

Hyperthermic intraperitoneal chemotherapy as palliative treatment for malignant ascites

A single-center experience and a review of the literature



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Malignant ascites is an abnormal accumulation of fluid in the peritoneal cavity of patients with intraperitoneal cancer dissemination. This clinical condition could represent the terminal evolution of a lethal disease and could influence the prognosis, severely impairing the patients' quality of life.

Treatment options include a multitude of different procedures with limited efficacy and some degree of risk; diuretics, paracentesis, peritoneo-venous shunts and intraperitoneal biologic agents like anti-VEGF molecules, metalloproteinase inhibitors and immunomodulators are included.

None of these approaches have been established as a standard of care because of their low efficacy or severe side effects. The last two decades saw the emergence of cytoreductive surgery with hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) as a viable therapeutic approach resulting in an effective cure against refractory malignant ascites. The following describes our experiences with 3 cases together with a literature review.

KEY WORDS: Chemotherapy, HIPEC, Laparoscopy, Malignant ascites

Introduction

Recently, Intraperitoneal Hyperthermic Chemotherapy (HIPEC) has been used as a promising therapeutic approach to control or to palliate the development of malignant ascites (MA) associated with peritoneal carcinomatosis although tumor reduction is unachievable. Investigators in both eastern and western countries have

continued to study potential treatment options for cancer patients with limited carcinomatosis encouraged by the results of cytoreductive surgery (CRS) and HIPEC for carcinomatosis of appendiceal and colorectal origin and showed that a small but meaningful number of patients can achieve long term survival^{1,2}.

Refractory MA is a debilitating condition affecting patients in their terminal stages of neoplastic disease and HIPEC seems to control this condition in more than 90% of patients.

Most gastrointestinal and gynecological tumors (ovarian, endometrial, colorectal, gastric, pancreatic cancer) and primitive peritoneal malignancy are often associated with MA; up to 15% of all patients with gastrointestinal cancers develop ascites at some stage of their disease³. In patients with peritoneal surface disease (PSD), MA is associated with a short life expectancy, ranging from weeks to a few months⁴.

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TABLE I - Patient's characteristics: intraoperative , postoperative results.

Patient	Sex	Age	Operation time (min)	Postoperative complication	Hospital stay(days)	Survival (months)
1	F	49	120	None	7	12
2	F	61	90	None	7	16
3	M	59	90	None	6	6

In addition to abdominal tumors originating by MA are breast cancer, lung cancer and pleural mesothelioma. The pathogenesis of malignant peritoneal effusion is a complex and multifactorial process; it involves both production and re-absorption of intraperitoneal peritoneal fluid. MA shows a variety of symptoms increasing patients' discomfort that could benefit from several treatments to improve their quality of life. The benefits of limited tumor resection combined with HIPEC for a palliation of the debilitating ascites have been extensively reviewed⁵. If cytoreduction is not feasible and MA is still well represented, laparoscopic HIPEC is a promising procedure that could be used as an effective approach in order to control peritoneal effusion and not increasing the tumor. The following describes our experiences with 3 cases in treating MA with HIPEC together with a literature review.

Case Introduction

A multidisciplinary team including a surgeon, an oncologist and a radiologist, selected patients that could benefit from laparoscopic HIPEC. Indication to perform HIPEC on these three patients was the need for an effective treatment for abundant debilitating ascites, secondary to peritoneal carcinomatosis from different kinds of tumors. All patients had ascites related symptoms (pain, vomiting, etc) requiring frequent paracentesis resulting in hydro-electrolytic disorders and severe protein depletion. In all 3 cases traditional treatments such as, diuretics and systemic chemotherapy, resulted ineffective. HIPEC procedure was then proposed both to diminish the frequency or to definitively avoid iterative paracentesis and to treat ascites related symptoms. Diagnosis of ascites, related to unresectable carcinomatosis, was made preoperatively in all 3 cases by standard clinical and radiological assessments (cytology, CT scan). The use of the laparoscopic approach was proposed in an attempt to diminish the invasiveness of the surgical procedure in patients undergoing HIPEC with a palliative intent. All patients were informed about the palliative role of the procedure.

Indications, risks, possible complications and expected benefits were discussed with the patients. Finally, an informed consent was accepted and signed by all patients. Since 2008 three patients have been treated in our ward

for malignant ascites, 2 women and 1 man with an average age of 56.3 ± 9.1 . Karnofsky performance status (PKS) scale was > 90 % before the treatment in all the patients (Table I).

Average survival is 11 ± 7.1 months, with one patient still alive after 16 months of treatment.

CASE N. 1

A 49 year old woman came to us due to an invalidating malignant ascites from a peritoneal localization of a right pleural mesothelioma that was diagnosed in July 2003 and treated with decortication and adjuvant chemotherapy with carboplatinum and pemetrexed. Due to a pleural recurrence and the onset of ascites in 2006 the patient started gemcitabine scheme chemotherapy and diuretics. A PET-CT showed the disease had progressed both, in the thorax and in the liver with conspicuous ascites (Fig. 1).

Medical treatment and repeated paracentesis were ineffective in controlling abdominal distension and the consequent dyspnea lead to the patient's hospitalization for acute respiratory distress. After a careful multidisciplinary assessment the patient was given a laparoscopic HIPEC treatment with cisplatin $25 \text{ mg/m}^2/\text{L}$ and doxorubicine $7 \text{ mg/m}^2/\text{L}$. The patient was discharged on postoperative day 7 in good clinical conditions and without any

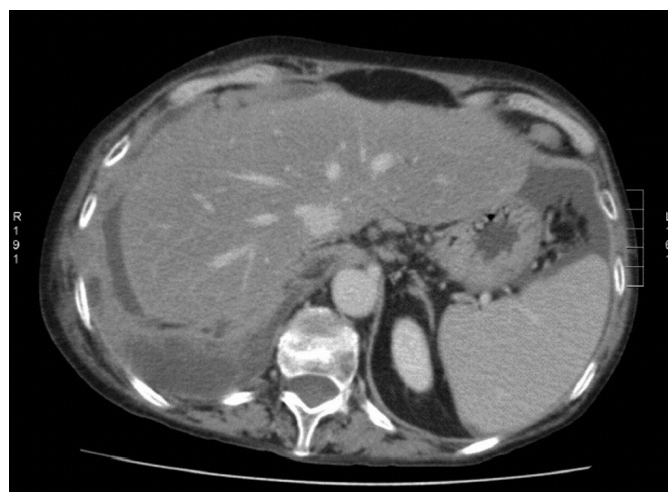


Fig. 1: Case one preoperative PET-CT scan.



Fig. 2: Case one postoperative CT scan.



Fig. 3: Case three preoperative CT scan, abundant ascites is shown.

diuretics therapy. The CT scan after one month confirmed the complete response to the treatment and the overall patients condition allowed the beginning of a third line chemotherapy (Fig. 2).

The patient died twelve months after treatment from a massive pulmonary embolism caused by a deep vein thrombosis.

CASE N. 2

A 61 year old woman came to our ward because of an invalidating malignant ascites from breast cancer diagnosed in 2011. She underwent a right radical mastectomy for a T2N1 tumor followed by chemotherapy. In 2013 she was referred to our surgical department for malignant ascites refractory for all conservative treatments.

The patient underwent laparoscopy that showed peritoneal dissemination in all the abdominal quadrants and in the small intestine, unsuitable for cytoreductive surgery. We performed HIPEC with cisplatin in a singular dose of 75mg/m^2 for 1 hour at the temperature of 40°C .

HIPEC procedure solved the malignant ascites; therefore paracentesis and other medical treatments were not necessary. Patient is alive, in good condition and she's continuing chemotherapy.

CASE N. 3

A 59 year old man came to us, because of an invalidating malignant ascites from a left pleural mesothelioma that was diagnosed in 2011. It had been treated with four cycles of carboplatinum and pemetrexed chemotherapy

until February 2014. The patient was in need of 7 liters of paracentesis every two days.

After a careful multidisciplinary assessment the patient was treated with a laparoscopic HIPEC using cisplatin $25\text{mg/m}^2/\text{L}$ and doxorubicin $15\text{mg/m}^2/\text{L}$. (Fig. 3).

The patient was discharged on postoperative day 6 in good clinical conditions. However he was in need of diuretics therapy in order to control the ascites. After the discharge, on day 30, a paracentesis due to abdominal distension was performed eliminating 2 liters. The CT scan after one month, confirmed the partial response to the treatment and the overall patient's good condition allowed for the beginning of a third line chemotherapy.

After 6 months, the patient died from a spontaneous bacterial peritonitis following a peritoneal catheter insertion.

Surgery Procedure

The surgical procedure was standardized in all three cases. The patients were in a supine position with both the superior and the inferior limbs adducted. Probes for monitoring temperatures were placed in the esophagus and in the axillary region. Pneumoperitoneum was induced by a Hasson trocar placed at the umbilical level and a scope was inserted in order to explore the abdominal cavity. PCI was then assessed. Four 10 mm trocars were introduced, respectively in the hypochondrium and iliac fossa bilaterally, and through them four (32 Fr) drainages were placed. The two input drainages were positioned in the right sub diaphragmatic space and between the intestinal loops. While the two suction drains were positioned in the left sub diaphragmatic space and in the pelvis. Having secured to the skin's sur-

face the drainages, input and output drains were connected to the HIPEC machine's circuit (Performer LTR, Rand, Mirandola, Italy), filled with a solution of 5% dextrose and set to a temperature of 44 °C and at a flow rate of 800 ml/min. (Fig. 4).

The Hasson trocar was removed and the skin was sutured to prevent any leakages. Moreover an intra-abdominal probe monitored the temperature during the procedure. Once the temperature reached 42 °C, chemotherapy drugs were added to the circuit in the following doses: cisplatin 25 mg/m²/L and doxorubicine 7 mg/m²/L. The perfusion was maintained for 60 minutes, at a body temperature between 42 °C and 43 °C, by monitoring continuously the flow of the perfusate and the temperature of the different probes. Esophageal temperature never exceeded 38.5 °C.

At the end of the perfusion the abdominal cavity was washed with 5 liters of saline solution and inspected for any places of bleeding or injury to the organs that could have occurred during the procedure.

Postoperative Course

After the operation, patients were put in the intensive care unit for the first 24 hours and afterward were readmitted to our ward. Patients were orally fed during their second postoperative day. Drainages were removed on the fourth postoperative day.

Malignant Ascites: Patho-Physiology

Peritoneal effusion associated with tumors is correlated to an altered vascular permeability and an obstructed lymphatic drainage ⁶.

Under physiologic conditions, transudation of plasma through the capillary membranes of the peritoneal serosa continuously produces free fluid to lubricate the serous surfaces.

Normally, the fluid balance is influenced by portal pressure, oncotic pressure, sodium–water equilibrium, and vascular channels' permeability to macromolecules and cells.

MA occurs when an altered balance between endothelial capillary permeability and intraperitoneal oncotic pressure happens ⁷.

In addition, an increased angiogenetic process characterizes MA, resulting in hyper permeability of the endothelial membrane and degradation of the basement membrane. When VEGF ⁶ is produced by neoplastic cells, it causes endothelial cells' proliferation and migration, leading to new blood vessels and capillaries' formation.

Other vascular factors, stimulating tumor cell growth and angiogenesis, have been identified in MA and include: Basic Fibroblast Growth Factor (b-FGF), angiogenin, Transforming Growth Factors α and β (TGF) and IL-8.

Cancer cells also produce metallo-proteases (MMP) causing a remodelling of non neoplastic tissue matrices enhancing the process of metastatic spread ^{8,9}.

Matrix metalloprotein inhibitors represent a new therapeutic approach for treatment of disseminated cancer. These inhibitors not only prevent metastatic spread, but they block angiogenesis, prevent local invasion, and enable stromal encapsulation of tumor cells. Increased matrix metalloproteinase activity is detected in a wide variety of cancers and seems to correlate to their invasive metastatic potential and aggressiveness.

The factors, mentioned above, induce plasmin secretion leading to endothelial and mesothelial tight junctions' break down. This allows the albumin transit in the peritoneal cavity and increases the oncotic pressure.

Under physiologic conditions, the presence of tight junctions prevent excessive fluid-filtration from the capillaries to the peritoneum. This maintains an effective barrier against leakage of negatively charged molecules such as albumin from plasma to the peritoneal cavity.

The increased oncotic pressure and, sometimes, the tumor burden can obstruct lymphatic drainage.

Treatment of Malignant Ascites

Currently, treatment of malignant ascites includes salt restriction, diuretics, paracentesis, and the implantation of peritoneovenous shunts.

However, there is objective evidence for the efficiency of each of these treatments, but there are no randomized, controlled trials evaluating their safety and efficacy in malignant ascites. Moreover, results achieved by the application of these conventional methods are variable, providing, only occasionally, prolonged relief from symptoms, but not improving survival.

Now, Laparoscopic Intraperitoneal Hyperthermic Chemotherapy, has become a valid and successful treatment for MA in patients in which cytoreduction is not possible.

INTRAPERITONEAL HYPERTHERMIC CHEMOTHERAPY (HIPEC)

Peritoneal dissemination remains a major problem waiting to be answered. Nor is the answer likely to come from adjuvant systemic chemotherapy alone, that can only be of influence on the extent of dissection. MA seems to be one of the symptoms that could be somehow addressed ¹⁰.

Patients with MA are considered to be in the terminal phase of their disease and the decision to perform a very aggressive treatment, such as surgery and heated chemotherapy, is often unreasonable. Moreover the presence of MA significantly decreases the chances of obtaining a complete R0/R1 macroscopic cytoreduction.

Palliative HIPEC is used in selected cases where CRS is not possible and a survival advantage unlikely will be

obtained from any extensive surgical approach. Laparoscopy and HIPEC, meaning the combination of a non-invasive surgical approach with the latest advanced oncological treatment, has been proposed as a palliative therapy for patients with MA of various origins.

To date, literature reports only a few studies about the use of laparoscopic HIPEC as a palliative approach for MA. Chang et al.¹¹ described two cases of malignant ascites from peritoneal and breast cancer treated with palliative laparoscopic HIPEC in 2001. Patient with MA from peritoneal mesothelioma had a complete resolution of his ascites. Whereas patient with MA from metastatic breast cancer did not achieve palliation from HIPEC. The authors did not observe any kind of complication from this procedure.

Valle et al reported the largest clinical study¹² of 52 patients affected with debilitating and refractory ascites originating from primary gastric, ovarian, breast or peritoneal mesothelioma malignancies who were not candidates for resection due to the high Peritoneal Cancer Index (PCI).

After minimal laparoscopically viscerolysis to optimize contact of chemotherapy with peritoneal surfaces, intraperitoneal chemotherapy was administered via a 10-mm infusion trocar and collected via three 5-mm suctioning drains. Drains were left in place and removed postoperatively.

Cisplatin 50 mg/m² and doxorubicin 15 mg/m² were used for ovarian cancer, peritoneal mesothelioma or breast cancer in equivalent doses in current standard practices for these malignancies after cytoreduction. Colorectal or gastric malignancies were treated with mitomycin C. Intraperitoneal chemotherapies were associated with an average temperature of 42°C. Intraperitoneal Perfusion time was of 90 min.

The intraoperative course was uneventful in all patients. The mean operative time was 147 min (range 133–210 min). No treatment related mortality was observed. Postoperative complications included two minor wound infections and 1 deep venous thrombosis. The mean hospital stay was 2.3 days (range 1–9 days). The authors of the study showed a resolution of ascites in all patients. The mean survival was 29 weeks.

Longest survival was observed in patients with underlying breast lobular carcinoma. The worst survival was observed in gastric carcinoma patients. An important improvement in performance status was observed postoperatively. The Karnofsky index increased with an average 20 points in the postoperative period.

In a second study by Facchiano et al.¹³, laparoscopic HIPEC using mitomycin and cisplatin, achieved successful palliation of symptoms related to malignant ascites from advanced, unresectable gastric cancer, with all 5 patients no longer requiring paracentesis. Intraoperative course was uneventful. A complete response of MA was found in all patients with no morbidity or mortality related to the treatment.

In the past, we¹⁴ reported our experience of MA with metastatic peritoneal mesothelioma of pleural origin in a young female patient.

We successfully treated our patient with laparoscopic HIPEC based on peritoneal instillation of cisplatin 50 mg/m² and Doxorubicin 15 mg/m². There was no further need for medication and the patient survived for 12 months. The final exitus was caused by pulmonary embolism and not because of tumour related causes.

Mestier L. et al.¹⁵ reported two cases of peritoneal carcinomatosis, from cardia adenocarcinoma and ovarian cancer, causing hemorrhagic peritoneal ascites and requiring iterative blood transfusions and paracentesis, treated by laparoscopic HIPEC. He obtained a successful reduction of debilitating ascites and cessation of peritoneal bleeding without postoperative complications.

Minchen B. et al.¹⁶ investigated the efficacy of combined continuous circulatory hyperthermic intraperitoneal chemotherapy (HIPEC) preceded or followed by cytoreductive surgery (CRS) for malignant ascites in 32 patients affected by PC from ovarian cancer.

Median follow-up was 29 months. All patients showed ascites regression (objective remission rates (ORR) = 100 %). Median survival time was 18 months.

Recently Reese W. et al.¹⁷ made an accurate retrospective analysis of a prospectively maintained database of 1,000 HIPEC and cytoreductive surgery procedures. Ascites was found in 299 patients.

Type of malignancy, resolution of ascites, duration and agent of chemo-perfusion, performance status, resection status, morbidity, mortality, and survival were analyzed. The authors demonstrated that CRS-HIPEC procedure was effective in successfully controlling ascites in 93 % of patients even when a complete cytoreduction was not achieved.

Malignant ascites was successfully resolved in the majority of cases regardless of primary tumor, duration and type of chemo-perfusion agent, and ascites score. So the ascites resolution was completely independent of resection status suggesting that it was more likely a function of HIPEC than CRS.

The authors concluded that MA was a strong but poor predictor of decreased feasibility, achieving a complete macroscopic cytoreduction. Ascites score could be a helpful indicator in selecting patients in which CRS-HIPEC is not feasible in terms of survival.

This study supports and enforces that laparoscopic HIPEC is able to control malignant ascites and its symptoms.

However, HIPEC is linked to morbidity and mortality, mostly determined by the extent of cytoreduction and peritoneal resection, the number of digestive anastomoses, the dose of chemotherapy and the operative time¹⁸. In patients with MA, the therapeutic goal is not to increase survival but to palliate symptoms thus an extended resection is not necessary decreasing morbidity related to HIPEC¹⁹.

In addition, laparoscopy is a less invasive surgical approach associated with low perioperative complications. The mechanism by which laparoscopic HIPEC could reduce cancer ascites is double: laparoscopy and high temperature synergistically increase drug absorption²⁰. Drugs used for intra-abdominal chemotherapy are various, depending on the different protocols and types of tumor.

Cisplatin seems to be one of the most effective and used agent in the treatment of ovarian cancers; given intraperitoneally, it is possible to reach high drug doses (about 30 times greater than when given intravenously) with low systemic toxicity and no cross resistance to other chemotherapeutic agents or significant peritoneal irritation.

Some experiences with cisplatin-based IC for MA due to gastric cancer, showed resolution of ascites in 50% of patients²¹.

Other reports showed an almost analogous response rate (47%) in treating MA from peritoneal mesothelioma with a combination of cisplatin and mitomycin delivered intraperitoneally²².

5-FU, alone or in combination with cisplatin, seems to offer the same response rate not exceeding 50%²³. Adriamycin is not commonly used because of its highly corrosive activity on the peritoneal surface²⁴. Other newer treatments currently under investigation to hinder formation of malignant ascites, include the intraperitoneal administration of VEGF inhibitor.

Kobols S et al.²⁵ reviewed current evidence suggesting that the Intraperitoneal (i.p.) application of the anti-VEGF antibody bevacizumab, which is already in use as an i.v. therapeutic drug for a variety of tumors, might represent an effective way to prevent local fluid accumulation²⁶⁻²⁹.

Ströhlein et al.³⁰ applied the trispecific antibody catumaxomab for the treatment of malignant ascites. This CD3 and epithelial cell adhesion molecule-specific antibody (Ep- CAM), is thought to stimulate the T-cell

immune system as well as to induce major histocompatibility complex-unrestricted cytotoxicity and phagocytosis of tumor cells³¹.

Goere D. et al. published a phase II randomized trial to assess the 2y- Overall-Survival in patients with limited peritoneal carcinomatosis treated with cytoreductive surgery and intraperitoneal infusion of catumaxomab at different doses³².

Cohorts of patients suffering from ovarian cancer and gastric cancer have experienced symptom relief after catumaxomab application, and, more recently, a phase II/III trial assessed catumaxomab in the treatment of malignant ascites, with significant results in terms of quality of life³³.

In conclusion, although these datas need to be confirmed in daily clinical practice, catumaxomab might represent a promising new approach for the therapy of malignant effusions.

However, the need for placement of an i.p. catheter for several days and the prolonged hospital admission required for the treatment, might limit its application in patients with end stage cancer who require palliative treatment.

Although our study was limited to the number of patients, we can confirm the successful palliation of MA in patients with a high peritoneal cancer index without post-surgical complications. We achieved a substantial ascites resolution at clinical and instrumental examinations in all three patients treated. All of them showed a regression of related symptoms. This suggests that a laparoscopic approach may be as effective as the traditional open procedure to perform HIPEC for treatment of debilitating malignant ascites. Finally, this resulted in an improved quality of life and in a general improvement of the clinical status related to a resolution of protein level and electrolytes loss.

In one patient, where massive ascites was present prior to the procedure, paracentesis were still needed less fre-

TABLE II - Palliative HIPEC for malignant ascites' state of art (n.r.: not reported)

Studies	Patients number and primitive tumour site	Drugs administered	Operative time (min.)	Hospital stay (days)	Mortality	Morbidity	Ascites resolution (%)	Median survival
Chang et al ⁹ .	2 (peritoneal, breast)	Cisplatin	280	Median 3-8	0	No grade III-IV	50	n.r
Valle et al ¹⁰ .	52 (various)	Cisplatin + Doxorubicin Mitomycin Doxorubicin	147	Mean 2.3	0	2 grade I 1 grade II	94	98 (days)
Facchiano et al. ¹¹	5 (gastric)	Mitomycin + cisplatin	n.r	23	0	1 grade I	100	89 (days)
Graziosi et al. ¹²	1 (pleural)	Cisplatin + Doxorubicin	120	7	0	No	100	6 (months)
Ba et al. ¹⁴	15 (gastric)	5-Fluorouracil + oxaliplatin	80	n.r.	0	1 grade I 3 grade II	100	5 (months)

quently. In fact this patient needed a paracentesis every five days with an evacuation of 7-10 liters before the procedure. After one month of HIPEC, paracentesis was necessary but less frequently, with an evacuation of no more than two liters every time. Abdominal distension was well tolerated by the patient and he could start a third line of chemotherapy until the death.

We recorded a rate of complications of 0% and our results are in accord with those reported in other published series reporting a laparoscopic approach to HIPEC (Table II).

The low rate of complications observed can be explained by analyzing the major factors responsible for the high morbidity and mortality. These are linked to the traditional open HIPEC related to the extension of the cytoreductive surgery.

Therefore, our conclusions are, the feasibility of the procedure, peri-operative morbidity and mortality were 0%; hospital stay after the procedure was acceptable and post-surgical analgesic therapy was limited.

One patient died from pulmonary embolism, 12 months after surgery, during chemotherapy treatment.

Venous thromboembolism (VTE) is a frequent cause of mortality and morbidity among surgical and medical cancer patients. The presence of cancer increases the risk of VTE by 4- and 7-fold for the patient-related risk factors, as well as risk factors related specifically to the cancer disease and cancer treatment. In addition the risk of developing VTE in these patients is strongly dependent on the type of cancer, tumor activity, and extent of the disease. Anticoagulant therapy is recommended for at least 4 weeks after surgery but a subgroup of patients at high risk (patients treated with chemotherapy, with an extensive neoplastic disease or with a history of VTE) could continue anticoagulant for a long time ³⁴.

Finally, we would like to underline the palliative role of this procedure. The treatment of ascites by laparoscopic HIPEC, not associated with cytoreduction, should only be performed when carcinomatosis is assessed either pre-operative or intraoperative, and not resectable. In addition, we treated MA originating from pleuric mesothelioma and breast cancer, where an aggressive surgical approach is contraindicated and HIPEC is only performed with palliative intent.

In selected cases, we think that VLS-HIPEC could be extended by safely and effectively administering to patients with disabling MA.

A future randomized trial could demonstrate a real improvement of Quality of Life with VLS-HIPEC compared to the other medical approaches.

Conclusions

To date there are no validated guidelines for preventing or reducing the production or re-accumulation of malignant ascites arising from different tumors.

Traditional therapies, including paracentesis, peritoneovenous shunt placement and diuretics, are successful and effective in varying degrees.

In patients with peritoneal carcinomatosis who do not qualify for surgical cytoreduction but suffer from the effects of malignant ascites, intraperitoneal chemotherapy can be safely and effectively administered via laparoscopic techniques with the intent to achieve palliative cure.

Short operative times, short hospital stays, low complication rates and, ultimately, symptomatic relief are the advantages of laparoscopically administering heated intraperitoneal chemotherapy, making it not only a valuable treatment modality but also the most successful treatment modality for achieving palliative cure of malignant ascites.

Further investigations into surveying quality of life remain to be formally studied establishing the real benefits of each newer treatment.

Riassunto

L'ascite maligna rappresenta il quadro avanzato di anormale accumulo di liquido intraperitoneale in pazienti con carcinosi peritoneale. Questa condizione clinica può rappresentare la condizione terminale di questa patologia a pessima prognosi inficiando inoltre la qualità di vita dei pazienti.

Le opzioni terapeutiche includono differenti procedure che hanno tuttavia una limitata efficacia e alcune criticità; diuretici, paracentesi, shunt veno-peritoneali, inibitori delle metallo proteasi, immunomodulatori e agenti biologici rappresentano alcuni esempi di queste procedure.

Nessuno di questi approcci terapeutici rappresenta a oggi lo standard of care per questa patologia data la scarsa efficienza e l'alto grado di effetti collaterali.

L'introduzione della chirurgia citoriduttiva e della chemio terapia ipertermica intraperitoneale sembra essere un approccio terapeutico valido nel trattamento dell'ascite maligna refrattaria, introdotto nelle ultime due decadi e che tutt'ora necessita di validazione scientifica.

In questo lavoro condividiamo la nostra esperienza di tre casi affetti da ascite maligna refrattaria trattati con HIPEC; facciamo inoltre una revisione della letteratura.

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