Is cholecystectomy and removal of the round ligament of the liver a necessary step in cytoreductive surgery and HIPEC, for peritoneal carcinomatosis?



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Evgenia Halkia*/**, Nikos Kopanakis*/**, Christos Valavanis°, George Nikolaou*, Andreas Zouridis*, Evangelos Vafias*, Anastasios Datsis°°, John Spiliotis*/**

*Department of Surgery, Metaxa Cancer Hospital, Piraeus, Piraeus, Greece **Hellenic Society of Peritoneal Surface Malignancy, Piraeus, Greece °Department of Anatomic pathology, Metaxa Cancer Hospital, Piraeus Greece °°Department of Surgery, Chatzikosta Hospital of Messolongi, Greece

Is cholecystectomy and removal of the round ligament of the liver a necessary step in cytoreductive surgery and HIPEC, for peritoneal carcinomatosis?

AIM: To determine if cholecystectomy and liver's round ligament removal is a necessary step during cytoreductive surgery (CRS) and HIPEC

METHODS: This was a retrospective observational study based on records from 180 patients treated in our center from 2005 to 2014. All patients have been offered CRS and HIPEC for peritoneal pseudomixoma (20 patients), peritoneal mesothelioma (7 patients), peritoneal carcinomatosis from ovarian cancer (66 patients), colorectal cancer (42 patients), gastric cancer (10 patients), mucinous adenocarcinoma of the appendix (28), and other abdominal malignancies (7 patients). We performed a cholecystectomy and we removed the round ligament of the liver in all patients, even if there wasn't a macroscopic tumor infiltration of the above anatomical structures. We reviewed the histological reports of all 180 patients.

RESULTS: Patients with peritoneal carcino matosis from mucinous adenocarcinoma of the appendix were treated more aggressively, due to the macroscopic appearance of the disease. Histologic report show no evidence of metastases at the round ligament of the liver in 21, 4% of the patients that were treated with CRS although it was estimated to be involved based on the macroscopic examination at the time of surgery. Tumor involvement of the gallbladder was overestimated, macroscopically, at the same patients in 25% of the cases. In patients with peritoneal carcinomatosis from ovarian cancer, macroscopic appearance of the gallbladder may be delusive. In 25% of the above patients there was a microscopic tumor involvement of the gallbladder, although there was not macroscopic evidence of the disease.

CONCLUSION: More extended cytoreductive surgery is needed in case of peritoneal carcinimatosis from ovarian cancer. In case of PC from mucinous adenocarcinoma of the appendix, it's difficult to calculate the extent of the disease and avoid unnecessary surgical excisions. More data is needed to confirm the above.

KEY WORDS: Cytoreductive surgery, Gallbladder, HIPEC, Peritoneal carcinomatosis, Round ligament of the liver

Introduction

Peritoneal carcinomatosis (PC) is a heterogeneous form of cancer that is generally regarded as a terminal stage. It is associated with a poor prognosis, and, once it is diagnosed, survival is generally less than 6 months ^{1,2}. Peritoneal Carcinomatosis (PC), can originate from the peritoneum membrane itself or more frequently is a direct extension of cancer originating from abdominal organs to the peritoneum.

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Correspondence to: Nikolaos Kopanakis, Department of Surgery, Metaxa Cancer Hospital, Piraeus, Botassi 51, 18537 Piraeus, Greece (e-mail: nikopanakis@gmail.com)

Tumours that originate from the peritoneum include mesothelioma and primary peritoneal serous carcinoma³. In the vast majority of PC, the primary origins of peritoneal implants are from malignancies of intra-abdominal organs including: appendix, colon, rectum, stomach, and ovaries ⁴.

For a long time PC was classified as a non-surgical advanced stage of the cancer disease process because of the wide territory of the peritoneum membrane and the frequent extension of the disease to multiple intraabdominal organ. Any attempt for complete surgical debulking, through a long complex surgery was aborted as per the high risk of such approach with limited benefits. Similarly, systemic intravenous chemotherapy had a little peritoneal penetration and effect on the peritoneal tumors, as the peritoneum membrane anatomically constitutes a compartment separate from the vascular compartment ⁵.

Over the last decade, with the advancements in surgical techniques, equipment, and postoperative care, cytoreductive surgery (CRS) has become a viable option for the treatment of PC 5. Furthermore a change in route of drug administration has occurred: Chemotherapy is given intraperitoneally, or by combined intraperitoneal (ip) and intravenous (iv) routes. The development of the intraperitoneal route of heated chemotherapy administration (HIPEC) allows for direct contact between the tumour cells and the chemotherapeutic agent to control all residual microscopic disease. In order to achieve maximum benefit meticulous cytoreductive surgery is necessary prior to the ip chemotherapy instillation. Aggressive treatment strategies for large-volume invasive carcinomatosis will not produce long-term benefits and are often the cause of excessive morbidity or mortality ⁶. IP chemotherapy gives high response rates within the abdomen because the peritoneal-plasma barrier provides dose-intensive therapy7

Currently, there are about 20 centers in USA performing CRS-HIPEC and 70 in Europe. Our center is performing CRS-HIPEC since 2005.

Patients and Methods

Our department is a national referral center for the CRS and HIPEC procedures. In the last 9 years (2005-2014), 180 patients underwent CRS and HIPEC for PC originating from peritoneal pseudomixoma, ovarian, colorectal or gastric cancer, peritoneal mesothelioma, mucinous adenocarcinoma of the appendix and few cases of other carcinomas. Patient's demographics can be found in Table I. Preoperative assessment included physical examination and CT scans of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) scan was performed to assess the extent of disease if necessary.

Treatment decisions were finalized in multidisciplinary team meetings, attended by surgical oncologists, medical

TABLE I - Patients characteristics

Ν	
Gender	
Male	61
Female	119
Age	21-77
Location of primary tumor	
Pseudomixoma	20
Ovarian	66
Colorectal	42
Gastric	10
Mesothelioma	7
Apendix	28
Various	7

oncologists, radiation oncologists, anaesthesiologists, cancer care nurses, and research staff.

All procedures were performed by a specialized surgical team, led by the same surgeon. The extent of disease was assessed with the use of the peritoneal cancer index (PCI) ⁸. All patients were offered a cholecystectomy and the hepatic round ligament removal, even if there wasn't a macroscopic tumor involvement of the above. Completeness of cytoreduction was assessed with the use of (CC) score ⁹. In cases of massive tumor extent or unresectable disease at time of scheduled CRS and HIPEC, standard palliative surgery was performed, including resection or bypass of small bowel/colon/rectum and tumor debulking.

After cytoreduction, HIPEC was performed, with the open or closed abdomen technique, for 45 to 90 minutes using drug protocols as we have already described ¹⁰.

Histology reports were collected and confronted with the intraoperative macroscopic image of the gallbladder and hepatic round ligament.

Results

Between 2005 and 2014, 180 CRS and HIPEC procedures were performed. Mortality rate was 5/180 (2.3%) and morbidity was 87/180 (48.3%). In most cases, the primary tumor was at the ovaries (66patients), colon (42 patients) and appendix (28 patients). In all patients the hepatic round ligament and the gallbladder was removed. Histology revealed that the hepatic round ligament was infiltrated by tumor in 94 patients (52.2%) and the gallbladder was infiltrated in 53 patients (29, 4%) (Table II). Retrospectively, we confronted the data from the histologic reports with the macroscopic evaluation we did during surgery, regarding tumor infiltration of the hepatic round ligament and the gallbladder (Table III).

Interestingly, we noticed that in case of peritoneal carcinomatosis from ovarian cancer, it's difficult to evaluate if the hepatic round ligament and its peritoneum, is infiltrated by the tumor. Indeed, in 16.6% of our patients, the histologic

TABLE II - Histologic reports

Cause of Peritoneal carcinomatosis	Patients with round ligament of the liver infiltration/total	Patients with gallbladder infiltration/total
Peritoneal pseudomixoma	16/20 (80%)	7/20 (35%)
Ovarian Cancer	32/66 (48. 4%)	10/66 (15.1%)
Colorectal Cancer	21/42 (50%)	16/42 (38%)
Peritoneal mesothelioma	3/7 (42.8%)	1/7 (14.2%)
Gastric Cancer	2/10 (20%)	6/10 (60%)
Mucinous adenocarcinoma of the appendix	18/28 (64.2%)	12/28 (42.8%)
Various	2/7 (28.5%)	1/7 (14.2%)
TOTAL	94/180 (52, 2%)	53/180 (29, 4%)

TABLE III - Macroscopic evaluation versus Histologic confirmation of tumor infiltration

Cause of Peritoneal carcinomatosis	Hepatic round ligament Infiltration Macroscopic evaluation-Histologic confirmation/total (%)	Gallbladder Infiltration Macroscopic evaluation-Histologic confirmation/total(%)
Peritoneal pseudomixoma	14-16/20	5-7/20
Ovarian Cancer	21-32/66 (16.6%)	7-10/66
Colorectal Cancer	16-21/42	14-16/42
Peritoneal mesothelioma	3-3/7	1-1/7
Gastric Cancer	2-2/10	5-6/10
Mucinous adenocarcinoma of the appendix	24-18/28 (21.4%)	19-12/28 (25%)
Various	1-2/7	1-1/7

report was positive for tumor cells infiltration, even if that was not macroscopically visible during surgery.

From the other hand, tumor spread in case of PC from mucinous adenocarcinoma of the appendix, is over-estimated, macroscopically, during surgery. In our patients, 21.4% of the histologic reports of the hepatic round ligament and 25% of the gallbladder were negative though it was expected to be infiltrated, based on the macroscopic evaluation.

To our knowledge, this is the first publication on this aspect of peritoneal carcinomatosis.

Discussion

Peritoneal Carcinomatosis (PC), is the presence of cancer cells on the surface of the peritoneum, and can originate from the peritoneum membrane itself or more frequently is a direct extension of cancer originating from abdominal organs to the peritoneum ³. Up to the turn of the century, the prognosis for patients with peritoneal carcinomatosis was considered to be hopeless. Series reporting the natural history of peritoneal tumors showed poor prognosis despite the best systemic therapy ^{11,12}. For a long time PC was classified as a non-surgical advanced stage of the cancer disease process because of the wide territory of the peritoneum membrane and the frequent extension of the disease to multiple intra-abdominal organ.

Over the last ten years, there has been a paradigm shift in the treatment of PC. With advancements in surgical techniques, equipment, and postoperative care, cytoreductive surgery has become a viable option for the treatment of PC⁵. It's important though to select the patients that will benefit from this procedure. Preoperative clinical staging of peritoneal carcinomatosis with computed tomography (CT) for predicting the stage is limited.

At present, the most reliable method of defining the extent of the disease is intraoperative staging using the Peritoneal Cancer Index ¹³. Lesion score is from 0 to 3, and it's based on the macroscopic evaluation of the peritoneum and the abdominal organs.

The cytoreduction operation consists of peritonectomy (parietal and visceral) of areas affected by tumor, omentectomy (greater and lesser omentum), and interventions/ resections in the stomach, spleen, small bowel, colorectum, liver, and urogenital tract ¹⁴. The gallbladder and hepatic round ligament can be removed also if there is tumor involvement.

When patients have undergone several operations, cytoreduction maybe a challenging act.

As a major operation that may involve resection of multiple abdominal organs, CRS-HIPEC as expected, carries a considerable postoperative morbidity of 12-56% and a mortality of 0-12% 15 . It seems that the lack of pain, caused by the absence of peritoneum, has a great role in the development of complications. We tried to evaluate, if macroscopic observation of tumor involvement of abdominal organs, in case of PC, correspond to histopathological findings, in order to avoid unnecessary organ resections. We removed the hepatic round ligament and performed a cholecystectomy in all our patients even if there was not a macroscopic evidence of tumor infiltration of the above organs.

We confronted retrospectively, all histopathologic reports with our observations made in time of surgery. In case of peritoneal carcinomatosis from ovarian cancer, macroscopic evaluation of tumor dissemination seems to underestimate the real extent of the disease. In fact in 16.6% of our patients we found histopathological tumor infiltration of the hepatic round ligament, while there was no sign of the disease macroscopically. Interestingly, in case of PC from mucinous adenocarcinoma of the appendix, macroscopic evaluation overestimates the extent of the disease. We found no sign of tumor infiltration in the gallbladder in 25% of our patients and in the hepatic round ligament in 21.4% of our patients. The reason is maybe, the nature of the disease. It's difficult to evaluate the real extent of the disease, because of the mucous that is found in large amounts in the peritoneal cavity.

Conclusion

More extended cytoreductive surgery is needed in case of peritoneal carcinimatosis from ovarian cancer. In case of PC from mucinous adenocarcinoma of the appendix, it's difficult to calculate the extent of the disease and avoid unnecessary surgical excisions. More data is needed to confirm the above.

Riassunto

La chemioterapia intraperitoneale ipertermica associata ad una chirurgia aggressiva vienne utilizzata nella terapia delle carcinosi peritoneali. Nel nostro studio abbiamo incluso i 180 pazienti operati nel nostro centro ed abbiamo confrontato le risposte istopatologiche, con l'aspetto macroscopico intraoperatorio della cistifellea e del legamento rotondo del fegato, cercando di verificare la necessita della loro asportazione in ogni intervento di citoriduzione per carcinosi peritoneale. In caso di carcinosi peritoneale da carcinoma delle ovaie, bisogna essere piu aggressivi nell'intervento di citoriduzione. Nel caso della carcinosi peritoneale dall'adenocarcinoma mucinoso dell'appendice e difficile calcolare l'estensione della malattia.

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