

## ANALYSIS OF RISK FACTORS OF POSITIVE PERITONEAL CYTOLOGY IN PATIENTS TREATED FOR GASTRIC CANCER – PRELIMINARY REPORT\*

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Presence of free gastric cancer cells in the peritoneal cavity of patients who underwent surgical treatment for gastric cancer is a negative prognostic factor and caused rapid disease recurrence, manifested as peritoneal metastases.

Positive peritoneal cytology despite lack of visible peritoneal metastases was regarded as M1 class in the TNM classification (7<sup>th</sup> edition) in 2010.

**The aim of the study** was to analyze factors associated with positive peritoneal cytology and identify groups of patients in whom diagnostic laparoscopy plus peritoneal lavage in the diagnostic process could affect therapeutic decisions.

**Material and methods.** The study enrolled patients with gastric cancer who underwent surgical treatment at the Department of Surgery, Wielkopolskie Oncology Center in Poznań. During the laparotomy, after opening of the peritoneal cavity, 200 ml of physiological saline at 37°C was administered in the tumor region. After this fluid was mixed, 100 ml of lavage fluid was collected. This fluid was subsequently spun many times to obtain sediment for cytology and immunohistochemistry investigation using anti-BerEp-4, CK 7/20, and B72.3.

Results of peritoneal cytology were analyzed jointly with clinical factors – patient's age, sex and pathology factors – tumor invasion, involvement of lymph nodes, histological grade, histological type according to Lauren and localization of the cancer in the stomach.

**Results.** Analysis of the peritoneal fluid for presence of free cancer cells was done in 51 patients. Positive peritoneal cytology was found in 12 (23.5%) patients. In the group of patients with positive cytology, all patients had T3/T4 tumors and all were found to have lymph node metastases, while G3 cancer was found in 83.3% of patients. In patients with positive cytology, diffuse gastric cancer according to Lauren predominated (9 of 12 patients, 75%), while in patients with negative cytology – intestinal type (20 of 39 patients, 51.2%). In the group of patients with positive histology, the whole stomach was involved by the cancer process in 7 of 12 patients (58.3%), while in the group with negative histology, in 29 of 39 patients the tumor was located in the gastric body and prepyloric part (74.4%).

**Conclusions.** Based on this study we can conclude that determinants of positive peritoneal cytology include: tumor stage T3/T4, N+, G3, cancer located in the whole stomach, diffuse histological type according to Lauren.

**Key words:** gastric cancer, peritoneal cytology

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Gastric cancer, despite reduction of incidence, remains a significant clinical problem. Results of treatment of this malignancy remain unsatisfactory. Therefore search continues for additional predictive factors that will allow for additional differentiation of patients with gastric cancer and further treatment individualization. Positive cytology of peritoneal fluid is one of negative prognostic factors. Positive cytology in patients who underwent surgical treatment for gastric cancer, is associated with shorter survival (12-15 months) of these patients and rapid disease recurrence, manifested as peritoneal metastases (1-4).

Adequate assessment of stage of cancer before initiation of treatment of patients with gastric cancer seems crucial in the context of more and more common neoadjuvant chemotherapy. Diagnostic laparoscopy that allows for lavage of the peritoneal cavity, is one of the stages of diagnostic work-up of a patients with gastric cancer. Diagnostic laparoscopy can detect subradiological disease foci in the peritoneal cavity and allows for more detailed assessment of local advancement of the cancer, reducing rate of needless laparotomies (5). Furthermore, image obtained during laparoscopy is a starting point for chemotherapy if radical resection is impossible at a given time.

In 1998 Japanese Gastric Cancer Association (JGCA) included positive cytology in the classification of gastric cancer staging. Result of cytological examination was also included in the 7<sup>th</sup> edition of TNM classification by International Union Against Cancer (UICC). Presence of gastric cancer cells in the peritoneal lavage fluid classifies the patient in the M1 category and concurrently stage IV cancer. To evaluate the cancer stage according to current edition of TNM classification, examination of peritoneal fluid for free cancer cells must also be performed.

Presence of gastric cancer cells in the peritoneal lavage fluid not only classifies the patient as M1, but also should result in a change of therapeutic decisions. Radical surgical treatment in this group of patients does not improve treatment results (1, 2, 3, 6); similar survival rate was observed among patients with positive cytology and potentially resectable tumor for palliative chemotherapy without surgical treatment (7). Lit-

erature includes papers on therapies that result in a change of cytological status of peritoneal fluid and that can improve results of gastric cancer treatment in the future in the group of patients with potentially resectable tumors but with positive peritoneal cytology (8, 9, 10). However, further prospective studies are required to establish universal standards of care.

The aim of this study was to analyze factors associated with positive peritoneal cytology and identify group of patients in whom diagnostic laparoscopy combined with peritoneal lavage in the diagnostic process could have a significant effect on therapeutic decisions.

## MATERIAL AND METHODS

Between April 2014 and July 2015, at the Department of Oncological and General Surgery, Wielkopolskie Oncology Center in Poznań 125 patients with gastric cancer underwent surgical treatment. The study enrolled 51 patients – 31 men and 20 women aged 39 to 81 years. The surgical treatment involved 39 gastric resections with lymphadenectomy D2, 1 resection with lymphadenectomy D3, 1 distal gastric resection with lymphadenectomy D2; in 10 cases the procedure was limited to laparotomy due to peritoneal metastases or local advancement that made radical resection impossible. Preoperative staging that did not reveal remote metastases or other features making the resection impossible, was conducted in all patients.

During the laparotomy, after opening of the peritoneal cavity, 200 ml of physiological saline at 37°C was administered in the tumor region. After approximately 30 seconds, approximately 100 ml of lavage fluid was collected and was transferred to the department of cancer pathology to undergo further assessment. At the first stage the fluid was spun and sediment was obtained that was passed into the paraffin. A 4.5 µm thick immunohistochemistry slices were used and stained using primary antibodies to Ber-EP4, CK7/20, and B72.3 and a detection system EnVisio (Dako). Results of peritoneal cytology were analyzed jointly with clinical factors – patient's age, sex and pathology factors – tumor invasion, involvement of lymph nodes, histological grade, histological type according to Lauren and location of the cancer

in the stomach. Statistical analysis included the following parameters: Lauren's class, tumor grading, TNM stage – T class, status of regional lymphatic system in the TNM classification – N class, location of the cancer in the stomach and presence of additional tumor markers – CEA, Ca 19-9, and Ca 72.4. Uni- and multivariate statistical analysis was performed using U Mann-Whitney test.

## RESULTS

Free cancer wells were found in the peritoneal fluid in 12 patients (23.5%) patients. Among T3/T4 cases, positive result was obtained in 12 of 40 (30%) patients. In 10 patients peritoneal cancer metastases or local disease advancement that made radical resection impossible, were found during laparotomy. Positive cytology was found in 4 (40%) patients from this group.

In the group of patients with positive cytology, all patients had T3/T4 tumors, metastases in lymph nodes, while the G3 grade was found only in 10 of 12 (83.3%) patients. In patients with positive cytology, diffuse gastric cancer according to Lauren predominated (9 of 12 patients, 75%), while in patients with negative cytology – intestinal type (20 of 39 patients, 51.2%). In the group of patients with positive histology, the whole stomach was involved by the cancer process in 7 of 12 patients (58.3%), while in the group with negative histology, in 29 of 39 patients the tumor was located in the gastric body and prepyloric part (74.4%).

Univariate analysis demonstrated a statistically significant correlation between positive cytology and lesion location in the stomach ( $p=0.04$ ), while the other factors did not reach statistical significance – Lauren's classification ( $p=0.34$ ), grading ( $p=0.21$ ), positive markers CEA ( $p=0.75$ ), CA-19.9 ( $p=0.18$ ), Ca 72-4 ( $p=0.85$ ) and tumor size T ( $p=0.06$ ) and lymphatic system status ( $p=0.23$ ).

Another stage involved a multivariate analysis that included the same parameters, but none of them reached statistical significance: Lauren's classification type ( $p=0.29$ ), grading ( $p=0.20$ ), tumor location in the stomach ( $p=0.18$ ), markers CEA ( $p=0.55$ ), Ca 72.4 ( $p=0.77$ ), Ca 19.9 ( $p=0.15$ ), tumor size T ( $p=0.79$ ), and lymphatic system status ( $p=0.28$ ) (tab. 1, 2, 3).

## DISCUSSION

Preoperative diagnostics workup of the gastric cancer, involving endoscopic examination and imaging studies, does not provide all required information to undertake correct therapeutic decisions in gastric cancer patients. The diagnostic algorithm in our country that includes laparoscopy and assessment of peritoneal cytology, is rarely used. According to recommendations of SAGES (Society of American Gastrointestinal and Endoscopic Surgeons), diagnostic laparoscopy should be performed in all patients with T3/T4 tumors

Table 1. Characteristics of the analyzed study group

	Positive cytology	Negative cytology
Number of patients	12 (23,5%)	39 (76,5%)
M:F	6:6	25:14
Age	44-76 (64.2)	39-81 (64,8)
Type of surgical procedure		
Gastrectomy D2	7 (58,3%)	32 (82%)
Gastrectomy D3	1 (8,3%)	0(0%)
Peripheral resection G2	0(0%)	1 (2,6%)
Laparotomy/palliative procedure	4 (33,3%)	6 (15,4%)
Stage		
I	0	8 (20,5%)
II	3 (25%)	8 (20,5%)
III	5 (41,6%)	17 (43,6%)
IV	4 (33,3%)	6 (15,4%)

Table 2. Detection ratio of free cancer cells in the peritoneum

Author/year	Number of patients	R0 resection	M1
Our own study /2015	51	14,7%	40%
Bonenkamp / 1996	457	4,4%	no data available
Ribeiro / 2006	220	6,8%	no data available
Burke / 1998	76	4%	59%

Table 3. Correlation between peritoneal cytology and the tumor stage, status of the lymphatic system, Lauren's classification type, differentiation grade and tumor location in the stomach

	Positive cytology	Negative cytology	Total
T1	0 (0%)	4 (7,84%)	4 (7,84%)
T2	0 (0%)	7 (13,73%)	7 (13,73%)
T3	7 (13,73%)	17 (33,33%)	24 (47,06%)
T4	5 (9,8%)	11 (21,56%)	16 (31,37%)
Total	12 (23,53%)	39 (76,47%)	51 (100%)
N+	12 (23,53%)	23 (45,1%)	35 (68,63%)
N-	0 (0%)	16 (31,37%)	16 (31,37%)
Total	12 (23,53%)	39 (76,47%)	51 (100%)
G1	0 (0%)	2 (3,92%)	2 (3,92%)
G2	2 (3,92%)	11 (21,57%)	13 (25,49%)
G3	10 (19,61%)	24 (47,06%)	34 (66,67%)
Undetermined	0 (0%)	2 (3,92%)	2 (3,92%)
Total	12 (23,53%)	39 (76,47%)	51 (100%)
Intestinal type	2 (3,92%)	20 (39,22%)	22 (43,14%)
Diffuse type	9 (17,65%)	14 (27,45%)	23 (45,1%)
Mixed type	1 (1,96%)	5 (9,8%)	6 (11,76%)
Total	12 (23,53%)	39 (76,47%)	51 (100%)
Cardia	2 (3,92%)	6 (11,76%)	8 (15,68%)
Whole stomach	7 (13,73%)	4 (7,84%)	11 (21,57%)
Body and prepyloric type	3 (5,88%)	29 (56,87%)	32 (62,75%)
Total	12 (23,53%)	39 (76,47%)	51 (100%)

in whom no peritoneal metastases were found in imaging studies (11). Use of diagnostic laparoscopy versus computed tomography imaging of abdominal cavity alone, resulted in a change of therapeutic decisions in 8.5% to 59.6% of patients (5, 12, 13), which supported widespread use of such management.

In an advanced gastric cancer, close to 50% of patients experience a disease recurrence after the surgical treatment, manifested as peritoneal metastases (10, 14). Survival in stage 4 cancer ranges 3-6 months (15). Free gastric cancer cells, desquamated from the surface of the tumor or metastatic lymph nodes are considered as a probable cause of peritoneal metastases. After separation from the tumor or lymph nodes, the cells may implant in the peritoneum where they undergo further divisions, causing metastatic spread in the peritoneum. Literature data unequivocally indicate that survival time and time free from the disease recurrence are much worse with positive peritoneal fluid. These results are worse both among patients who underwent radical surgical treatment (R0) and in patients in whom visible cancer foci were found in the peritoneum during a laparotomy. Bando et al. in their study analyzed cytology of peritoneal fluid in 1297 patients who underwent surgical

treatment for the gastric cancer. Positive peritoneal cytology was found 30 of 411 (7.3%) patients after R0 resection. There was a disease recurrence manifested as peritoneal metastases in all patients with positive cytology; one-year survival in this group was 37%, while no one survived 3 years after the gastrectomy. In a group of 296 patients in whom the procedure was stopped at laparotomy due to detected peritoneal metastases, positive peritoneal cytology was found in 49% (146 of 296) patients. One year survival in patients with positive cytology was only 18%. On the other hand, 43% of patients survived more than one year, when the cytology was negative (2). Similar results were presented by Bonenkamp et al. who performed an analysis of the peritoneal lavage fluid in 457 patients who underwent surgical treatment for the gastric cancer. Positive peritoneal fluid was obtained in 4.4% of patients receiving radical treatment (R0). An average survival time in this group was 13 months, while patients lived on average more than 3 years with negative results. None of the patients with positive cytology who received only a palliative procedure, survived more than one year (16).

Most of the publications concerning investigation of the peritoneal fluid is based on

conventional cytological analysis, in which cellular sediment obtained from the spun peritoneal fluid is smeared on the microscopic slide and evaluated using a staining method under a microscope by an experienced pathologist. This method is considered as a golden standard in cytological assessment due to high specificity, simple execution, low costs and relatively short duration of the analysis that does not exceed 20-30 minutes. The detection rate of free cancer cells in the peritoneum using this method in patients, who underwent a potentially radical treatment, was 4.4% – 11%. If we only include cases with infiltration of the serous membrane, this rate rises to 22% – 30% and with coexisting peritoneal metastases it is 44% – 68%. We obtained similar results in our study – in cases of R0 resection, positive cytology was obtained in 5 of 34 patients (14.7%), in cases with coexisting peritoneal metastases – in 4 of 10 (40%) of patients. Limitations of this method are related to low sensitivity and interpretational problems in differentiation between well differentiated tumor cells and benign mesothelial cells (17, 18).

Immunohistochemistry methods, characterized by higher sensitivity and specificity, supplement conventional cytological assessment. Monoclonal antibodies (Ber Ep4, HEA 125) allow for identification of antigens occurring in the gastric cancer cells implanted in the peritoneum. Increase of sensitivity over that of conventional cytological analysis is 14% (19). Molecular examination that involves identification of mRNA for carcinoembryonal antigen (CEA) in the peritoneal lavage fluid using RT-PCR is considered as the most sensitive method. In this case, increase of sensitivity over that of conventional cytology is 20% (20, 21). Limitations of this method are related to high rate of false positive results caused by low quality of mRNA in peritoneal lavage fluid (inflammatory cells, mesothelium, other), fact that it is highly time consuming and expensive. Therefore this method is not utilized as a standard in the diagnostic work-up of gastric cancer cells in the peritoneum.

Our results indicate correlation between invasion grade, involvement of lymph nodes, histological grade, cancer location in the whole stomach, diffuse type according to Lauren and presence of cancer cells in the peritoneum. All patients with positive free cancer cells in the peritoneal fluid had T3/T4 tumor (100%) and

metastases in the lymph nodes as well as grade G3 was found in 10 of 12 (83.3%) patients. We found positive result in none of the T1/T2 and N(-) patients. La Torre et al. in their study obtained similar results: in the group with positive cytology, 86% of patients had T3/T4 and 100% N(+) and 71% G3 (22). Based on preliminary assessment of a group of 51 patients we can conclude, based on the literature data, the be greatest benefit from diagnostic laparoscopy with the peritoneal lavage can be obtained by the patients with T3/T4N(+) stage disease.

Positive result of peritoneal fluid cytology is classified as M1 feature. In such situation there are questions of correct therapeutic management of patients with resectable gastric cancer who have positive peritoneal cytology. Lorenzen et al. demonstrated that systemic chemotherapy based on cisplatin, fluorouracil and folinic acid before radical surgical treatment in patients with positive cytology may result in conversion of cytological status of the peritoneal fluid to negative. Conversion of the cytological status was associated with longer survival – 36.1 months versus 9.2 months in patients in whom no changes were found in cytological examination both before and after chemotherapy ( $p=0.002$ ). Authors paid attention to a group of patients in which the disease progression was found during the neoadjuvant chemotherapy, manifested as conversion of previously negative to positive cytology of the peritoneal fluid. Survival of these patients was only 18.5 months (8). A potential therapeutic option used by Yang et al. was combination of cytoreductive therapy with intraperitoneal chemotherapy under hypothermic conditions [Hyperthermic Intraperitoneal Chemotherapy (HIPEC)]. The author randomized a group of 68 patients with stage 4 gastric cancer. The first group received surgical treatment with HIPEC procedure and cisplatin and mitomycin C, while the second group received surgical treatment alone. In patients who received HIPEC, prolongation of survival to 11 months was observed versus 6.5 months in the second group ( $p=0.046$ ) (23). Another therapeutic option for patients with positive cytology was presented by Kuramoto et al. They divided the patients to three groups: those who received surgical treatment alone, those who received surgical treatment in combination with intraperitoneal chemotherapy and systemic chemotherapy and the third

group that received surgical treatment with intensive peritoneal lavage with ten liters of physiological saline in combination with intraperitoneal chemotherapy and systemic chemotherapy. Five-year survivals in these groups were 0%, 4.6%, and 43.8%, respectively ( $p < 0.0001$ ) (24). Due to lack of large randomized studies of the best management of patients with gastric cancer with positive peritoneal fluid cytology, further analysis of factors associated with it is required. Multivariate analysis may identify patients who will benefit the most from preoperative chemotherapy or surgical treatment in combination with intraperitoneal chemotherapy.

### CONCLUSIONS

Results of this study and presented literature data unequivocally indicate that in pa-

tients with an advanced gastric cancer, preoperative diagnostic workup should be supplemented with laparoscopy in combination with cytological investigation of fluid for free cancer cells. Prognosis of patients with positive cytology despite lack of clear peritoneal metastases is poor and radical surgical in such settings may be inadequate.

We conclude, based on our own studies and literature data, that adequate patient selection should be done and indications to a diagnostic laparoscopy in combination with fluid investigation should include local and regional disease stage – patients with tumor stage T3/T4, N+, G3, diffuse histological type according to Lauren cancer located in the whole stomach. Previously suggested therapeutic strategies for patients with positive cytology require further prospective studies and eventually determination of proper algorithm to improve the treatment results.

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