Pressurized intraperitoneal aerosol chemotherapy in nonresectable carcinomatosis from colorectal cancer

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Abstract

Peritoneal carcinomatosis colorectal cancer unfortunately represents a frequently encountered condition during the natural history of this malignancy which has been considered for a long period of time as a terminal event. However, once new surgical and oncological therapies have been reported significant changes have been reported in the management of these cases. Therefore, cytoreductive surgery to no residual disease as a stand-alone procedure or in association with intraperitoneal hyperthermic chemotherapy has been proposed and significant benefits in terms of survival have been reported; unfortunately not all patients with peritoneal carcinomatosis are candidates for this combined approach, especially if extended, non-resectable lesions are present. In such cases pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been proposed with promising results. The aim of the current paper is to review the most important studies conducted on this issue.

Keywords: PIPAC, peritoneal carcinomatosis, morbidity, survival

INTRODUCTION

Colorectal cancer represents one of the most commonly encountered malignancies worldwide and, in the meantime an important cause of cancer related death (1). Although rectal cancer usually leads to the apparition of alarming signs such as constipation, rectal bleeding, abdominal pain and modifications of the aspect of the stool, a significant number of patients ignore these signs and are submitted to colonoscopy only late during the course of the disease (2-4); therefore, the final diagnosis is established lately during the course of the disease, when local invasion of the surrounding organs or distant metastases are already present. When it comes to the ways of dissemination, the most commonly encountered routes are represented by the peritoneal and hematogenous ones, leading to the apparition of peritoneal nodules and parenchymatous metastases respectively (5-8). While the development of parenchymatous, lesions is considered as the sign of systemic spread of the disease, the apparition of peritoneal lesions is rather considered as the...
sign of local spread of the malignant cells via the peri-
toneal route, facilitated by the presence of small 
amounts of free peritoneal liquid (9,10).

**THERAPEUTIC STRATEGIES IN PATIENTS 
WITH PERITONEAL CARCINOMATOSIS 
FROM COLORECTAL CANCER**

Once the above mentioned theory has been widely 
approved, patients presenting peritoneal carcinomato-
sis have been considered lately as cases with locally 
disseminated disease and were therefore submitted to 
surgery with curative intent (11). The most efficient 
such therapeutic strategy is represented by cytoreduc-
tive surgery to no residual disease in association with 
intraperitoneal heated chemotherapy (12-14). The 
method proved to be an efficient one and the results in 
terms of survival demonstrated a significant benefit; 
therefore, it became widely accepted. However, the 
most important condition in order to maximize the ef-
fects in terms of survival is represented by achieving a 
complete cytoreductive surgery, desiderate which 
might be difficult to be obtained especially when dis-
seminated and extended peritoneal lesions are pres-
ent. In order to diminish the number of cases in which 
this method is not feasible and to minimize the effects 
of systemic therapies, attention was focused on identi-
fying other therapeutic strategies which might provide 
a direct administration of the chemotherapeutic agent. 
Therefore, direct introduction of the cytostatic agent 
into the peritoneal cavity is expected to maximize the 
local effect of drug and to minimize the level of system-
ic adverse effects. Meanwhile, certain authors pro-
posed the administration of pressurized agents in or-
der to increase the rate of local absorption and the 
bioavailability (15-17).

**THE PRINCIPLES OF PRESSURIZED 
INTRAPERITONEAL AEROSOL 
CHEMOTHERAPY (PIPAC)**

PIPAC represents a laparoscopic controlled proce-
dure of intraperitoneal administration of low dose cy-
tostatic agent as an aerosol which combines multiple 
advantages: therefore local instillation of pressurized 
chemotherapeutic agents provides low systemic ab-
sorption, low systemic toxicity, homogenous intraperi-
toneal distribution and more appropriate tissue pene-
tration when compared to standard intravenous 
chemotherapy (18-20).

The method has been initially investigated in the 
setting of unresectable peritoneal carcinomatosis from 
different origins, the type of the administered cytotoxic 
agent depending on the origin of the peritoneal le-
sions. Due to the relatively low number of cases sub-
mitted to this therapeutic strategy, specific analysis 
according to the type of tumor and to the type of cyto-
toxic agent were initially impossible to be performed 
(21-24). Therefore at that moment it was very difficult 

to establish which cases could benefit most from this 
therapeutic strategy.

**THE EFFECT OF PIPAC ON UNRESECTABLE 
PERITONEAL CARCINOMATOSIS FROM 
COLORECTAL CANCER**

The first studies which aimed to investigate the role 
of PIPAC in treating unresectable peritoneal meta-
estases from colorectal cancer were conducted by Teixeira 
and Demtröder on 20 patients and respectively 17 pa-
ients submitted to oxaliplatin based PIPAC for unre-
sectable peritoneal metastases from colorectal cancer. 
In the first group the total number of performed proce-
dures was of 37 while in the second group 48 proce-
dures were performed. Both studies demonstrated 
into a retrospective manner that this procedure is asso-
ciated with low morbidity rates due to a low systemic 
toxicity and to improved rates of cytoreductive surgery; 
however, the exact percent of cases in which the proce-
dure was effective was difficult to be established as 
long as in certain cases the intraperitoneal route of ad-
ministration was associated with intravenous systemic 
chemotherapy (25,26). However other studies came to 
demonstrate that performing such therapies might in-
duce a significant degree of local inflammation, making 
more difficult a future cytoreductive procedure (27).

An interesting study which has been recently pub-
lished on this issue was conducted by Gockel et al. and 
cluded 13 patients with unresectable carcinomatosis 
from intestinal origin who were submitted to 26 PIPAC 
procedures between 2015 and 2018. The median peri-
toneal cancer index before the first procedure was 14 
while the median volume of free intraperitoneal fluid 
was of 10 l; among the 13 cases there were six patients 
who received at least two procedures of PIPAC and re-
ported significant decrease of the ascites volume, while 
the increase of the amount of ascites was reported in a 
single case. Meanwhile, peritoneal biopsies which 
were retrieved during each PIPAC procedure demon-
strated the decrease of the number of tumoral cells in 
seven cases, a constant number of malignant cells in 
five cases while in three cases no respond was ob-
erved, increased number of malignant cells being re-
ported after 2 PIPAC procedures. Meanwhile the au-
thors demonstrated a strong correlation ship between 
the number of tumoral cells and the amount of free 
asites. When it comes to the postoperative outcomes, 
no severe complications were reported; therefore, 
one of the cases developed systemic renal or hepatic
toxicity; meanwhile transient modifications of the circulating levels of leukocytes and C reactive protein have been reported. As for the long term outcomes, the authors reported an overall survival of 303 days (28).

THEROLEOFREPEPETITIVED & ELECTROSTATIC PIPAC

In order to maximize the effect of PIPAC, recent studies proposed a new technique for PIPAC (29,30). Electrostatic precipitation of the aerosols during PIPAC represents a novel therapeutic strategy which aims to increase the amounts of the cytotoxic agent at peritoneal level and to increase in the meantime tissue penetration of the drug (29). However, at the present moment data published so far underlined the fact that the procedure is associated with a significant deterioration of the quality of life especially within the first week after the administration of the cytotoxic agent, the systemic absorption of the drug being considerably higher than initially expected (30). Therefore the method is still under evaluation.

CONCLUSIONS

PIPAC represents a novel therapeutic strategy which has been tested in the last years in cases with unresectable peritoneal metastases from different primaries including colorectal cancer in order to offer a more efficient palliative effect and even to convert the lesions from unresectable to resectable and therefore to maximize the possibility of performing complete cytoreductive surgery. The method is associated with lower rates of systemic toxicity due to the low rates of systemic absorption; however, in the meantime it can induce local modifications such as severe intraperitoneal inflammation leading in this way to a more difficult surgical procedure whenever cytoreduction is tempted. However, larger, prospective studies are still needed in order to identify which cases could benefit most from this novel therapeutic strategy.

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