Review

PREDICTIVE AND PROGNOSTIC VALUE OF PERITONEAL WASHING IN COLORECTAL CANCER: A LITERATURE REVIEW

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Summary

Over the last decade, there has been a steady trend in increasing the incidence of colorectal cancer on a global scale. The relative share of patients under the age of 40 increases with each year. There is also a tendency for the incidence to be almost the same in males and females. Despite the efforts of the National Cancer Institute (NCI) to establish and implement adequate screening for disease prevention, 45.8% of patients were diagnosed in the advanced (third and fourth) stages of the disease. In 44.7% of patients, it was in the first and second stages, and the stage was unspecified in the remainder [1].

The prognosis in patients with colorectal cancer has been significantly improved. Precise staging of the tumor, adequate interpretation of predictive and prognostic factors is essential in the choice of therapeutic behavior. On the other hand, an inappropriate therapy administered to a patient with a diagnosed cancer can lead to disease progression, metastasis, and death, which can be avoided by adequate, patient-specified treatment.

Key words: peritoneal washing, colorectal cancer, predictive value

Introduction

The peritoneum is a common site of metastatic colorectal carcinoma (CRC). Intraperitoneal dissemination has a poor prognosis and is often considered a terminal stage of the disease. In CRC, the peritoneum is the second site of metastasis after the liver. Studies have shown that nearly 40-80% of those who die of CRC have developed peritoneal metastases [2].

Peritoneal dissemination, in this case, occurs as a result from direct tumor cell disruption from the primary tumor, because of insufficient volume of surgical resection, or incorrect dissection of the vessels and lymph nodes from and to the tumor. Making the diagnosis of CRC is not enough, and it is advisable to use all results from image, clinical and laboratory investigations to have a detailed picture of the colon, adequate staging of the tumor process and follow the progress of the disease. Metastases are most commonly detected by computed tomography of the liver and chest, PET-CT, as well as by using endorectal ultrasound or magnetic resonance imaging (MRI) [3].

What is 'Peritoneal Wash?'

In this study, the predictive value of the peritoneal wash (PW) in patients treated for colorectal cancer is also discussed. PW was introduced in the 1950s as a method of identifying proliferation of tumor cells of the peritoneal surface invisible macroscopically. In some patients, positive PW cytology may be the only evidence of advanced stage of the disease process. This cytological analysis is included in the staging of ovarian and fallopian tube tumors, as well as of endometrial carcinoma. The positive results from the investigation of PW result in changes of staging in 3% to 5% of the cases [4].

PW is used as a golden standard to prove primary ovarian carcinomas and peritoneal dissemination. It can help identify clinically unresolved peritoneal dissemination and provide adequate staging and prognosis in ovarian tumors, especially the non-serous histological variants [5]. This review is on studies involving PW in patients with colorectal cancer. It presents various methodologies for carrying out the research and the possibility of choosing one of the methods that meet the requirements of our study. The review shows the advantages and disadvantages of PW and what can be expected if PW is adopted as a predictive and prognostic factor. The analysis of PW offers an opportunity to refine our study.

PW has been used for many years in gynecological surgery for staging tumors and detecting tumor metastasis. It implies a minimal risk for the patient and can be useful in detecting early dissemination of the tumor. These combined results are not inherent to colorectal surgery due to the considerable variability of the results obtained. Although PW can be easily made during laparoscopic surgery, it is often overlooked in patients with benign disease in the attempts to avoid stress in case of false-positive results. It is not yet fully understood how to interpret the results obtained with PW. False positive results cause unnecessary strain, and this, in turn, leads to using other more expensive and sophisticated diagnostic tools unnecessarily [5, 6]. An essential role in the metastatic process is shown by free tumor cell in the peritoneal cavity, but this needs further refinement [7].

Our goal was to make a detailed literature review of all the techniques of implementing PW alone or in combination with other laboratory tests. This can provide an opportunity to standardize the technique and introduce PW in routine clinical practice.

Materials and Methods

A search was undertaken of PUBMED/Medline and Cochrane databases such as SCOPUS and Science Direct for English language articles for the last 10 years using a predefined search strategy. The key words we used were: PW, CRC, predictive and prognostic value, peritoneal. The synonyms and the extensions of the research were based on automatic term mapping. We found 103 articles, of which 71 matched the search criteria.

Variety

The literature review showed a wide variety of studies and different approaches to the research. The methodology of the study is as follows: in the area around the tumor, 100 ml physiological serum at 37°C is applied. After gentle stirring, the material obtained is aspirated. Because of the rapidly occurring autolytic changes of the cells outside the human body, the material is transported to a cytology laboratory immediately after it is taken [4, 8].

Several morphological characteristics make PW different from ascites. Firstly, PW mechanically peels off mesothelial cell fields that have not been seen in ascites fluid. Secondly, fatty tissue and skeletal muscle fibers are common in PWs, which are absent in ascites fluid. The cytomorphology of benign PW may be represented by membrane cells, collagen fibers, histiocytes, skeletal muscle cells, adipose tissue [9].

All the authors of the articles we studied were unanimous about the criteria for determining a sample as positive according to direct signs: i.e., the presence of tumor cells in the sample, or indirect signs, i.e., the abundance of leukocytes. The aim is to determine the relationship between positive cytology and recurrence rates and survival rates.

Of the 3805 articles we reviewed, 18 met the required criteria (3197 patients, 59.5% with

colon cancer and 40.5% with rectal cancer). We found reports on a variety of methods for PW wash. There were reports about using more than one method. Reports on the conventional method were found in 14 articles, on the immunology method – in 6 studies, and molecular engineering was presented in 4 studies [10].

From a study on 697 patients who received PW intraoperatively by the above-described conventional method, four characteristics were identified as a risk factor for the release of tumor cells into the peritoneal cavity: depth of invasion, regional lymph nodes, lymphatic invasion, and invasion of vessels [1].

The mean follow-up of patients was 90.5 months. A total of 15 (2.2%) of 697 patients had a positive result. In the analysis of 697 patients and a subgroup of 374 patients with pT3 or T4 disease stage, the patients with positive cytology from PW had a significantly more unfavorable prognosis and survival than those with a negative one ($p<0.0001$). Thus, the peritoneal sputum appears to be a useful prognostic factor in patients referred for cytoreductive surgery. It may be used in making decisions regarding the choice of systemic chemotherapy or HIPEC. More studies are needed to elucidate the problem further [1].

The diagnostic significance of free intraperitoneal tumor cells (FITCs) is still unclear. The primary objective of the multicenter prospective study (EVOCAPE2) was to determine the significance of FITCs in the onset of colorectal and gastric carcinoma [2].

Given the proven applicability of PW in patients with gastric carcinoma, our attention was focused on patients treated with colorectal cancer. Patients were followed for two years after the treatment.

For the period 2002-2007, 1364 patients were enrolled in the study, and 956 were followed up for 2 years. The presence of FITCs was 5.7% in colon cancer, 0.6% in rectal cancer, and 19.5% in gastric cancer. The two-year survival in patients with positive FITCs was 34.7% vs. 86.8% in patients with negative cytology ($p<0.0001$). According to results from the multivariate analysis, the positive PW of FITCs was not an independent prognostic factor. There was no correlation between cytological analysis data and relapse. The lack of correlation does not add any additional prognostic information to the usual prognostic factors associated with the tumor – pathological tumor-node-metastasis (pTNM) and differentiation. Furthermore, the presence of FITCs found with this method does not seem to be predictive for the development of peritoneal carcinoma. Peritoneal cytology, using conventional staging, is not a useful tool for colorectal and gastric cancer. While proving the correlation of positive PW with survival, the study considers the method not sufficiently informative and necessary at the onset of the disease [2].

Another such prospective study involving 20 patients was performed at Kasr Al Ainy Hospital, Cairo University Hospitals, from March 2012 to March 2013. The study confirmed the findings of EVOCAPE2. The gender of the patients did influence the results of peritoneal lavage cytology ($p=0.062$). There was no significant relationship between the Tumor Node Metastasis classification system of malignant tumors (TNM) and cytology in colorectal cancer patients ($p=0.253$). Complete surgical removal of the affected intestinal segment in colorectal cancer was the most effective primary treatment. The main prognostic factors for colorectal cancer are penetration of the tumor into various layers of the intestinal wall and the regional involvement of the lymph nodes [11]. Positive rinsing cytology has been used to predict peritoneal relapse, but its effectiveness remains contradictory. This study was conducted to evaluate the prevalence of positive cytology of PW in correlation with tumor stage in colorectal cancer patients [2].

Conclusions

Free malignant cells are an indicator of an unfavorable prognosis and are involved in the onset of tumors in upper GIT sections, but not in CRC [1].

Our review aimed to evaluate the role of PW in colorectal cancer. Positive PW is a negative prognostic factor in CRC. It appears to be a useful tool at the onset of the tumor process, but its application is still limited due to the substantial difference in positivity from different studies. This difference is mainly due to the various techniques of PW analysis.

Although the positive PW does not always

have clinical significance, it is useful for detecting malignant cells in the peritoneum. The poor prognosis is associated with positive PW. Although positive PW cannot be considered as an independent factor, it should not be underestimated, because its positivity can be associated with other prognostically significant factors such as lymph node involvement, depth of involvement, and presence of distant metastases, to mention a few.

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