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Review

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

Radosław Lisiecki[a,*], *Małgorzata Kruszwicka*[b], *Arkadiusz Spychała*[c], *Dawid Murawa*[c]

[a] *Department of General Surgery, Pleszewskie Medical Center in Pleszew, Poznańska Street 125a, 63-300 Pleszew, Poland*
[b] *Department of Oncology, Pleszewskie Medical Center in Pleszew, Poznańska Street 125a, 63-300 Pleszew, Poland*
[c] *Department of General and Oncological Surgery, Greater Poland Cancer Center in Poznań, Garbary Street 15, 61-866 Poznań, Poland*

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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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* *Corresponding author.*
E-mail addresses: lisurlis@gmail.com (R. Lisiecki), gosiawalczewska@op.pl (M. Kruszwicka), spychala@me.com (A. Spychała), dmurawa@gmail.com (D. Murawa).
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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%

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