Preliminary results of prophylactic HIPEC in patients with locally advanced gastric cancer

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BACKGROUND: *The prognosis of locally advanced Gastric Cancer following surgical therapy alone is poor. Peritoneum represents a preferential site of dissemination in such neoplasm. Hyperthermic intraperitoneal chemotherapy (HIPEC) has been used in association with cytoreductive surgery (CRS) in the treatment of GC peritoneal carcinomatosis (PC). Aim of our preliminary experience is reporting our data on prophylactic HIPEC (P-HIPEC) in patients with GC at high risk of developing PC.*
METHODS: *Eleven patients underwent P-HIPEC at our General and Emergency Surgery Department. All the patients were affected of high risk GC: serosa invasive tumors (T4), conventional cytology-positive or quantitative PCR detection of CEA mRNA on peritoneal lavage. Seven subtotal and four total gastrectomies with D2 or D2+ were performed. All the anastomoses were made before HIPEC. The procedure was carried out for 60 minutes with Mytomicin C and Cisplatin in all patients. Post-operative monitoring in Intensive Care Unit least for 24-48 hours. Oral nutrition was started precociously (day 5) also according with bowel movements and stool/gas passage. Follow-up took place in all patients at 1 month from surgery then every 6 months for 2 years and every 12 months for the following years.*
RESULTS: *In four patients a neoadjuvant treatment was scheduled due to T or N stage at pre-operative evaluation. Gastric resection was guided on tumor location while the choice of performing a D2 or D2 + lymphadenectomy was up to pre-operative imaging and intra-operative nodal status. No intra-operative complications were recorded. Median operation time was 398 minutes. In our series we recorded 20 adverse events. Median number for each patient was 1 adverse effect (range 0-2). Eight patients experienced a surgical adverse effect (G2-G3) that did not require any surgical treatment. Only one patient with duodenal stump dehiscence and intra-abdominal sepsis (G4-G5) underwent re-operation and died for severe hemorrhagic pancreatitis. Another patient died for ARDS. Per-operative mortality was 18%. Both patients were older then 70 years old. Median hospital stay was 14 days. Median follow-up was 15.9 months. Median survival was 29.6 months and median DFS was 20 months. Only one patient developed a peritoneal recurrence at 12 months and died for disease progression. Seven patients are still alive and disease free at last follow-up. One patient affected of variable immunodeficiency died at 9 months for pulmonary sepsis without any sign of local recurrence.*
CONCLUSIONS: *Peritoneal dissemination appears to be a strong determinant in defining GC patients prognosis. Even after curative resection, peritoneal recurrence develops in about 60% of the patients with T3 and T4 tumors, and up to 40% of resected gastric cancer patients die as a direct result of peritoneal dissemination. Clinical trials showed that surgery plus HIPEC was associated with a significant improvement in survival compared to surgery alone in patients affected of GC with resectable PC. At present day there are not studies evaluating the role of P-HIPEC in patients at high risk of developing PC. The rationale of P-HIPEC is based on the concept that positive peritoneal lavage is considered an M1*

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(stage IV) similarly to macroscopic PC by the 7th TNM classification. Also analogous is the median survival of this 2 groups of patients. Detection of peritoneal micrometastases with cytologic examination has been considered a major method to predict peritoneal recurrences; the sensitivity of this assay is low. Recently, molecular approaches using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique has made possible the increase in the sensitivity.
We can conclude, although the preliminary experience, that prophylactic HIPEC in locally advanced gastric cancer is feasible, increasing median survival compared to surgery alone. For sure this procedure need to be performed in the highly specialized centres strongly respecting the eligibility criteria.

KEY WORDS: Gastric Cancer, Hipec, Peritoneal dissemination

Introduction

Gastric adenocarcinoma (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide [1].
The current treatment paradigm includes surgical resection with D2 lymphadenectomy for non metastatic GC, and palliative systemic therapy for disseminated tumors. In patients with locally advanced GC with serosal invasion, lymph node metastasis or positive peritoneal washing cytology the prognosis following surgical therapy alone is poor [2].
The lack of efficient systemic therapy combined with the fact that the peritoneum is a preferential site for locally advanced GC dissemination, has been the aim for many investigators to study Hyperthermic intraperitoneal chemotherapy (HIPEC) in an adjuvant setting [3].
Actually, CRS (Cytoreductive Surgery) combined with HIPEC and/or EPIC has been accepted worldwide as the treatment of choice in several tumor types: Pseudomyxoma Peritonei, carcinoma of the appendix, colorectal cancer and malignant peritoneal mesothelioma [4].
Only a few centers offer HIPEC plus CRS for the treatment of established GC peritoneal carcinomatosis [5].
In our study we wanted to show the role of HIPEC in gastric cancer patients at high risk to develop peritoneal recurrences.

Patients and Methods

From August 2007 to November 2011 eleven patients underwent hyperthermic intraperitoneal chemotherapy (HIPEC) with prophylactic intent. Five out of eleven were females. Median age 61 years (range 41-76 years). All the patients were affected by gastric cancer with high risk of peritoneal dissemination represented by serosa-invasive tumors (T4a according to the 7th TNM edition) and cytology-positive peritoneal lavage without macroscopic peritoneal dissemination.
Peritoneal lavage was analized with conventional cytology (Papanicolau test) and intraoperative quantitative PCR detection of CEA mRNA.
Gastric cancer was diagnosed in all patients by superior endoscopy with biopsies confirming an adenocarcinoma. Five out of eleven were intestinal type, one was signet ring cell carcinoma, 4 were diffuse and one mucinous type. A thoracic-abdominal and pelvic CT scan and total body FDG-PET were performed for tumor staging. The T parameter was assessed with superior endoscopy ultrasound. All patients underwent spirometric and cardiac pre-operative evaluation. Operative risk was assessed by an anesthesiology specialist.
Inclusion criteria were: Karnowsky Performance Status (KPS) ≥ 90, age < 75 years old, gastric cancer with high risk features for peritoneal carcinomatosis, white blood cells >3500/mm3, neutrophiles >1500/mm3, platelets > 100.000/mm^3, good renal functions, creatinine values being < 1.5 mg/dl, informed consent.
Exclusion criteria were: metastatic disease or high suspicion for peritoneal carcinomatosis at pre-operative staging, presence of co-morbidity, including severe chronic diseases or organ insufficiency, insufficient renal functions, serum creatinine being > 1.5mg/dl, gastric stump neoplastic relapse, previous malignant tumors, excluding conditions with 100% cure rate, serum bilirubin > 2 mg/dl, impaired haematopoiesis, poor performance status Karnofsky < 90%. All patients underwent i.v. rehidration and N-acetilcistein administration 48 hours before surgery.

Procedure

A midline incision was performed with the patient in supine position. Sovramesocolic and Douglas pouch lavage with 100 ml of sterile saline solution were performed. Sixty milliliter of the solution were collected from both the areas and send for Papanicolau and quantitative PCR detection of CEA mRNA. A complete abdominal exploration was performed to reveal any peritoneal macroscopic nodules of carcinomatosis.
A 2/3 gastrectomy or a total gastrectomy were carried out depending on tumor location. In all patients D2 lymphadenectomy or D2+ (lymph node stations beyond those incorporated in a D2 standard) were performed. All the anastomoses were done before starting HIPEC. Two inflow drains were placed in the upper left and lower right quadrant while the outflow ones were placed in the upper right and lower left quadrants. The skin was sutured in a continuous fashion. Before starting HIPEC, plasma (10 ml/kg) was administered intravenously in all patients.

The Performer (RanD-Medtronic) was used in all HIPEC procedures. A solution (Emagel 5 l + Saline solution 0.9% 1 l) of Mitomycin C (3.3 mg/m2/Lt of perfusate) and Cisplatin (25mg/m2/Lt of perfusate) were delivered intraperitoneally for 60 minutes with an inflow temperature of 43.5°C in order to obtain an intrabdominal temperature of 41-42°C. Patient temperature was monitored during all the procedure by an oesophageal catheter. At the end of the treatment a peritoneal lavage was performed with 5 L of saline solution. Four drains were left in place. Abdominal wall was closed with resorbable suture in a continuous fashion.

Postoperative monitoring

All the patients were monitored for 24-48 hours in the Intensive Care Unit. From postoperative day 1, patients underwent daily monitoring of blood test for at least 5 days. On postoperative day 3, in all patients a thoracic radiogram was performed. Nasogastric tube was removed after the bowel function was fully recovered. In 80% of the patients a semiliquid diet was started from the fifth post-operative day. After that they started a customized diet. The wound was examined every two days, and cutaneous sutures were removed in all patients after 12-14 days.

Follow-up

All patients were evaluated by the same physician 1 month after surgery and every 6 months for the first two years, once a year for the following 5 years. They underwent clinical examination, dosage of tumor markers, upper GI endoscopy and PET-CT scan. An adjuvant chemotherapy was performed in eight patients (DCX). In two patients the chemotherapy was stopped at the end of the second cycle for hematologic toxicity.

Results

Four patients were enrolled in a neoadjuvant chemotherapy treatment (DCX) due to T stage or nodal involvement at pre-operative stadiation.
A total amount of seven subtotal gastrectomies was performed. Four patients underwent total gastrectomy according to the proximal location of the tumor in the stomach. A D2 lymphadenectomy or D2+ was performed in all patients. The choice of performing a D2+ was related to the pre-operative imaging and to intraoperative nodal status.
The intraoperative course was uneventful in all patients. The median operation time was 398 minutes (range 300-570 minutes).
Postoperative adverse effects were evaluated according to CTCAE (Common Terminology Criteria of Adverse Events – Grade 1 to 5) and are summarized in the table below (Tab 1). Median hospital stay was 14 days (range 9-30). In our series we recorded 20 adverse events. Median number for each patient was 1 adverse effect (range 0-2). Eight patients experienced a surgical adverse effect (G2-G3) that did not require any surgical treatment. Only one patient with duodenal stump dehiscence and intra-abdominal sep-

TABLE I - *Patients features.*

Patient	Sex	Age	Tumor Location	Histology	Stage (c)	Cytology	Surgery/Lymphadenectomy	Operation Time(minutes)	Surgical adverse effects	Toxicity	Hospital stay (days)	Follow up (months)	Local/Peritoneal recurrence	Status	Survival (months)
V.R.	M	70	Fundus + body	Mucinous type	IIIA	Cy+/PCR +	TG + J /D2	300		Transient hepatic failure (G1)	10	21	No	DF	21
M.P.	M	58	Fundus+body	Diffuse type	IIIA	Cy-/PCR -	TG + J /D2+	360	Intrabdominal collection (G2)	Anemia (G2)	17	9	No	Dead for pulmonary sepsis	9
B.G.	M	62	Antrum	Diffuse type with signet ring cells	IIIB	Cy-/PCR -	2/3G /D2	570	Anemia (G3) Fever (G2)	Leucopenia (G2) Piastrinopenia (G3)	30	36	No	DF	36
C.F.	F	61	Body + antrum	Diffuse type	IIB	Cy-/PCR -	2/3G /D2	300	Anemia (G2) Pleural effusion	Hepatic toxicity (G1)	12	36	No	DF	36
V.T.	F	41	Antrum	Diffuse type	IIIC	Cy-/PCR +	2/3G /D2	360	Pleural effusion	Neutropenia (G4) Piastrinopenia (G2)	9	12	Yes	Dead for disease progression	12
B.G.	M	58	Body + antrum	Intestinal type	IIIC	Cy-/PCR +	2/3G / D2+	420	Pleural effusion		13	7	No	DF	7
G.N.	F	50	Antrum	Intestinal type	IIB	Cy+/PCR +	2/3G /D2	360	Anemia (G2) Pleural effusion		11	7	No	DF	7
B.R.	F	59	Fundus+body	Intestinal type	IIIA	Cy-/PCR +	TG + J /D2	360			11	15	No	DF	15
M.F.	F	72	Fundus+body	Intestinal type	IIIA	Cy-/PCR +	TG + J /D2+	480	Duodenal stump deiscence (G4) Sepsis (G5)		65			Dead for intrabdominal sepsis and PANE	
G.A.	M	62	Antrum	Intestinal type	IIIC	Cy+/PCR +	2/3G /D2	420	Anemia (G2)		16	9	No	DF	9
M.R.	M	75	Antrum	Diffuse type	IIIC	Cy+/PCR +	2/3G /D2+	360	Anemia (G2)		20	8	No	DF	8
	TG + J: total gastrectomy + jejunostomy														
	2/3 G: Subtotal gastrectomy														

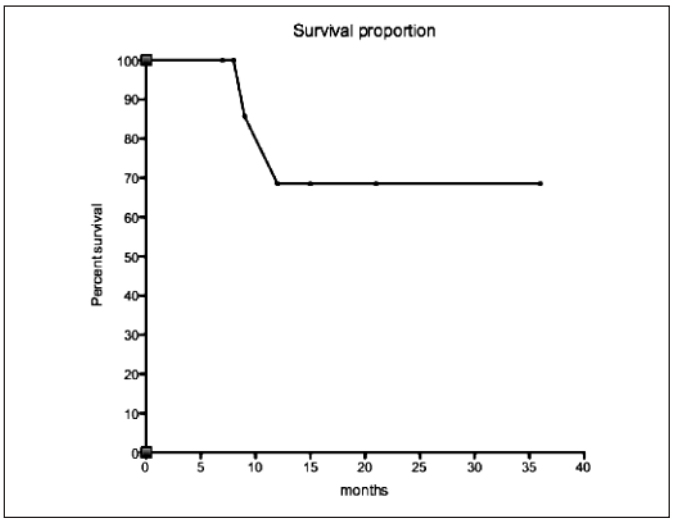

Fig. 1: Survival curve in Prophylactic HIPEC.

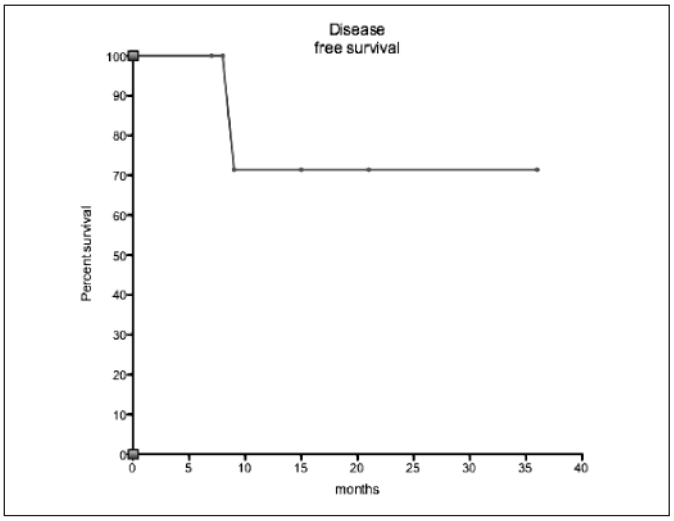

Fig. 2: DFS in Prophylactic HIPEC.

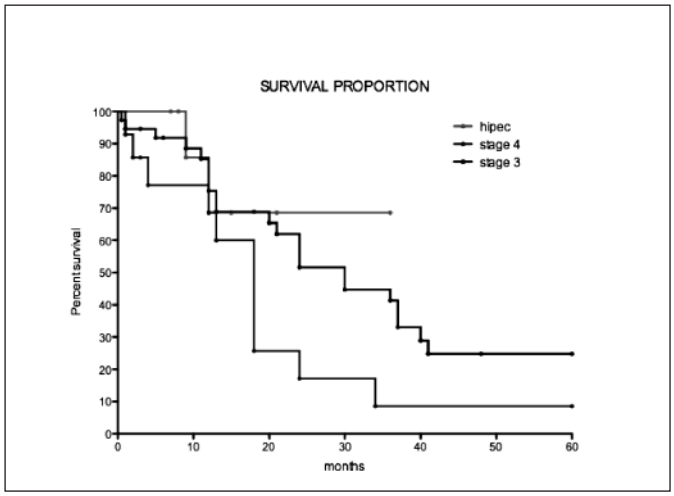

Fig. 3: Survival curve in Prophylactic HIPEC and resected stage III-IV GC (7th TNM Edition) in our series.

sis (G4-G5) underwent re-operation and died for severe hemorrhagic pancreatitis. Another patient died for ARDS. Peri-operative mortality was 18%. Both patients were older then 70 years old. Median follow-up was 15.9 months (range 7-36). Median survival was 29.6 months and median DFS was 20 months.

Discussion

Gastric cancer caused more deaths than any other type of cancer 60 years ago in the US, even if over the past several decades its incidence has decreased progressively throughout the western countries. Nonetheless, it remains a major public health issue as the fourth most common cancer and the second leading cause of cancer death worldwide, including 1,000,000 new cases per year throughout the world [1].

In most cases the preferential site of recurrences after surgical resection is peritoneum, in particular for the diffuse histological subtype. Free intraperitoneal cancer cells shed from the primary tumor involved serosa before resection, contribute to the peritoneal recurrence of resectable gastric cancer. The other source of free cancer cells is tumor cells shed with blood and lymph into the surgical field, also arising from metastatic nodes. As matter of fact, with the surgical trauma produced in excising the primary tumor, cancer emboli are released into the peritoneal cavity and readily implant on the raw surface from which the tumor was removed. Both the resection site and abraded peritoneal surfaces become layered in the immediate post-operative period by fibrinous exudates, which entrap the tumor cells and protect them from host defences. These events are collectively referred by Sugarbaker as the "tumor cell [6]. Not only is it important in understanding of the pathogenesis of both resection site and peritoneal surface recurrence, but also in an appreciation of the beneficial effects of adjuvant perioperative intraperitoneal chemotherapy.

As a matter of fact, peritoneal dissemination is a major pattern of therapeutic failure, and its recurrence rate ranges from 38% to 60%, being 53,3% in a recent exhaustive study issued by Chen-Wun Wu et al. 7 These Authors found that serosal invasion, scirrhous-type stromal reaction and female gender were three independent factors associated with peritoneal dissemination. They confirmed both the observation that peritoneal recurrence appeared once the cancer cells involved the serosa and the concept that once the tumor has spread through the gastric wall, complete surgical removal of all subclinical deposit is impossible. The main cause of treatment failure is the tendency of gastric cancer to disseminate in the peritoneal cavity, as Yonemura recently states [8].

Even after curative resection, peritoneal recurrence develops in about 60% of the patients with T3 and T4 tumors, and up to 40% of resected gastric cancer patients die as a direct result of peritoneal dissemination.

Peritoneal dissemination remains a major problem awaiting to be answered. Nor is the answer likely to came from adjuvant systemic chemotherapy alone, that can only be of influence on the extent of dissection.
Most studies evaluating the incremental value of intraperitoneal chemotherapy added to systemic therapy or surgery, were conducted in the adjuvant setting [10,11].
Yan et al reviewed all clinical randomized trials studying HIPEC in GC with resectable peritoneal carcinomatosis. They showed that surgery plus HIPEC was associated with significantly improved survival compared to surgery alone [12].
Actually there are not any studies evaluating the role and the value of prophylactic HIPEC in patients at high risk to develop peritoneal dissemination.
We enrolled in our preliminary experience patients featuring high risk of peritoneal recurrences: serosal invasion (T4) and positive peritoneal washing.
Lee S.D. et al demonstrated that the positive peritoneal washing cytology is a poor prognostic factor of survival in patients with resectable gastric cancer. According to the 7th TNM classification patients with positive peritoneal washing is classified as M1 (stage IV) as a patient with peritoneal carcinomatosis macroscopically evident [13].
Previous studies showed that the median survival of patients at stage P0 C1 is similar to that of those at stage P1 C1 [14].
The treatment of patients with positive peritoneal lavage citology is controversial. In the West the neoadjuvant chemotherapy is recommended and the need for the surgery is evaluated after chemotherapy.
In Korea and Japan the treatment of choice is gastric resection and D2 lymphadenectomy and adjuvant chemotherapy. However, no satisfactory and efficient chemotherapy regimen has been established for P0 C1.
Sun Z. et al. in their study concluded that serosal involvement sensitively predicts the presence of peritoneal micrometastases. Serosal invasion could be considered a good indicator to guide intraperitoneal adjuvant therapy for patients with high risk of peritoneal micrometastases.
Detection of peritoneal micrometastases with cytologic examination has been considered a major method to predict peritoneal recurrences; the sensitivity of this assay is low. Recently, molecular approaches using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique has made possible the increase in the sensitivity [15].
Also, carcinoembryonic antigen (CEA) has been considered the most valuable indicator to predict peritoneal recurrence [16-18]. In our series we observed that peritoneal lavage cytology and RT-PCR were both positive in 27.3% of the patients. In 36,4% of patients we evaluated a discrepancy in the results. In all the last cases RT-PCR was positive and the cytology was negative. Positive mRNA CEA RT-PCR dosage was associated with macroscopic serosal invasion.
Patient selection is one of the utmost importance criteria to ensure acceptable per-operative morbidity.
Kusamura et al observed that patients elegible for CRS and HIPEC must have good ECOG performance status, good nutritional status and low Charlson Comorbidity Index [20]. In our small series we showed that per-operative complications are also correlated with patient's age. Both the two dead patients were older than 70 years old. Considering that in our preliminary experience we reported few patients, we obtained a satisfactory median survival of 29.6 months compared to only 7.5-12 months in patients with advanced GC as reported by Van Cutsem [21].
The only dead patient of the progressive disease experienced a distant metastatic recurrences without peritoneal involvement.

Conclusions

We can therefor conclude, although the preliminary experience, that prophylactic HIPEC in locally advanced gastric cancer is feasible, increasing median survival compared to surgery alone. For sure this procedure needs to be performed in the highly specialized centres strongly respecting the eligibility criteria.

Riassunto

INTRODUZIONE: Il cancro gastrico localmente avanzato presenta una prognosi scarsa. La chemioipertermia intraperitoneale ipertermica (HIPEC) in associazione alla citoriduzione chirurgica (CRS) viene utilizzata nella terapia della carcinosi peritoneale. Il nostro studio riporta l'esperienza preliminare di pazienti con neoplasia gastrica localmente avanzata trattati con HIPEC profilattica.
MATERIALI E METODI: Undici pazienti affetti da cancro gastrico localmente avanzato sono stati sottoposti a chemioipertermia addominale presso il Dipartimento di Chirurgia Generale d'Urgenza. Tutti i pazienti considerati presentavano una neoplasia gastrica localmente avanzata con invasione della sierosa (T4), citologia convenzionale peritoneale positiva e/o positività del CEA mRNA al liquido di lavaggio peritoneale con PCRa. Sette pazienti sono stati sottoposti a gastrectomia totale e 4 pazienti a gastroresezione con linfectomia D2. Tutte le anastomosi sono state eseguite prima della HIPEC. La proceduta è stata eseguita per 60 minuti e sono stati usati il cisplatino e la mitomicina come chemioterapici ad uso intraperitoneale. I pazienti sono stati monitorizzati nell'immediato post-operatorio in Unità di Terapia Intensiva per 24-48 ore. L'alimentazione è iniziata precocemente in quinta giornata post-operatoria in media compatibilmente con la canalizzazione ai gas ed alle feci. Il follow-up, cui i pazienti sono stati sottoposti, si è svolto ogni 6 mesi per i primi due anni dall'intervento ed ogni 12 mesi per i successivi anni.
RISULTATI: Nessuna complicanza intraoperatoria è stata

riportata. Il tempo medio della procedura chirurgica è stata di 398 minuti. Sono stati osservati 20 eventi avversi nel post-operatorio. In 8 pazienti sono stati osservati eventi avversi (G2-G3) che non hanno richiesto un reintervento chirurgico risoltosi con la sola terapia medica. Un paziente ha presentato un quadro di pancreatite necrotico-emorragica e deiescenza del moncone duodenale per cui ha richiesto un reintervento chirurgico. Un paziente è deceduto nell'immediato post-operatorio. La mortalità postoperatoria è del 18% (2 pazienti). Il follow-up medio è stato di 29,6 mesi ed il tempo libero da malattia di 20 mesi. Solo un paziente ha presentato recidiva peritoneale dopo 12 mesi dall'intervento chirurgico. Un paziente affetto da Immunodeficienza Comune Variabile tipo II è deceduto dopo 9 mesi dall'intervento chirurgico per sepsi polmonare.

CONCLUSIONI: La carcinosi peritoneale si presenta in circa il 60% dei pazienti sottoposti ad intervento chirurgico curativo per neoplasia gastrica localmente avanzata e presenta una sopravvivenza alquanto scarsa di 6-9 mesi in media. Vari studi clinici hanno dimostrato l'efficacia in termini di aumento della sopravvivenza globale della chemioipertermia intraperitoneale associata a citoriduzione chirurgica nei pazienti affetti da cancro gastrico con carcinosi peritoneale limitata resecabile. Attualmente non vi sono studi che valutino il ruolo dell'HIPEC profilattica nei pazienti ad alto rischio di sviluppare carcinosi peritoneale. La settima edizione della stadiazione TNM considera la positività della citologia peritoneale malattia metastatica come la carcinosi macroscopicamente evidente vista la simile sopravvivenza media che i due gruppi di pazienti presentano. La determinazione della presenza di cellule neoplastiche nel liquido di lavaggio peritonele con la citologia convenzionale presenta una bassa sensibilità. Recenti approcci molecolari quali la determinazione della rMNA del CEA nel liquido peritoneale con tecnica Reral-Time PCR ha aumentato la sensibilità nella diagnosi di micrometastasi peritoneali. La nostra preliminare esperienza ha dimostrati la fattibilità della procedura rispettando i criteri di eleggibilità ed il raggiungimento di una buona sopravvivenza nei pazienti con neoplasia localmente avanzata paragonata a quelli trattati con la sola chirurgia.

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