INTRODUCTION

Malignant ascites is a debilitating condition affecting cancer patients in their terminal stage of disease. Recently, laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) was introduced as a new approach. From September 2001 to August 2008, 52 patients were treated with this new modality. No treatment-related mortality was observed. Median survival was 98 days. One patient developed a clinical recurrence. Laparoscopic HIPEC is a safe and effective method for palliating malignant ascites.

KEY WORDS: malignant ascites; laparoscopy; chemotherapy; intraperitoneal

MATERIALS AND METHODS

Patients

Between September 2001 and August 2008, 52 patients with debilitating malignant ascites due to peritoneal extension of their primary malignancy, were treated with laparoscopic HIPEC at the Ziekenhuis Oost-Limburg, Genk (Belgium) and the ‘‘Regina Elena National Cancer Institute’’, Rome (Italy). Fifty-three procedures were performed in 52 patients. IRB approval was obtained. Selection of the patients was done by a multidisciplinary team of oncologists, surgeons, nuclear physicians and radiologists. All patients were symptomatic at the time of surgery with discomfort, dyspnoea and anorexia being the most common presenting symptoms. Diagnosis was made on clinical grounds and confirmed by ultrasound, computed tomography (CT) or videolaparoscopic staging. Some patients were excluded for laparoscopic HIPEC during laparoscopic staging because of the extent and density of the adhesions, which would require an extensive adhesiolysis with a high risk of bowel perforation.

All patients had undergone previous conventional treatment including paracentesis, diuretics and radio-isotopes (n = 2) and were refractory to conservative treatment. Further exclusion criteria were

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TABLE I. Primary Malignancy in 52 Patients With Refractory Malignant Ascites Treated With Laparoscopic Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

<table>
<thead>
<tr>
<th>Primary malignancy</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric carcinoma</td>
<td>15</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td>11</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>13</td>
</tr>
<tr>
<td>Breast lobular carcinoma</td>
<td>8</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
</tr>
</tbody>
</table>

American Society of Anesthesiologists (ASA) classification grade 5 patients and patients in whom curative approach was still deemed feasible. The median age was 61 (range 31–79). The male/female ratio was 0.78.

Table I shows the variety of underlying primary malignancies in these patients.

Procedure

After induction of general anesthesia all patients were placed in standard supine position. A variety of trocar positions was used; it was based on review of the CT scans, in order to determine the safest positions to enter through the abdominal wall in the peritoneal cavity. Midline incisions were preferred, whenever possible in the Genk experience. On the contrary, in the Italian experience, lateral incisions for trocar positioning were always chosen. In all these Italian patients the first 10 mm Hasson trocar was placed with the open technique: the Endopath Tristar (Ethicon, a Johnson & Johnson Company, Piscataway, NJ) was preferred in 28 patients because its radiolucent sleeve helps in avoiding damages on neoplastic implants. In two patients where preoperative CT suggested a difficult entry, intraoperative ultrasound was used to guide placement of the first trocar. Care was taken not to contaminate the abdominal wall with the ascitic fluid. After introduction of the first trocar a 14 mm-Hg CO₂ pneumoperitoneum was induced, followed by the placement of an additional two or three trocars under direct laparoscopic vision. All ascitic fluid was drained. A sample of the fluid was obtained for cytology and culture. A laparoscopic exploration was followed by a limited laparoscopic adhesiolysis in order to allow a communication among all the abdominal quadrants and a wide circulation of the perfusate over all the peritoneal surfaces.

In 28 patients (Fig. 1) this was followed by placement of three closed-suction drains as outflow catheters and one closed-suction drain as inflow catheter via the trocar incisions according to the technique described by Garofalo et al. [26]. All drains were secured with purse-string sutures to the skin. Intracavitary temperature was measured at the inflow catheter and at the junction of the outflow catheters. The patient’s body temperature was monitored by means of three probes: at the skin, in the external ear canal, and in the bladder. The peritoneal cavity was filled with 2,000 ml of 1.5% dextrose solution. Perfusion was started and after reaching the target intracavitary temperature of 42°C, chemotherapy was added to the perfusion circuit. At 15 min intervals the position of the operating table was modified to facilitate homogeneous distribution of the cancer chemotherapy solution. After 90 min of perfusion the chemotherapy was retrieved and a lavage with 2,000 ml of 1.5% dextrose solution performed. The drains were connected to gravity bags. When drainage dropped to less than 50 ml/day, drains were removed and the patient discharged.

In 24 patients (Fig. 2) three 10 mm trocars (TYCO/United States Surgical Corporation [USSC], Norwalk, CT) were placed and secured on the midline. One inflow catheter was placed through the inferior trocar. One outflow catheter was positioned above the right liver lobe through the superior trocar. Intracavitary pressure and temperature probes were positioned through a handport device (Ethicon, a Johnson & Johnson Company) which replaced the third trocar. A hydroperitoneum with 1.5% dextrose solution was established by passive infusion: when the intracavitary pressure reached 15 mm Hg, perfusion was started. The surgeon usually takes care of stirring the solution. At 42°C the chemotherapy solution was added. At the end of the procedure, the chemotherapy solution was evacuated in a closed container, and two drains were left in place. Patients were usually discharged on the second postoperative day and the drains removed in the outpatient clinic on day 5–7.

Chemotherapy

The chemotherapy solution used was cisplatin 50 mg/m² and doxorubicin 15 mg/m² for malignant ascites from ovarian cancer, mesothelioma or breast cancer. In ascites from colorectal or gastric cancer, mitomycin C 12.5 mg/m² was used. In 10 patients regardless of the underlying pathology the drug of choice was doxorubicin 20 mg/ m². The perfusion time was 90 min.
treatment and resolved over an average of 1.4 cycles. Intraperitoneal instillations with mitoxantrone could decrease ascites by more than 50% [37].

Small series in literature report the feasibility of laparoscopic HIPEC in the treatment of malignant ascites [26–28,38]. We report the largest series of laparoscopic HIPEC in palliating refractory malignant ascites.

Pharmacokinetic Rationale

Laparoscopic HIPEC may result in deeper penetration of the cancer chemotherapy drug in the peritoneal layers and tumor nodules. Animal experiments confirmed the increased intratumoral accumulation of intraperitoneal chemotherapy when the intra-abdominal pressure was raised during HIPEC [39,40]. Gesson-Paute and coworkers reported in a pig model that increased intra-abdominal pressure during laparoscopic HIPEC as compared to open HIPEC facilitated drug penetration into the plasma compartment and peritoneal tissues [41,42]. The question remains if increased chemotherapy penetration into tumor nodules is the underlying mechanism explaining efficacy of laparoscopic HIPEC in palliating malignant ascites. In the absence of cytoreductive surgery during these palliative laparoscopic HIPEC procedures one can assume that the direct cytotoxic effect of this single chemotherapy instillation will be limited. The heated chemotherapy may eradicate viable cancer several cell layers deep on all the peritoneal surfaces. Then, a thin layer of fibrosis may develop on the exposed surfaces. The fibrous layer may direct the cancerous fluid into the capillary bed and thereby into the systemic circulation, causing a resolution of the problematic reaccumulation of ascites [26]. Abdominal sclerosis and induction of dense adhesions are probably the major factor of efficacy of this technique. Otsols et al. [43] in their phase I study reported sclerozing peritonitis and subsequent pain as the dose-limiting factor at 18 µM when performing intracavitary chemotherapy with doxorubicin in patients with advanced ovarian cancer. Our data in 10 patients where laparoscopic HIPEC with doxorubicin 20 mg/m² was used, regardless of the underlying primary malignancy, support this working hypothesis.

The absence of major complications and treatment-related mortality in our patients suggests that laparoscopic HIPEC is a safe technique. Proficiency in both laparoscopy and performing HIPEC procedures is a prerequisite for centers who consider starting a laparoscopic HIPEC program for their patients with malignant ascites.

Our retrospective analysis provides data that show an excellent radiological and clinical resolution of the ascites regardless of the underlying primary tumor. In all but one patient, no readmissions or outpatient visits were noted in relation with their previous condition. The consistent increase of the performance status of these patients postoperatively suggests a better quality of life in their remaining life span. A quality of life study using EORTC QLQ-C30 has been started in the last 10 patients to substantiate these assumptions.

CONCLUSIONS

Malignant ascites is a debilitating condition affecting patients in their terminal stages of disease. Our data establish this procedure as a low morbidity and no mortality palliative treatment with high impact on the performance status of these patients. In our experience with laparoscopic HIPEC in the management of refractory malignant ascites a complete and definitive disappearance of the ascites was observed in 94% of patients. Laparoscopic HIPEC is safe and feasible and results in excellent radiological and clinical resolution of the ascites.

REFERENCES


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