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TOPIC HIGHLIGHT

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Intra-operative peritoneal lavage for colorectal cancer

Guillaume Passot, Kayvan Mohkam, Eddy Cotte, Olivier Glehen

Guillaume Passot, Kayvan Mohkam, Eddy Cotte, Olivier Glehen, Departement of General and Surgical Oncology, Hospices Civils de Lyon, 69495 Pierre Bénite, France
Guillaume Passot, Kayvan Mohkam, Eddy Cotte, Olivier Glehen, EMR 3738, Université Lyon 1, F-69364 Lyon, France
Author contributions: All authors contributed to the design and editing for the manuscript; Mohkam K and Passot G wrote the article.
Correspondence to: Olivier Glehen, MD, PhD, Departement of General and Surgical Oncology, Hospices Civils de Lyon, CH Lyon Sud, 69495 Pierre Bénite, France. olivier.glehen@chu-lyon.fr
Telephone: +33-7-8865742 Fax: +33-7-8863343
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Abstract

Free cancer cells can be detected in peritoneal fluid at the time of colorectal surgery. Peritoneal lavage in colorectal surgery for cancer is not used in routine, and the prognostic significance of intraperitoneal free cancer cells (IPCC) remains unclear. Data concerning the technique of peritoneal lavage to detect IPCC and its timing regarding colorectal resection are scarce. However, positive IPCC might be the first step of peritoneal spread in colorectal cancers, which could lead to early specific treatments. Because of the important heterogeneity of IPCC determination in reported studies, no treatment have been proposed to patients with positive IPCC. Herein, we provide an overview of IPCC detection and its impact on recurrence and survival, and we suggest further multi-institutional studies to evaluate new treatment strategies.

Key words: Peritoneal carcinomatosis; Colorectal cancer; Free intraperitoneal cells; Immunocytochemistry

Core tip: We provide an overview of intraperitoneal free cancer cells (IPCC) detection and its impact on recurrence and survival, and we suggest further multi-institutional studies to evaluate new treatment strategies. Moreover, while current literature is sufficient to consider positive IPCC as a pejorative prognostic factor, further studies are also needed to propose adjuvant treatment for patients with positive IPCC.

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INTRODUCTION

Intra-operative peritoneal lavage can be used to detect intraperitoneal free cancer cells (IPCC) in order to determine the presence of peritoneal spread in intra abdominal malignancies. IPCC are considered as an important prognostic tool in ovarian[1-3] and gastric cancers[4-7]. Colorectal cancer is one of the most frequent cancers worldwide[8], with development of peritoneal carcinomatosis in 10%-30% of patients[9,10]. The development of curative treatments for peritoneal carcinomatosis, such as cytoreductive surgery and intraperitoneal chemotherapy showed effective outcomes, especially in malignancies of colorectal origin[11,12], and thus raised the interest for free malignant cells detection. In colorectal cancer, different therapeutic strategies could be proposed if IPCC were confirmed to be an important prognostic factor. Several techniques, such as pathological examination, immunocytochemistry (ICC) and polymerase chain reaction (PCR) have been described to determine the presence of IPCC and were used at various times before or after resection. The heterogeneity of peritoneal lavage techniques, timing and samples analysis were the main issues to clarify the impact of IPCC on prognosis and risk to develop recurrence. The aim of this review was to report and discuss

the significance of IPCC detection in patients treated for a colorectal cancer in a curative intent.

PERITONEAL CYTOLOGY TECHNIQUE

Techniques used

Peritoneal cytology can be performed without lavage when free peritoneal fluid is present. In the absence of peritoneal fluid, a lavage with saline serum (NaCl 0.9%) is needed. The volume of fluid used was extremely variable, ranging from 50 to 1000 mL[13-25], but most authors proposed a small amount of liquid (100-200 mL) delivered around the tumor, where most cells are supposed to be.

IPCC were usually sought in peritoneal fluid by conventional cytology. After peritoneal lavage, the collected fluid was centrifuged and the sediment was smeared on slides and stained by the Giemsa or/and Papanicolaou methods. If at least one cancer cell was identified, cytology was considered positive. A clear-cut identification between benign and malignant cases could be achieved in most cases, but in 2% of cases, the analysis was still inconclusive[26]. Yield rate of positive IPCC detection by conventional cytology varied from 4% to 35.5%[14,15,20,26-30]. To increase the sensitivity of conventional cytology, ICC has been proposed with various monoclonal antibodies evaluated Ks20.8, Lu5 and Ber-Ep4[18], C1P83, Ra96, CA19-9[31], CK20[32] and 17-lA14 and Kl-1[22], along with PCR or reverse transcriptase PCR to detect cytokeratin 20, carcinoembryonic antigen, laminin g2, ephrin B4, matrilysin mRNA[17,33], Kras mutation on exon 1 or 2, Braf mutation[34] or human mammaglobin (hMAM) and hMAM-B expression[35], or even fluorescence in situ hybridization[35]. Yield rate of positive IPCC detection varied from 20%-30% and 8%-40% for ICC and PCR, respectively. Bosch *et al*[18] reported one case of positive ICC within a control group of benign lesion, resulting in a specificity of 97% for ICC. PCR techniques present a similar issue by detecting DNA from benign cells[36]. Other techniques such as immunofluorescence for epithelial markers[37] or serosal stamp[38,39] have been proposed and evaluated by a few teams. Even if serosal stamp cytology appeared to be more sensitive than conventional cytology to detect IPCC, its clinical impact was insufficiently evaluated, and its impact on recurrence or survival remains uncertain[39].

To the best of our knowledge, no prior study has compared the different techniques of IPCC detection. Due to the important heterogeneity of these techniques, conventional cytology may be proposed as the standard IPCC detection technique in further clinical trials, given that it is reproducible and widely used. Its specificity is high (100%), while its sensitivity is variable. To improve diagnostic accuracy and sensitivity of conventional cytology, inconclusive cases could be reviewed by an expert panel as suggested by Piaton *et al*[26], or ICC could be associated as suggested by Yang *et al*[32] with the added risk of decreasing specificity[35]. In a study detailing improved effusion analysis, Fiegl *et al*[35] suggested that for gastrointestinal carcinomas, the addition of real time-PCR for hMAM-B to conventional cytology enhanced diagnostic sensitivity from 25.8% to 51.7% and could be considered as the most effective association.

Timing of peritoneal lavage

Peritoneal lavage was mainly performed after the abdomen was opened and before any manipulation of the tumor, but a few series also reported analysis after tumor resection. Two studies reported both pre and postresection IPCC detection by PCR[17,33]. The detection rate before resection was similar in both studies (12%-14%), but the post resection detection rate were contradictory, as it was lower than the pre resection rate in one study (3%)[33], and higher in the other (20%)[17]. Data are missing to recommend a precise timing of sampling. However, the evolution of IPCC detection rate between before and after resection could be a prognostic factor suggesting that peritoneal lavage analysis should be performed before and after resection.

PROGNOSTIC IMPACT

For colorectal cancer, as well as in gastric and ovarian cancer, the objective of IPCC detection was to evaluate the impact on survival and local recurrence, in order to discuss intraperitoneal treatment or adjuvant systemic chemotherapy. Few studies[14,22,31,34,38,40], with less than 200 patients included in each, reported a trend between cancer stage and positivity of peritoneal lavage. The study by Noura *et al*[13] on 697 patients reported a significant correlation between cancer stage and positivity of peritoneal lavage.

Rekhraj *et al*[41] reported a meta-analysis in 2007 in order to determine the impact of IPCC on local and general recurrence of patients treated with curative intent. They analyzed 9 studies for a total of 1182 patients. Three studies included patients with stage Ⅳ colorectal cancer. They reported a significantly higher risk to develop overall recurrence for patients with positive IPCC. The risk rose from 25% for negative pre-resection IPCC to 46% for pre-resection positive IPCC and from 17% for negative post-resection IPCC to 52% for post-resection IPCC. Pre-resection positive IPCC was a significant risk factor for local recurrence (21% *vs* 12% for negative post-resection IPCC), while the risk for post-resection positive IPCC was not significant (18% for positive IPCC *vs* 8% for negative IPCC). Two studies[28,42] demonstrated a higher rate of peritoneal recurrence for positive IPCC compared to negative IPCC.

Alex *et al*[43] reported a more recent meta-analysis that a mean weighted yield of 8.4%, 28.3% and 14.5% for conventional cytology, ICC and PCR, respectively, which aimed to determine the outcome of patients with positive peritoneal lavage treated for colorectal cancer with curative intent. The authors excluded studies that included patients presenting with synchronous peritoneal carcinomatosis. Twelve studies including 6 published after 2007 were analyzed, with 1880, 1711 and 1096 patients for mortality analysis, peritoneal recurrence analysis and

Table 1 Demographic and outcome data from studies involved more than 100 patients

Ref.	Patients (*n*)	Method of IPCC detection	Lavage	Timing of sampling	Yield rate of positive IPCC	Significant impact	
						Overall survival	Global recurrence
Noura *et al*[13]	697	Cyto	100 mL NaCL	Before	2.20%	Yes (5 yr 87% *vs* 50%)	ND
Nishikawa *et al*[21]	410	Cyto	200 mL NaCl	Before	7.60%	Yes (5 yr 68% *vs* 20.6%)	Yes (30% *vs* 60%)
Fujii *et al*[15]	293	Cyto	200 mL NaCl	Before	6.00%	NS	NS
Kristensen *et al*[34]	237	PCR	200-600 mL NaCl	After	8.00%	Yes (median 47 mo *vs* 22 mo)	ND
Lee *et al*[16]	234	Cyto	1000 mL NaCl	Before	8.00%	Yes (mean 32 mo *vs* 25 mo)	ND
Katoh *et al*[14]	226	Cyto	100 mL NaCl	Before	14.60%	Yes (5 yr 79% *vs* 14%)	Yes
Yamamoto *et al*[42]	189	Cyto	50 mL NaCl	Before	5.80%	Yes (5 yr 76% *vs* 46%)	ND (26% *vs* 55%)
Temesi *et al*[23]	145	Cyto		Before	17.00%	ND	ND (23% *vs* 56%)
Vogel *et al*[31]	135	ICC	100 mL NaCl	Before	23.00%	Yes (5 yr 85% *vs* 23%)	ND
Lloyd *et al*[17]	125	PCR	100 mL NaCl	Before After	13.00% 20.80%	NS pre Yes post (mean 88 mo *vs* 44 mo)	ND (4% *vs* 22%)
Schott *et al*[22]	109	ICC	1000 mL NaCl	Before	31.00%	Yes (4 yr 60 mo *vs* 28 mo)	Yes (47% *vs* 85%)

Global recurrence range at end of study follow up. IPCC: Intraperitoneal free cancer cells; ND: Not determinable; NS: Not Significant; Cyto: Conventional cytology; PCR: Polymerase chain reaction; ICC: Immunocytochemistry.

overall recurrence analysis, respectively. Positive peritoneal lavage was associated with an increase in all 3 parameters. Mohan *et al*[24] reported the same findings in a recent review. Other studies reported opposite results[15,19,33,44], but only one[15] of these included more than 200 patients. All other studies including more than 200 patients[13,14,16,21] found a significant impact of positive peritoneal lavage on survival and recurrence. A large multi institutional study is needed to confirm the impact of positive peritoneal lavage on survival and recurrence.

Table 1 reports lavage techniques, yield rate of positive IPCC detection and impact on survival and global recurrences in the main studies.

HOW CAN PERITONEAL CYTOLOGY BE INTEGRATED IN THE OVERALL MANAGEMENT OF COLORECTAL CANCER

Positive peritoneal lavage for stage Ⅰ, Ⅱ and Ⅲ of colorectal cancer appears to be a prognostic factor of local recurrence, overall recurrence and poor survival, but the studies discussed here present an important heterogeneity in lavage techniques and analysis. Standardization is needed in order to integrate peritoneal lavage into routine clinical practice. Peritoneal lavage might be realized twice, after the abdomen has been opened and before closure with 100-200 mL of saline (NaCl 0.9%). Conventional cytology remains the standard to determine positive IPCC, and a panel analysis or ICC or PCR could increase the sensitivity for inconclusive cases.

Positive IPCC appeared to be a pejorative prognostic factor of overall recurrence and survival. These findings might be explained by cell exfoliation into the peritoneal cavity along with systemic diffusion. According to this hypothesis, the presence of IPCC during a curative surgery for stage Ⅰ, Ⅱ or Ⅲ colorectal cancer could be considered as a pejorative prognostic factor. Even if the rate of patients with positive IPCC was variable among the reported studies, adjuvant chemotherapy should be evaluated for these patients in a large multi-institutional study.

The other treatment that could be proposed for patients with positive IPCC could be prophylactic intraperitoneal chemotherapy. Local recurrences were not well described and included lymphatic, anastomotic or peritoneal recurrences. However, the low sensitivity of morphological examinations for peritoneal carcinomatosis diagnosis[45] could under-estimate the rate of peritoneal recurrence in patients with positive IPCC. In a systematic review, Honoré *et al*[46] assumed that patients with positive IPCC have an unknown risk of developing peritoneal carcinomatosis. One issue was the average risk to develop peritoneal carcinomatosis for patient with positive IPCC, with an important variability among reported studies. But this risk remains probably under estimated because of the low sensitivity of morphological examinations to diagnose peritoneal carcinomatosis. Another issue was the large heterogeneity in positive IPCC incidence in reported studies with a mean yield rate of 8%-15%[41,43], raising the question of the efficacy of conventional cytology in routine. Intraperitoneal chemotherapy combined with surgery is an aggressive treatment[47] associated with

an increased morbidity, and therefore requires expertise. Data available about peritoneal recurrence and the impact of intra-peritoneal chemotherapy are insufficient to propose intraperitoneal chemotherapy routinely. The risk to develop peritoneal carcinomatosis for this patient population could be evaluated by a second look surgery, as proposed by Sugarbaker[48]. In the author's series, patients treated for stage Ⅰ, Ⅱ or Ⅲ colorectal cancer with limited surgical history underwent a laparoscopic second look in order to limit morbidity. The exploration enabled the detection of limited carcinomatosis and could lead to a curative treatment combining systemic chemotherapy, cytoreductive surgery +/- intraperitoneal chemotherapy. This study showed that patients with positive IPCC had a higher risk of developing peritoneal carcinomatosis, and could therefore benefit from a prophylactic treatment with intra-peritoneal chemotherapy.

CONCLUSION

Positive intraperitoneal free cancer cells are a prognostic factor of recurrence and survival for patients treated for stage Ⅰ, Ⅱ and Ⅲ colorectal cancer. These findings should be supported by a large multi-institutional study to determine the real prevalence of positive IPCC. Moreover, while current literature is sufficient to consider positive IPCC as a pejorative prognostic factor, further studies are also needed to propose adjuvant treatment for patients with positive IPCC.

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http://www.wjgnet.com

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