Patient Selection for Cytoreductive Surgery and HIPEC, and Role of Laparoscopy in Diagnosis, Staging, and Treatment

Mario Valle, MD, Orietta Federici, MD, Alfredo Garofalo, MD*

KEYWORDS
- Peritoneal carcinomatosis • Staging • Staging laparoscopy • Refractory ascites
- Intraperitoneal hyperthermic chemotherapy

KEY POINTS
- Peritoneectomy + hyperthermic intraperitoneal chemotherapy (HIPEC) shows good late results only for patients in whom a complete cytoreductive surgery was performed; the expected completeness of cytoreduction (CC0) is the cornerstone of the indications to the treatment.
- Imaging (computed tomography [CT] and CT/positron emission tomography [PET]) is still considered the first-choice diagnostic test in the workup of peritoneal carcinomatosis, but video-laparoscopic (VLS) staging is the only presidium that allows a correct staging and a reliable forecast of the expected CC0.
- The VLS staging technique is safe and reliable, not presenting major complications and mortality.
- In refractory malignant ascites not suitable for surgery, laparoscopic HIPEC shows encouraging results regarding both the ascites and the improvement in the Karnofsky index.
- VLS peritonectomy might be used in minimal carcinomatosis, confined to 1 or 2 sectors and well-defined histologic types. At present, in the absence of comparative data with open surgery, it is not possible to consider it as a gold standard in minimal carcinomatosis.

INTRODUCTION

The integrated approach to peritoneal carcinomatosis is based on the change of paradigm introduced by Paul Sugarbaker, who considers this abnormality as a locoregional disease in which only the abdominal compartment is involved.1 Following this
approach, and carrying out an accurate assessment of locoregional tumor burden, patients can be selected for treatment with a procedure that combines surgery (peritonectomy) and hyperthermic intraperitoneal chemotherapy (HIPEC).

The first step of selection consists in excluding from the integrated treatment all the patients with hematogenous metastases in the extra-abdominal districts and with nonresectable liver metastases.

Of paramount importance is the qualitative and quantitative assessment of locoregional tumor burden and the forecast of the extent of resection needed to achieve complete cytoreduction; the main purpose of this assessment is to select for treatment those patients who can achieve a real improvement in survival, also carefully evaluating the operative risk.2

Peritonectomy + HIPEC, when a complete cytoreduction is accomplished, permits an overall survival (OS) and a disease-free survival (DFS) that cannot be achieved by any other kind of treatment.3–7

**DIAGNOSIS AND EXCLUSION OF PATIENTS WITH EXTRAREGIONAL DISEASE OR HIGH PERITONEAL CANCER INDEX: IMAGING**

The first role of imaging is to rule out the presence of distant metastases in extra-abdominal areas, which is an absolute criterion of exclusion. The lesions pertaining to peritoneal carcinomatosis can be demonstrated directly through ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT.

Ultrasonography is useful in detecting ascites, large abdominal masses, or liver metastases. CT gives valid topographic representation of the abdominal cavity and a precise definition of site, type, and extent of the pathologic process.

The main findings for peritoneal carcinomatosis on CT scan are focal or diffuse thickening of peritoneal folds, appearing as sclerotic, jelly-like, reticular, reticulonodular, nodular, or in large plaques. According to such an appearance, it is possible to identify different types of peritoneal carcinomatosis, namely infiltrative, micronodular (miliary), and macronodular (nodosal) forms, with some overlapping among them.

Nodular or plaque lesions can show various levels of enhancement after intravenous injection of contrast media, or even a little attenuation, with cyst-like appearance; sometimes it is possible to see calcification deposits inside the lesions.

Mesenteric involvement is often of the sclerotic type, with thickening and retracted appearance of the single layers. In the greater omentum it is often possible to see reticular/micronodular, or a nodular aspect and/or large plaques, in some cases where a huge and thick neoplastic tissue layer of inhomogeneous density is located between the abdominal wall and the bowel loops (“omental cake”).

Chances of identifying nodular lesions depend on the anatomic location; small nodules (<5 mm) are more easily recognized on the surfaces of liver or spleen. Image visualization on different planes (multiplanar reconstruction sagittal, coronal, oblique) can help in searching for lesions on curved structures such as diaphragm, paracolic gutters, and small-intestine loops.

Small-bowel and large-bowel loops can be warped and attached to each other, capable of causing stenosis and mechanical intestinal obstruction. Ascites is present in more than 70% of cases, free or entrapped; CT scan can demonstrate free ascites if the amount is more than 50 mL. In the upper part of the abdomen the fluids collect first in the hepatorenal space and in the subphrenic right and left spaces; in the lower part the initial collection is in the Douglas pouch, then around urinary bladder and in paraocolic gutters.
Primary tumor can also be identified (if it has not yet been surgically removed); if not possible, the synchronous peritoneal lesion can be assumed as primary, or a spread from an extra-abdominal focus (eg, breast cancer, melanoma) might be hypothesized.

In the differential diagnosis, some rare diseases causing similar lesions should be considered: tuberculous peritonitis, mesenteric panniculitis, diffuse peritoneal leiomyomatosis, and extramedullary hematopoiesis.

Pseudomyxoma peritonei can grow close to the original lesions (localized form) or spread to most of the peritoneal surface (diffuse form). CT shows solid, inhomogeneous tissue, mostly hypodense, localized around the peritoneal sides, which usually appears thickened by the irritating action of mucin; ascites is often present. As for peritoneal carcinomatosis, even a pseudomyxoma peritonei fibrotic reaction can cause adhesions with obstruction of the intestinal transit.

CT can help in the evaluation of intra-abdominal metastatic diffusion, and in choosing the best treatment option when involvement of liver or head of pancreas is present and when the mesenteric root is grossly infiltrated; in the preoperative evaluation of the peritoneal cancer index (PCI), it shows 88% sensitivity and 12% accuracy. CT shows low sensitivity in assessing small-bowel lesions (8%–17%), which decreases to 11% for lesions smaller than 5 mm in all quadrants with a significant underestimation of clinical PCI. When the CT scan is positive, mainly in patients with bulky tumors, its specificity reaches 100% in all regions. CT is very helpful during the early postoperative period because it can identify complications such as fluid collections, abscesses, perforations, fistulae, and pancreatitis.

Magnetic nuclear resonance shows no advantages when compared with CT in the evaluation of PCI and in the prediction of achievable cytoreduction index. 18F-FDG PET, if used alone, underestimates PC. 18F-FDG PET/CT shows instead 90% sensitivity and preoperative specificity of 77% for degree II and III lesions; nevertheless it underestimates small lesions in all locations, when the size of the nodules is less than 5 mm. In the follow-up period, CT can detect early recurrences, even if a differential diagnosis between true relapses and fibrotic scars caused by treatments is often difficult; in these patients 18F-FDG PET/CT can help to make a differential diagnosis. Usually 18F-FDG PET/CT is positive after completeness of cytoreduction index grade 2 (CC2) to CC3 and negative after CC0 to CC1.

Not all histologic types show good glucose uptake at 18F-FDG PET/CT; it could therefore be advisable to perform a preoperative examination to assess the initial glucose uptake to exclude false negatives in the follow-up period of nonuptaking tumors. Recent studies showed that both CT and 18F-FDG PET/CT were unable to give a correct staging of carcinomatosis. One may conclude that nowadays there is no noninvasive procedure that can correctly evaluate PCI and expected cytoreduction index after treatment, especially if the lesions are small (Figs. 1 and 2).

INDICATIONS FOR INTEGRATED TREATMENT: LOCOREGIONAL STAGING

The first attempt at defining locoregional staging of peritoneal carcinomatosis was conducted by the Japanese, after the first studies completed in the 1990s about the association of surgery and locoregional chemotherapy for the treatment of locally advanced gastric cancer.

A staging format for carcinomatosis from gastric cancer was proposed:

- P1 (few nodules above the mesocolon)
- P2 (moderate amount of nodules even below transverse mesocolon)
- P3 (many spread nodules)
This classification is simple, shows a good prognostic value, with a 2-year survival rate that falls from 21% for P1 to 4% for P3 and, with slight modifications, can be used even for different forms of carcinomatosis; notwithstanding, it is not accurate enough concerning the distribution and localization of neoplastic lesions.

Gilly’s classification is also very simple, but more modern:

- Stage 0: no macroscopic signs of disease
- Stage I: nodules smaller than 5 mm, confined to one abdominal region
- Stage II: nodules smaller than 5 mm, disseminated through the abdomen
- Stage III: size of nodules between 5 mm and 2 cm
- Stage IV: lesions larger than 2 cm

Even so, this classification is not detailed enough about the distribution of the lesions. Sugarbaker’s classification is more useful for both prognosis and research, and is based on the PCI (Fig. 3). The abdomen is divided into 9 sectors and the small bowel
into 4 more parts; for each sector a score is assigned (Lesion Size score [LS]) related to the actual disease:

- LS 0: no macroscopic evidence
- LS 1: maximum diameter of the lesions up to 0.5 cm
- LS 2: maximum diameter up to 5 cm
- LS 3: maximum diameter larger than 5 cm or confluent nodules

The total of the scores for all sectors gives the PCI.

Stage P1 to P2 of the Japanese classification is equivalent to Gilly’s Stage I to II and to Sugarbaker’s PCI of less than 13.

The expected achievement of CC0 remains, however, the main prognostic factor:14 patients who achieve CC1 cytoreduction have a markedly worse outcome, whereas those classified as CC2 to CC3 show very poor results.

If one has to consider Peritonectomy + HIPEC as a curative treatment of peritoneal carcinomatosis, patients who cannot be classified as expected CC0 should be excluded from the procedure. CC1 cases (residual lesions between 0.25 and 2.5 mm) in HIPEC-responder patients can also be considered CC0 after cytoreduction. In CC1 HIPEC nonresponders, CC2, and CC3, the integrated treatment offers limited increase in OS but a marked improvement in quality of life; it can therefore be considered as advanced palliative surgery.

Histology of the primary tumor plays a crucial role in the selection of patients affected by peritoneal carcinomatosis, because it noticeably modifies the cutoff value of PCI during the decision-making process. Selection of patients cannot therefore leave out of consideration the following factors:

- PCI
- Histology of the primary tumor
- Expected CC index
These factors must be related to:

- Age
- Karnofsky Index
- Comorbidities (cardiovascular, respiratory)
- Carcinomatosis-related complications at the time of surgery (intestinal obstruction, ascites)
- Active infections
- Previous systemic chemotherapy, chemoresistance, toxicity
- Disease-free interval from previous surgery

Previous evaluation of resectable hepatic metastases and of possible involvement of other organs, such as pancreas, is mandatory, because an eventual pancreatic resection greatly increases morbidity.

Infiltration of small bowel and its mesentery by lesions that cannot be reduced to CC0 even after HIPEC (and therefore requiring surgical resection) can be treated, providing the remaining healthy small-bowel length is at least one-third of the total.\textsuperscript{15-20}

**ROLE OF STAGING LAPAROSCOPY**

Video-laparoscopy (VLS) is considered an excellent diagnostic procedure, but its wide application in peritoneal carcinomatosis has been discouraged, the objections to this technique being related to:

- Difficulty of trocar positioning in the presence of abdominal wall tumor masses or adhesions from previous surgery
- Skepticism about the reliability and efficacy of the procedure in the staging phase
- Fear of neoplastic contamination of the port sites, supported by the finding of 52\% of recurrences for pseudomyxoma peritonei along the surgical scar\textsuperscript{21}

Notwithstanding the aforementioned considerations, in their extensive experience the authors have documented a possibility of trocar positioning near 100\% (even in patients with multiple previous surgery), the absolute reliability of VLS staging, and the complete absence of neoplastic contamination of the abdominal wall around the port sites, if trocars are inserted using a standardized technique.\textsuperscript{20,22,23}

Since the beginning of their experience in 2000, the authors have related the information from VLS staging with PCI with the possibility of obtaining complete cytoreduction. Using this methodology, almost one-half of the patients were excluded from the treatment, many of them being submitted to a second staging laparoscopy after systemic neoadjuvant chemotherapy.

**LAPAROSCOPY IN THE STAGING OF PERITONEAL CARCINOMATOSIS**

Main aim of laparoscopic staging is to carefully assess the patient’s prognosis and the surgical feasibility, considering that the simple surgical exploration is often dangerous in such patients: in advanced abdominal tumors treated with laparotomy alone morbidity from 12\% to 23\% and mortality from 20\% to 36\% have been reported.\textsuperscript{2}

Diagnostic imaging (CT and CT/PET) is still considered the first and mandatory diagnostic test for peritoneal carcinomatosis: when imaging-based PCI is in favor of enrolling the patient for treatment, VLS staging allows assessment of the true PCI, granting a correct selection of patients according to the expected CC index and a cost/benefit assessment in terms of DFS, OS, and quality of life.
**Surgical Technique**

The Hasson trocar is introduced and the ascites completely sucked out of the peritoneal cavity, taking care not to contaminate the port sites.

Considering the high incidence of adhesions both from previous surgery and from tumor masses infiltrating the midline, the choice is to avoid median or paraumbilical access; the authors prefer a trocar positioned in the right or left flank or iliac fossa on the mid-axillary line after carrying out clinical evaluation and ultrasound scan of the considered quadrants.

This access allows for a better exposure of the small bowel and its mesentery even in presence of a large omental cake; it also offers the possibility of improving visualization by inserting a second trocar (5 mm) beneath the first one or in the contralateral iliac fossa.

A 30° scope is routinely used; division of adhesions should be kept to a minimum to avoid the risk of lesions to abdominal organs, but should be enough for a complete evaluation of the PCI. In case of tenacious adhesions or neoplastic infiltrations of the median line, it is advisable to explore the right and left sections separately and to carry out a second open access to view the quadrants of the opposite side.

Cytology samples should be taken under direct view. Highly mucinous carcinomatosis sometimes requires a 10-mm trocar in port II to admit insertion of a larger suction cannula. In peritoneal surface malignancies where the pathologic findings are unknown or doubtful, it is important to collect multiple biopsy specimens from the parietal, omental, and pelvic cavity lesions. Diaphragmatic biopsies can cause perforation and infiltration of the muscular wall and should be avoided. When liver metastases or the involvement of major hepatic veins are suspected, as in diaphragmatic lesions larger than 2 cm, VLS ultrasound imaging can be helpful.

To accomplish the laparoscopic definition of PCI, which is determined on the basis of the distribution and size of the tumor nodules, the operating table has to be moved into at least 4 positions: steep anti-Trendelenburg left tilt, steep anti-Trendelenburg right tilt, steep Trendelenburg left tilt, and steep Trendelenburg right tilt.20

**Personal Experience and Results**

The authors’ group performed 351 diagnostic VLS procedures in patients with peritoneal surface malignancies (Table 1). The average time needed for a diagnostic and staging VLS procedure was 30 minutes (range 15–45 minutes). In one patient the access to the abdominal cavity was impossible because of thick cancerous adhesions between the small-bowel loops and the abdominal wall: this patient underwent midline laparotomy, which confirmed the impossibility of reaching into the abdominal cavity because of massive involvement of the small-intestine loops tightly adherent to the abdominal wall.

In 335 cases, 2 trocars (10 mm and 5 mm, respectively) were enough to carry out the procedure, whereas in 13 cases a third 10-mm trocar was necessary to gain a full view of the abdominal cavity.

In 121 patients the primary tumor was ovarian, in 76 gastric, in 73 recurrent colorectal, in 10 recurrent pancreatic, in 8 cancer of the uterine cervix, and in 1 prostatic; 24 patients had pseudomyxoma peritonei syndrome from appendiceal adenocarcinoma, 14 were affected by mesothelioma, 6 by abdominal sarcomatosis, and 2 by intra-abdominal desmoplastic small round cell tumors. In 15 patients carcinomatosis was the peritoneal progression of a primary breast tumor.

In 5 cases (1.42%) VLS understaged the carcinomatosis (1 mesothelioma, 2 gastric cancers, 1 pseudomyxoma, and 1 ovarian tumor) and, at laparotomy, massive infiltration of the pancreas was detected in gastric cancer and mesothelioma, which resulted in a CC2 peritonectomy. In the pseudomyxoma and ovarian cancer the value of VLS PCI
Table 1
Personal experience of staging laparoscopy in peritoneal surface malignancy

<table>
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<tr>
<th>Pathology</th>
<th>Cases</th>
<th>Diagnostic</th>
<th>Unfeasible</th>
<th>Understaging</th>
<th>2-Trocar</th>
<th>3-Trocar</th>
<th>Site Infection</th>
<th>Bleeding</th>
<th>Bowel Perforation</th>
<th>Diaphragm Perforation</th>
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<td>5</td>
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<td>21</td>
<td>2</td>
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<td><strong>%</strong></td>
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<td>1.42</td>
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<td>6.02</td>
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was lower than open-surgery PCI, but it was nonetheless possible to carry out a CC0 cytoreduction.

In 244 cases (69.5%) advanced carcinomatosis was found with PCI greater than 17; in 62 cases PCI was in the range 0 to 13, in 22 between 14 and 16, in 87 between 17 and 23, in 95 between 24 and 33, and in 85 between 34 and 39. One hundred four patients were excluded from surgical exploration because of massive infiltration of the small bowel or its mesentery basis detected by VLS.

Of patients on whom a diagnostic VLS procedure was performed, 250 of 351 (71.22%) had had at least one previous laparotomy. One hundred seventy-six (50.1%) patients were treated with peritonectomy and HIPEC. Four (2%) patients, who were not eligible for a peritonectomy because of massive infiltration of the small bowel and occlusion, underwent a VLS decompressive ileostomy.

Regarding morbidity, in VLS surgical exploration 5 complications were observed (1.4%), 2 of which (0.56%) were intraoperative: one was a perforation of the diaphragm during biopsy, sutured with laparoscopic technique, whereas the other patient sustained early postoperative bleeding treated by a blood transfusion. Of the remaining 3, 2 (0.56%) showed delayed postoperative infections of the trocar site, treated by topical antibiotic therapy; 1 patient (0.28%) had a small-bowel perforation that was sutured through the port site. No neoplastic seeding was detected at the trocar sites, and all patients who underwent peritonectomy showed negative results regarding port-site metastasis 10 to 40 days after the procedure. No mortality was observed.

### Points of Strength

- Evaluation of the small-bowel mesentery (superficial lesions and retractions) (see Fig. 2)
- Evaluation of all the sectors according to the PCI scoring system (Fig. 4)
- Evaluation of small-bowel lesions on the antimesenteric margin (Fig. 5)
- Evaluation of the omental bursa, pelvic cavity, diaphragm, and abdominal wall
- Possibility of peritoneal washing and biopsies for defining the histology of the primary tumor
- Predictive evaluation of the CC index following peritonectomy

### Points of Weakness

- Evaluation of the thickness of lesions of the diaphragm
- Evaluation of pancreatic involvement

These issues have been overtaken by coupling VLS examination with VLS ultrasonography.

### Indications

- Staging of a carcinomatosis already diagnosed via imaging technology (CT, MRI)
- Staging of a carcinomatosis of unknown origin (biopsy)
- Restaging following neoadjuvant chemotherapy
- Restaging during follow-up in case of dubious imaging
- Restaging following adjuvant chemotherapy

The use of VLS staging as a second look for patients who have already undergone a peritonectomy is not easy, because the presence of adhesions might not allow for a comprehensive evaluation of an eventual relapse nor a good evaluation of all abdominal quadrants. Nevertheless, the presence of ascites often facilitates the insertion of the trocars, provided that \(^{18}\text{F-FDG PET/CT}\) gives sufficient information about the origin and entity of the relapse and its possible treatment.
Fig. 4. Complete staging laparoscopy: peritoneal carcinomatosis from colonic cancer.

Fig. 5. Small bowel involvement. (A) Massive mesenterial infiltration. (B) Micronodular infiltration antimesenteric margin. (C) Micronodular infiltration of bowel mesentery. (D) Macronodular infiltration of bowel mesentery.
Algorithm of the Decision-Making Process for a Correct Indication for Radical Cytoreductive Surgery Based on Laparoscopic Staging

Step 1: Rule out the absolute criteria of exclusion
- Mesenteric root infiltrated or not liable to a complete cytoreduction
- Pancreatic capsule massively infiltrated, not liable to a complete cytoreduction, or requiring major pancreatic resections
- Expected small-bowel resection for more than one-third of the whole length
- Liver metastases: more than 3 on the same lobe, or multiple bilateral, unresectable

Step 2: Determination of relative inclusion criteria
- Ratio between PCI and histology (natural history of the primary)
- Possibility of downstaging by line of systemic chemotherapy

Step 3: Final decision about the possibility of reaching CC0 based on the following:

Ruling out Absolute Exclusion Criteria

Relative Inclusion Criteria (ratio between PCI and histology of the primary)

= Possibility of reaching CC0

The “Small Bowel Factor”

A critical review of the authors’ experiences allows some conclusions to be reached.

In the sectors 0 to 8, notwithstanding 59,049 possible combinations of scores of the single sectors, it is theoretically almost always possible to achieve stage CC0 even with the highest PCI (lesions larger than 2.5 cm or merging lesions).

The situation changes when sectors from 9 to 12 (those pertaining to the small bowel in Sugarbaker’s classification) are analyzed. Drawing on a mathematical model that considers cytoreduction chances for these 4 sectors, the authors obtained 256 possible combinations. Among all these, only in 68 groups (27%) will it be possible to achieve CC0; in 106 (41%) it will only be possible to achieve CC1 or CC2; while in the remaining 82 combinations (32%) only CC3 will be achieved, or surgery will be impossible.

Because it is possible to reach CC0 only in fewer than 30% of cases in the sectors 9 to 13, the degree of involvement of small bowel turns out to be the true cutoff point about chances to achieve CC0; once pancreatic infiltration and multiple nonresectable hepatic metastases are excluded, the correct evaluation of lesions of the small bowel and its mesentery remains the main goal.24

If one considers that imaging techniques show low specificity in the evaluation of these sectors, VLS can be considered essential to the achievement of the correct indication to peritonectomy + HIPEC and the only way to have a correct forecast of the expected degree of cytoreduction.

LAPAROSCOPY IN THE TREATMENT OF PERITONEAL CARCINOMATOSIS

Operative Laparoscopy

Recent studies describe the treatment of a small number of patients with minimal carcinomatosis by laparoscopic peritonectomy + HIPEC,25,26 showing that it is possible to use this procedure in carefully selected cases. The authors are of the
opinion that the methodology deserves further studies in larger series of patients, with special attention paid to the association of cytoreductive surgery to HIPEC because, at least theoretically, the spread of neoplastic cells at the induction of pneumoperitoneum could be wide, resulting in a higher risk of diffusion of a minimal carcinomatosis.

Laparoscopy in the Treatment of Refractory Ascites

Laparoscopy in the restaging of peritoneal carcinomatosis allows the use of a peritoneectomy procedure in responders to adjuvant and neoadjuvant chemotherapy; on the other hand, a reevaluation of nonresponders brought to consideration a group of patients with debilitating intractable ascites, with a very poor quality of life. Thirty-three patients underwent hyperthermic intraperitoneal chemotherapy for the palliation of ascites through a minimally invasive approach.27–30

Methods

A Hasson trocar was inserted in the right or left pararectal area through a 1-cm incision, taking care not to contaminate the abdominal wall with ascites. The ascites was completely sucked out of the peritoneal cavity through the trocar before insufflation with CO₂. After positioning the 30° 5-mm scope under direct vision, a second 5-mm trocar was introduced in the contralateral iliac fossa. When deemed necessary, release of adhesions was performed to grant free access to the abdominal cavity. If extended adhesiolysis was considered too dangerous, only few adhesions were divided to ensure communication between all abdominal quadrants and to allow free contact of the hyperthermic chemotherapy with all the peritoneal surfaces. Then 3 additional 5-mm trocars were sequentially placed on the right and left side into the free iliac fossa.

A 5-mm grasper was passed out from the peritoneal cavity through the 5-mm trocar to place closed-suction drains into the pelvic cavity and into the right and left subdiaphragmatic spaces. These 3 suctioning drains were connected together to provide a single outflow. The 5-mm trocars were removed and an infusion trocar was placed directly through the 10-mm site where the camera had been inserted. To make the peritoneal space watertight, all drains were secured with a purse-string suture to the skin and connected to the perfusion machine, which was set at an inflow temperature of 43°C to 44°C. The aim was to achieve an average temperature of 42°C in the whole peritoneal cavity (Fig. 6). The temperature of the infusion was measured by 2 probes, located at the inflow site and at the junction between the 3 outflow drains. The patient’s body temperature was monitored by 3 additional probes placed over the skin, in the external ear canal, rectum, and bladder. The average length of laparoscopic preparation was 45 minutes, with a range of 30 to 120 minutes depending on the extent of adhesiolysis.

To allow the spread of the chemotherapy solution throughout the whole peritoneal surface, the tilt of the operating table was changed at 15-minute intervals during perfusion as follows:

1. Straight
2. Trendelenburg + left tilt
3. Trendelenburg + right tilt
4. Straight
5. Reverse Trendelenburg + left tilt
6. Reverse Trendelenburg + right tilt

After a 90-minute perfusion, the chemotherapy agent was recovered and washed out with 2000 mL of 1.5% dextrose. The drains were connected to gravity bags and
removed postoperatively, when the amount drained was small enough. After removing all drains, the patient was discharged from the hospital.

The drugs used were cisplatin, 50 mg/m² and doxorubicin, 15 mg/m² for ascites due to ovarian cancer, peritoneal mesothelioma, or breast cancer. In ascites from rectal colon and stomach cancer mitomycin, 12.5 mg/m², was used. The volume of perfusion given was 2000 mL and consisted of a peritoneal dialysis solution containing 1.5% dextrose. Fresh frozen plasma (1200 mL) was infused during perfusion. Furosemide was administered along with intravenous fluids to maintain a diuresis of 400 mL/h.²⁸

Results
Among the 33 patients treated, the cause of malignant ascites was untreatable peritoneal carcinomatosis from gastric cancer in 12 cases, colon cancer in 7, breast lobular cancer in 5, ovarian cancer in 6, and mesothelioma in 3. In all cases a complete disappearance of the ascites within 9 days after the procedure was observed. The average postoperative increase in the Karnofsky index was 20 points. Even though the treatment was palliative, the disappearance of the refractory ascites had an impact on average survival rate, which in this series averaged 152 days (range 21–796 days). The longest survival times were observed in 3 of 5 cases of breast lobular cancer (807, 736, and 216 days) and in a case of mesothelioma (726 days) (Fig. 7), whereas the shortest survival times were observed in patients with gastric cancer. Follow-up ultrasonography or CT 1 month after the laparoscopic HIPEC revealed complete resolution of ascites in 31 of the 33 patients; 1 patient died on the 21st postoperative day, free from ascites. In one case a CT scan 1 year later showed a small, clinically undetectable, fluid effusion in the pelvis. In 2 cases of coexisting neoplastic intestinal obstruction, a laparoscopic ileostomy was performed before the hyperthermic intraperitoneal chemotherapy procedure.

Fig. 6. Treatment of refractory ascites. Laparoscopic HIPEC procedure.
No intraoperative or postoperative complications and no mortality related to the procedure were observed.32,33

Rationale of Palliative Treatment of Refractory Ascites with HIPEC

Laparoscopic HIPEC results in deeper penetration of the drugs in the peritoneal layers and tumor nodules. In the absence of cytoreductive surgery, during the palliative laparoscopic HIPEC procedures one can assume that the direct cytotoxic effect of this single chemotherapeutic instillation will be limited: heated chemotherapy is able to eradicate only some layers of cancer cells, with penetration on all the peritoneal surface. As a result of this process a thin layer of fibrosis may develop, which directs the cancerous fluid into the capillary bed and, from there, into the systemic circulation, determining a resolution of the problematic collection of ascites.27–30,34

Peritoneal sclerosis and induction of dense adhesions are possibly the major factor regarding the effectiveness of this technique. Ozols and colleagues,32,35 in their phase I study, reported sclerotic peritonitis and subsequent pain at the dose-limiting factor of 18 μM when performing intracavitary chemotherapy with doxorubicin in patients with advanced ovarian cancer. The absence of major complications and treatment-related mortality in the patients studied herein suggests that laparoscopic HIPEC is a safe technique. Such treatment is to be considered palliative for untreated ascites and must be performed exclusively on patients with peritoneal carcinomatosis who are not eligible for peritonectomy with HIPEC.

The treatment’s goal is to improve the Karnofsky index, ultimately having some impact on the patient’s quality of life. With this perspective in mind, even some patients affected by peritoneal carcinomatosis from lobular breast cancer were treated.

SUMMARY

In the treatment strategy of peritoneal carcinomatosis, VLS is located at the beginning of a critical path of analysis to classify the patient and provide a correct indication for integrated treatment. The technique is safe and reliable, does not lead to major complications and mortality, and is the only presidium that allows for correct staging of peritoneal carcinomatosis and a correct forecast of the expected CC0.

Laparoscopic peritonectomy might be used in minimal carcinomatosis, with PCI confined to 1 or 2 sectors and well-defined histologic types (carcinoma of appendix).
At present, there are no comparative data with open surgery; it is not yet possible, therefore, to consider the former as a gold standard in minimal carcinomatosis. The use of laparoscopy as treatment is indicated in refractory malignant ascites not suitable for surgery by HIPEC. This method shows encouraging results regarding both the ascites and the improvement in the Karnofsky Index.

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