Positive Peritoneal Lavage Cytology –Implications for Staging and Management of Gastric Cancer

Suman B. Koganti^{1,2} · Satish Boddepalli¹ · Muralidhar Nambada¹ ·
Venu madhav Thumma¹ · Bheerappa Nagari¹ · R. A. Sastry¹

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Abstract The survival rates of gastric cancer patients with cytology-positive peritoneal lavage fluid without macroscopic dissemination (CY+/P-) is the same as that of patients with overt peritoneal metastasis. The 5-year survival rate of such patients is only 2%. The current study aims to highlight its significance in the staging of gastrointestinal malignancies and its implications for patient care. Prospective nonrandom analysis of peritoneal wash cytology in patients with gastrointestinal malignancies was conducted in the department of Surgical Gastroenterology, Nizams Institute of Medical Sciences, Hyderabad from January 2012 to June 2013. Descriptive statistics and ANOVA variance analysis was performed to estimate incidence, risk factors and the effect of surgery in causing peritoneal dissemination of malignancy. A total of 60 patients with operable gastric cancer underwent peritoneal lavage for evaluation of malignant cells. The incidence of Positive peritoneal lavage cytology was 8.3% (5/60). Four patients with positive lavage fluid belong to T3 stage (11.7%, $p=0.309$). Poorly differentiating and mucinous tumors had a higher incidence of positive cytology (18.1% and 25%). None of the patients with positive cytology had positive resection margin. Tumors with advanced T stage, lymph nodal involvement, lympho-vascular and perineural invasion have higher incidence of positive peritoneal cytology. Surgical handling has a negligible effect in peritoneal dissemination of tumor.

Large scale studies are warranted to validate the findings and define its role in management of gastric cancer.

Keywords TNM-tumor, node, metastasis · PPC-positive peritoneal wash cytology · AJCC-American joint committee on cancer

Introduction

Peritoneal metastases are a common finding at the time of diagnosis for many intra-abdominal malignancies and a common site for recurrence after resection. Washing the peritoneal cavity at the time of operation and examining the fluid cytology has been performed in a variety of gastrointestinal malignancies including stomach, colorectal and pancreatic cancers.

The survival rates of patients with cytology-positive peritoneal lavage fluid and without macroscopic peritoneal dissemination (CY+/P-) in gastric cancer is similar to that of patients with overt peritoneal metastasis. The 5-year survival rate of such patients in gastric cancer is only 2% [1] with a median survival of 9.2 months [2]. Notwithstanding such poor prognosis in these patients, a suitable standard regimen for treating such patients has not yet been established. Furthermore, the current AJCC staging system for gastric cancer includes this category of patients in stage IV. Recently, several studies have demonstrated the incidence and prognostic significance of positive peritoneal cytology in colorectal and pancreatic cancers [3, 4]. Patients with negative cytology (CY-) had significantly better five-year survival rate than patients with positive cytology (CY+); (68.0% vs. 20.6%; $P=0.0001$) in rectal carcinoma [5]. Data are limited, from Indian subcontinent however, with respect to the prevalence of

✉ Suman B. Koganti
sumankoganti@gmail.com

¹ Surgical Gastroenterology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad 500082, India

² Present address: Department of Surgery, Bronx-Lebanon Hospital Center, Ichan School of Medicine at Mount Sinai, 1650 Grand Concourse, New York, NY 10457, USA

positive peritoneal cytology and its implications for staging and management of gastric cancer. We purposed to study the significance of these findings at our center.

Aim & Objectives

The study objectives were to evaluate the incidence of positive peritoneal cytology for malignant cells in the peritoneal cavity in patients with all operable cancers of gastric cancer without macroscopic peritoneal dissemination, to compare quantitatively the cytological positivity of malignant peritoneal cells before and after surgery as a measure of the effect of surgery in causing peritoneal dissemination of malignancy and to identify the risk factors for positive peritoneal cytology.

Material and Methods

This prospective study was conducted in the department of surgical gastroenterology, Nizam's Institute of Medical Sciences, Hyderabad from January 2012 to June 2013.

Inclusion Criteria

All preoperatively identified patients with operable gastric cancer.

Exclusion Criteria

1 Patients with gastric cancer having overt liver or peritoneal metastasis. 2. Cytologically confirmed malignant ascites preoperatively or intra-operatively. 3. All locally advanced inoperable cases.

Intraoperative Collection of Fluid

Immediately after opening the abdomen in all patients, operability was confirmed. If ascitic fluid was found, it was sent for cytology for malignant cells and if the same is positive, the procedure was abandoned. If the disease is deemed operable peritoneal lavage cytology analysis was performed. A total of 100 ml was used altogether in the three spaces (both the subphrenic spaces and pelvis). After sufficient stirring for 10 min all the lavage fluid was collected and sent to the pathology lab. A 5 mL representative sample was taken and subjected to fixation for one hour by mixing with 5 mL of 10% alcohol-formalin. This was termed **S1**. After one hour, this 10 ml fluid was centrifuged at 2500 rpm for 15 min. The supernatant was discarded and a further 3–5 mL of fresh 10% alcohol-formalin was added to the sediment and it was kept for 12–18 h. On the following day, the sediment containing the cell button of the peritoneal fluid sample was

processed for paraffin embedding. The paraffin embedded cell button (cell block) sections of 4–6 μ thickness were prepared and stained with the Geimsa & Papanicolaou for analysis by senior cyto-pathologist. A minimum of four (4–8) cytospins were made from each sample. Later, on the completion of surgery another sample collected in an identical manner as stated above was sent for analysis of malignant cells (termed **S2**).

Surgical Procedure

An appropriate surgery adhering oncological principles was performed regardless of the possibility of positive cytology findings on S1.

Cytological Examination

The samples were examined by an experienced pathologist. Four to eight cytospins were made from a representative sample of the peritoneal lavage fluid. The cytospins were stained using the Giemsa and Papanicolaou methods for cytological evaluation. Cytospins were classified as either positive (cytology positive for malignant cells) or negative (cytology negative for malignant cells).

The following clinicopathological features were noted for analysis: age, sex, histologic type and grade of tumor, pathologic stage of disease (depth of tumor invasion and lymph node metastasis) and lympho-vascular invasion.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean $\pm$ SD (min-max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level ($p < 0.05$).

The following assumptions on data were made. Dependent variables should be normally distributed. Samples drawn from the population should be random, and cases of the samples should be independent. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. One proportion Z test has been performed under the binomial assumption of 0.50 for frequency distribution of variables studied.

Significant *P* Value

+Suggestive significance (P value: $0.05 < P < 0.10$).

* Moderately significant (P value: $0.01 < p < 0.05$).

**Strongly significant (P value: < 0.01).

Statistical Software The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables.

Results

During the study period a total of 60 patients underwent peritoneal lavage for evaluation of malignant cells. Of the 60 patients included in this study, there were 17 females and 43 males with an average age of 50.80 ± 13.66 years. Study group included patients with operable carcinoma of stomach. Majority of patients had distal growths in carcinoma stomach (distal-42, proximal-18(70% 30%). Type III Siewert GE junction tumors were also included in the analysis.

Peritoneal Lavage Cytological Findings The incidence of Positive peritoneal lavage cytology in our study was 8.3% (5/60). All the samples sent after resection of the tumor were negative for malignant cells.

Peritoneal Lavage Cytological Findings – Correlation with TNM Staging In the current study (Ref Table 1) 20% of T4 tumors had positive cytology whereas only 11.7% of tumors belong to T3 stage (4/34, $p=0.309$) stage. Though the absolute number of positive peritoneal cytology is higher in T3 compared to T4, the proportion of tumors with positive cytology is higher in T4 over T3. Also T4 stage is a statistically significant factor ($p=0.09$) in determining positive peritoneal cytology. One patient with N1 (1/21, 4.7%, $p=0.344$), three patients with N2 (2/8, 37.5%, $P=0.061$) and one patient with N3 (1/4, 25%, $P=0.067$) had positive cytology.

Peritoneal Lavage Cytological Findings – Correlation with Grade of Tumor (Ref Table 2) Poorly differentiating carcinomas and mucinous secreting adenocarcinoma had high incidence of positive peritoneal lavage cytology (18.1% and 25%) respectively.

Peritoneal Lavage Cytological Findings – Correlation with Lymphovascular and Perineural Invasion (Ref Table 2) Patients with lymphovascular invasion had more incidence of positive peritoneal cytology compared to those without invasion. (12.5% and 3.5%).

Peritoneal Lavage Cytological Findings Correlation with Resection Margin (Ref Table 2) None of the Patients with positive cytology had positive resection margin.

Discussion

Despite progress in recent years towards the early detection of gastric cancer, most patients have advanced disease at diagnosis [6, 7]. The majority of patients will die of recurrent disease, even if the patient had an R0 resection. Relook laparotomy and post-mortem studies have demonstrated that the majority of patients who have recurrent disease will have peritoneal metastases [8]. Peritoneal recurrence presumably stem from transcoelomic dissemination of malignant cells in the pre- or perioperative period. Despite this, the role of peritoneal cytological evaluation in predicting failure of gastric cancer resections has garnered little interest [9]. The Dutch Gastric Cancer trial demonstrated positive cytology in only 7.1% of all patients with gastric cancer and 12% of cases with serosal invasion [10]. These estimates of incidence suggest transcoelomic dissemination occurs more frequently than is demonstrated by

Table 1 Positive cytology according to Tumor, Nodal and Metastasis stage

	Number of patients (<i>n</i> = 60)	Positive Cytology (<i>n</i> = 5)	Percentage (%)	P- value
Tumor stage				
T1	5	0	-	NS
T2	16	0	-	NS
T3	34	4	11.7	0.309
T4	5	1	20	0.09 ⁺
Nodal stage				
N 0	27	0	-	NS
N I	21	1	4.7	0.344
N II	8	3	37.5	0.061*
N III	4	1	25	0.067*
Metastasis stage				
M 0	60	–	-	NS

+ Suggestive significance (P value: $0.05 < P < 0.10$)* Moderately significant (P value: $0.01 < P \leq 0.05$)** Strongly significant (P value: $P < 0.01$)

Table 2 Correlation of clinical variables with positive cytology

Clinical variable	Gastric cancer <i>n</i> = 60 (%)	Positive cytology <i>n</i> = 5 (%)	<i>P</i> -value
Age in years	50.8 ± 13.66	53.58 ± 13.78	0.270
Gender(M:F)	43:17	4:1	0.065+
Cytology(Before surgery)			
Negative	55 (91.7%)	NA	0.784
Positive	5 (8.3%)	NA	
Grade of tumor			
Well differentiated	25(41.6%)	-	-
Moderately differentiated	8(13.3%)	-	
Poorly differentiated	22(36.6%)	4 (18.1%)	0.009**
Mucinous secreting	4(6.6%)	1(25%)	0.021*
Signet ring	1(1.6%)	-	-
Lymphovascular invasion			
Absent	28(46.7%)	1(3.5%)	0.044*
Present	32(53.3%)	4 (12.5%)	
Margin			
Negative	56 (93.3%)	5	0.354
Positive	4(6.7%)	0	

Chi-Square test/Fisher Exact test for No(%) For Mean(SD), ANOVA

cytology of pre-resection lavage fluid. The first step of peritoneal carcinomatosis is considered to be detachment of cancer cells from the serosal surface of the primary tumor, followed by their dissemination within the peritoneal cavity. These floating cancer cells reach the peritoneal surface, invade the sub peritoneal connective tissue, and proliferate to form a peritoneal metastasis. Other studies have suggested that a metastatic route through the lymphatic system might be involved in peritoneal dissemination. Peritoneal metastases are the most common type of metastasis in patients with advanced gastric cancer. The prognosis of patients with peritoneal metastases is dismal with a median survival of 9.2 months [2, 9]. In addition to overt metastases, positive peritoneal washing cytology has been shown to predict peritoneal metastases and recurrence. Positive peritoneal washing cytology is included in the American Joint Committee on Cancer (AJCC) staging system (7th edition) as M1 disease. For this reason, peritoneal wash cytology of the abdominal cavity is obtained during gastric cancer surgery at many institutions. The outcome of cytological examination of abdominal washings is not used uniformly in the assessment of curability of cancer. Japanese investigators have demonstrated that, in a small proportion of patients deemed to have been treated curatively, cytological examination reveals free abdominal tumor cells and these patients had a considerably worse prognosis than those without such free cells [9, 11–13].

Nakajima et al. found a positive cytology result in 16% of patients undergoing macroscopic curative resection and in 47% of those having non-curative operations [9]. Boku et al. detected a positive result in 34.4% of those with macroscopic serosal invasion, but free tumor cells were absent in patients in whom the serosa was not involved [11].

In the present study the rate of positive cytology was 8.3% in patients having curative resection. We found an interesting association between the T stage and intraperitoneal free cancer cells. The most distinctive increase of free malignant cells was found between T3 and T4 stages. This appears to be the result of serosal invasion, which is defined as T4 in gastric cancer cancer. However, free cancer cells were also found in the peritoneal cavity in T3 carcinomas without breaching the serosa. Peritoneal wash cytology positivity in T2, T3 tumors is well described in literature. It has been reported that approximately 0.5% of patients with early gastric carcinoma and 5% of patients with muscularis propria invasive gastric carcinoma developed peritoneal recurrence after a curative operation [14–16]. The reasons for peritoneal dissemination in non-serosal-invasive carcinoma have been postulated as lymph node dissection opening lymphatic channels and spreading viable cancer cells and metastatic lymph nodes shedding cancer cells [17, 18]. No patient without sub serosal and serosal invasion has positive cytology result, whereas free abdominal tumor cells were found in 12.8% of those with tumors invading the sub-serosa and serosa. This is in agreement with the work of Nakajima et al., who also found free intraperitoneal malignant cells in patients with tumors without infiltration of the serosa [9].

Peritoneal cancer cell exfoliation might also be influenced by lymphatic spread. In the present study we found significant association between N staging and cytology with a positive correlation between extent of lymphatic spread and positive cytology. Poorly differentiated carcinomas and tumors with lymphovascular invasion had higher incidence of positive cytology. This possibly explains the theory of noncontiguous lymphatic dissemination of tumor cells.

It is surprising that none of the S2 samples showed a positive cytology since the association of surgical trauma in dissemination of intraperitoneal free cancer cells is well documented [19–21]. There are technical and analytical differences between the above quoted papers and from our study which could explain the difference. The amount of lavage fluid was more in the above quoted than that used in our study. The large quantity (500–1000ml) of fluid might have enhanced the dissemination and the detection rate. Lavage was performed in the areas of lymph node dissection beds which potentially harbor malignant cells. On the contrary in our study the lavage sites were in the subphrenic spaces and in the pelvis. In the above mentioned studies a two tier or three tier system was used to detect cancer cells in the lavage fluid if conventional staining is negative for malignant cells (IHC, RT-PCR and quantitative PCR). These techniques are more sensitive in picking up cancer cells at an earlier stage. This explains that conventional cytological staining alone used in our study may have been subject to a false negative detection bias. The positive cytology in the paper by Han et al. [19] is 2.6%. Only one patient had post lavage fluid cytology positive which is more consistent with the current study. All the above quoted papers are from centres which practice extensive lymph node dissection (D2, D3). It is possible that the more radical lymph node dissections may have caused tumor cell dissemination which reflected in a higher cytology positivity rate.

As the current study is not aimed at studying the survival differences we do not acknowledge the poor survival rates of patients with positive cytology as noted in the lorenzen study and the Japanese literature [2, 7, 9]. Aside lack of survival figures, the small number of patients with positive cytology and lack of external validity of the sampling assay might have precluded the statistical power ($1-\beta$) of the study.

Despite the endorsement by major societal guidelines like NCCN [22] and AJCC the acceptance of positive peritoneal cytology alone as M1 disease is not uniform across all the centres. At present the highest yield of peritoneal wash cytology is for T3/T4, N+ tumors which is 25% [23]. It seems reasonable to include peritoneal wash cytological analysis in the pre-op staging work-up for these tumors as a routine.

The management decisions of these patients however are challenging in view of the limited existing data. Should these patients receive neo-adjuvant chemotherapy upfront?, Should the peritoneal wash be repeated after the neo adjuvant chemotherapy?, Is CY + /P0 in itself enough to deem the cancer metastatic?. What is the best strategy for these patients?. These are some of the pressing questions that demand strong evidence based recommendations.

Data on neoadjuvant therapy do not greatly influence the elimination of free peritoneal tumor cells. Tumor positivity to negative and vice versa can be observed during the preoperative chemotherapy period, irrespective of response to the systemic treatment [2]. Studies on cytoreduction and HIPEC

pertain mostly to gross peritoneal disease [24]. Perhaps the best solution for this would be to enroll these patients in a randomized clinical trial studying the effects of upfront neo-adjuvant chemotherapy, intra-operative adjuvant therapy and determine the long term survival.

Cost implications and workflow limitations of peritoneal wash cytology are not yet studied but intuitively does not appear to have great burden on the resources. Notwithstanding these limitations peritoneal wash cytology has extended beyond the realms of gastric cancer to encompass other G.I malignancies like colon and pancreatic cancer in the recent past. Preliminary data suggest a promising role, however at this point it's role in the staging and prognosis of these cancers remains unclear [4, 25, 26]. Peritoneal lavage cytology is certainly useful for the prognosis of some gynecologic, gastric, and pancreatic cancers. Positive lavage cytology in these cases will identify those patients who need more frequent postoperative follow-up and possibly adjuvant chemotherapy.

Conclusions

The incidence of positive peritoneal cytology in Gastric cancer is not so uncommon (8.3%). Advanced Tumor and Nodal (T&N) stage has higher incidence of free peritoneal malignant cells along with higher grade, lymphovascular and perineural invasion. The effect of surgery in peritoneal dissemination of tumor was not observed. Peritoneal wash cytology should be considered in the pre-op staging work up of advanced gastric cancers. Adjuvant therapies upfront or post-resection have a promising role in the management of these advanced cancers.

Compliance with Ethical Standards

Ethics Approval Informed consent was obtained from all patients and the study was approved by Institutional ethics committee and the protocol approved by IRB.

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