

Assessment of Prognostic Value of Peritoneal Lavage Cytology in Patients with Resectable Gastric Cancer

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ABSTRACT

The gastric cancer generally is considered a geriatric disease, which occurs commonly among lower socioeconomic levels of the populations. There are wide differences in the gastric cancer occurrence among different geographical regions. In Iran, the northern and the northwestern regions are with the most higher risk of gastric cancer occurrences. In spite of the recent gastroscopical examinations, almost of the gastric cancers are diagnosed in the advanced stages. Peritoneal relapse is the most common form of gastric cancer recurrence after the surgery and it is the leading cause of the mortality in the gastric cancers. The peritoneal relapse is formed from the micrometastases originated of free peritoneal tumor cells (FPTCs) in the peritoneal space. It is a bad prognostic aspect for the patients with gastric cancer. The randomized clinical trials suggest that adjuvant intraperitoneal chemoperfusion demonstrated significant median survival difference in comparison with simple surgery group. In this study we tried to compare the prognoses and the time and location of the recurrence of gastric cancer between the patients with negative and positive cytology. Patients who were eligible were those who were deemed fit enough for a general anesthetic and those with potentially resectable and curable disease, i.e. no CT evidence of metastatic disease or unresectable invasion into adjacent structures. Pre-laparoscopic staging in all cases involved upper gastrointestinal endoscopy and biopsy, followed by CT of the chest and abdomen. Staging laparoscopy was performed within six weeks of CT in all cases. For target patients peritoneal lavage and cytological examination were performed. Nineteen of 62 patients who underwent staging laparoscopy and peritoneal lavage cytology had malignant cells within the lavage fluid, i.e. FPTC-positive (30.6%). The median age was 62.27 ± 12.87 years (range 24–89) with a male:female ratio of 2.6:1. Fourteen of these patients (73.7%) subsequently underwent laparotomy for an attempted curative resection. In five out of these 14 patients, incurable disease was found (unresectable local invasion or extensive lymph node, peritoneal and liver metastases) and no procedure or a palliative procedure was performed. There was a significant difference between peritoneal lavage cytology and resectable gastric cancer ($p=0.002$). Of the 12 patients with positive cytology, seven cases (58.3%) had recurred gastric cancer and the rest five cases (41.7%) had no recurrences. Of the patients with negative cytology, only a single patient had recurred gastric cancer (2.56%). There was a significant relationship between gastric cancer recurrence with positive cytology results ($r=0.78$; $p=0.001$). The mean recurrence time in the seven patients who had recurred gastric cancer was 6 months ± 1.41 . In two cases with negative cytology, there was recurred gastric cancer after 6 months. There was a significant relationship between gastric cancer recurrence with positive cytology results ($r=0.89$; $p=0.02$). Considering above, we may come to the end that there is a significant relationship between positive peritoneal lavage cytology and cancer recurrence, common recurrence location of the tumor and the probability of cancer recurrence. Based on the results of abdominal lavage cytology, the appropriate therapeutic method may be selected for improving the life quality of the patients with gastric cancer.

KEYWORDS: Peritoneal lavage cytology, resectable gastric cancer.

INTRODUCTION

During the several past decades, the mortality and morbidity due to gastric cancer have been strikingly decreased in the western industrialized countries. However, in the Asia and Eastern Europe, gastric cancer still is a leading death cause due to the cancer. The gastric cancer generally is considered a geriatric disease, which occurs commonly among lower socioeconomic levels of the populations (1).

There are wide differences in the gastric cancer occurrence among different geographical regions. The regions with higher risk of occurrence are Japan, Korea and China in a rate of more than 20 cases in hundred thousand people, and the regions with lower occurrence rate (less than 10 cases in hundred thousand people) in the USA and Canada. In Iran, the northern and the northwestern regions are with the most higher risk of gastric cancer occurrences. Ardebil with a incidence rate of 49 cases in hundred thousand people, has the highest rank

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of the gastric cancer occurrence in Iran (2). In spite of the recent gastroscopical examinations, almost of the gastric cancers are diagnosed in the advanced stages (3).

Peritoneal relapse is the most common form of gastric cancer recurrence after the surgery and it is the leading cause of the mortality in the gastric cancers. The peritoneal relapse is formed from the micrometastases originated of free peritoneal tumor cells (FPTCs) in the peritoneal space. It is a bad prognostic aspect for the patients with gastric cancer (4). As the primary tumor invades directly to the serosal and subserosal layers, the dissemination probability of the cancer cells in the abdominal cavity increases (3). The mentioned free peritoneal tumor cells originate from the primary lesion or metastatic lymph nodes (4). No doubt that the free peritoneal tumor cells are not so long alive in the peritoneal space to produce implants (3). Iitsuka *et al.* found that the presence of free peritoneal tumor cells indicates that the cancer have invaded the serosa, because the positive cytological test do not occur in the patients without serosa involvement (6). Detection of the free peritoneal tumor cells before and during the surgical procedure is difficult, however, their detection and controlling by appropriate methods, e.g. adjuvant intraperitoneal chemoperfusion, is essential for preventing the recurrence of postoperative peritoneal involvement and increasing the survival rate in the patients. Although laparotomy peritoneal lavage cytology is the gold standard for the evaluation of peritoneal dissemination of gastric cancer, the sensitivity of the test is low and the rate of false negative results is relatively high (4).

The randomized clinical trials suggest that adjuvant intraperitoneal chemoperfusion demonstrated significant median survival difference in comparison with simple surgery group. Having a diagnostic result, whilst the surgery is going on, may be more helpful in guiding the adjuvant palliative surgery (5). Although there are more sensitive methods for detection of peritoneal distribution, these modern, sophisticated methods are time-consuming, slow and expensive, and they need more specialized laboratory facilities and related expert staffs. However, the definite diagnosis is not made during the surgery.

In the European countries the lavage is done for cytological study in the patients with gastric cancer. In a study conducted in the Netherlands, the rate of positive cytology was less than the results of a study done in Japan, and it may be due to the controversial analysis of both studies (5).

According to the recommendations of JCGC (Japanese Committee of Gastric Cancer), lavage should be done in the pouch of Douglas. Almost the earlier studies were done only based on lavage in one cavity (6). The followings are the reasons for low sensitivity of lavage cytology: 1) using non-standard peritoneal lavage, 2) presence of inter-observer bias among the cytopathologists for staging the cytopathological findings, 3) low number of the cancer cells in the peritoneum, which are hardly detected in the cytology (5,6).

There is a significant consistency between tumor stage, tumor extension extent, nodular involvement and general mortality with the positive peritoneal cytology (5). It is still controversial whether the patients with positive cytology are suitable candid for gastrectomy or not. If gastrectomy is done for the patients with positive cytology, some adjuvant therapies especially concentrating on peritoneal distribution will be needed (3). If we accept the peritoneal recurrence as the main failure reason of surgical procedure and also for mortality after palliative resection, then chemotherapy during surgery will be as a modality for eradication of microscopic residuals of the malignancy or as recurrence prevention (5).

Randomized studies revealed that intraperitoneal chemoperfusion caused a significant survival in comparison with only surgery procedure. Adjuvant systemic chemotherapy or intraperitoneal chemoperfusion are expensive and not suitable for patients without residual disease. Additionally, it has its side effects and mortality. Diagnosis of free peritoneal tumor cells may have reasonable value for selecting the patients, who will profit the invasive chemotherapeutic methods (5).

In this study we, using modern high-tech cytology called liquid-based, collected that samples from different peritoneal cavities (right subdiaphragmatic, left subdiaphragmatic, lesser sac, and pouch of Douglas), which in the earlier studies the samples were from one cavity. We, in addition to increasing the sensitivity of the cytological method, tried to compare the prognoses and the time and location of the recurrence of gastric cancer between the patients with negative and positive cytology.

MATERIALS AND METHODS

A prospective study of staging laparotomy with accompanying peritoneal lavage was undertaken between March 1999 and February 2000 on patients with gastric cancer. Patients who were eligible were those who were deemed fit enough for a general anesthetic and those with potentially resectable and curable disease, i.e. no CT evidence of metastatic disease (lymph node, peritoneal or distant metastases) or unresectable invasion into adjacent structures. Pre-laparoscopic staging in all cases involved upper gastrointestinal endoscopy and biopsy, followed by CT of the chest and abdomen. Staging laparotomy was performed within six weeks of CT in all cases. The study was discontinued following the results of this initial analysis.

Once the upper part of the peritoneal cavity had been assessed, peritoneal lavage was carried out. Two hundred ml of warmed normal saline was used to irrigate the pelvic part of the peritoneal cavity via a combined suction/irrigation catheter inserted through the left and right upper quadrant parts. The irrigant was not

administered over primary tumor. After gentle agitation of the lower abdomen, 100 ml of fluid was aspirated through the same introducer. The fluid was transported in universal containers with no additive.

The peritoneal lavage fluid was concentrated using a bench top centrifuge (1500 rpm). Four cytospin preparations were made on slides coated with 0.1% poly-L-lysine hydrobromide. One was fixed in 99% alcohol and stained using the Papanicalou method; the remaining three were then rapidly air-dried. The slides were examined for the presence of adenocarcinoma cells by a Senior Lecturer in pathology and the results were announced as positive, negative and indescribable. The patients were followed for 9 months after the surgery. The results were analysed by SPSS version 17. The chi-square test and Student t-tests were used and the p value less than 0.05 was considered as statistically significant.

RESULTS

Nineteen of 62 patients who underwent staging laparoscopy and peritoneal lavage cytology had malignant cells within the lavage fluid, i.e. FPTC-positive (30.6%). The median age was 62.27 ± 12.87 years (range 24–89) with a male:female ratio of 2.6:1. Fourteen of these patients (73.7%) subsequently underwent laparotomy for an attempted curative resection. In five out of these 14 patients, incurable disease was found (unresectable local invasion or extensive lymph node, peritoneal and liver metastases) and no procedure or a palliative procedure was performed. There was a significant difference between peritoneal lavage cytology and resectable gastric cancer ($p=0.002$) (See **Table 1**). For microscopical sections of the peritoneal lavage cytology see the **Figure 1** and **Figure 2** for the mesothelial and inflammatory cells and the clumps of malignant cells.

In order to determine the recurrence rate, the patients underwent gastric cancer resection were followed for 9 months. Of 62 patients, five cases did not undergo the gastric cancer resection. Two patients missed in the follow-up, due to lack of referring. During the follow-up process, we received notification of four patient's death, in the third and seventh days after surgery. The death causes were two cases pneumonia, one case of sepsis, and single other case of pulmonary embolus. Finally, the rest of the patients (51 cases) were followed up for the recurrence of gastric cancer. Of these 51 patients, 12 cases had positive cytology and the rest 39 patients had negative cytology. Of the 12 patients with positive cytology, seven cases (58.3%) had recurred gastric cancer and the rest five cases (41.7%) had no recurrences. Of the patients with negative cytology, only a single patient had recurred gastric cancer (2.56%). There was a significant relationship between gastric cancer recurrence with positive cytology results ($r=0.78$; $p=0.001$) (See **Table 2**). Of seven cases with recurred gastric cancer, 6 patients had peritoneal metastases (85.7%) and a single case had chest metastases (14.3%). There was also a case of recurred gastric cancer with negative cytology. However, there was a significant relationship between gastric cancer recurrence with cytology results ($p=0.018$). The mean recurrence time in the seven patients who had recurred gastric cancer was 6 months ± 1.41 . In two cases with negative cytology, there was recurred gastric cancer after 6 months. There was a significant relationship between gastric cancer recurrence with positive cytology results ($r=0.89$; $p=0.02$).

Table 1: Data of the frequency of peritoneal lavage cytology of the patients with resectable gastric cancer

peritoneal lavage cytology	gastric cancer resection		Total
	with surgery	no surgery	
positive	14 (73.7%)	5 (26.3%)	19 (100%)
negative	43 (100%)	0 (0%)	43 (100%)
Total	57 (91.94%)	5 (8.06%)	62 (100%)

Table 2: Data of the frequency of gastric cancer recurrence of the patients with positive cytology results

peritoneal lavage cytology	gastric cancer recurrence		Total
	recurred	not recurred	
positive	7 (58.3%)	5 (41.7%)	12 (100%)
negative	1 (2.56%)	38 (97.44%)	39 (100%)
Total	9 (17.6%)	42 (82.4%)	51 (100%)

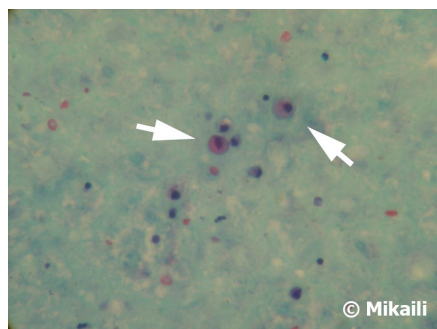


Figure 1: The micrograph depicts the mesothelial and inflammatory cells (arrows), H&E, x40.

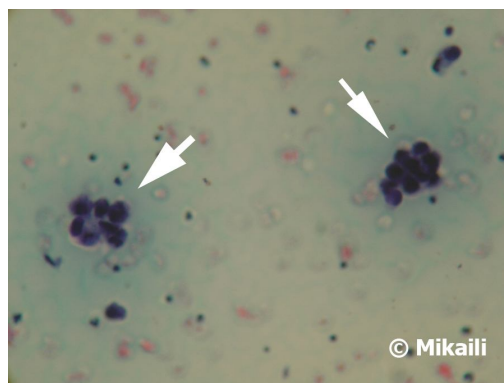


Figure 2: The micrograph depicts the clumps of malignant cells (arrows), H&E, x40.

DISCUSSION AND CONCLUSION

The stomach usually is a target location for distal metastases of other organ tumors, like duodenum and breast. Almost malignant tumors of adjacent organs (e.g. pancreas and colon) directly invade the stomach, or they are transplanted in it through peritoneum (e.g. ovary). In 1930, gastric cancer was the number one leading death cause in USA, among cancers of men and the third death cause in women cancers. Today, however, it is not even among the first ten death causes.

Genetic cancer is common among the lower socioeconomic levels of the populations. Generally, gastric cancer is a geriatric disease; however, it rarely occurs in the younger people (30-40 years old).

According to the results of our study, the percentage of gastric cancer was more common among men than women, with a minimal age 24 and maximal 89 year old (regardless intervening factors, e.g. smoking, socioeconomic situations etc.).

In general, surgical procedure is the only therapeutic method for gastric cancer. Therefore, the patients with gastric adenocarcinoma should undergo gastrectomy, unless in the exceptional conditions, in which the patient cannot endure the additional surgery or the presence of extensive metastatic involvements.

In our study, there was a significant relationship between resectable gastric cancer and positive cytology of the peritoneal lavage, so that five patients, due to having advanced cancer did not undergo the resection.

In this study, as we followed the patients for cancer recurrence for 6 months, we found patients with positive cytology had 58.3% cancer recurrence. It demonstrated significant relationship between positive cytology and cancer recurrence, which agrees with the study conducted by Eshter *et al.* (5). In our study, if the patients had clinical signs during the following period of 9 months, they already underwent imaging procedures including chest radiography and pelvic and abdominal sonography, and monitoring for cancer recurrence. Of seven cases with cancer recurrence (with positive cytology) in 85.7% of the peritoneum was reported as the common location of cancer recurrence. There was a significant relationship between positive cytology and the common location of cancer recurrence.

In a study conducted by Ribeiro *et al.*, the positive cytology meant bad prognosis in the patients underwent potential palliative for gastric cancer and peritoneal lavage cytology caused improving staging to modify the palliative therapy. Comparing to our study, the cancer recurrence was demonstrated 58.3% in the patients with positive cytology. Considering the cancer recurrence time in patients with positive cytology, our study showed shorter cancer recurrence time (6 ± 1.41) comparing the patients with negative lavage cytology. Dina *et al.* suggested the poor prognosis before surgery, e.g. peritoneal positive cytology in resectable gastric cancer is of great importance.

These results are agreed with our results in a shorter time and higher rate of cancer recurrence in patients with positive peritoneal lavage cytology, who underwent gastric cancer resection.

Homma Y. *et al.* suggested that peritoneal lavage cytology in several cavities is more sensitive than a single cavity, and the number of positive cavities may suggest the grade of tumor extension in peritoneum and imply the poor prognosis for patients with positive lavage cytology (11). These were also agreed with our results in the rate of cancer recurrence in patients with positive cytology, additionally, the common location of cancer recurrence, where it occurred commonly in the peritoneum. Considering above, we may come to the end that there is a significant relationship between positive peritoneal lavage cytology and cancer recurrence, common recurrence location of the tumor and the probability of cancer recurrence. Based on the results of abdominal lavage cytology, the appropriate therapeutic method may be selected for improving the life quality of the patients with gastric cancer.

In this study, we did not evaluate the number of free peritoneal tumor cells as a factor of progress and recurrence of the gastric cancer, therefore, we suggest to plan other case-control studies for investigating the

predicting value of the abdominal lavage cytology in patients with resectable gastric cancer with more sample numbers and in a larger study periods.

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