Surg Today (2018) 48:388–394
https://doi.org/10.1007/s00595-017-1598-3

ORIGINAL ARTICLE

Serum carbohydrate antigen 125 is a significant prognostic marker in patients with unresectable advanced or recurrent gastric cancer

Tsutomu Namikawa[1] · Yasuhiro Kawanishi[1] · Kazune Fujisawa[1] · Eri Munekage[1] · Jun Iwabu[1] · Masaya Munekage[1] · Hiromichi Maeda[2] · Hiroyuki Kitagawa[1] · Michiya Kobayashi[2,3] · Kazuhiro Hanazaki[1]

Received: 8 May 2017 / Accepted: 20 September 2017 / Published online: 17 October 2017

Abstract
Purpose We evaluated the diagnostic and prognostic value of three tumor markers: carcino-embryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 125 (CA125), in the pretreatment serum of patients with unresectable advanced or recurrent gastric cancer.
Methods The subjects of this retrospective analysis were 245 patients with unresectable advanced or recurrent gastric cancer diagnosed at Kochi Medical School between 2007 and 2015. We ascertained the sensitivity of CEA, CA19-9, and CA125 to identify a certain survival time and then evaluated the relative prognosis of the patients.
Results The overall positive rates for each tumor marker in the study group were as follows: 57.6% (141/245) for CEA, 38.4% (94/245) for CA19-9, and 34.3% (84/245) for CA125; the sensitivity of these three biomarkers in combination was 73.1% (179/245). The median survival time of the CA125-positive patients was 4.5 months, which was significantly shorter than that of a normal range group (18.3 months, $P < 0.001$). Multivariate survival analysis identified that high CA125 was independently associated with a worse prognosis (HR 3.941; 95% CI 2.544–6.106; $P < 0.001$).
Conclusions Pretreatment serum CA125 is a useful prognostic biomarker in patients with unresectable advanced or recurrent gastric cancer. Evaluating a panel of serum tumor biomarkers is a useful diagnostic tool as elevated values might be associated with poor survival.

Keywords Gastric cancer · Tumor marker · Biomarker · Prognosis · Chemotherapy

Introduction

Gastric cancer is the third most commonly diagnosed cancer worldwide and one of the leading causes of cancer-related deaths [1]. Gastrectomy with regional lymphadenectomy is the most effective treatment for advanced gastric cancer, when curative resection is possible; however, the development of minimally invasive surgery with precise evaluation of the postoperative complications is also important to achieve satisfactory outcomes [2, 3]. For patients with recurrent, metastatic, or advanced gastric cancer, chemotherapy can prolong survival and improve quality of life compared to providing only even the best supportive care.

Serum tumor markers are blood-based biomarkers used to diagnose disease, predict survival rates, and monitor recurrence following surgery for malignant cancer [4, 5]. Carcino-embryonic antigen (CEA) is a glycoprotein that belongs to the immunoglobulin superfamily and was originally described by Gold and Freedman in 1965 [6]. Carbohydrate antigen 19-9 (CA19-9) is a carbohydrate tumor-associated antigen, initially isolated from a human colorectal cancer cell line by Koprowski et al. [7]. Carbohydrate antigen 125 (CA125) is a sensitive tumor marker for ovarian cancer, as reported by Bast et al. [8]. Although tumor markers, such as CEA, CA19-9, and CA125, are used widely for patients with

Electronic supplementary material The online version of this article (doi:10.1007/s00595-017-1598-3) contains supplementary material, which is available to authorized users.

✉ Tsutomu Namikawa
tsutomun@kochi-u.ac.jp

[1] Department of Surgery, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan

[2] Cancer Treatment Center, Kochi Medical School Hospital, Kochi, Japan

[3] Department of Human Health and Medical Sciences, Kochi Medical School, Kochi, Japan

gastric cancer, their specificity and sensitivity to identify gastric cancer patients with short survival times are poor. Furthermore, information about any association between tumor marker values and patient prognosis is limited and the usefulness of measuring these tumor markers in a clinical setting remains controversial [4, 9, 10].

In this study, we examined the proportions of elevated pretreatment serum biomarker values in patients with unresectable advanced or recurrent gastric cancer, evaluated clinicopathological differences, and correlated these three biomarkers with patient prognosis.

Patients and methods

Patients

We reviewed retrospectively patients with unresectable advanced or recurrent gastric cancer who were treated with systemic chemotherapy. Patients with unresectable advanced or recurrent gastric cancer, who were treated with chemotherapy at Kochi Medical School during the period between January, 2007 and December, 2015, were identified from a medical information database. Gastric cancer diagnoses were made based on the findings of esophagogastroduodenoscopy, biopsy specimen analysis, computed tomography, magnetic resonance imaging, ultrasonography of the abdomen, and positron emission tomography. We reviewed the clinicopathological features of these patients, including age, gender, disease status, tumor histology, and metastatic sites. The histological type of each tumor was categorized as intestinal (well differentiated, moderately differentiated, and papillary adenocarcinoma) or diffuse (poorly differentiated, mucinous adenocarcinoma, and signet ring cell carcinoma), according to the Lauren classification [11].

Measurement of tumor markers and survival analysis

The serum levels of CEA, CA19-9, and CA125 were measured in 245 patients with advanced gastric adenocarcinoma, using a commercially available immunoradiometric assay kit, prior to any treatment. The recommended normal upper limits of serum tumor markers were as follows: 3.4 ng/mL for CEA, 37 U/mL for CA19-9, and 35 U/mL for CA125. A result was considered positive when the marker serum value was higher than the upper limit for this marker in serum from healthy patients. Positive combined detection for the three tumor markers was defined as one or more tumor markers having values above the upper limit found in the serum of healthy patients.

The survival curves of patients were examined following treatment. The overall survival time was defined as the interval between the date of chemotherapy initiation and the date of death or last contact. Surviving patients were censored at the last follow-up date.

Statistical analysis

We tested the serum biomarker differences for significance, using the Mann–Whitney *U* test for continuous variables and Pearson's Chi square test for categorical variables. We used the Kaplan–Meier method to generate cumulative survival rates and compared them using the log-rank test to evaluate significant differences. A multivariate Cox proportional hazards regression analysis was used to identify factors independently associated with survival. The hazard ratio (HR) and 95% confidence interval (CI) within each subgroup were summarized for the subgroup analysis of overall survival. When the various factors were considered in a multivariate analysis, all were dichotomized according to the univariate analysis. Statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

We identified 245 patients with unresectable advanced or recurrent gastric cancer, comprising 159 men and 86 women, with a median age of 69 years (range 19–89 years). The clear majority of patients were treated using S-1, an oral fluoropyrimidine, plus cisplatin, administered as in recent large-scale randomized controlled trials [12, 13], while 15 patients received concomitant trastuzumab with chemotherapy consisting of capecitabine plus cisplatin as in the ToGA trial that validated the additive effects of trastuzumab for HER2-positive tumors [14]. Subsequently, 163 patients were shifted to second-line chemotherapy using taxanes and irinotecan after the evidence of disease progression. The median survival time for the total study cohort was 11.5 months (range 1.3–74.1 months), and the overall 1-, 3-, and 5-year survival rates after therapy were 48.2, 16.0, and 0.4%, respectively. At the time of the analysis, the median observation period in our hospital was 8.1 months.

Diagnostic value of tumor markers

In the 245 patients with unresectable advanced or recurrent gastric cancer, the median values of the tumor markers were as follows: 4.0 ng/mL for CEA (range 0–12917 ng/mL), 21.8 U/mL for CA19-9 (range 0–4899 U/mL), and 18.8 U/mL for CA125 (range 0–7070 U/mL). The overall positive rates for each tumor marker were as follows: 57.6% (141/245) for CEA, 38.4% (94/245) for CA19-9, and 34.3% (84/245) for CA125; the sensitivity of these three

biomarkers in combination was 73.1% (179/245). Positivity for CEA was significantly higher than positivity for CA19-9 or CA125 ($P = 0.008$ and $P = 0.002$). The rates of positivity for CA125 combined with other tumor markers were as follows: 17.1% (42/245) for CA125 and CEA, 13.1% (32/245) for CA125 and CA19-9, 9.8% (24/245) for all tumor marker, 64.5% (158/245) for CA125 or CEA, 69.8% (171/245) for CA125 or CA19-9, and 73.1% (179/245) for CA125, CEA or CA19-9.

Table 1 summarizes the results of serum tumor marker values for the different categories of clinicopathological variables in patients with advanced gastric cancer. The rate of positivity for CEA was significantly higher in patients with intestinal-type gastric carcinoma than in those with diffuse-type (72.4 vs. 49.4%, $P < 0.001$). On the other hand, the rate of positivity for CA125 was significantly higher in patients with the diffuse-type of gastric cancer than in those with the intestinal-type (40.1 vs. 23.9%, $P = 0.010$). With regard to the site of metastasis, there were significant differences in the rates of positivity for CEA and the combined marker group. Eleven patients had multiple metastatic sites and the median CA19-9 level was significantly higher in the patients with multiple metastatic sites than those with a solitary metastatic site (45.9 vs. 21.3 U/mL, $P < 0.001$). There were no significant differences in the rates of positivity for each tumor marker between patient subgroups based on age, gender, and disease status.

Relationship between the value of tumor markers and patient survival

Although there was a tendency for a negative relationship between the tumor marker values and patient survival time, no significant association existed between serum values and survival times (Supplemental data). A significantly positive correlation was identified between serum values for CEA and CA125 ($r = 0.339$, $P < 0.001$), but there were no significant correlations between values for CEA and CA19-9 or CA19-9 and CA125.

Association of tumor markers and survival

The median survival time for the CEA-positive group was 11.4 months, which was slightly less than that for the CEA-normal range group, although the difference was not significant (12.3 months, $P = 0.424$; Fig. 1). Similarly the median survival time for the CA19-9-positive group was also slightly shorter (9.6 months) than that of the CA19-9-normal range group, although again the difference was not significant (12.6 months, $P = 0.157$; Fig. 2). The median survival time for the CA125 positive group was 4.5 months, which was significantly shorter than that of the CA125-normal range group (18.3 months, $P < 0.001$; Fig. 3). When the median survival time based on the results of CA125 levels was compared by stratification according to the metastatic sites, peritoneal metastasis was the strongest significant factor associated with worse survival (3.4 vs. 18.5 months, $P < 0.001$).

The median survival times were significantly shorter for patients with positive combined tumor markers prior to treatment than for those with values in the normal range (10.7 vs. 15.7 months, $P = 0.037$; Fig. 4). The median survival times were also significantly shorter for patients with positive values for all tumor markers prior to treatment than for those with positive values for one or two tumor markers (3.5 vs. 14.6 months, $P < 0.001$; Fig. 5). The median survival time of the patients with multiple metastatic sites was shorter than that of those with solitary metastatic site, even though the differences did not reach significance (6.7 vs. 11.6 months, $P = 0.068$).

Univariate analysis of the prognostic factors among the subgroups identified by each predictive factor identified the following as significantly associated with a poor outcome: diffuse-type histology and CA125 $\geq$ 35 U/mL. Multivariate analysis revealed a high CA125 value to be independently associated with poor survival (HR 3.941; 95% CI 2.544–6.106; $P < 0.001$) (Table 2). Histologic type had no significant influence on the survival rate.

Discussion

We found that patients with unresectable advanced or recurrent gastric cancer who received chemotherapy and who had serum CA125 values above the reference interval for healthy people were at higher risk of dying. Additionally, increased values of all the tested serum tumor markers; namely, CEA, CA19-9, and CA125, were a significant prognostic indicator of survival for these patients. Thus, while the prognosis for unresectable advanced or recurrent gastric cancer patients is largely affected by performance status and tumor characteristics, including depth of invasion and lymph node metastasis [12–15], evaluating a panel of tumor markers might also be a useful predictor of the risk of mortality for these patients.

Although CA125 was originally considered as a specific biological marker for ovarian cancer, it might also play an important role in diagnosing different types of cancer, including gastric, colorectal, and pancreatic carcinoma [16–18]. In the present study, the rate of CA125 positivity was 34.3% in gastric cancer patients, which was lower than that of CEA and CA19-9; however, the median survival time of the CA125-positive patients was significantly shorter than that of the CA125-normal range group patients. Kim et al. [18] demonstrated an increased serum CA125 value as an independent prognostic risk factor with a hazard ratio of

Table 1 Results of serum tumor marker values for different categories of clinicopathological variables in patients with unresectable advanced gastric cancer

	CEA		*P* value	CA19-9		*P* value	CA125		*P* value	Combined marker		*P* value
	Positive ($n = 141$)	Negative ($n = 104$)		Positive ($n = 94$)	Negative ($n = 151$)		Positive ($n = 84$)	Negative ($n = 161$)		Positive ($n = 179$)	Negative ($n = 66$)	
Age, median (range), years	70 (19–89)	69.5 (34–89)	0.339	71 (19–89)	69 (34–89)	0.934	70 (42–89)	68 (34–89)	0.316	70 (19–89)	68 (34–88)	0.058
Gender			0.137			0.999			0.322			0.284
Male	97	62		61	98		51	108		119	39	
Female	44	42		33	53		33	53		60	27	
Disease status			0.179			0.382			0.191			0.141
Initially metastatic	99	81		72	108		66	114		127	53	
Recurrent after curative resection	42	23		22	43		18	47		52	13	
Histologic subtype			< 0.001			0.069			0.013			0.665
Intestinal	63	24		40	47		21	66		65	22	
Diffuse	78	80		54	104		63	95		114	44	
Metastasis sites			< 0.001			0.123			0.345			0.025
Hematogeneous	68	20		41	47		25	63		73	15	
Peritoneum	47	61		35	73		41	67		71	37	
Lymph node	26	23		18	31		18	31		35	14	

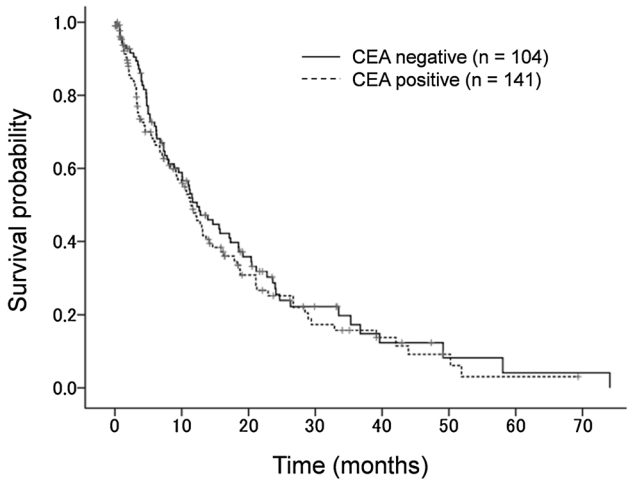

Fig. 1 Kaplan–Meier estimates of survival time for patients with unresectable and recurrent gastric cancer and carcino-embryonic antigen (CEA)-negative serum values ($n = 104$, solid line) or CEA-positive values ($n = 141$, dotted line). There was no significant difference in survival times between the groups ($P = 0.424$; stratified log-rank test)

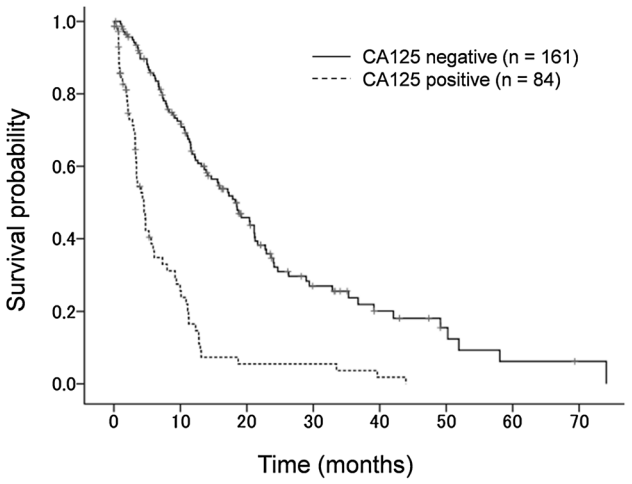

Fig. 3 Kaplan–Meier estimates of the survival time of patients with unresectable and recurrent gastric cancer and carbohydrate antigen 125 (CA125)-negative serum values ($n = 66$, solid line) or CA125-positive values ($n = 179$, dotted line). There was a significant difference in survival times between the groups ($P < 0.001$; stratified log-rank test)

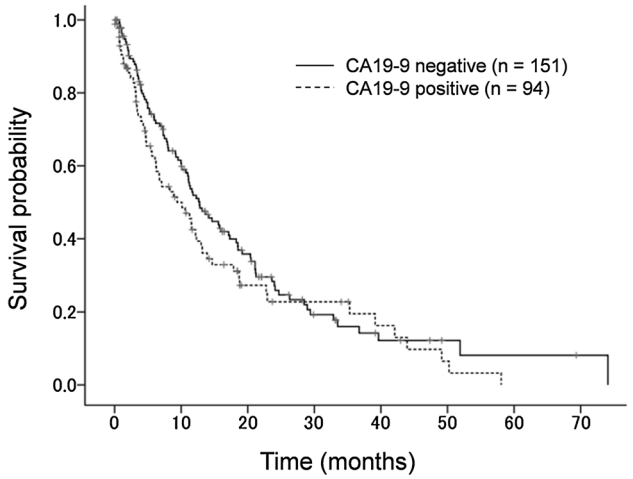

Fig. 2 Kaplan–Meier estimates of overall survival for patients with unresectable and recurrent gastric cancer and carbohydrate antigen 19-9 (CA19-9)-negative serum values ($n = 151$, solid line) or CA19-9-positive values ($n = 94$, dotted line). There was no significant difference in survival times between the groups ($P = 0.157$; stratified log-rank test)

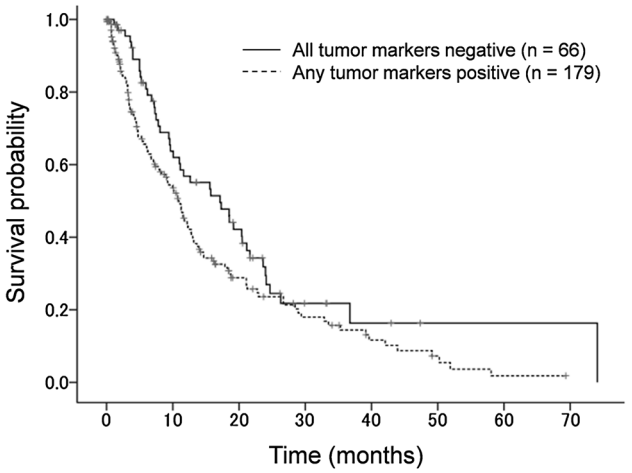

Fig. 4 Kaplan–Meier estimates of survival times for patients with unresectable and recurrent gastric cancer and negative values for all tumor markers ($n = 66$, solid line) or positive combined detection of any tumor markers group ($n = 179$, dotted line). There was a significant difference in survival times between the groups ($P = 0.037$; stratified log-rank test)

2.431 for the recurrence of gastric cancer in 679 patients who had undergone resection believed to have been curative. In our study, positive values of CA125 were significantly more likely in diffuse-type than intestinal-type gastric carcinoma, despite relatively fewer cases of positive CA125 values. Furthermore, peritoneal metastasis was the strongest significant factor associated with worse survival for the patients with positive CA125 values according to stratified analysis of the metastatic sites. In patients who have undergone what was believed to be curative surgery, CA125 positivity may reflect peritoneal dissemination [16, 18, 19].

Wang and colleagues reported that preoperative serum CA125 was an independent prognostic factor for patients with gastric cancer who underwent gastrectomy [20]. The results of the present study showed that a high CA125 value was an independent factor associated with poor prognosis for patients with unresectable advanced or recurrent gastric cancer. Thus, CA125 might be an important biomarker for

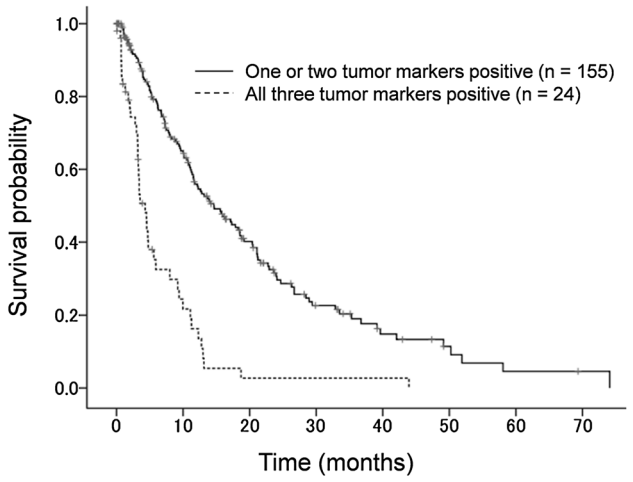

Fig. 5 Kaplan–Meier estimates of survival times for patients with unresectable and recurrent gastric cancer and one or two positive tumor markers (n = 155, solid line) or all positive tumor markers (n = 24, dotted line). There was a significant difference in survival times between the groups ($P < 0.001$; stratified log-rank test)

Table 2 Clinical characteristics and survival of patients with unresectable advanced gastric cancer using multivariate survival analysis

Variable	Hazard ratio	95% confidence interval	P value
Histologic type (intestinal/diffuse)	1.377	0.866–2.140	0.155
CA125 (< 35/≥ 35)	3.941	2.544–6.106	< 0.001

evaluating patient outcomes and predicting prognosis more precisely, not only for patients who have undergone curative surgery for gastric cancer, but also for patients with unresectable advanced or recurrent gastric cancer who have been treated with systemic chemotherapy, particularly if it is used with other tumor markers.

CEA is one of the most commonly used biomarkers in clinical practice, both for monitoring patients with gastrointestinal malignancies and for predicting recurrence [9, 17, 21]. Previous studies indicate that pretreatment serum CEA values are associated with an adverse prognosis for gastrointestinal cancer [5, 22, 23]. A meta-analysis reported by Deng et al. [24] demonstrated that elevated pretreatment serum CEA values were an independent predictor of poor prognosis for patients with gastric cancer. In the present study, there were significantly more patients with a positive CEA value than with a positive CA19-9 or CA125 value. The median survival time of the CEA-positive patients was also slightly shorter than that of the CEA-normal range patients, although the difference did not reach significance.

Our study found that patients with intestinal types gastric carcinomas were significantly more likely to have a positive CEA value than those with diffuse-type gastric carcinomas, and that this trend was significantly more likely in patients with hematogeneous metastasis than in those with peritoneal or lymph node metastasis. Similarly, several reports have documented that elevated CEA values were significantly associated with histologically diagnosed intestinal-type tumors [17, 25], while one study reported an association with diffuse-types tumors [26]. Ikeda et al. also reported that an elevated CEA level was an independent risk factor for liver metastases in 68 patients with stage IV gastric cancers [27].

CA19-9 is a widely used biochemical marker for diagnostic and prognostic purposes in patients with digestive system tumors, especially pancreatic cancer, and has a reported sensitivity and specificity of around 80% [28]. However, high levels of CA 19-9 can be caused by benign obstructive jaundice or cholangitis. A multivariate analysis of 663 patients with gastric cancer who underwent surgery by Kodera et al. [29] indicated that serum CA19-9 was a better prognostic factor than CEA, although with a reported sensitivity of only 16.0%. In the current study, there were no significant differences in median survival time between the CA19-9-positive and -negative patient groups. Moreover, as there was no significant correlation between the value of each of the tumor markers and survival, it cannot be concluded that patients with higher values of tumor markers were more likely to have a higher tumor burden and reduced chances of survival. This disparity in study findings could be due to differences in patient characteristics such as whether resection was curative, whether metastatic disease was present, or different sample sizes among studies.

We recognize the following limitations of the present study. First, it was a retrospective study, so results may be affected by errors and biases inherent in such a design. Second, it consisted of patients from a single institution, possibly leading to patient selection bias. Further studies with adequate statistical power and a larger number of patient subgroups are needed to establish the reliability and accuracy of tumor markers in assessing patient prognosis of advanced gastric cancer. Despite this, the current study showed positive rates for CEA, CA19-9, and CA125 of 57.6, 38.4, and 34.3%, respectively; similar to those of previous investigations where overall positive rates of tumor markers in patients with gastric cancer were 16–68% for CEA, 14–68% for CA19-9, and 23–65% for CA125 [4, 16, 17, 30].

In conclusion, while few effective biomarkers have previously been used in clinical practice to investigate and manage patients with gastric cancer [21, 31, 32], this study found that measuring pretreatment CA125 might be a useful biomarker for predicting the prognosis of patients with unresectable advanced or recurrent gastric cancer who have received chemotherapy. Furthermore, the combined measurement of the tumor markers, CEA, CA19-9, and CA125, might be useful to improve the management of these

patients. Further studies, including prospective studies, are required to confirm and better understand the prognostic value of these biomarkers in clinical practice.

Compliance with ethical standards

Conflict of interest None of the authors received funding or have any competing interests to disclose.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.
2. Yamashita K, Miyazaki Y, Takahashi T, Masuike Y, Motoori M, Kimura Y, et al. Safety and feasibility of laparoscopic gastrectomy for gastric cancer patients with a history of abdominal surgery. Surg Today. 2017. doi:10.1007/s00595-017-1506-x.
3. Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, et al. Extended Clavien–Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surg Today. 2016;46:668–85.
4. Shimada H, Noie T, Ohashi M, Oba K, 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.
5. Wada N, Kurokawa Y, Miyazaki Y, Makino T, Takahashi T, Yamasaki M, et al. The characteristics of the serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer cases. Surg Today. 2017;47:227–32.
6. Gold P. Freedman So. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med. 1965;121:439–62.
7. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genet. 1979;5:957–71.
8. Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Investig. 1981;68:1331–7.
9. Jiexian J, Xiaoqin X, Lili D, Baoguo T, Ting S, Xianwen Z, Cunzhi H. Clinical assessment and prognostic evaluation of tumor markers in patients with gastric cancer. Int J Biol Markers. 2013;28:192–200.
10. Yamao T, Kai S, Kazami A, Koizumi K, Handa T, Takemoto N, et al. Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. Jpn J Clin Oncol. 1999;29:550–5.
11. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
12. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
13. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
14. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
15. Namikawa T, Munekage E, Munekage M, Maeda H, Yatabe T, Kitagawa H, et al. Evaluation of a trastuzumab-containing treatment regimen for patients with unresectable advanced or recurrent gastric cancer. Mol Clin Oncol. 2016;5:74–8.
16. Sun Z, Zhang N. Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. World J Surg Oncol. 2014;12:397.
17. Maehara Y, Sugimachi K, Akagi M, Kakegawa T, Shimazu H, Tomita M. Serum carcinoembryonic antigen level increases correlate with tumor progression in patients with differentiated gastric carcinoma following noncurative resection. Cancer Res. 1990;50:3952–5.
18. Kim DH, Yun HY, Ryu DH, Han HS, Han JH, Yoon SM, et al. Preoperative CA 125 is significant indicator of curative resection in gastric cancer patients. World J Gastroenterol. 2015;21:1216–21.
19. Wang Q, Yang Y, Zhang YP, Zou Z, Qian X, Liu B, et al. Prognostic value of carbohydrate tumor markers and inflammation-based markers in metastatic or recurrent gastric cancer. Med Oncol. 2014;31:289.
20. Wang W, Chen XL, Zhao SY, Xu YH, Zhang WH, Liu K, et al. Prognostic significance of preoperative serum CA125, CA19-9 and CEA in gastric carcinoma. Oncotarget. 2016;7:35423–36.
21. Kalniņa Z, Meistere I, Kikuste I, Tolmanis I, Zayakin P, Linē A. Emerging blood-based biomarkers for detection of gastric cancer. World J Gastroenterol. 2015;21:11636–53.
22. Chapman MA, Buckley D, Henson DB, Armitage NC. Preoperative carcinoembryonic antigen is related to tumour stage and long-term survival in colorectal cancer. Br J Cancer. 1998;78:1346–9.
23. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230:309–21.
24. Deng K, Yang L, Hu B, Wu H, Zhu H, Tang C. The prognostic significance of pretreatment serum CEA levels in gastric cancer: a meta-analysis including 14651 patients. PLoS One. 2015;10:e0124151.
25. Fan B, Xiong B. Investigation of serum tumor markers in the diagnosis of gastric cancer. Hepatogastroenterology. 2011;58:239–45.
26. Kim DY, Kim HR, Shim JH, Park CS, Kim SK, Kim YJ. Significance of serum and tissue carcinoembryonic antigen for the prognosis of gastric carcinoma patients. J Surg Oncol. 2000;74:185–92.
27. Ikeda Y, Mori M, Adachi Y, Matsushima T, Sugimachi K, Saku M. Carcinoembryonic antigen (CEA) in stage IV gastric cancer as a risk factor for liver metastasis: a univariate and multivariate analysis. J Surg Oncol. 1993;53:235–8.
28. Kato Y, Takahashi S, Gotohda N, Konishi M. Prognostic impact of the initial postoperative CA19-9 level in patients with extrahepatic bile duct cancer. J Gastrointest Surg. 2016;20:1435–43.
29. Kodera Y, Yamamura Y, Torii A, Uesaka K, Hirai T, Yasui K, et al. The prognostic value of preoperative serum levels of CEA and CA19-9 in patients with gastric cancer. Am J Gastroenterol. 1996;91:49–53.
30. Yu J, Zhang S, Zhao B. Differences and correlation of serum CEA, CA19-9 and CA72-4 in gastric cancer. Mol Clin Oncol. 2016;4:441–9.
31. Namikawa T, Fukudome I, Ogawa M, Munekage E, Munekage M, Shiga M, et al. Clinical efficacy of protein-bound polysaccharide K in patients with gastric cancer undergoing chemotherapy with an oral fluoropyrimidine (S-1). Eur J Surg Oncol. 2015;41:795–800.
32. Namikawa T, Munekage E, Munekage M, Maeda H, Yatabe T, Kitagawa H, et al. Evaluation of systemic inflammatory response biomarkers in patients receiving chemotherapy for unresectable and recurrent advanced gastric cancer. Oncology. 2016;90:321–6.