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FIELD OF VISION

Prognosis and treatment of patients with positive peritoneal cytology in advanced gastric cancer

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Core tip: Gastric cancer staging is still matter of debate as it evolves along with introduction of new diagnostic tools. Use of laparoscopy and washing cytology in gastric cancer staging has identified a particular category of patients with no macroscopic peritoneal disease but with positive peritoneal cytology. Prognosis and management of such patients still remains a controversial issue.

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Abstract

Positive peritoneal cytology in gastric cancer is classified as M1 disease by the 7th Edition of American Joint Committee on Cancer staging system. With the introduction of laparoscopy and peritoneal washing cytology in the staging of gastric cancer a new category of patients has been identified. These are patients with no macroscopic peritoneal metastases but with peritoneal cytology positive (P0C1). Prognosis and treatment of such patients represent a controversial issue. We evaluate the state of the art of staging system in gastric cancer and discuss standardisation in staging and treatment procedures. There is still a lack of uniformity in the use of laparoscopy with peritoneal cytology in clinical decision making and in the surgical treatment for gastric cancer. Survival of this patient subset remains poor. Multimodal therapies and new therapeutic strategies are required to improve the survival of these patients.

Key words: Advanced gastric cancer; Peritoneal washing cytology; Staging laparoscopy; Reverse transcription-polymerase chain reaction

COMMENTARY ON HOT TOPICS

Gastric cancer is the second most frequent cause of cancer death worldwide[1]. Unfavourable prognosis, mainly in Western countries, is related to the advanced stage of the disease at the diagnosis. The peritoneum is the most common site of metastasis in patients with gastric cancer. Since accurate staging of patients with locally advanced disease is critical for selecting the appropriate treatment strategy, in addition to visible macroscopic peritoneal metastases, only positive peritoneal washing cytology is included in the American Joint Committee on Cancer (AJCC) staging system (7th edition) definition of M1 disease[2]. The standardization of peritoneal cytological examination is essential, and staging laparoscopy is necessary in patient selection for neoadjuvant chemotherapy. The management of patients with positive peritoneal cytology as the only evidence of M1 disease is largely unknown. Though patients with intraperitoneal free cancer cells (IFCC) have traditionally been offered palliative care, prognosis could be improved by a multimodal approach. Both neoadjuvant and adjuvant treatment strategies are

currently being evaluated.

How should we regard patients negative for macro/microscopic peritoneal seeding, but with positive peritoneal cytology: locally advanced disease or metastatic disease? What is the best treatment option for this subset of patients: neoadjuvant therapy or resection and adjuvant therapy?

In their retrospective study Lee *et al*[3] included 1072 patients who underwent surgery for gastric cancer and peritoneal washing cytology: 84% had negative cytology, 16% positive cytology. The patients were stratified into four subgroups: P0C0 (no peritoneal metastases, negative cytology), P0C1 (no peritoneal metastases, positive cytology), P1C0 (peritoneal metastases, negative cytology), P1C1 (peritoneal metastases, positive cytology). Median overall survival was best in the P0C1 subgroup (20 mo) and decreased to 14 and 10 mo respectively for P1C0 and P1C1 subgroups. Patients with P0C1 disease seem to have significantly better survival than those with P1C1 disease. This is probably due to the combination of aggressive surgical resection with lymph node dissection and adjuvant chemotherapy. This is confirmed by the reduction in peritoneal recurrence with associated improvement survival using the aggressive approach reported by Kuramoto *et al*[4].

On the other hand, Mezhir *et al*[5] have essentially abandoned gastrectomy as positive peritoneal cytology even in absence of gross peritoneal disease suggests a poor outcome.

So identifying prognostic factors within P0C1 patients may be crucial for planning the most suitable therapeutic option. Again, the multivariable analysis by Lee *et al*[3] showed that P0C1 group (with N0/2 patients) after resection and adjuvant chemotherapy had a significantly better prognosis.

Lorenzen *et al*[6] demonstrated that gastric cancer patients, whose IFCC status was converted from positive to negative following neoadjuvant therapy, had an improved median survival after surgery, suggesting that surgeons should selectively offer aggressive resection in patients in whom there is a response to induction chemotherapy.

A recent study by Mezhir *et al*[5] has proposed a new approach to patients with M1 disease based solely on IFCC positivity. After chemotherapy for 6-12 mo, if there is no clinical progression, repeat cytology is performed. Patients who remain positive for IFCCs are treated palliatively. Patients who become IFCCs negative have repeat laparoscopy after a further 3-6 mo. If they revert to M1 status, they are treated palliatively. If they remain IFCC-negative and have good performance status, they are considered for gastrectomy. Using this strategy, the authors reported a resection rate of 74% for ICC-positive patients who were converted to negative cytology.

A third option, not included in the analysis, is intraoperative chemotherapy (IPC). Some studies have demonstrated the efficacy of this procedure in patients with advanced peritoneal dissemination and have shown improvement in survival rates and a decrease in the incidence of peritoneal recurrence[7].

Currently there are no level 1 data to support a specific treatment plan. As reported by the review of Matharu *et al*[7] the methodological quality of most studies on intraperitoneal chemotherapy is poor, owing to selection and observer bias. Intraperitoneal chemotherapy can be administered preoperative, intraoperative and postoperative. Yano *et al*[8] treated with neoadjuvant IPC, 25 patients with T3/T4 tumors, no macroscopic carcinomatosis, (in only one case positive peritoneal lavage cytology) and achieved disease T downstaging in 48% of cases.

The use of extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy has been demonstrated, in a randomized controlled trial, to improve the 5-year survival in patients with positive peritoneal cytology and no macroscopic peritoneal carcinomatosis[4]. So, IPC may reduce the frequency of peritoneal recurrence in patients with locally advanced gastric cancer in the absence of macroscopic peritoneal seeding, but is clearly unable to prevent recurrence or disease progression completely. Studies seem to demonstrate that IPC is more effective in preventing peritoneal carcinomatosis than in treating macroscopic carcinomatosis.

The methods for detecting IFCCs represent yet another controversial issue. The sensitivities of conventional cytology, immunoassay, immunohistochemistry (IHC), and reversetranscription polymerase chain reaction (RT-PCR) in predicting peritoneal recurrence are low and vary considerably[8]. Such low sensitivities suggest that a significant number of patients negative for IFCCs are developing recurrent disease. RT-PCR for the detection of a single tumor marker, CEA mRNA, in the peritoneal lavage increases the detection of subclinical peritoneal disease and is more sensitive than conventional cytology. PCR was positive in a significantly greater number of patients with advanced-stage disease or vascular and perineural invasion than in those who were cytology positive. Multiple studies have shown that patients with no visible peritoneal disease at laparoscopy (LAP-) and positive for PCR have a worse survival and earlier recurrence than PCR-patients[9].

A significant challenge when applying such a sensitive technique is to determine the best threshold and the true predictive role of PCR, thus avoiding overinterpretation of the clinical significance of a false-positive PCR[10]. Future studies will also help determine whether analysis of multiple tumor markers rather than a single gene may increase the diagnostic yield and independent predictive value of RT-PCR.

In conclusion, the evaluation of peritoneal cytology in gastric cancer patients is still a grey zone with regards to staging and treatment options. There is lack of uniformity in the utilization of peritoneal cytology in the algorithm of gastric cancer treatment. The optimal management of patients with IFCCs still remains debatable. Therefore, identifying prognostic factors and stratifying patients with IFCCs will be crucial in targeting therapeutic options.

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