Percy C, Jack A, Shanmugaratnam A, Sobin L, Parkin DM, et al. International classification of diseases for Oncology. 2013.
[10] Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101–12.
[11] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113–23.
[12] Russo A, Li P, Strong VE. Differences in the multimodal treatment of gastric cancer: East versus west. J Surg Oncol 2017;115:603–14.
[13] Brenkman HJ, Goense L, Brosens LA, Haj Mohammad N, Vleggaar FP, Ruurda JP, et al. A high lymph node yield is associated with prolonged survival in elderly patients undergoing curative gastrectomy for cancer: a Dutch population-based cohort study. Ann Surg Oncol 2017;24:2213–23.
[14] Afaneh C, Levy A, Selby L, Ku G, Tang L, Yoon SS, et al. Ex vivo lymphadenectomy during gastrectomy for adenocarcinoma optimizes lymph node yield. J Gastrointest Surg 2016;20:165–71.
[15] Schoenleber SJ, Schnelldorfer T, Wood CM, Qin R, Sarr MG, Donohue JH. Factors influencing lymph node recovery from the operative specimen after gastrectomy for gastric adenocarcinoma. J Gastrointest Surg 2009;13:1233–7.
[16] Haverkamp L, Ruurda JP, van der Sluis PC, van Hillegersberg R. Surgical treatment of gastric cancer: focus on centralisation and laparoscopic resections. Ned Tijdschr Geneeskd 2013;157:A5864.
[17] Busweiler LA, Wijnhoven BP, van Berge Henegouwen MI, Henneman D, van Grieken NC, Wouters MW, et al. Early outcomes from the Dutch upper gastrointestinal cancer audit. Br J Surg 2016;103:1855–63.
[18] 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;30:3834–40.
[19] Haga Y, Hato S, Ikenaga M, Yamamoto K, Tsuburaya A, Doi K, et al. Validation of an assessment tool: estimation of postoperative overall survival for gastric cancer. Eur J Surg Oncol 2018 Apr;44(4):515–23.
[20] Bencivenga M, Verlato G, Han DS, Marrelli D, Roviello F, Yang HK, et al. Validation of two prognostic models for recurrence and survival after radical gastrectomy for gastric cancer. Br J Surg 2017;104:1235–43.
[21] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.