

# Is intraperitoneal chemotherapy beneficial in pancreatic cancer?

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## ABSTRACT

*The role of intraperitoneal chemotherapy has been widely investigated in locally advanced malignancies which serosal involvement as well as in cases in which disseminated peritoneal nodules are present. However, its benefits have been widely contested by the higher rates of perioperative complications and therefore, the guidelines did not include it as part of standard therapy. Meanwhile, the better control of the intraperitoneal spread which has been demonstrated in certain cases enabled surgeons to propose performing intraperitoneal chemotherapy in particularly aggressive malignancies such as pancreatic cancer. The aim of the current paper is to discuss about the efficacy and the preliminary results of intraperitoneal chemotherapy in pancreatic cancer.*

**Keywords:** pancreatic cancer, intraperitoneal chemotherapy, local control, survival

## INTRODUCTION

Pancreatic cancer remains the most aggressive malignancy affecting patients worldwide which is associated with poor rates of survival especially in cases diagnosed in advanced stages of the disease; therefore, in such cases the five years survival rate is lesser than 5% [1]; this fact is particularly worrisome due to the fact that most cases remain asymptomatic for a long period of time, being therefore diagnosed in advanced stages

of the disease when local invasion of vascular structures or distant metastases are already present [2]. While in cases in which vascular invasion is present large studies came to demonstrate that radical resection might provide an efficient local control of the disease, the long-term survival rates of such patients being similar to those reported in cases submitted to standard pancreatoduodenectomy [3-5], patients presenting disseminated lesions are rather candidates for systemic, palliative therapy. Even if an aggressive chem-

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otherapeutic treatment is performed, metastatic pancreatic cancer patients usually present extremely poor rates of long-term survival, only few cases surpassing 12 months from the initial diagnostic [6]. In this respect, attention was focused on identifying other therapeutic strategies which might improve the long-term outcomes in such cases. Meanwhile, these therapies were further analyzed in the setting of locally advanced pancreatic cancer after radical surgery in order to achieve a better local control of the disease. The aim of the current paper is to review the possible benefits of intraperitoneal chemotherapy (HIPEC) in the field of pancreatic cancer.

## THE CONCEPT OF HIPEC

The concept of HIPEC has been widely studied in patients diagnosed with advanced stage malignancies presenting serosal involvement of the abdominal primaries, positive peritoneal fluid or even peritoneal carcinomatosis. The method consists of introducing intraperitoneal heated chemotherapeutic agents and maintain them inside the peritoneal cavity, at a constant temperature of 41-43° for 30-60 minutes; the duration of the process as well as the temperature differ accordingly to the type of the chosen therapeutical agent [7-10]. However, depending on the type of associated surgical procedure, of the biological parameters of the patient and of the cytotoxicity of the administrated chemotherapeutic agent, the rates of success as well as the rates of perioperative morbidity and mortality significantly differ [8-10].

## THE RATIONALE OF USING HIPEC IN ADVANCED STAGE PANCREATIC CANCER

Cytoreductive surgery following by HIPEC has been proposed as part of the therapeutic strategy in patients with resectable pancreatic cancer presenting positive peritoneal fluid cytology or limited peritoneal disease. Therefore, cases presenting pancreatic head adenocarcinoma with no visible peritoneal metastases have been proposed for prophylactic HIPEC, cases presenting limited peritoneal lesions have been proposed for debulking surgery to no residual disease followed by HIPEC while cases presenting locally advanced tumors have been proposed for neoadjuvant intraperitoneal chemotherapy [11-13]. When it comes to the most frequently proposed chemotherapeutic agents, there were represented by gemcitabine, cisplatin and mitomycin C [12].

An interesting review conducted on this issue has been recently published in 2021 in *Clinical and Experimental Metastasis*. The authors reviewed eight studies and 85 patients which were included in one of the

above mentioned situations (prophylactic HIPEC, HIPEC after debulking for pancreatic carcinoma with limited peritoneal lesions and neoadjuvant intraperitoneal chemotherapy). Among the 37 patients diagnosed with peritoneal carcinomatosis from pancreatic cancer the peritoneal cancer index ranged from 2 to 23, complete debulking surgery being achieved in 28 out of the 37 cases. When it comes to the most commonly preferred cytotoxic agents, they were represented by gemcitabine, mitomycin and cisplatin. As for the rates of perioperative complications, they were reported in 37,8% of cases while the perioperative mortality was null. Meanwhile the authors demonstrated a median overall survival rate ranging between 4 and 62 months; as expected the most significant factor influencing the long-term outcomes was represented by the completeness of cytoreduction. Moreover, certain patients were also submitted to intraoperative radiotherapy with promising results but the follow up period was rather short in order to establish a preliminary conclusion. When it comes to patients submitted to prophylactic HIPEC, the authors identified 33 such cases, the postoperative morbidity rate being of 24%; the median 5 year overall survival rate was of 24%. As for the last group, it included 33 patients submitted to neoadjuvant intraperitoneal chemotherapy in association with neoadjuvant systemic chemotherapy, the main administered substances being represented by paclitaxel and S-1 for 14 consecutive days; by using this protocol eight patients were converted into resectable disease, the median overall survival was 27,8 months, significantly higher when compared to 14,2 months in cases in which no conversion therapy was performed [14].

## FACTORS INFLUENCING THE LONG TERM OUTCOMES AFTER HIPEC IN PANCREATIC CANCER

As expected, the most important prognostic factors which influence the long-term survival after such procedures are related to the extent of the intraperitoneal disease, to the absence of the extraperitoneal disease, to the completeness of cytoreduction and to the biology of the tumor [15-17]. Accordingly to the above presented data, significant benefit in terms of survival has been reported so far in cases submitted to curative surgery in association with concomitant or neoadjuvant intraperitoneal chemotherapy. These data are impressive especially when comparing them to those reported after oncological systemic therapy, in which the overall survival rarely surpasses 12 months. However, we should not omit the fact that patients submitted so far to this combined approach consisting of intraperitoneal chemotherapy and radical surgery are in fact highly selected cases, in which a lower tumoral burden, absence

of extraperitoneal disease and a good general status were presented. In this respect, we cannot draw evident conclusions, larger prospective and randomized studies being still needed.

## CONCLUSIONS

Intraperitoneal chemotherapy has been recently proposed as part of the therapeutic armamentarium for advanced stage pancreatic cancer with three differ-

ent purposes: with prophylactic purpose after radical surgery, in cases in which no evident metastatic lesions are present, with curative purpose in cases presenting a low peritoneal carcinomatosis index and with neoadjuvant purpose in order to convert unresectable lesions to resectable disease. The method, although is associated with a certain degree of perioperative complications, seems to offer a good control of the disease, especially in highly selected cases in which limited tumoral burden is present.

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