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Evaluation of Peritoneal Lavage for Gastric Cancer Staging in Patients Without Ascites Based on Cytology and Carcinoembryonic Antigen

Fezzeh Elyasinia[1], Faramarz Karimian[2], Fatemeh Samiei[3], Ehsan Sadeghian[1]*

1. Department of Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
2. Department of Surgery, Imam Khomeini Hospital, Tehran University of Medical Sciences.
3. Department of Surgery,Tehran University of Medical Sciences.

***Corresponding Author:**
Ehsan Sadeghian
Department of Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Tel: (+98)2184902455
Email: ehsan810@yahoo.com

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ABSTRACT

Background: Imaging, cytological examination of ascites (if present), laparoscopy, and peritoneal lavage are performed before surgery for gastric cancer staging. Peritoneal lavage aims to diagnose the microscopic presence of tumor cells on the peritoneal surface. Positive cytology may have a prognostic value that classifies the disorder as stage IV, in which the patient is no longer an elective surgical candidate. Thus, our study was designed to assess the ability of peritoneal lavage to stage gastric cancer in non-ascitic patients based on cytological evaluation and carcinoembryonic antigen (CEA) level measurement.

Methods: In our prospective study, we examined gastric cancer patients who were candidates for elective surgery. Upon entering the abdominal cavity and before tumor manipulation, normal saline (500 ml) was applied, and the abdominal cavity was thoroughly dispersed. After three minutes, the fluid was drained and addressed to cytological analysis and CEA measurement by radioimmunoassay (RIA). Study variables including age, sex, family history, tumor position, pathology, staging, grading, the original tumor size, regional lymph node involvement, and distant metastases were recorded during the pre- and postoperative staging. The association between positive peritoneal lavage cytology and various patients' characteristics was investigated.

Results: In this study, 94 patients were screened. Due to lymphoma and gastrointestinal stromal tumor (GIST), two patients were excluded. We examined 92 patients, including 63 males (68.5 %) and 29 females (31.5 %). The mean age of patients was 58.52 ± 11.87 years. The most common tumor location was the esophagogastric junction. Moderately differentiated adenocarcinoma was the most frequent microscopic diagnosis. T3 was the most prevalent primary tumor size in 51 patients. Seventy-two patients (78.26%) were operable, of whom 18 (19.6 %) were positive for peritoneal lavage cytology. Positive cytology of peritoneal lavage was significantly related to tumor size, tumor grade, serosa/adjacent organ invasion (T4), laparoscopic staging findings, locally advanced disease (R0), and stage of the disease ($P < 0.05$). In the peritoneal lavage fluid, elevated CEA titers were significantly related to the high-grade tumor ($P = 0.012$).

Conclusion: Our study demonstrated that positive cytology and high CEA titers in peritoneal lavage fluid of gastric cancer patients without ascites are significantly correlated to the advanced stages.

Keywords: Gastric Cancer, Peritoneal Lavage, Carcinoembryonic Antigen (CEA), Cytology

INTRODUCTION:

Gastric cancer is one of the most frequent cancers in the world. Despite recent developments in gastric cancer treatment, the cumulative 5-year survival rate is considerably low (1). Gastric cancer is an invasive disease that can hardly be clinically diagnosed in its early stages. Most patients are diagnosed with limited survival in the advanced stage due to metastatic disease (2). In the early stage, gastric cancer is asymptomatic and can be treated while it is only a local disease if an early diagnosis is made (3). Gastric cancer is the most common cancer in men and the second most frequent among women in some Middle East countries (4).

It is necessary to diagnose gastric cancer when it is still a local disease by considering clinical symptoms such as weight loss, loss of appetite (anorexia), indigestion, postprandial fullness, nausea, and vomiting (5,6). Treatment of gastric cancer requires surgery, chemotherapy, and radiotherapy. Chemotherapy and radiotherapy should be performed in advanced stages to alleviate the symptoms. As the early diagnosis may improve survival, assessment and identification of gastric cancer stages are prominent (7). Preoperative gastric cancer staging includes imaging, cytological assessment of ascites (if present), laparoscopy, and peritoneal lavage. There has been a strong association between elevated levels of CEA and the presence of malignant cells in ascites fluid, which indicates poor prognosis and invasive disease in patients with gastric cancer. However, there is not much information on this correlation in non-ascitic patients (8, 9). Peritoneal lavage aims to diagnose the microscopic presence of tumor cells on the peritoneal surface in patients without ascites. In our study, the peritoneal lavage fluid was evaluated based on CEA level and cytology to assess its relationship to the stage of gastric cancer in non-ascites patients.

METHODS:

Patients

Our prospective study was conducted after obtaining ethical approval from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran. The required information was collected from the medical records of patients. The study population included patients with gastric cancer who were candidates for surgical treatment. The inclusion criteria were: age > 18 years, tissue diagnosis of gastric adenocarcinoma, and being a candidate for surgery. The exclusion criteria were: the existence of ascites, peritoneal seeding, and distant metastasis. Normal saline (500 ml) was applied and extensively distributed in the entire abdominal and pelvic cavity upon entering the abdomen and before manipulating the tumor. After three minutes, the fluid was removed and addressed to cytological evaluation and CEA level measurement by radioimmunoassay (RIA).

Statistical Analysis

Variables including age, sex, family history, tumor location, tissue pathology diagnosis, tumor size, tumor grade, regional lymph node involvement, distant metastasis, and staging were assessed during pre- and postoperative staging. Statistical analysis was performed with SPSS (version 16.0). Mean, median, and standard deviation (SD) were used to characterize quantitative data. Qualitative data was explained by frequency (%). Based on the type of distribution, quantitative variables were compared by the independent t-test or Man-Whitney U test, and qualitative variables were compared using the Chi-square test. P values <0.05 were considered significant.

RESULTS:

In this study, 94 patients were screened. Due to lymphoma and gastrointestinal stromal tumor (GIST), two patients were excluded. We examined 92 patients in-

cluding 63 males (68.5 %) and 29 females (31.5 %). The mean age of patients was 58.52 ±11.87 years. Among the patients studied, 26 (28.3%) had a positive family history of gastric cancer.

The esophagogastric junction was the most frequent tumor location in 40 patients (43.5%), and the antrum was the second position in 28 patients (30.4%). Thirty-three patients (35.9%) had moderately differentiated adenocarcinoma, the most common pathological variant, accompanied by well-differentiated adenocarcinoma in 25 patients (27.2 %).

In the primary tumor size (T) analysis, T3 with 51 patients (55.4%) was recognized as the most common subgroup, and T2 and T4 with 20 patients (21.7%) were both ranked second. Besides, in the study of regional lymph node involvement (N), 79 patients (85.9%) were identified as regional lymph node metastases (N1, N2, or N3). The number of lymph nodes in the affected areas was less than three in most patients (57%). Also, 17 patients (18.5%) were diagnosed with distant metastasis (M1).

Preoperative staging showed that most patients (46.7%) were at stage II (**Table 1**). At intraoperative staging, R0 resection could be achieved in 72 patients (78.26%). In the other 20 patients, the most common barrier to achieving R0 was extensive omental involvement.

Peritoneal lavage cytological evaluation revealed that malignant cells were present in 18 patients (19.6%). Also, CEA titer was measured in peritoneal lavage fluid by RIA, which was higher than 2.5 (ng/ml) in 5 patients (5.43%) and was considered positive (**Figure 1**).

The mean age of patients with positive cytology was significantly lower than patients with negative cytology ($P = 0.024$). The positive cytology of peritoneal lavage had a statistically significant relationship with tumor size, tumor grade, serous/adjacent organ invasion (T4), findings from laparoscopic staging, locally advanced disease, and disease stages ($P < 0.05$) (**Table 2**).

Notwithstanding, the mean age of patients with high CEA titers in peritoneal lavage fluid was not significantly different from those with low CEA titers ($P = 0.08$). Moreover, among the study variables, only the high tumor grade had a significant association with the high CEA titers in the peritoneal lavage fluid (P =

Table 1. Preoperative staging in gastric cancer patients without ascites

Pathological Stage	N	Percent
IA	1	1.1
IB	4	4.3
IIA	22	23.9
IIB	21	22.8
IIIA	21	22.8
IIIB	6	6.5
IV	17	18.5
Total	**92**	**100**

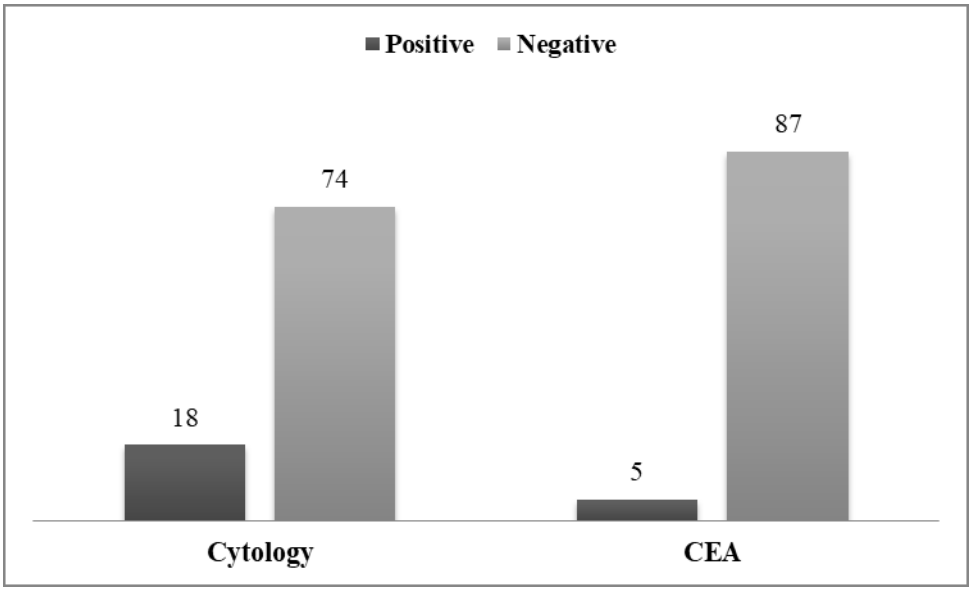

Figure 1. Comparison of carcinoembryonic antigen (CEA) level and positive cytology in peritoneal lavage fluid of gastric cancer patients without ascites

0.012) (**Table 3**).

DISCUSSION:

Gastric cancer is the third most prevalent cause of cancer death in the world (10). Since gastric cancer is typically diagnosed in late stages, it is complicated to cure gastric cancer, although significant cancer therapy advances have occurred. Some countries, such as Japan, with a high incidence of gastric cancer, have implemented screening programs that resulted in early diagnosis of gastric cancer with a better outcome. However, the prognosis is poor if the gastric tumor invades the serosal layer (11). Advanced imaging methods have not assisted much in delineating gastric cancer resectability. There are indeed periods when laparoscopy demonstrates the unresectable condition. Some patients have resectable tumors without ascites, and R0 resection will be achieved with free microscopic longitudinal and circumferential margins. They do not return shortly afterward with peritoneal carcinomatosis. It is presumed that these patients had microscopic seeding at the primary surgery. Indeed, they may have had stage IV disease in the first place that can be determined through peritoneal lavage. The peritoneum is the most common site of gastric cancer relapse and metastasis following tumor resection. There is a significant association between positive cytology in peritoneal lavage fluid and local gastric tumor invasion (12). In some studies, peritoneal cytology findings are considered as an independent prognostic factor. Evaluating peritoneal cytology for gastric cancer staging has shown to be recommended by the research community of gastric cancer in Japan. Cytology of peritoneal lavage fluid has been recognized as the gold standard in the peritoneal cavity for detecting free malignant cells. Positive cytology has been reported in 14-40 % of patients (with or without ascites, resectable, or not). Statistically, positive cytology of peritoneal lavage fluid is found in 4.4-10% of resectable and 22-30% of unresectable patients (13).

Table 2. Correlations between peritoneal lavage cytology and clinicopathological findings of gastric cancer patients without ascites

Variables	Peritoneal lavage Cytology				P value
	Negative (N=74)		Positive (N=18)		
	n	(%)	n	(%)	
Age at diagnosis (years)					
mean ± SD	59.89 ±11.63		52.89 ±11.48		0.024*
Sex					
Male	53	(84.1%)	10	(15.9%)	0.302
Female	21	(72.4%)	8	(27.6%)	
Tumor location					
Cardia	27	(67.5%)	13	(32.5%)	0.95
Fundus	2	(100.0%)	0	(0.0%)	
Body	11	(84.6%)	2	(15.4%)	
Lesser curvature	9	(100.0%)	0	(0.0%)	
Antrum	25	(89.3%)	3	(10.7%)	
Pathologic findings					
Well-differentiated adenocarcinoma	25	(100.0%)	0	(0.0%)	<0.001*
Moderately differentiated adenocarcinoma	33	(100.0%)	0	(0.0%)	
Poorly differentiated adenocarcinoma	4	(19.0%)	17	(81.0%)	
Undifferentiated	2	(100.0%)	0	(0.0%)	
Signet cell carcinoma	10	(90.9%)	1	(9.1%)	
Adenocarcinoma grade					
Low-grade	58	(100.0%)	0	(0.0%)	<0.001*
High-grade	16	(26.1%)	18	(73.9%)	
Primary tumor size (T)					
T1	1	(100.0%)	0	(0.0%)	0.038*
T2	19	(95.0%)	1	(5.0%)	
T3	42	(82.4%)	9	(17.6%)	
T4	12	(60.0%)	8	(40.0%)	
Primary tumor size (T)					
T1/T2	20	(95.2%)	1	(4.8%)	0.063
T3/T4	54	(76.1%)	17	(23.9%)	

Table 2. Continue...

Variables	Peritoneal lavage Cytology				P value
	Negative (N=74)		Positive (N=18)		
	n	(%)	n	(%)	
Serosal/ Adjacent invasion					
No (T1-T3)	62	(86.1%)	10	(13.9%)	0.021*
Yes (T4)	12	(60.0%)	8	(40.0%)	
Regional lymph nodes (N) (n=72, 14 with positive cytology)					
N0	8	(80.0%)	2	(20.0%)	0.065
N1	25	(80.6%)	6	(19.4%)	
N2	22	(81.5%)	5	(18.5%)	
N3	3	(75.0%)	1	(25.0%)	
Regional lymph node metastasis (n=72, 14 with positive cytology)					
No (N0)	8	(80.0%)	2	(20.0%)	0.065
Yes (N1-N3)	50	(80.6%)	12	(19.4%)	
Distant metastasis (M)					
M0	63	(84.0%)	12	(16.0%)	<0.001*
M1	11	(64.7%)	6	(35.3%)	
Operative findings					
Resectable	62	(86.1%)	10	(13.9%)	0.004*
Unresectable, omentum involvement	4	(50.0 %)	4	(50.0%)	
Unresectable, liver metastasis	4	(100.0%)	0	(0.0%)	
Unresectable, peritoneal seeding	3	(60.0%)	2	(40.0%)	
Unresectable, T4M0	1	(33.3)	2	(66.7)	
Resectable tumor					
Yes	62	(86.1%)	10	(13.9%)	0.004*
No	12	(60.0%)	8	(40.0%)	
Peritoneal seeding					
Yes	3	(60.0%)	2	(40.0%)	0.171
No	71	(81.6%)	16	(18.4%)	

Data are presented as mean ± SD.
*P value< .05 indicates statistical significance.

Table 3. Correlations between carcinoembryonic antigen (CEA) level in peritoneal lavage fluid and clinicopathological findings of gastric cancer patients without ascites

Variables	Peritoneal lavage CEA				P value
	Low (N=87)		High (N=5)		
	n	(%)	n	(%)	
Age at diagnosis (years)					
mean ± SD	58.45±12.15		59.80±5.16		0.80
Sex					
Male	59	(93.7%)	4	(6.3%)	0.940
Female	28	(96.6%)	1	(3.4%)	
Tumor location					
Cardia	36	(90.0%)	4	(10%)	0.526
Fundus	2	(100%)	0	(0%)	
Body	13	(100%)	0	(0%)	
Lesser curvature	9	(100%)	0	(0%)	
Antrum	27	(96.4%)	1	(3.6%)	
Pathologic findings					
Well-differentiated adenocarcinoma	24	(96.0%)	1	(4.0%)	0.073*
Moderately differentiated adenocarcinoma	31	(93.9%)	2	(6.1%)	
Poorly differentiated adenocarcinoma	21	(100%)	0	(0.0%)	
Undifferentiated	2	(100.0%)	0	(0.0%)	
Signet cell carcinoma	9	(81.8%)	2	(18.2%)	
Adenocarcinoma grade					
Low-grade	58	(100.0%)	0	(0.0%)	0.012*
High-grade	29	(85.3%)	5	(14.7%)	
Distant metastasis (M)					
M0	1	(100.0%)	0	(0.0%)	0.038*
M1	19	(95.0%)	1	(5.0%)	

Table 3. Continue...

Variables	Peritoneal lavage Cytology				P value
	Negative (N=74)		Positive (N=18)		
	n	(%)	n	(%)	
Operative findings					
Resectable	69	(95.8%)	3	(5.6%)	0.903
Unresectable, omentum involvement	7	(87.5%)	1	(12.5%)	
Unresectable, liver metastasis	4	(100.0%)	0	(0.0%)	
Unresectable, peritoneal seeding	5	(100.0%)	0	(0.0%)	
Unresectable, T4M0	3	(100.0%)	0	(0.0%)	
Resectable tumor					
Yes	69	(95.8%)	3	(5.6%)	1.000
No	19	(95.0%)	1	(5.0%)	
Peritoneal seeding					
Yes	5	(100%)	0	(0.0%)	1.000
No	82	(94.3%)	5	(5.7%)	

Data are presented as mean ± SD.
*P value< .05 indicates statistical significance.

This study examined the cytology and CEA titers of peritoneal lavage fluid in gastric cancer patients. We only included non-ascitic patients, and positive cytology was detected in 19.6% of the patients. There was a significant correlation between positive cytology and tumor size, tumor grade, serosa/adjacent organs invasion (T4), laparoscopic staging findings, locally advanced disease, and stage of the disease ($P < 0.05$). According to these findings, peritoneal lavage fluid cytology can be considered an effective method for gastric cancer staging. Bryan et al. could diagnose only 11% of unresectable tumors with conventional preoperative staging. However, 70% of unresectable tumors had positive cytological examination (14). Kanetaka et al. evaluated 100 patients with locally advanced gastric cancer. They found that laparoscopic staging accompanied by peritoneal lavage cytology upstaged 44% of patients (15).

Hyperthermic chemotherapy during operation can have a beneficial impact on patients with positive cytology. It can increase survival and reduce peritoneal relapse in patients with advanced stages of gastric cancer or with tumors invading the serosal layer.

We found elevated CEA titers in the lavage fluid of 5.43% of patients. However, it has been reported in up to 30% of patients by Oh et al. (16). This discrepancy

may be due to the application of different measurement methods. Although other studies used the polymerase chain reaction (PCR) technique to evaluate the CEA titers, we measured CEA titers by RIA. It seems that RIA is not a sufficiently sensitive method to measure CEA titers in lavage fluid and could not accurately determine the prognosis and survival of patients with gastric cancer (17). We observed a significant correlation between the occurrence of high-grade tumors and the elevated CEA titers (P = 0.012). Burke et al. also demonstrated high-grade tumors in patients with elevated CEA levels (18). It can be concluded that using sensitive and specific methods for measuring the level of CEA in peritoneal lavage fluid can help in staging and determining the prognosis and survival of gastric cancer patients without ascites (19).

The presence of undiagnosed concomitant malignancies in the abdominal cavity is a possible downside to the diagnosis of peritoneal lavage. While this is not common, it can lead to an over-staging of gastric cancer. In our study, intraoperative peritoneal lavage was performed. Diagnosing peritoneal lavage (DPL) using a laparotomy-free catheter could also be utilized for staging before surgery. Thus, further prospective research is needed to provide evidence for the effectiveness and feasibility of peritoneal lavage in gastric cancer patients without ascites.

CONCLUSION:

In gastric cancer patients without ascites, positive cytology and elevated CEA titers in peritoneal lavage fluid are substantially related to more advanced and invasive disease. The efficacy of these variables in predicting prognosis and survival needs to be established by further investigations with more specific laboratory methods, more patients, and long-term follow-up.

CONFLICT OF INTERESTS:

The authors declare no conflict of interest and have not received any grant from the institution

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