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Original Article

High expression of serum carcinoembryonic antigen (CEA) associated with poor prognosis in early gastric cancer: a single-center retrospective study

Zai-Sheng Ye[1,2], Lu-Chuan Chen[2], Sheng-Hong Wei[2], Jun Xiao[2], Shuai Han[1], Zhai Cai[1], Zhou Li[1]

[1]Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou 510280, Guangdong Province, China; [2]Department of Gastrointestinal Surgery, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350001, Fujian Province, China

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Abstract: Background: The level of carcinoembryonic antigen (CEA) in the diagnosis of early gastric cancer (EGC) seems obscure. This study is aimed to assess whether a high level of CEA is associated with the inferior prognosis for EGC. Methods: About 203 EGC patients, who received endoscopic mucosal resection or submucosal dissection or radical gastrectomy, were reviewed retrospectively. All the EGC cases were evaluated based on their clinicopathological features and surgical outcomes. The X-tile program was used to calculate the optimal cut-off points for the CEA using minimum *P*-value from log-rank ÷ 2 statistics. In the analysis of the overall cumulative probability of survival, the Kaplan-Meier method was employed. Their differences were evaluated through the log-rank test. The Cox multiple factors analysis was carried out using the logistic regression method. Results: The X-tile plots cut-off points for CEA were 15.54 ng/ml in EGC patients. They were classified as CEA-low and CEA-high groups. The percentage of the vessel carcinoma embolus was higher in CEA-high groups compared to their CEA-low counterparts (20% vs. 16.29%, P = 0.000). The five-year overall survival rate (OS) of the patients under CEA-high group was markedly inferior compared to the CEA-low group (68.95% vs. 99.42%, P < 0.05). The multivariate survival analysis showed that CEA (OR = 1.674), N stage (OR = 2.436) were significant prognostic factors for EGC (all P < 0.05). In the CEA-low subgroup, not signally risk factors were found (all P > 0.05), while N stage (OR = 2.632) was an independent risk factor in the CEA-high group by multivariate analysis (P < 0.05). Conclusion: The CEA, categorized by the cut-off points of 15.44 ng/ml could develop the best prognostic discriminatory ability and predictive accuracy for the EGC patients. It could be a reliable prognostic factor when combined with tumor node metastasis (TNM) evaluation system.

Keywords: Early gastric cancer, TNM classification, X-tile plots, carcinoembryonic antigen

Introduction

The early gastric cancer (EGC) was defined as adenocarcinoma involving mucosa or submucosa irrespective of the nodal status [1]. According to the 7th edition NCCN guidelines, EGC was divided into stage T1N0 and stage T1N1-3 (clinical stage of IA, IB, IIA and IIB) [2]. With increased public awareness of the early diagnosis and treatment of cancer, including the development of the endoscopic imaging and image enhanced techniques, the ECG proportion in diagnosis is rising [3]. The prognosis of EGC treated with the proper therapies has been reported to be exemplary [4-7], with a reported five-year overall survival (OS) rates of more than 92% [4-8]. Also, the differences in the clinical prognosis were found because of the negligible risk of lymphopoiesis invasion, which leads to an inferior prognosis [9].

The techniques of the endoscopic treatment for EGC include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), and radical gastrectomy [3]. The perioperative chemotherapy is recommended (category 1) after the R0 resection for patients with resectable T1b [2]. The NCCN guidelines had no visible hints whether the chemotherapy among patients with T1a stage alone has high-risk factors and also it lacks related clinical data. Thus, the subgroups with the malignant biological behavior showed different survival times. These

Table 1. Demographic data of the 203 patientswith early gastric cancer

Characteristic	CEA-Low group (N = 178)		CEA-High group (N = 25)		*P*
Age (years)	57.74±10.29		55.2±12.26		
Mean ± SD	59 (27-79)		54 (32-78)		
Gender					
Female	64	35.96%	6	24%	0.239
Male	114	64.04%	19	76%	
Family history					
Y	3	1.69%	2	8%	0.056
N	175	98.31%	23	98%	
HP infection status					
Y	16	8.99%	4	16%	0.271
N	162	91.01%	21	84v	
BMI					
Less than 18.5	10	5.62%	2	8%	-
18.5-24.99	129	72.47%	23	92%	
More than 25	39	21.91%	-	-	
T category					
T1a	75	42.13%	12	48%	0.579
T1b	103	57.87%	13	52%	
N category					
N0	135	75.84%	20	80%	0.647
N1	43	24.16%	5	20%	
Nerve invasion					
Y	16	8.99%	3	15%	0.217
N	162	91.01%	22	85%	
Vessel carcinoma embolus					
Y	29	16.29%	5	20%	0.000*
N	149	83.71%	20	80%	

SD: standard deviation, Y: yes, N: not, HP: helicobacter pylori. *: $P < 0.05$: statistically significant meaning.

may be vital to improving the effect of the treatment by selecting high-risk groups from EGC patients, and taking a clinical intervention in time.

The carcinoembryonic antigen (CEA), one of the tumor markers, is most widely used in identifying gastric cancers [10]. Increased preoperative serum CEA varied greatly among the small percentage of the patients [11]. A previous study has found that extremely elevated preoperative serum CEA in a small group of patients [11], showing a worse biological behavior usually indicated a poor prognosis [11-14]. So far, limited numbers of ascites have examined the ability of CEA to predict prognosis of EGC, and this required to determine the CEA cut-off level. In the current study, the subgroups were separated by CEA-low and high subgroups. The objective of this study was to evaluate the effectiveness of preoperative CEA values among the EGC patients.

Patients and methods

Patients

From January 2000 to December 2010, a retrospective analysis was conducted of 1,050 consecutive patients with advanced GC who underwent D_2 lymphadenectomy, at the Department of gastrointestinal surgery, Fujian tumor hospital. All of the surgery was operated by Lu-Chuan Chen. Among them, 203 patients suffered with early stage gastric cancer according to the 7th edition of the UICC/TNM classification. Data from these patients were enrolled into a prospectively maintained database.

The inclusion criteria were as follows: 1) early GC; 2) adenocarcinoma confirmed by histopathology; 3) physical fitness suitable for surgery; 4) D_2 lymphadenectomy; and 5) no prior history ofany type of adjunctive therapy.

The exclusion criteriawere as follows: 1. older than 80 years of age; 2. previous or concomitant other cancer; 3. previous or concomitant gastrectomy for benign disease; 4. previous chemotherapy or radiotherapy; 5. esophageal involvement; or 6. distant metastatic disease; 7. non-curative resection, 8. multiple primary malignancies, 9. remnant GC, 10. mortality within 30 days after surgery.

All of the above patients were followed up by posting letters or by telephone interviews. The last follow-up was 1 January 2016. The cardiopathy logical and follow-up findings were collected andrecorded in the database. All subjects gave written informed consent to the study protocol, which was approved by the Ethical Committees of Fujian Provincial Tumor Hospital.

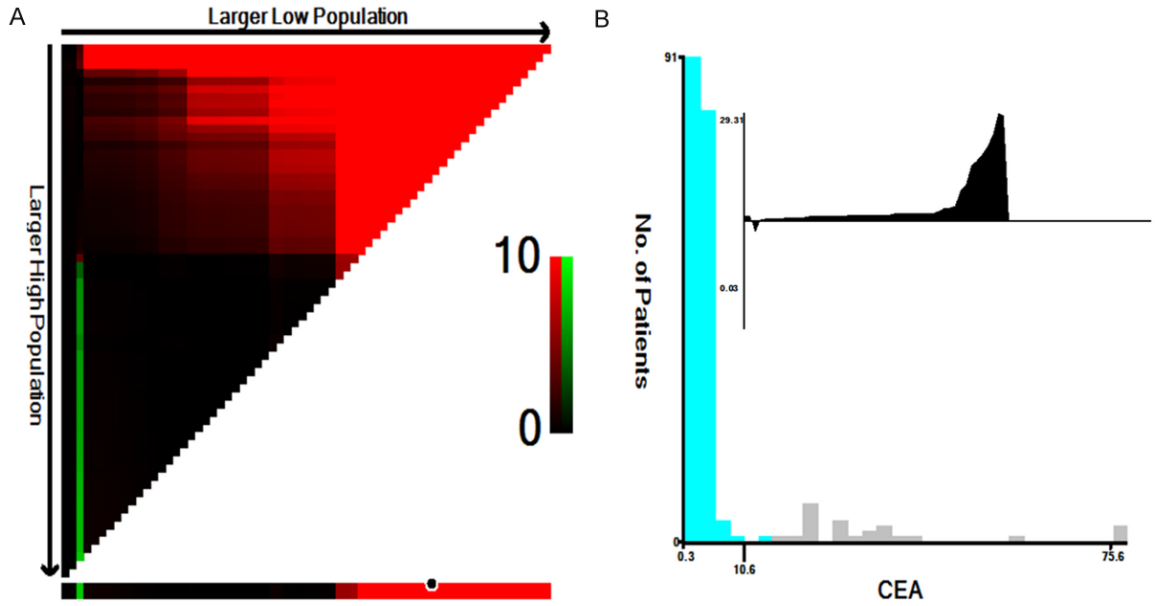

Figure 1. Division of patients by the cut-off points produced by X-tile plot. A. X-tile plots for CEA. The plots illustrate that the produced log-rank ÷ 2 value stratify the EGC patients into two groups by a cut-off points, 15.54 ng/ml. B. Survival curves generated by X-tile plots, show a strong discriminatory capacity, with a ÷ 2 value of 105.95 and a relative risk ratio of 1:2.45.

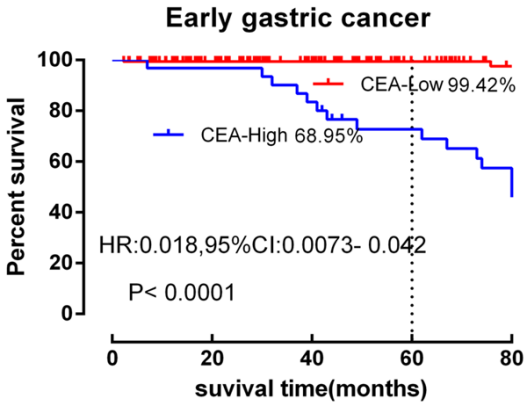

Figure 2. Survival analysis of early patients with gastric cancer undergoing curative intent surgery. The *P* values for the survival comparison was determined by the log-rank test.

Surgery

According to the 7th edition NCCN guidelines [2], EMR or ESD is the primary treatment option for patients with Tis or T1a tumors. Besides, surgery with lymph node dissection is the primary treatment option for medically fit patients with resectable T1b, any N tumors. All patients in the study underwent standard total ordistal gastrectomy, depending on the location andmacroscopic appearance of the primary tumor (**Table 1**). The strategy for LN dissections wasdetermined using a standardized technique accordingto the guidelines of the 2010 Japanese Classification of Gastric Cancer and Gastric Cancer Treatment Guidelines edited by the Japanese Gastric Cancer Association [15].

Clinicopathological characteristics

The clinicopathological findings, including depth of tumor invasion and LN metastases, were utilized to stage tumors according to the 7th edition NCCN guidelines [2]. LNs were dissected and described according to the Japanese Classification of Gastric Carcinoma [15], which was also used to classify the location, histological type, and lymphatic invasion of tumors.

Statistical analysis

Statistical analyses were conducted using Statistical Product for Social Sciences (SPSS) 19.0 software (SPSS, Inc., Chicago, IL, USA). The distribution of baseline characteristics was compared by using either Fisher's exact test orthe chi-square test. The CEA cut-off points were produced and analyzed using the X-tile program which identified the cut-off with the minimum *P* values from log-rank ÷ 2 statistics for the categorical CEA in terms of survival.

Table 2. Multivariate analysis for early gastric cancer patients with D_2 resection

	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI used for Exp (B)	
							Lower	Upper
Family history	-.183	.825	.049	1	.825	.833	.165	4.195
HP infection status	-.670	.533	1.577	1	.209	.512	.180	1.456
Gender	-.392	.424	.851	1	.356	.676	.294	1.553
CEA	1.546	.492	5.943	1	.000*	1.674	1.219	2.951
T category	-.558	.399	1.951	1	.163	.573	.262	1.252
N category	-.454	.291	2.351	1	.000*	2.436	1.362	3.521
Nerve invasion	-9.898	541.246	.000	1	.985	.810	0.711	1.147
Vessel carcinoma embolus	.492	.709	.481	1	.488	1.636	.407	6.566
BMI	-.188	.694	.074	1	.786	.828	.212	3.229

HP: Helicobacter Pylori. *: P < 0.05: statistically significant meaning.

Table 3. Multivariate analysis for early gastric cancer patients with D_2 resection separated by level of CEA

	CEA-low group				CEA-high group			
	Sig.	Exp (B)	95.0% CI		Sig.	Exp (B)	95.0% CI	
			Lower	Upper			Lower	Upper
Family history	.992	1.175	.873	2.694	.938	1.075	.173	6.694
HP infection status	.519	2.121	.715	3.874	.309	.517	.145	1.842
Gender	.586	.651	.139	3.047	.851	.894	.278	2.877
T category	.809	1.204	.268	5.408	.122	.431	.148	1.253
N category	.661	.573	.362	1.212	.000*	2.631	1.461	3.622
Nerve invasion	.990	1.114	.668	2.408	.981	.821	0.801	1.341
Vessel carcinoma embolus	.831	1.282	.732	2.488	.356	2.522	.353	18.018
BMI	.105	.313	.077	1.274	.064	2.282	0.980	4.781

HP: Helicobacter Pylori. *: P < 0.05: statistically significant meaning.

Meaningful factors were extracted for further analysis, which was conducted byusing the logistic regression method. The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and differences were evaluated by using the log-rank test. A *P* value less than 0.05 was regarded as statistically significant.

Results

Correlation analysis between the clinicopathologic factors and CEA

X-tile plots, constructed in **Figure 1**, illustrated that the optimal cut-off point for CEA was 15.54 ng/ml in EGC patients using minimum *P* value from log-rank ÷ 2 test, according to which patients were categorized into CEA-low and CEA-high groups, with the strongest discriminatory capacity.

Clinicopathological characteristics

Depending on the 7th editions of the TNM system, a total of 203 patients with EGC underwent surgery. **Table 1** summarizes their demographic and clinicopathological features. No difference in these characteristics, including age, gender, BMI, family history, HP infection status, T category, N category (all P > 0.05). The percentage ofvessel carcinoma embolus was higher in CEA-High group than CEA-Low group (20% vs. 16.29%, P = 0.000).

Survival analysis

The 5-year OS of EGC patients with CEA-high was significantly inferior than CEA-low groups (68.95% vs. 99.42%, P < 0.05, **Figure 2**).

Multivariate analysis

Multivariate survival analysis showed that CEA (OR = 1.674), N stage (OR = 2.436) were signifi-

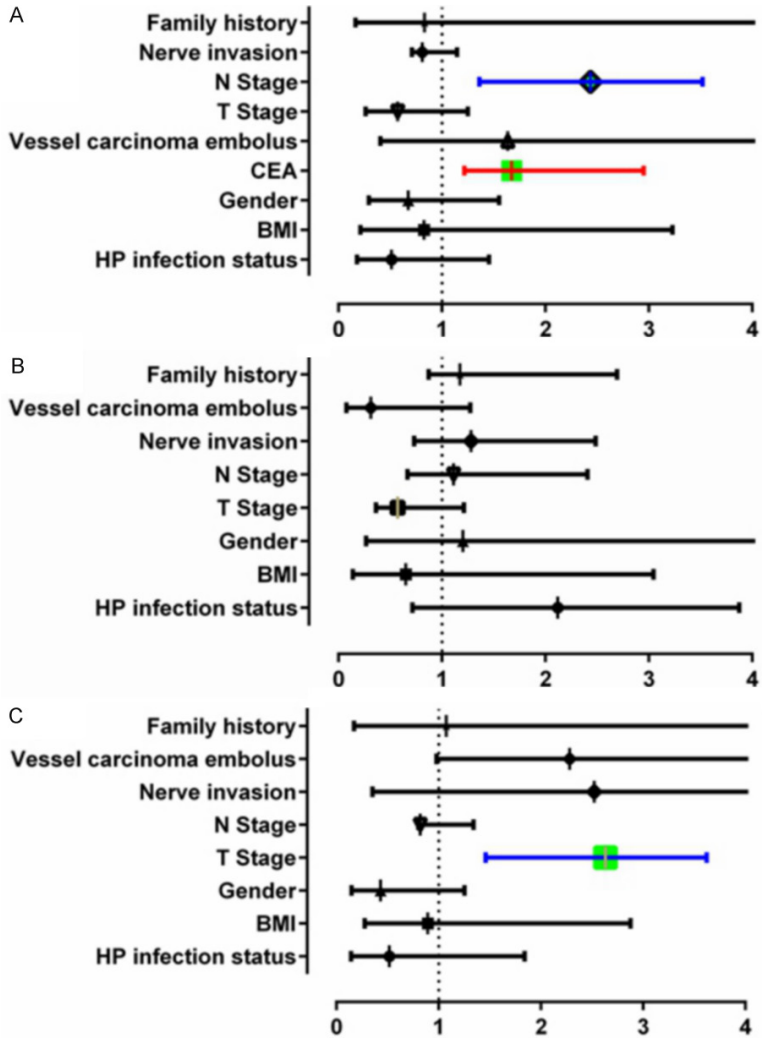

Figure 3. Multivariate analyses for EGC patients by the Cox regression model. A. Ultivariate analyses calculated by OR for early gastric cancer cases. B. Multivariate analyses calculated by OR for CEA-low group. C. Multivariate analyses calculated by OR for CEA-high group.

cant prognostic factors for early GC (all P < 0.05, **Table 2; Figure 2A**). In the CEA-low subgroup, no signally risk factors were found (all P > 0.05), while N Stage (OR = 2.632) was an independent hazard factor in CEA-high group by multivariate analysis (P < 0.05, **Table 3**; **Figure 3A-C**).

Discussion

Despite the availability of many studies, evaluating the prognostic significance of CEA among the EGC patients showed that the antigen was an independent predictor and more focus should be put into it. No agreement has been reached yet by far because of the limitation of the different cut-off points and evaluation criteria [16-18]. In particular, there existed no unified and well-recognized cut-off points CEA in EGC. In this present study, a cut-off point was applied of about 15.54 ng/ml, produced by X-tile, which showed better discriminatory ability and more prognostic accuracy than those proposed in the past studies [19]. The patients with high CEA were found to have worse biological behavior and more aggressive features than patients with low CEA when comparing both the training and validation set. Specifically, the patients with a high level of CEA were found more frequently in the presence of vessel carcinoma embolus (20% vs. 16.29%, P = 0.0). Also, the five-year OS of patients with CEA-high was markedly inferior compared to CEA-low groups (68.95% vs. 99.42%, P < 0.05).

The multivariate survival analysis in the study highlighted that CEA (OR = 1.674), N stage (OR = 2.436) were significant prognostic factors for EGC (all P < 0.05), suggesting that these two factors were closely associated with the survival and multicollinearity might exist between them. Acting in accordance with the X-tile, the EGC patients were separated into CEA-high and CEA-low subgroups. In the CEA-low group, not signally risk factors were found (all P > 0.05), while N stage (OR = 2.632) was an independent hazard factor in the CEA-high group by the multivariate analysis (P < 0.05). Only N stage was confirmed to be positively correlated with the CEA-high group in the analysis. It was found consistent in the previous studies, which was the reason the CEA was substituted with N stage in the current tumor node metastasis (TNM) staging system to come up with a modified staging system.

A useful staging system, which is essential for the EGC patients in clinical practice, should be

able to distinguish the survival difference among the several subgroups of patients and provide accurate prognostic estimation and beneficial guidance in the selection of the applicable adjuvant therapy [20]. As a powerful independent prognostic factor, the N stage in the current TNM staging system is based on the number of metastatic lymph nodes, regardless of the total number of retrieved lymph nodes in the surgery [21]. However, the prognosis of the EGC patients will be underestimated because of the appropriate staging in the case of the insufficient retrieved number of lymph nodes. CEA was developed as biologically active substances in the tumor tissue or cancer cells. Thanks to the abnormal expression of genes as it can identify indirectly the tumor's malignant behavior. It is an effective supplement to the current TNM evaluation system.

There were several limitations inherent in this study. First, it was designed as a retrospective study and a clinical bias could potentially occur. Also, follow-ups were made through phone calls and a recall bias existed. The most obvious pitfall was that there was an inadequate number of patients in the subgroups such as T1N3 subcategorized (one case).

To show the improvement in this study, the various cut-off points attained in the past studies were validated which were not usually done by previous authors. As observed, the CEA, categorized by the cut-off points of 15.44 ng/ml, could produce the best prognostic discriminatory ability and predictive accuracy.

Conclusion

The CEA, categorized by the cut-off points of 15.44 ng/ml, could produce the best prognostic discriminatory ability. It could be considered as a reliable prognostic factor when combined with TNM evaluation system. A large sample study is necessary to evaluate the long-term oncological safety in the future.

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Disclosure of conflict of interest

None.

Authors' contribution

Design of the study and approval of the final version: CLC. Data collection and analysis: CLC, SHW, JX. Contributed reagents/materials/analysis tools: SH, ZC. Critical revision: ZL. Writing of the manuscript: ZSY.

Abbreviations

EGC, early gastric cancer; OS, overall survival rate; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; CEA, Carcinoembryonic antigen; SD, standard deviation; Y, yes; N, not; HP, Helicobacter Pylori.

Address correspondence to: Dr. Zhou Li, Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou, China. E-mail: leezhou888@yeah.net

References

[1] Murakami T. Early cancer of the stomach. World J Surg 1979; 3: 685-692.

[2] Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Korn WM, Leong S, Linn C, Lockhart AC, Ly QP, Mulcahy MF, Orringer MB, Perry KA, Poultsides GA, Scott WJ, Strong VE, Washington MK, Weksler B, Willett CG, Wright CD, Zelman D, McMillian N and Sundar H. Gastric Cancer, Version 3.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016; 14: 1286-1312.

[3] Zhu L, Qin J, Wang J, Guo T, Wang Z and Yang J. Early gastric cancer: current advances of endoscopic diagnosis and treatment. Gastroenterol Res Pract 2016; 2016: 9638041.

[4] Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S and Kaminishi M. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer 2013; 16: 1-27.

[5] Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J and Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut 2009; 58: 331-336.

[6] Gotoda T, Iwasaki M, Kusano C, Seewald S and Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. Br J Surg 2010; 97: 868-871.
[7] Park CH, Shin S, Park JC, Shin SK, Lee SK, Lee YC and Lee H. Long-term outcome of early gastric cancer after endoscopic submucosal dissection: expanded indication is comparable to absolute indication. Dig Liver Dis 2013; 45: 651-656.
[8] An JY, Heo GU, Cheong JH, Hyung WJ, Choi SH and Noh SH. Assessment of open versus laparoscopy-assisted gastrectomy in lymph node-positive early gastric cancer: a retrospective cohort analysis. J Surg Oncol 2010; 102: 77-81.
[9] Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T and Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219-225.
[10] Shimada H, Noie T, Ohashi M, Oba K and Takahashi Y. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the task force of the Japanese Gastric Cancer Association. Gastric Cancer 2014; 17: 26-33.
[11] Bagaria B, Sood S, Sharma R and Lalwani S. Comparative study of CEA and CA19-9 in esophageal, gastric and colon cancers individually and in combination (ROC curve analysis). Cancer Biol Med 2013; 10: 148-157.
[12] Hwang GI, Yoo CH, Sohn BH, Shin JH, Park YL, Kim HD, Kim YS, Han WK and Pae WK. Predictive value of preoperative serum CEA, CA19-9 and CA125 levels for peritoneal metastasis in patients with gastric carcinoma. Cancer Res Treat 2004; 36: 178-181.
[13] Wang W, Seeruttun SR, Fang C, Chen J, Li Y, Liu Z, Zhan Y, Li W, Chen Y, Sun X, Li Y, Xu D, Guan Y and Zhou Z. Prognostic significance of carcinoembryonic antigen staining in cancer tissues of gastric cancer patients. Ann Surg Oncol 2016; 23: 1244-1251.
[14] Zhou YC, Zhao HJ and Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer–a single tertiary hospital study of 1,075 cases. Asian Pac J Cancer Prev 2015; 16: 2685-2691.
[15] Sano T. [Evaluation of the gastric cancer treatment guidelines of the Japanese Gastric Cancer Association]. Gan To Kagaku Ryoho 2010; 37: 582-586.
[16] Jung M, Jeung HC, Lee SS, Park JY, Hong S, Lee SH, Noh SH, Chung HC and Rha SY. The clinical significance of ascitic fluid CEA in advanced gastric cancer with ascites. J Cancer Res Clin Oncol 2010; 136: 517-526.
[17] Liang Y, Wang W, Fang C, Raj SS, Hu WM, Li QW and Zhou ZW. Clinical significance and diagnostic value of serum CEA, CA19-9 and CA72-4 in patients with gastric cancer. Oncotarget 2016; 7: 49565-49573.
[18] Wang W, Chen XL, Zhao SY, Xu YH, Zhang WH, Liu K, Chen XZ, Yang K, Zhang B, Chen ZX, Chen JP, Zhou ZG and Hu JK. Prognostic significance of preoperative serum CA125, CA19-9 and CEA in gastric carcinoma. Oncotarget 2016; 7: 35423-35436.
[19] Distler M, Pilarsky E, Kersting S and Grutzmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of the pancreas-a retrospective tumor marker prognostic study. Int J Surg 2013; 11: 1067-1072.
[20] Liao R, Tang ZW, Li DW, Luo SQ, Huang P and Du CY. Preoperative neutrophil-to-lymphocyte ratio predicts recurrence of patients with single-nodule small hepatocellular carcinoma following curative resection: a retrospective report. World J Surg Oncol 2015; 13: 265.
[21] Zhao LY, Li CC, Jia LY, Chen XL, Zhang WH, Chen XZ, Yang K, Liu K, Wang YG, Xue L, Zhang B, Chen ZX, Chen JP, Zhou ZG and Hu JK. Superiority of lymph node ratio-based staging system for prognostic prediction in 2575 patients with gastric cancer: validation analysis in a large single center. Oncotarget 2016; 7: 51069-51081.