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Review

Prognostic significance, diagnosis and treatment in patients with gastric cancer and positive peritoneal washings. A review of the literature

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ABSTRACT

Peritoneal dissemination is a common consequence of a relapse following a radical surgical treatment of gastric cancer. The development of the disease in the peritoneum depends not only on its stage, but also on free cancer cells exfoliated from the tumor mass or from involved lymph nodes, and which are capable of being implanted in the peritoneum. According to the latest TNM (7 edition; 2010) classification, patients with free cancer cells in the peritoneal washings qualify for stage IV of the disease. Patients in whom free cancer cells were found during the operation – have a recurrence of gastric cancer – mainly in the peritoneum, and the majority of them die within two years of the diagnosis. To properly assess the prognosis, it is vital to determine the stage of cancer by additionally assessing the washings for the presence of free cancer cells before taking a therapeutic decision. This also allows identifying those patients who require different medical procedures to obtain the best treatment results possible. Medical literature describes various methods of examining peritoneal washings aimed at detecting free cancer cells. The methods apply different cancer cell detection rates, sensitivity and specificity in prediction of a peritoneal relapse. Oncological Departments performing the evaluation of the washings employ non-standard methods of treatment in this group of patients and the results presented are promising.

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1. Introduction

The aim of the assessment of peritoneal washings in patients treated for gastric cancer is to identify patients with free cancer cells in the peritoneal cavity. The positive result of the examination applies to 4–11% of the patients in whom no peritoneal dissemination of the disease is visible during the diagnostic report. The presence of free cancer cells in the peritoneal cavity is a negative factor as far as the prognosis is concerned, as it is connected with a short survival status (12–15 months) and a quick relapse of the disease is reported in all the patients.[1–3]

The result of peritoneal cytology was included in the 7th edition of the TNM by the International Union Against Cancer (UICC) and according to its directives the patients with a positive result are classified as M1 category, that is grade IV of advanced disease.[4] According to the current TNM directives, to properly determine the stage of gastric cancer, endoscopic and imaging examinations should be supplemented with the result of a diagnostic laparoscopy along with a lavage of the peritoneum for free cancer cells.[5–7]

The European Society For Medical Oncology (ESMO) recognizes the examination of the peritoneal washings as an option in preoperational diagnosis,[8] while the American Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommends carrying out peritoneal cytology during laparoscopic diagnosis in patients with T3/T4 tumor if no peritoneal dissemination is found in their imaging diagnosis.[9] Similarly, the NNCN (National Comprehensive Cancer Network) directives also recommend laparoscopic diagnosis combined with the examination of peritoneal washing before surgical treatment in advanced T3/T4, N+ patients, and in all patients who receive perioperative chemotherapy as the first line of treatment.[10] Yet, despite the fact that we have knowledge on the significance of the presence of free cancer cells in the peritoneum, currently there is no gold standard treatment for the patients.[11] There appeared articles in medical literature, which take into account therapeutic strategies aimed at conversing the cytological status in the peritoneum. The results described are promising–they affect the lengthening of survival time of the examined patients which can in the future improve the results of the treatment of patients with stomach cancer at this level of advancement.[12–14]

2. Pathomechanism of peritoneal dissemination and diagnostic methods of free cancer cells in the peritoneum

The presence of free cancer cells is the result of the spontaneous exfoliation of cancer cells from the main tumor or from the metastatic lymph nodes.[15] It can also be the result of a perioperative trauma (tumor manipulation, intraoperative perforation, severing the lymphatic vessels, blood vessels, lymphadenectomy).[16] While circulating in the peritoneal fluid, the cells become implanted on the surface of the peritoneum with the participation of adhesive molecules and then they penetrate the sub-peritoneal layer where they further divide.[17–19] Another mechanism of cell implantation is connected to the so-called lymph channels (stomata) on the peritoneum – responsible for the elimination of all the exfoliated cell elements from the peritoneal cavity (including the cancer cells), which, due to their size, are not absorbed by the blood-peritoneum barrier.[20] So far, in the diagnostics of free cancer cells in the peritoneum, medical literature has accepted classical peritoneal cytology, the immunohistochemical method with the use of antibodies against antigens present in cancer cells. (Ber-Ep4, HEA 125, B72.3), the immune-enzymatic method [(level CEA (carcinoembryonic antigen) in peritoneal washings)] and the molecular method in which the CEA level is examined with the use of RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction Technique).

Most publications concerning the examination of washings from the peritoneal cavity are based on the classical cytological analysis in which the cellular sediment obtained from the spun peritoneal liquid is smeared on a glass side. It is then examined under a microscope by an experienced pathologist using the pigmentary method. The method is recognized to be the gold standard method[21] due to its high specificity (Table 4), easiness, low cost and the relatively short analysis time of 20–30 min. Using this method, the detection rate of free cancer cells in the peritoneum in patients subjected to potentially radical surgery treatment is 4–11%. If one considers only the cases where the serous membrane is infiltrated, then the rate rises to between 22% and 30%. If peritoneal dissemination happens alongside as a concomitant, then the rate applies to 23–83% of the patients (Table 1).

Immunohistochemical methods are complementary to classical cytological evaluation. They are characterized by higher sensitivity but at the cost of specificity (Table 4). The use of monoclonal antibodies (Ber Ep4, HEA 125, B72.3) allows one to identify antigens appearing on the surface of the cancer cells of the stomach in the peritoneum. In 1998 Benevolo and co-workers[22] published a study in which, in addition to classical cytology employed for identification of free cancer cells in the peritoneum, they used monoclonal antibodies directed against the antigens on the surface of the cancer cells. He

Table 1 – Rate of cancer cells detection in the peritoneum using the peritoneal cytology.

Author/year	Number of patients subjected to examination	Cyt +R0	Cyt+ – peritoneal dissemination
Bonenkamp 1996	535	4.4%	23%
La Torre 2010	64	11%	Data not available
Bando 1999	1297	7.3%	49%
Kodera 1999	91	11%	40%
Bentrem 2005	371	6.5%	Data not available
Ribeiro 2006	220	6.8%	Data not available
Suzuki 1999	347	8.4%	Data not available
Burke 1998	76	4%	59%
Lee 2012	1072	10.3%	52%
Nath 2008	255	7.2%	83%

Table 2 – Rate of cancer cells detection in the peritoneum using the immunohistochemical method.

Author/year	Presence of free cancer cells – classical cytology	Presence of free cancer cells Immunohistochemistry
Benevolo 1998	21%	35%
Rosenberg 2006	Not carried out	21.4%
Nekarda 1999	6%	20%
Vogel 1999	20%	30%

observed a 14% increase in the detection of cells in comparison with the cytological method. In the group of patients identified exclusively with the use of the immunohistochemical method, he observed similar recurrence rates of the disease and long survival periods as in the group of patients with positive cytology. Other tests in which immunohistochemical methods were used also showed higher detection rates (Table 2).[23–25]

The other two diagnostic methods described in medical literature with reference to stomach cancer cells in the peritoneal cavity are based on the identification of the cancerous marker of the carcinoembryonic antigen (CEA) in peritoneal washings. In the immune enzymatic method, the CEA level is determined in the supernatant left following the spinning of the sediment from the washing liquid, whereas in the molecular test, the RT-PCR technique is employed (Table 3). In his work Wang and co-workers[26] compared the conventional peritoneal cytology with the marking of the CEA level in the peritoneal washings using immunoenzymatic methods and RT-PCR. The detection rates of cancer cells for the three methods were 15%, 20% and 27.5%, respectively. Kodera and co-workers[27] indicate in their study that the difference between cytology and RT-PCR CEA was 10% in favor of the latter method (28% versus 18%).

3. Presence of free cancer cells in the peritoneal cavity and risk of peritoneal dissemination

Peritoneal dissemination in the cancerous process is the most common cause of failure after radical surgery for gastric cancer. It affects about 60% of patients receiving surgery when the tumor is at the advance T3/T4 level and the average survival period is 3 months.[14,28,29] One of the factors for peritoneal dissemination, apart from the degree of tumor invasion, the involvement of lymph nodes by cancer, the degree of diversity,

Table 3 – Rate of cancer cells detection in the peritoneum for CEA dependant methods (immunoenzymatic and molecular).

Author/year	RT-PCR	Cyt +	CEA – protein
Wang 2005	27.5%	15%	20%
Kodera 1998	28%	18%	–
Katsuragi 2007	40%	–	–
Yamamoto 2007	–	–	17.5%
Abe	–	–	17.9%
Ji-Kun Li 2005	–	23.4%	40.6%

Table 4 – Sensitivity and specificity in anticipating peritoneal relapse for particular diagnostic methods.

Diagnostic method	Sensitivity (%)	Specificity (%)
Cytology	11–80	86–100
Immunohistochemistry	23–100	81–93
CEA level	22–75	77–96
RT-PCR CEA	31–100	59–95

and the histological type according to the Lauren classification – is the presence of free cancer cells in the peritoneum during the surgery. Data from medical literature pertaining to the sensitivity and specificity of particular diagnostic methods in anticipating peritoneal relapse are shown in Table 4.[3]

The highest sensitivity of conventional cytology was obtained by Kodera (80%) in a study published in 1999. In a group of 10 patients who had a relapse of peritoneal dissemination, 8 had a positive cytology result of peritoneal washings. In a group of 81 patients with a negative result, 2 patients had peritoneal dissemination (specificity – 97.5%).[30] In their study Li and co-workers[31] obtained a similar high sensitivity and specificity of cytology in anticipating peritoneal relapse (73.7% and 97.8%). It should however be noted that most available medical literature presents a lower sensitivity of the method – the result being a big percentage of patients with peritoneal relapse of the disease with negative cytology result.[3] The restrictions of the method stem from the low sensitivity and interpretational difficulties in the differentiation between well diversified cancerous cells and benign mesothelium cells. Its indubitable advantage is the specificity, which reaches almost 100%.[32] At present, molecular tests based on the detection mRNA CEA have become the standard procedure at centers performing the assessment of peritoneal washings. The presence of the marker in peritoneal washings is linked to the depth of the invasion of the cancerous tumor, to the involvement of lymph nodes by cancer and to the stage of the cancer.

In medical literature there are studies, which compare various diagnostic methods used in anticipating peritoneal relapse. In a publication of 2005[26] Wang and co-workers, when comparing conventional cytology with dependent CEA methods (immunoenzymatic and molecular), obtained 33.3% cytology sensitivity at 93% of specificity. For comparison, the sensitivity of the enzymatic and monocular methods in this study was 67% and 50%, respectively, at specificity of 93% and 89%. Similar results have been obtained by other authors who published data comparing the two diagnostic methods – Table 5.[27,33,34]

The comparative results obtained indicate that the molecular method, which uses CEA mRNA, boasts a higher sensitivity than the classical cytology of peritoneal washings in anticipating peritoneal relapse.

Nevertheless, it is to be noted that in some studies the rate of sensitivity[26] and of specificity[34] is low in the molecular method. Falsely negative results of RT-PCR tests with the use of mRNA CEA are a result of a lack of expression of the CEA marker in the cells of stomach cancer in peritoneal washings. Falsely positive results, however, are linked to the production of CEA by other cells of peritoneal fluid–leucocytes, macrophages, endothelium cells, etc.[27]

Table 5 – Comparison of sensitivity and specificity of the cytological and molecular method in anticipating peritoneal relapse.

Author of test	Number of patients	Molecular method (RT = PCR CEA)		Classical cytology	
		Sensitivity	Specificity	Sensitivity	Specificity
Wang 2005	40	50%	89%	33%	93%
Kodera 1998	284	88%	81%	47%	96%
Tokuda 2003	136	93%	87.5%	31%	100%
Fuji 2002	49	100%	64%	33%	97%

Table 6 – Survival after surgery with positive and negative results of peritoneal washings examinations.

Author/year	Method of identification	Survival after resection – positive cytology (months)	Survival after resection – negative cytology (months)	Statistical coefficient (p)
Ribeiro/2005	Cytology	10.5	61	0.00001
Vogel/1999	Immunohistochemistry	25.7	40	0.007
Kodera/1999	Cytology	12.8	Data not available	<0.0001
La Torre/2010	Cytology	19	38	0.0001
Bentrem 2005	Cytology	14.8	98.5	<0.0001
Lee/2011	Cytology	15.7	78	0.001
Bonenkamp/1996	Cytology	13	Data not available	0.0001

4. Prognostic significance of the results of peritoneal washings test

Medical literature data clearly shows a difference in the survival of patients who had free cancer cells in the peritoneum as compared to the group of patients with negative peritoneal cytology. The results are worse both in the case of patients who received radical surgery (R0) and those who showed visible cancer symptoms during laparotomy. Bando and co-workers[35] analyzed the cytology of fluid from the peritoneum in 1297 patients operated for gastric cancer. The result of the cytological test of peritoneal washings was positive in 296 patients (24%). In this group only 2% of the patients lived up to 5 years after surgery, whereas in the case of negative result the rate was 58% ($p < 0.001$). Patients with a positive result of peritoneal cytology included those who had radical surgery and those whose surgery was restricted to exploratory laparotomy due to the dissemination of the disease. In patients who underwent resection, one year and three-year survival rates were 37% and 0%, respectively. However, with peritoneal dissemination present, one and three-year survival rates were 18% and 2% ($p < 0.001$). In patients with peritoneal dissemination and negative washing cytology result, one year and three-year survival rates were 43% and 9% ($p < 0.001$). A similar, negative influence of the peritoneal fluid examination on survival with a concurrent dissemination of the disease was also observed by Fukigawa and co-workers.[1]

In a Dutch study[36] 535 patients who received surgical treatment for stomach cancer had their peritoneal washings analyzed and a positive result of the fluid examination was obtained in 4.4% of those who received radical treatment (R0). However, when peritoneal dissemination was found and when the only treatment applied was palliative treatment, the rate was 23%. Median survival for patients with a positive peritoneal cytology was 13 months; patients with a negative cytology lived, on average, longer than 3 years ($p < 0.001$). No patient with a positive cytology result and who underwent palliative treatment lived longer than a year.

Table 6 contains data on the survival periods of patients depending on the results of the examination of peritoneal washings. Each of the authors who presented their findings evidently confirmed the statistical dependence between a positive and negative result of the fluid examination despite considerable differences in the survival rates between the particular studies.[2,25,30,36–38]

5. Suggested therapeutic strategies for patients with positive examination results of the peritoneal washings for the presence of free cancer cells

At present, there is no standard for treating gastric cancer patients with a positive result of peritoneal lavage for free cancer cells. Nevertheless, due to poor prognosis for patients, attempts have been made to introduce some methods of treatment (Table 7).

Asian patients with a positive peritoneal fluid examination have a good alternative of receiving S1 chemotherapy. Ako and co-workers[39] evaluated the effect of S1 chemotherapy (tegafur, gimeracyl, oteracil) administered as an adjuvant

Table 7 – Suggested therapeutic strategies for patients with positive examination result of the peritoneal washings.

Type of therapy	Author/year
Surgical treatment with intensive lavage of the peritoneum with physiological saline	Kuramoto/2009
Surgical treatment with intraperitoneal chemotherapy with adjuvant chemotherapy	Shimada/2002 Kuramoto/2009 Imano/2011
Surgical treatment with S1 chemotherapy	Ako/2008 Yonemura/2006
Neoadjuvant chemotherapy with surgical treatment	Lorenzen/2010 Mezhir/2010 Badgwell/2008
Cytoreductive operation HIPEC	Yang/2011

therapy after surgical treatment. In the S1 group, a 3-year survival rate was indeed statistically higher and was 71.6%, whereas of the patients who underwent only surgery merely 17.1% survived that period of time ($p = 0.0002$). Yonemura and co-workers[40] obtained similar results in their study. Two years after surgery. 53% of the patients who received S1 chemotherapy survived; with no S1 chemotherapy applied, only 9% of the patients survived the same period of time ($p = 0.0002$). Unfortunately, the differences in the pharmacokinetics S1 stemming from different CYP2A6 properties (the enzyme responsible for S1 metabolism) in the Caucasian population do not allow to achieve appropriately high concentration of the medication, which accounts for its low effectiveness in non-Asian countries.

Shimada and co-workers in a publication of 2002[41] pointed out that an intensive lavage of the peritoneal cavity with physiological saline decreases the CEA level as a marker of the presence of cancer cells in the peritoneal washing. The study conclusions were used by Kuramoto and his co-workers.[42] He divided patients in whom the presence of free cancer cells was detected into three groups: those who were treated surgically, those treated surgically with a follow-up of intra-peritoneal chemotherapy and systemic chemotherapy, and those treated surgically with intensive peritoneal lavage using ten liters of physiological saline combined with intra-peritoneal chemotherapy and systemic chemotherapy. A five-year survival rates of the above groups were 0%, 4.6% and 43.8% ($p < 0.0001$), respectively. It is worth noting that in the group of patients subjected to an intensive peritoneal cavity lavage and who had a good result of 5-year survival, 90% had a poorly differentiated cancer or a sub-type signet ring cell (SRC) adenocarcinoma, and in 60% the cancer infiltration affected the serous membrane of the stomach.

In the second segment of the study, intra-peritoneal chemotherapy was applied after surgical treatment. 4.6% of the patients survived 5 years after surgery which is a slightly better result than that obtain with surgery alone (none of the patients lived up to 5 years). This indicates that the application of this therapeutic method positively affects the survival rate.

Good results obtained in the treatment of other types of peritoneum cancer (ovary cancer, colon cancer) support the notion of applying intra-peritoneal chemotherapy in stomach cancer. Moreover, the application of intra-peritoneal medicines allows one to obtain a higher degree of concentration for a longer period of time with fewer undesired effects in comparison with the systemic application.

The influence of intra-peritoneal chemistry on the results of the treatment of patients with positive peritoneal cytology was also analyzed by Imano and co-workers.[43] The study included ten patients (all of them T3/T4 and 7 from 10 – N3). Gastrectomy with lymphadenectomy D2 was performed, then paklitastel was used intra-peritoneally, postoperatively S1 – a 2-year survival rate was 70%. In the control group who received only surgical treatment, the 2-year survival rate was 20% ($p < 0.01$).

Another potential therapeutic option is a cytoreductive treatment with intra-peritoneal chemotherapy in hyperthermia (Hyperthermic Intraperitoneal Chemotherapy (HIPEC)). Yang and co-workers[44] subjected a group of 68 patients with an IV stage cancer to randomization. The first group was treated surgically using the HIPEC procedure with cisplatin and mitomycin C, and the other group was treated with surgery alone. It transpired that the patients treated with HIPEC had their survival rate extended to 11 months versus 6.5 months for the other group.

Lorenzen and co-workers,[12] in turn, proved that using systemic chemotherapy prior to radical surgery, based on cisplatin, fluorouracil and folic acid in patients with positive cytology, can converse the status of the cytological liquid to negative. The change in the cytological state was connected with lengthening the survival rate to 66.1 months versus 9.2 months for patients in whom no change in cytology was noticed prior to and after chemotherapy ($p = 0.002$).

The authors noted that in a group of patients who had cancer progression during neoadjuvant chemotherapy in the form of conversion from negative to positive cytology of the peritoneal cavity liquid, the survival rate was only 18.5 months.

Mezhir and co-workers[45] came to similar conclusions while studying a group of 291 patients with positive peritoneal cytology. The patients' cytological status of the peritoneum liquid was examined during a diagnostic laparoscopy. The patients with positive result were qualified for neoadjuvant chemotherapy, whereupon 48 of them again underwent diagnostic laparoscopy and had their liquid examined. The neoadjuvant treatment changed the status of the cytological fluid from positive to negative in 27 patients, while 21 patients had the same positive result. For the patients who responded positively to the treatment, the median time free of relapse was 2.5 years versus 1.4 years ($p = 0.0003$) for patients who did not respond to the treatment. Out of 27 patients with negative cytology after treatment, 20 were subjected to radical surgery, 7 were not operated, moreover, survival time was comparable for the two groups.

The treatment results are promising, but require further randomized study on large groups of patients, so that the most effective way of treating patients with positive peritoneal cytology can be obtained.

6. Summary

The data presented in medical literature clearly indicate that in patients with gastric cancer preoperational diagnosis should be obligatorily supplemented with diagnostic laparoscopy combined with tests for the presence of free cancer cells. The prognosis for patients who have free cancer cells in the peritoneum despite the absence of visible peritoneal dissemination is poor, and employing radical surgery as the only method must be regarded as palliative treatment.

The therapeutic strategies proposed so far for patients with positive cytology require further perspective studies leading to finding an appropriate algorithm which could improve the results of the treatment.

Conflict of interest

None declared.

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