Original article

Peritoneal and serum tumor markers predict recurrence and survival of patients with resectable gastric cancer

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Abstract:

Background. Laparoscopy has become a useful adjunct for the staging of gastric cancer; yet, other than standard TNM staging, few additional variables can be used to predict survival. This study evaluated the utility of serum and peritoneal tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA]-125) as predictors of locoregional recurrence and distant disease-free survival in patients with gastric cancer.

Methods. During the period June 1990 to February 1994, 86 patients with gastric cancer were evaluated and deemed resectable by preoperative imaging studies. Serum levels of CEA and CA-125 were determined, and all patients underwent laparoscopic staging. Peritoneal washings were obtained from all patients, and 56 of these samples were evaluated for levels of CEA and CA-125.

Results. Sixteen (19%) of the 86 patients were found to have metastatic disease at laparoscopy; 67 of the remaining 70 patients underwent potentially curative gastrectomy. Serum CEA and CA-125 levels were predictive of survival in the entire group of patients. In patients who underwent curative gastrectomy, serum CEA predicted survival, whereas peritoneal CA-125 predicted peritoneal recurrence.

Conclusions. Elevated serum levels of CEA and CA-125 are predictive of decreased survival in patients with gastric cancer. Furthermore, determination of peritoneal CA-125 helps to identify those patients at an increased risk for recurrent peritoneal disease.

Key words: tumor markers, CEA, CA-125, gastric cancer

Introduction

Despite progress in surgical techniques and the development of adjuvant chemotherapeutic regimens, sur-

vival from gastric cancer remains poor [1]. Although morbidity and mortality from surgical resection have decreased significantly in the past 40 years, the overall 5-year survival in patients who undergo curative resection remains less than 40% [2]. Despite advances such as endoscopic ultrasonography (EUS) and laparoscopic staging, the selection of patients to undergo curative resection remains difficult, as a significant fraction of these patients will still have locoregional recurrences in addition to disseminated metastases [3]. The only accepted prognostic variables for gastric cancer are the pathologic TNM staging criteria, yet these are not entirely accurate in predicting either locoregional or distant recurrence or in separating the risk of site-specific recurrence [4].

Common sites of recurrence following curative resection for gastric cancer include the peritoneal surface, the liver, and lymph nodes [2]. Laparoscopy with cytologic examination of peritoneal washings has been advocated to detect small-volume peritoneal or hepatic disease that could not be identified with preoperative imaging studies [5–7]. However, microscopic peritoneal disease remains a significant problem, as carcinomatosis is a frequent occurrence following curative resection of gastric cancer. However, as many as 50% of patients who have negative peritoneal cytology will ultimately develop peritoneal recurrence, and, conversely, up to 20% of patients with macroscopic peritoneal disease will have negative cytology [5]. Therefore, it is clear that cytological examination of peritoneal fluid is insufficient for detecting or predicting microscopic peritoneal disease.

Various tumor markers have been described since Gold and Freedman [8] first reported the discovery of carcinoembryonic antigen (CEA) in 1965. The utility of these tumor markers has been assessed in a variety of studies to predict various clinical parameters (stage, response to neoadjuvant therapy, progression and recurrence of the cancer) [9,10]. Specifically, these tumor

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markers have been studied in an effort to identify those patients who may be at increased risk for recurrence despite curative resection and therefore are appropriate candidates for adjuvant therapy. Although CEA may be useful in the follow-up of colon cancer to identify tumor recurrence, it is presently unclear what role tumor markers may have in predicting or identifying those patients with gastric cancer who will develop recurrence following curative resection [11]. Although many studies have examined tumor markers in gastric cancer, most have focused on the correlation of tumor marker level with tumor stage. Studies that have examined the utility of tumor markers such as CEA, carbohydrate antigen (CA) 19-9, and CA72-4 in gastric cancer have been limited by the heterogeneous patient population, which ranged from patients with mucosal disease to those with metastatic disease [12–16]. Finally, most of these studies did utilize current staging modalities such as EUS and laparoscopy to fully define those patients with localized, resectable gastric cancer.

The purpose of the present study was to determine whether preoperative serum levels of the tumor markers CEA and CA-125 predicted recurrence in patients with gastric cancer who underwent complete staging, utilizing helical computerized tomographic (CT) scanning, EUS, and laparoscopy, followed by standardized treatment of surgical resection, including D2 nodal dissection. Furthermore, levels of CEA and CA-125 were determined in peritoneal washings in an effort to determine whether elevated levels of these tumor markers predicted peritoneal recurrence following curative resection.

Patients and methods

Between June 1990 and February 1994, 104 patients were referred for evaluation to the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center (Houston, TX, USA) for potentially resectable gastric cancer. All patients had histologically proven adenocarcinoma of the stomach. All patients underwent a standard screening program consisting of a physical examination, CT scan of the lower chest and abdomen, and esophagogastroscopy with an EUS scan of the tumor and adjacent nodal basins. Eighteen patients were found to have extra-nodal metastases and were excluded from this data analysis. Routine blood samples were evaluated for the levels of the tumor markers CEA and CA-125.

The 86 eligible patients underwent laparoscopic staging before planned curative resection. Peritoneal washings were obtained by the instillation of at least 600 ml of sterile saline solution into the upper abdomen

with subsequent aspiration to determine levels of the tumor markers CEA and CA-125. At the time of laparoscopy, 16 patients were found to have gross visible extranodal metastases within the liver or on the peritoneal surface. These patients were excluded from the analysis, leaving 70 patients eligible for curative resection of localized gastric cancer. Standard treatment for resectable gastric cancer at M. D. Anderson Cancer Center has been described previously [17]; in brief, the regimens used in preoperative chemotherapy included continuous infusion of 5-fluorouracil, cisplatin, and etoposide, Adriamycin, cisplatin (EAP). Three patients had medical diseases that precluded gastrectomy; hence, 67 underwent gastrectomy with spleen-preserving D2 nodal dissection (Fig. 1) [18].

Of the patients undergoing gastrectomy, 38 were men and 29, women; their median age was 55 years (range, 27–86 years). The tumor and nodal stage, as determined by preoperative EUS, of these patients is summarized in Table 1. Of the 67 eligible patients, there were 6 stage IA patients, 7 stage IB, 14 stage II, 23 stage IIIB, 12 stage IIIB, 1 stage IV, and 4 patients in whom precise staging was not completed prior to neoadjuvant therapy. The level of CEA in the peritoneal washing was available for 56 of these patients; the level of CA-125 in the peritoneal washing was available for 27 of these patients. Patients were followed at 3-month inter-

Fig. 1. Schema of the 104 patients evaluated for treatment of gastric cancer. Upon staging with computed tomography (CT) and endoscopic ultrasound (EUS) scans, 18 patients were found to harbor metastatic disease, leaving 86 patients with potentially resectable gastric cancer. These patients then underwent staging laparoscopy, and an additional 16 patients were found to harbor metastatic disease. Of the remaining 70 patients, 67 underwent curative resection; 3 patients did not undergo resection for medical reasons

Table 1. Demographics of 67 patients who underwent curative resection for gastric cancer following laparoscopic staging

Sex	38 Men; 29 women
Median age (range)	55 (27–86) Years
No. T stage (% of patients)	
1	9 (13)
2	22 (33)
3	29 (43)
4	3 (4)
Unknown	4 (6)
No. N Stage (% of patients)	
0	14 (21)
1	28 (42)
2	21 (31)
Unknown	4 (6)
Median follow-up (range)	28 (2–66) Months

Tumor and nodal stages were determined preoperatively by endoscopic ultrasound (EUS) during upper endoscopy. The precise tumor and nodal stage was unclear in four patients who underwent resection following neoadjuvant chemoradiation without a pre-treatment EUS

vals for 2 years, then every 6 months, and disease status was determined by physical examination and routine CT scans of the abdomen. Clinico-pathologic data were maintained in a prospective database, which served as the source for subsequent analysis. The median follow-up of all patients was 28 months.

Statistical methods

Survival curves for disease recurrence and disease-specific survival were calculated according to the Kaplan-Meier method. Disease-specific survival is used as a direct analysis of the variables and tumor behavior, although in this population in which survival is directly related to the disease process, overall survival is nearly identical to disease-specific survival. Cutoff points for serum levels were chosen for CEA and CA-125 according to the range of levels of these tumor markers in healthy patients as determined by the Department of Laboratory Medicine at M. D. Anderson Cancer Center (CEA, normal range, <3 ng/ml, CA-125, normal range, <35 IU/ml). Cutoff points for peritoneal levels were chosen through the use of a stepwise, backward linear regression model examining various breakpoints to achieve statistical significance. The optimal breakpoints for the peritoneal markers occurred at 1 ng/ml for CEA and 35 IU/ml for CA-125. Statistical significance was calculated by the log-rank test. Analysis of mean tumor marker levels and tumor stage was performed using Kruskal-Wallis analysis of variance (ANOVA). Statistical significance was assumed for a *P* value less than 0.05.

Fig. 2. Disease-free survival curves for patients with potentially resectable gastric cancer before laparoscopic staging as a function of serum carcinoembryonic antigen (CEA) level ($n = 86$). A significant difference was demonstrated between patients with elevated (>3 ng/ml) and normal serum CEA levels ($P = 0.013$). Median survival of patients with an elevated CEA level was approximately 10 months, whereas that of patients with a normal serum CEA level was 28 months

Results

In patients deemed to be eligible for resection according to preoperative radiographic imaging modalities, the serum level of CEA was elevated in 21 (24.4%) and normal in 65. Elevation of the preoperative serum level was a significant predictor of poor survival in patients with potentially resectable gastric cancer (Fig. 2). The median survival of patients with an elevated serum CEA level was approximately 10 months, whereas that of patients with a normal serum CEA level was 28 months. Preoperative elevation of the serum CEA level was also found to predict peritoneal disease: 7 of the 16 patients who were found at laparoscopic staging to harbor metastatic disease had elevated serum levels of CEA, whereas only 14 of the remaining 54 patients without metastatic disease at laparoscopy had elevated serum CEA levels ($P = 0.046$ by χ^2).

Results for serum levels of CA-125 were similar to those for serum CEA levels, although data were available for only 53 patients. Preoperative serum levels of CA-125 were elevated in 28 patients (52.8%), normal in 25 patients, and not determined in 33 patients. Similar to the results for CEA levels, elevation of the preoperative serum level of CA-125 predicted poorer survival in patients with potentially resectable gastric cancer before staging using laparoscopy (Fig. 3). Elevations of the serum levels of CEA and CA-125 were unrelated; of the 28 patients with elevated CA-125, 11 had elevated CEA, whereas of the 25 patients with normal CA-125, 5 had elevated CEA levels ($P = 0.10$ by χ^2 analysis). Median survival for those patients in whom both serum CEA and CA-125 levels were elevated was

Fig. 3. Disease-free survival curves for patients with potentially resectable gastric cancer before laparoscopic staging as a function of serum carbohydrate antigen (CA)-125 level. A significant difference was demonstrated between patients with elevated (>35 IU/ml) and normal serum CA-125 levels ($P = 0.043$)

9 months, compared with 26 months when only one marker was elevated (data not shown).

In the 67 patients who underwent curative resection, the serum level of CEA was elevated in 13 patients (19.4%) and normal in 54 patients. In this same group of patients, the serum level of CA-125 was elevated in 17 patients (45.9%), normal in 20 patients, and not obtained preoperatively in 30 patients. Elevation of the serum CEA level significantly predicted a poorer survival following curative resection (Fig. 4). The median survival for those patients with an elevated serum CEA level was approximately 14.5 months, whereas the median survival for patients with a normal serum CEA level was 43 months. In contrast, serum levels of CA-125 did not predict survival. This may have been due to the small number of patients or to the exclusion of those patients with metastatic disease at laparoscopic staging.

Levels of CEA and CA-125 were determined in peritoneal washings in patients who underwent laparoscopic staging. For those patients who subsequently underwent curative gastrectomy, the level of CEA was >1 ng/ml in the washings of 14 patients and <1 ng/ml in 39 patients; CEA levels were not determined for 14 patients. The level of CA-125 was >35 IU/ml in the washings of 21 patients and <35 IU/ml in 28 patients; CA-125 levels were not determined for 18 patients. Elevated levels of CA-125 in the peritoneal washings significantly predicted peritoneal recurrence in patients who underwent curative gastrectomy (Fig. 5). The median time to the development of metastatic peritoneal disease was 20 months in patients with high levels of CA-125 in the peritoneal washings and 54 months in patients with normal levels. The level of CEA in the peritoneal washings did not have a significant predictive

Fig. 4. Disease-free survival curves for patients who underwent curative resection for gastric cancer after laparoscopic staging as a function of serum CEA level. A significant difference was demonstrated between patients with elevated (>3 ng/ml) and normal serum CEA levels ($P = 0.007$)

Fig. 5. Peritoneal disease-free survival curves for patients who underwent curative resection for gastric cancer after laparoscopic staging as a function of peritoneal levels of CA-125. A significant difference was demonstrated between patients with elevated (>35 IU/ml) and normal peritoneal levels of CA-125 ($P = 0.047$)

value for the occurrence of peritoneal disease following curative gastrectomy (data not shown).

The median levels of both serum and peritoneal tumor markers were then correlated with the T and N stage for all patients (Fig. 6). Surprisingly, there was not a significant correlation between any of the tumor markers and T or N stage, with the exception of T4 lesions. Of interest is the lack of correlation between the tumor markers and T1–T3 disease, without a specific elevation observed between any of these tumor subgroups. The correlation of advanced T stage (T4) and tumor markers must be interpreted cautiously, as there were very few patients in this group. As both serum CEA and peritoneal CA-125 levels were prognostic factors for survival following curative resection, these fac-

Fig. 6a,b. Correlation of **a** tumor (T) and **b** nodal (N) stage with levels of serum and peritoneal tumor markers in patients who underwent curative resection for gastric cancer after laparoscopic staging. Mean values (ng/ml) are shown for serum CEA (*diamonds*) and peritoneal CEA (*triangles*), as well as serum CA-125 (*small squares*) and peritoneal CA-125

($\times 10^{-1}$) *large squares* (IU/ml). For T stage, only T4 demonstrated significant correlations with elevated levels of serum CEA, serum CA-125, and peritoneal CEA ($P < 0.05$); for N stage, a generalized, but nonsignificant trend ($P > 0.05$) toward lower tumor marker levels was observed during nodal stage progression

Table 2. Relationship of abnormalities in either serum CEA levels or peritoneal CA-125 levels to various clinicopathologic variables in the 67 patients who underwent curative resection for gastric cancer following laparoscopic staging^a

	Serum CEA		Peritoneal CA-125	
	Normal	Elevated	Normal	Elevated
Preoperative chemotherapy				
Administered	15	6	8	1
Not administered	39	7	9	12*
Peritoneal cytology				
Positive	7	2	2	1
Negative	47	11	16	12
Nodal metastasis				
Present	40	9	13	10
Absent	12	3	3	4

* $P < 0.05$ by χ^2 analysis

CEA, Carcinoembryonic antigen; CA-125, carbohydrate antigen-125

^aNot all patients had peritoneal levels of CA-125 determined; thus, the number of patients for that parameter does not total the 67 patients included in the current study

tors were examined in relation to other variables which may influence survival (Table 2). These data indicate that elevation of serum CEA was not associated with the administration of preoperative chemotherapy, the presence of microscopic peritoneal disease as detected by peritoneal cytology, or the presence of nodal metastases. The current practice protocol at M. D. Anderson Cancer Center excludes patients with positive peritoneal cytology from treatment for localized gastric cancer, including curative gastrectomy, and, therefore, few patients with positive peritoneal cytology are available for analysis. There was an association between the administration of preoperative chemotherapy and peritoneal levels of CA-125, with fewer patients

who received preoperative chemotherapy exhibiting an elevation of peritoneal CA-125. However, there was no association of peritoneal cytologic positivity or nodal metastases with peritoneal levels of CA-125.

Discussion

These data have demonstrated that elevated serum levels of the tumor markers CEA and CA-125 are predictive of poor survival in patients who are deemed eligible for resection based upon preoperative imaging studies in the absence of or prior to the performance of laparoscopic staging. Furthermore, in patients who un-

dergo laparoscopic staging with a subsequent curative gastrectomy, elevated preoperative levels of CEA, but not CA-125, predict disease recurrence and poorer survival. Finally, determination of the level of CA-125 in the effluent following laparoscopic peritoneal washing is useful in predicting those patients who are at an increased risk for the development of peritoneal recurrence following a curative gastrectomy. It would appear from our data that determination of peritoneal levels of CA-125 is complementary to cytologic evaluation of peritoneal washings, as most patients in this study had negative peritoneal cytology. These data indicate that serum and peritoneal tumor markers may identify patients who are at increased risk for the development of metastatic disease utilizing current methods of management of localized gastric cancer, including CT, EUS, and laparoscopic staging.

Since the description of CEA and its secretion by gastrointestinal tumors [19], various other tumor markers have been identified that are specifically produced by neoplastic tissues. These tumor markers have been studied for applicability in terms of tumor detection, staging, and identification of recurrence. Numerous reports have examined the utility of CEA and other tumor markers, including CA19-9, CA72-4, CA-50, CA-125, and serum interleukin-6, in gastric cancer [9,11,20–23]. Some have indicated the usefulness of one or more tumor markers in predicting specific clinical outcomes (i.e., prognosis, response to treatment, and monitoring for recurrence), although the studies have not provided consistent results. Furthermore, the studies have been hampered by several methodologic flaws: (1) the inclusion of patients with a variety of tumor stages ranging from localized to metastatic (2) a heterogeneous treatment regimen, including both surgical and chemotherapeutic methods, and (3) the lack of laparoscopy for uniform staging.

CEA has been shown in several studies to correlate directly with the depth of invasion of the tumor and the presence of nodal or disseminated metastasis [12–14,18,22,24]. Furthermore, CEA has demonstrated some role as an independent prognostic marker; however, this has not been confirmed in all studies [20,23,25]. This is likely due to the heterogeneous nature of patients included in these studies, including those with localized disease who undergo gastrectomy and those with locally advanced and disseminated disease who may not undergo resection. The prognostic utility of tumor markers in patients with metastatic disease is limited; these markers may be more useful to assess treatment response rather than long-term survival. Finally, in most of these studies, the exact treatment regimen is not fully detailed, including the extent of nodal resection and the inclusion of adjuvant chemotherapy and radiotherapy following curative resection.

Our study cohort was composed of a clinically homogeneous group of patients; that is, patients with gastric cancer who underwent staging laparoscopy and potentially curative gastrectomy with regional lymph node dissection. Nearly 75% of the patients had stage II or stage III disease, which represents those at greatest risk for locoregional recurrence after potentially curative gastrectomy. No patients with identified extranodal metastatic disease were included in the current study, and fewer than 10% of the patients were stage IA. Laparoscopy has been shown in other studies to be an effective staging tool and has been incorporated into many treatment regimens for gastric cancer, especially in the setting of preoperative or neoadjuvant chemotherapy [5,7,26]. This is the first reported study that we are aware of that examined tumor markers for prognostic value in patients undergoing preoperative laparoscopy and who only had resectable disease.

The levels of a variety of tumor markers have been examined in gastric luminal washings and stool specimens in an additional attempt to quantitate tumor burden and, hence, to predict the risk of disseminated disease. The peritoneal cavity is a significant site of disease recurrence following potentially curative resection for gastric cancer. A variety of regimens are being developed, some of which include peritoneal chemotherapy [27–30]. Therefore, it would be helpful to identify those patients who undergo potentially curative gastrectomy but have a significant risk for the development of peritoneal metastases [31]. A single study has examined peritoneal CEA levels in patients with gastric cancer and found a correlation between these variables; however, almost 20% of the patients included in the analysis by Asao et al. [32] had carcinomatosis identified at laparoscopy. Laparoscopic washing with cytologic examination has been shown in a limited number of studies to identify patients at risk for peritoneal and disseminated disease [5,7]; however, our study did not compare the cytologic staging with levels of tumor markers. This study found that peritoneal levels of CA-125, but not CEA, were predictive of peritoneal recurrence, thereby potentially identifying those patients in whom peritoneal-specific therapy may be warranted. In summary, the results from our data are significant for two separate reasons: (1) Tumor markers may allow for preoperative prognostic stratification of patients based upon non- or minimally invasive techniques, (2) specifically peritoneal tumor markers in the setting of a negative laparoscopy (including negative peritoneal cytology) may allow for stratification of patients at increased risk for peritoneal failure following curative gastrectomy and therefore allow for possible administration of peritoneal-based therapy.

It is becoming clear that tumor markers are clinically useful in the treatment of patients with gastric cancer,

whether in terms of stratification for risk of recurrence, assessment of treatment response, or monitoring for recurrence. It would appear that CEA may not be the optimal marker, but until further investigation identifies a better tumor-associated antigen, it may be worthwhile to obtain a baseline level of CEA preoperatively and at intervals during routine follow-up. Finally, extreme elevation of a tumor marker in the setting of a resectable gastric cancer should alert the oncologist of the high potential for recurrence, and may warrant aggressive adjuvant therapy following curative gastrectomy.

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