

REVIEW ARTICLE

HIPEC in controversial digestive tumors

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Summary

Local-regional and peritoneal metastases still develop despite improvements in surgical techniques. Intraperitoneal chemotherapy has been proved to be effective in reducing the rate of local-regional and peritoneal metastases in many malignancies. There is adequate evidence that intraperitoneal perioperative chemotherapy after aggressive resection of locally advanced tumors of the digestive system may be helpful in decreasing the rate of local-regional and peritoneal metastases. Prospective trials and meta-analyses have shown that patients with locally advanced gastric or colorectal carcinomas are offered significant survival ben-

efit and develop reduced number of local-regional metastases with surgery combined with perioperative intraperitoneal chemotherapy. In pancreatic cancer the preliminary results have shown that these patients do not develop local-regional recurrences with R₀ resection in combination with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Further studies are required to document these findings.

Key words: colorectal cancer, gastric cancer, HIPEC, pancreatic cancer, prevention

Introduction

HIPEC integrated in cytoreductive surgery has been considered the standard of care for pseudomyxoma peritonei, diffuse malignant peritoneal mesothelioma, colorectal cancer with peritoneal carcinomatosis, gastric cancer with peritoneal carcinomatosis, peritoneal sarcomatosis, and recurrent ovarian cancer in many countries. Peritoneal malignancy is present at initial diagnosis of an abdominal tumor in 10-15% of the cases. Tumors of the digestive tract are likely to develop local-regional or peritoneal metastases in approximately 40-50% of the cases [1].

Recent improvements in surgical technology have decreased the incidence of local-regional failures or peritoneal metastases in patients with gastrointestinal carcinomas. D₂ gastrectomy has been shown to offer significant survival benefit in patients with gastric cancer and decrease the rate of local-regional recurrences [2,3], although it has been strongly questioned by western surgeons [4]. In rectal cancer, total mesorectal excision has

drastically decreased the rate of local-regional recurrences [5]. Aggressive surgical lymphadenectomy with an intact mesocolon and a wide resection in colon cancer has also been shown to decrease the local-regional failures [6]. Such surgical improvements do not allow tumor cell contamination in the abdominal cavity. Despite these improvements in surgical strategy the rate of local-regional failures in colorectal cancer has still been as high as 10-20%. The integration of aggressive surgical interventions including peritonectomy procedures in combination with HIPEC may decrease even more the rate of local-regional and peritoneal metastases.

Data indicating high-risk of local-regional recurrence and peritoneal metastases

The pathophysiology of local-regional failures has not been clearly explained. These fail-

Table 1. Patients with colorectal cancer at high risk to develop local-regional and peritoneal metastasis

1.	Visible evidence of peritoneal metastases
2.	Ovarian cysts showing adenocarcinoma suggested to be of gastrointestinal origin
3.	Perforated cancer
4.	Positive cytology either before or after cancer resection
5.	Positive lateral margins of resection
6.	Adjacent organ involvement or cancer induced fistula
7.	T ₃ mucinous cancer
8.	T ₄ cancer or positive imprint cytology of the primary cancer
9.	Cancer tumor ruptured with the excision
10.	Obstructed cancer

ures are probably the result of cancer emboli that are exfoliated during surgical manipulations. The exfoliated emboli are entrapped into fibrinous exudate during wound healing and in approximately 2-3 years after initial surgery give rise to local-regional tumors. Progression of the disease onto the peritoneal surfaces is more rapid than progression to liver. Liver recurrence results from the entrance of cancer emboli into the portal circulation [7]. The peritoneal metastatic implants do not respond adequately to systemic chemotherapy and are less amenable to complete surgical resection [8]. Significantly shorter overall survival of patients with peritoneal metastases has been reported [9].

Improved local-regional control and probably reduction of peritoneal carcinomatosis will be possible if HIPEC is integrated in selected high-risk patients. Intraperitoneal chemotherapy is effective in eradicating microscopic tumor in peritoneal malignancy.

Data indicating significant benefit for local-regional and peritoneal metastases with perioperative intraperitoneal chemotherapy

Gastric cancer

The first publication in 1988 concerning the use of HIPEC in gastric cancer reported a significant survival benefit although the study was considered to be underpowered [10]. A second publication in 1994 confirmed the same results by adding that HIPEC was more beneficial compared to EPIC and surgery alone [11]. The same year another controlled randomized trial did not prove any benefit in survival but showed that the rate of peritoneal carcinomatosis was significantly less in the HIPEC group [12]. One year later another publication showed that patients with

gastric cancer and infiltrated serosa undergoing gastrectomy and HIPEC had significantly better survival than patients undergoing gastrectomy alone [13]. In 1999 another publication showed that long-term survival was significantly better in patients undergoing gastrectomy and HIPEC compared to patients undergoing gastrectomy alone [14]. The same favorable results were shown in another controlled randomized trial in which EPIC was used [15]. Later, several meta-analyses showed that the use of perioperative intraperitoneal chemotherapy offered significant benefit in overall survival and in decrease of local-regional recurrences [16,17].

Colorectal cancer

Clinical findings in the subgroup of patients with colorectal cancer at high risk to develop local-regional or peritoneal metastases indicate the need for further treatment besides surgical resection and systemic chemotherapy. The patients at high risk for local-regional or peritoneal metastases are listed in Table 1 [18].

Intraperitoneal chemotherapy integrated in surgical tumor resection has been proposed by Sugarbaker to control the local-regional failures or the development of peritoneal carcinomatosis in colorectal cancer patients. Phase I/II studies showed a marked pharmacokinetic advantage of intraperitoneal chemotherapy with disseminated cancer cells as the targets of this treatment strategy [19]. Noura et al. showed that colon cancer patients with positive peritoneal cytology were offered significant survival benefit and peritoneal recurrence free survival undergoing intraperitoneal chemotherapy with Mit-C [20].

In a prospective study patients with locally advanced colorectal tumors (T₃,T₄) undergoing resection in combination with HIPEC were shown to develop significantly less recurrences than pa-

tients that underwent resection only. In addition, it was shown that patients that underwent surgery in combination with HIPEC did not develop any local-regional recurrence [21].

In another prospective randomized trial in colon cancer patients it was shown that the disease-free survival in patients with T₃, T₄ tumors, mucinous histology, or signet-ring cell histology that underwent resection in combination with HIPEC was significantly better compared to the disease-free survival of those patients that underwent resection alone [22].

Pancreatic cancer

Patients with pancreatic cancer have an unfavorable prognosis even though R₀ resection is possible. The overall 5-year survival rate does not exceed 15% [23]. The sites of recurrence after potentially curative resection are the liver in 50-60%, the peritoneal surfaces in 40-50%, and the bed of resection in 50% of the cases [24]. Gemcitabine in high-risk patients undergoing potentially curative resection has been proved very effective

given as systemic adjuvant chemotherapy [25]. However, systemic chemotherapy has not been confirmed to be helpful in the control of the local disease. In contrast, both laboratory and clinical studies have shown that the intraperitoneal use of gemcitabine effectively controls the local disease [26].

The preliminary results of the intraperitoneal use of gemcitabine have shown effective control of the local disease in a prospective clinical trial. There was no local-regional recurrence after potentially curative resection of pancreatic cancer when gemcitabine was used as adjuvant treatment. In the same study it was shown that the overall 5-year survival rate was 23% [27].

Conclusions

These data show that patients with locally advanced tumors of the gastrointestinal tract may be offered significant benefit with aggressive surgery in combination with HIPEC. Further studies with larger numbers of included patients are required to document these optimistic findings.

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