



Selection criteria for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer

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Abstract

Peritoneal carcinomatosis in gastric cancer is associated with a dismal prognosis. Systemic chemotherapy is not effective because of the existence of a blood-peritoneal barrier. Cytoreductive surgery and intraperitoneal chemotherapy can improve survival and quality of life in selected patients. Patient selection for this multimodal approach is one of the most critical issues, and calls for interdisciplinary evaluation by radiologists, medical and surgical oncologists, and anaesthetists. This article sets forth criteria for selection of gastric cancer patients suffering from peritoneal carcinomatosis.

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Key words: Peritoneal carcinomatosis; Gastric cancer; Hyperthermic intraperitoneal chemotherapy; Cytoreductive surgery; Selection criteria

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INTRODUCTION

Gastric cancer is one of the most frequent causes of cancer-related mortality worldwide^[1,2]. Surgical resection after neoadjuvant chemotherapy in primary locally extended cases remains the mainstay for treating patients suffering from this disease. Surgery is limited by various factors: impaired general status, severe concomitant diseases, and distant metastases. One form is peritoneal dissemination of cancer cells within the abdominal cavity. Peritoneal carcinomatosis (PC) is detected in more than 30% of patients with advanced gastric cancer, and almost 60% of deaths are caused by peritoneal dissemination. In contrast to lymphatic and hematogenous metastasis, peritoneal carcinomatosis can be considered a local disease limited to the peritoneal cavity. Based on this rationale, cytoreductive surgery and intraabdominal chemotherapy have become a relevant treatment option for patients.

Various intraabdominal chemotherapy protocols have been established, varying from hyperthermic intraperitoneal chemotherapy (HIPEC), to early postoperative intraperitoneal chemotherapy, normothermic intraperitoneal chemotherapy, and delayed postoperative intraperitoneal chemotherapy^[3]. They differ in the heat of the administered agent, the chemotherapy dosage, and time of administration of the chemotherapy. HIPEC seems to have the most beneficial impact on overall survival^[3]. Retrospective analyses of patients treated with cytoreductive surgery plus HIPEC show a clear survival benefit when complete cytoreduction was possible. The randomized trial by Fujimoto *et al*^[4] in 141 gastric cancer patients, who were curatively resected, showed a significantly reduced peritoneal recurrence rate and improved long-term survival when HIPEC was part of the treatment as

compared to the “surgery alone” group. This observation was confirmed by Kim *et al*^[5], who showed a significantly lower peritoneal recurrence rate and an improvement in the five-year survival rate in the multimodally treated patients as compared to the “surgery alone” group.

Systemic chemotherapy is not as effective as surgery plus HIPEC because of the blood-peritoneal barrier^[6].

For metachronous peritoneal carcinomatosis from gastric cancer, there is no evidence to show which patient should be treated with the presented multimodal strategy. The dilemma arises when patients are very young and systemic chemotherapy is ineffective. In such cases, an individual approach with maximal tumor debulking may be an option and is justified in highly selected patients. However, in metachronous peritoneal carcinomatosis, the tumor often extensively involves the abdominal cavity with infiltration of the retroperitoneum, liver hilus, etc., which makes surgery impossible.

The aim of this article is to summarize the recent knowledge on patient selection for cytoreductive surgery and perioperative intraperitoneal chemotherapy for primary gastric cancer with peritoneal carcinomatosis or positive cytology.

GENERAL STATUS

Patients with limited peritoneal carcinomatosis from gastric cancer do not suffer from symptoms such as dysphagia or dysmotility, and PC is frequently found even in low T and negative N stages. Therefore, if the general status is acceptable, the option of radical surgical treatment should always be considered.

A detailed preoperative anesthesiological check-up is of importance and all patients should undergo a preoperative lung and cardiac function test. Concomitant diseases, that may influence surgical and anesthesiological risks, should be identified. As for most general elective operations, a low ASA score is mandatory. Age is still a matter of concern, because biological age does not always correlate with numerical age. However, most groups dealing with cytoreductive surgery and HIPEC restrict patient selection to an age below 65. Most importantly, informed consent with discussion of all alternative therapies must be obtained from the patients, and patients should be offered psychooncological support.

PREOPERATIVE DIAGNOSTICS

A high-end computed tomography is actually the standard and should be performed also to exclude extraabdominal spread and liver metastases. Recently, we demonstrated that positron emission tomography computed tomography (PET-CT) correlates well with intraoperative tumor load in peritoneal carcinomatosis^[7]. However, gastric cancer with PC is frequently of mucinous character; therefore, PET-CT is not helpful in selecting candidates for radical resection. Nodules smaller than 5-8 mm cannot be consistently detected^[8,9]. In particular, nodules on the small bowel and its mesentery are difficult to diagnose, but relevant for indication.

To date, there is no imaging method that can sufficiently predict intraoperative tumor load. Therefore, explorative laparoscopy is an invasive alternative for candidates in whom radiological work-up was not sufficient to determine operability.

Laparoscopy permits determination of the peritoneal carcinomatosis index (PCI) and cytology in locally advanced cases. Laparoscopy is highly accurate for the diagnosis of peritoneal carcinomatosis, with good correlation to the open surgical exploration found by Yonemura *et al*^[9].

Therefore, every patient should undergo explorative laparoscopy before neoadjuvant therapy or primary gastrectomy. As the first step of treatment, some groups even administer HIPEC *via* laparoscopy in patients with synchronous PC or positive cytology^[10,11].

PCI

PCI describes the tumor load in the abdomen and varies from 0 to 39, depending on the compartments involved^[12].

In contrast to colorectal cancer, where the PCI should be lower than 20 so that patients potentially profit in terms of overall survival^[13], in gastric cancer, the PCI should be much lower, because the biological behaviour of the tumor is more aggressive.

In a recent work by Yonemura *et al*^[14], complete cytoreduction was achieved in 91% of the patients when the PCI was lower than 6, but in only 42% of the patients with a PCI ≤ 7 . Overall survival was also better in the PCI ≤ 6 group. In gastric cancer with peritoneal carcinomatosis, lymph nodes should be removed only if they are infiltrated; however, prophylactic D2 lymphadenectomy is unnecessary.

Patients with liver metastasis, involving para-aortic lymph nodes and extraabdominal metastases, are not candidates for cytoreductive surgery and HIPEC. The treatment of metachronous metastases remains controversial, and cancer masses tend to infiltrate the retroperitoneum and liver hilus with vascular structures, which makes surgery impossible.

COMPLETENESS OF CYTOREDUCTION SCORE

The completeness of cytoreduction score CC score describes the completeness of cytoreduction after operation. Ideally, all tumor nodules can be removed macroscopically (CC0). Otherwise, a CC1, CC2 or CC3 score describes non-resectable tumor nodules that vary in size and influence on prognosis. Non-resectability is caused either by diffuse peritoneal carcinomatosis with a high PCI, where surgical resection is oncologically not justified, or by diffuse infiltration of the small bowel or the mesenteric axis, and infiltration of the retroperitoneum.

NEW PROTOCOLS

Neoadjuvant intraperitoneal systemic chemotherapy pro-

TOCOL (NIPS) is a newly developed neoadjuvant intraperitoneal treatment modality developed by Yonemura *et al*^[15]. A good predictor of the possibility of achieving a CC0 status is preoperative cytology. Yonemura *et al*^[16] performed NIPS and achieved CC0 status in 27 of 52 patients with negative cytology, but only in four of 27 with positive cytology. Peritoneal wash cytology may, therefore, be a good predictor of the potential for CC0 status.

SUMMARY AND FUTURE PERSPECTIVES

Gastric cancer with peritoneal carcinomatosis is a biologically aggressive tumor, and surgery is still the gold standard of treatment if abdominal spread is limited and PCI is low, ideally < 10. HIPEC may have a potential impact on remaining free cancer cells, although it has not been proven in randomized trials. In metachronous peritoneal carcinomatosis, the surgical approach is often limited by the extensive intraabdominal tumor load and by the aggressive biological behaviour of the tumor itself. NIPS is a promising therapy, and may improve resectability and survival. Intense research is currently being done in experimental peritoneal carcinomatosis, which will eventually modulate current indications.

Concerning promising biomarkers, Phosphoglycerate-kinase 1 (PGK1), an adenosine-triphosphate (ATP)-generating enzyme of the glycolytic pathway, which also affects DNA replication and repair, seems to be an interesting enzyme that is significantly involved in the pathogenesis of gastric cancer and PC^[17-19]. Concerning tumorigenesis, it is assumed that genes involved in the glycolytic pathway are responsible for providing solid tumor cells with ATP. A newly discovered link between metabolic changes, including PGK1, and differentiation, has intriguing connections to an old hypothesis advocated by Otto Warburg for tumor metabolism. Further, recent *in vitro* and *in vivo* studies showed that PGK1 overexpression is associated with an elevated tumor invasion and metastatic rate in gastric cancer^[17-19]. Those results demonstrate that PGK1 might be a crucial enzyme enabling cancer cells to metastasize, and, therefore, may serve as a target molecule for therapy in gastric cancer in the near future.

CONCLUSION

Nowadays, a radical combined treatment should be considered for a motivated patient with good performance status and low-grade peritoneal carcinomatosis. In addition, the patient should be sent to a peritoneal surface malignancy center.

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