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ORIGINAL ARTICLE – REVIEW ARTICLE

Laparoscopic Hyperthermic Intraperitoneal Chemotherapy: Indications, Aims, and Results: A Systematic Review of the Literature

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ABSTRACT

Purpose. To evaluate laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) with neoadjuvant, adjuvant, or palliative purpose in order to discuss potential clinical implications.

Methods. A systematic search of PubMed's Medline through August 2011 using the keywords *laparoscopic, hyperthermic,* and *chemotherapy.*

Results. Eight studies encompassing a total of 183 patients were considered. The indications for laparoscopic HIPEC was neoadjuvant in 5 patients, adjuvant in 102 patients, and palliative in 76 patients. There were 13 minor complications not requiring repeat operation, and no deaths related to procedure were recorded. When performed to treat refractory malignant ascites, the procedure was effective in 95 % of cases.

Conclusions. Laparoscopic HIPEC appears to be a safe and effective procedure when performed to treat malignant ascites refractory to less aggressive treatments. The effectiveness of laparoscopy to perform HIPEC with neoadjuvant or adjuvant purpose needs to be confirmed by further studies.

Peritoneal carcinomatosis occurs as the terminal stage of many malignancies. It represents a poor prognostic factor, with a life expectancy of few months without treatment.[1] The use of hyperthermic intraperitoneal chemotherapy (HIPEC), eventually preceded by an extended cytoreductive surgery, has been widely reported in the medical literature for two decades with excellent results in terms of survival improvement for carcinomatosis from different types of cancer.[2,3] Even if this treatment can be considered effective in terms of survival, it is associated with high morbidity and mortality.[4] The use of laparoscopy to perform HIPEC may be an interesting option because it permits reduction of surgical trauma and faster recovery.[4] Laparoscopy for the treatment of intra-abdominal cancer has been reported for several years in both therapeutic and diagnostic roles, and its use has expanded rapidly.[4–6] Its application for new indications seems to be the natural evolution of the technique.

The safety and effectiveness of laparoscopy to perform complex operations such as cytoreduction and HIPEC with neoadjuvant, adjuvant, or palliative purpose have been discussed in the literature.[4,7–13]

The aim of this review was to analyze the published series reporting the laparoscopic HIPEC to evaluate the potential indications and results and to assess its role in the treatment or prevention of peritoneal carcinomatosis.

METHODS

A search in PubMed's Medline (National Library of Medicine) was performed for English-language articles through August 2011 using the keywords *laparoscopic, hyperthermic,* and *chemotherapy.* We then hand-searched the reference lists of pertinent articles. A full-text copy of each publication was obtained. All the clinical studies reporting the use of laparoscopy to perform HIPEC with prophylactic, curative, or palliative aim were considered. Experimental studies performed on animals were excluded from the analysis. When multiple reports were found from a single institution, only the most recent one including a larger number of patients was considered. A procedure was considered laparoscopic only if it was carried out completely by

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TABLE 1 Published series reporting laparoscopic HIPEC

Study	Patients with total laparoscopic procedure	Aim	Patients with carcinomatosis	Patients with ascites	Ascites treated	Primary malignancies	Chemotherapy drugs	Mean total operative time (min)	Duration of hyperthermic perfusion (min)	Complications	Mean hospital stay (days)
Chang[8]	7	Neo-adjuvant (5) palliative (2)	2	2	1	4 pancreatic, 1 gastric, 1 peritoneal mesothelioma, 1 breast	Cisplatin (250 mg/m^2) + mitomycin C (8 mg/l)	282 (range 180–360)	90	1 diarrhea and biliary sepsis (patient with pancreatic cancer and biliary stent)	3–8 (mean not available)
Knutsen[10]	5	Adjuvant	0	0	0	3 appendiceal adenocarcinoma, 1 ileal, 1 gallbladder	Mitomycin C (30 g/m^2)	216 (range 165–259)	90	1 cellulitis at a port site	1.4 (range 1–2)
Facchiano[9]	5	Palliative	5	5	5	5 gastric	Mitomycin C (120 g/m^2) + cisplatin (200 mg/m^2), sodium thiosulfate i.v. (16 g/m^2)	161 (range 130–195)	60–90	1 delayed gastric empting	23 (range 8–75)
Patriti[12]	1	Palliative	1	1	1	1 peritoneal mesothelioma	Cisplatin (25 mg/m^2/l) + doxorubicin (7 mg/m^2/l)	Not available	60	1 transient postoperative hyponatremia	7
Valle[13]	52 (53 procedures)	Palliative	52	52	49	15 gastric carcinoma, 11 colon carcinoma, 13 ovarian carcinoma, 8 breast lobular carcinoma, 4 peritoneal mesothelioma, 1 melanoma	Ovarian, mesothelioma, breast: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) colorectal, gastric: mitomycin C (12.5 mg/m^2), 10 patients: doxorubicin 20 mg/m^2	147 (range 133–210)	90	2 minor wound infections, 1 deep venous thrombosis	2.2 (range 1–9)
Ba[7]	16	Palliative	16	16	16	Gastric cancer	5-fluorine (1,500 mg), oxaliplatin (200 mg)	Not available	90	3 bone narrow suppression of I–II degree, 1 slight gastrointestinal reaction	
Esquivel[4]	10	Adjuvant (after laparoscopic cytoreduction)	10	0	0	1 peritoneal mesothelioma, 3 appendiceal neoplasm, 1 primary peritoneal carcinoma	Cisplatin, adriamycin	Not available	90	1 small bowel obstruction, 1 dehydration	6
Lygidakis[11]	87	Adjuvant (prophylactic, no carcinomatosis)	0	0	0	Stage III rectal carcinoma	Oxaliplatin, 5-fluorouracil, leucovorin, irinotecan	Not available	60	0	Not available
Total	183 (184 procedures)	Not applicable	86	76	72	Not applicable	Not applicable	Not applicable	Not applicable	13	Not applicable

laparoscopy, without conversion to open surgery. Conversions to the open procedure were excluded from the analysis. For each article, the following data were collected: year of publication, number of patients, aims of the procedure, presence or not of carcinomatosis, presence or not of malignant ascites, success or not in the treatment of ascites (when applicable), primary malignancy, chemotherapy drugs, mean operative time, duration of hyperthermic perfusion, mortality and morbidity rate, type of postoperative complications occurred, and mean hospital stay.

RESULTS

A total of 8 clinical studies reporting the use of laparoscopy to perform HIPEC have been published to date.[4,7–13] Data are summarized in Table 1. There are 7 retrospective series and 1 case report encompassing a total of 183 patients who underwent 184 procedures.[4,7–13] In 5 of the 8 series, laparoscopic HIPEC was performed in at least 1 case with the specific purpose of treating malignant ascites.[7–9,12,13] In 1 article, some of the reported procedures were performed with neoadjuvant purpose.[8] In 3 articles, the procedure had an adjuvant aim.[4,10,11] Peritoneal carcinomatosis was present in 86 of the 183 patients at the time of the laparoscopic procedure.[4,7–9,12,13] In 10 of these patients, laparoscopic HIPEC was preceded by an extensive laparoscopic cytoreduction.[4]

In 5 patients, laparoscopic HIPEC was performed with a neoadjuvant purpose, as a prophylactic act before an extended complete cytoreductive surgery (4 pancreatic adenocarcinomas, 1 gastric adenocarcinoma).[8] In these patients peritoneal carcinomatosis was not found at the time of laparoscopy, and the primary malignancies were considered completely resectable.[8]

Laparoscopic HIPEC was performed with an adjuvant aim in 102 patients.[4,10,11] In 5 of these patients, laparoscopic HIPEC was performed several weeks after extended open cytoreductive surgery.[10] In 10 patients, this procedure was performed during the same operation after a complete laparoscopic cytoreduction.[4] In 87 others, the procedure was performed 22 weeks after a primary cancer resection without evidence of peritoneal carcinomatosis.[11]

Among the 86 patients with peritoneal carcinomatosis, 76 presented malignant ascites, and laparoscopic HIPEC was performed with a palliative intent in order to treat the debilitating symptoms originating from intractable ascites.[7–9,12,13]

Primary malignancies originating carcinomatosis were gastric cancer in 37 cases, breast cancer in 9 cases, peritoneal mesothelioma in 7 cases, ovarian cancer in 13 cases, colorectal cancer in 11 cases, pancreatic cancer in 4 cases, appendiceal neoplasm in 3 cases, and primary peritoneal carcinoma and melanoma in 1 case each.[4,7–9, 12,13]

Mean operative time was clearly reported in only 4 studies; it ranged from 161 to 282 minutes comprehensive of 60–90 min of hyperthermic perfusion.[8–10,13]

The drugs used to perform HIPEC procedures were cisplatin, mitomycin C, doxorubicin, 5-fluorine, oxaliplatin, adriamycin, 5-fluorouracil, leucovotin, and irinotecan, used alone or in different combination.[4,7–13]

Among the 76 patients treated to palliate debilitating malignant ascites, the procedure was considered successful, with a complete regression of ascites in 72 patients (95 %).[7–9,12,13]

There were no deaths linked to the procedure. Among the total of 183 patients who underwent the procedure with neoadjuvant, adjuvant, or palliative intent, only 13 minor complications were recorded, and they did not require repeat operation.[4,7–10,12,13] These minor complications included 3 wound infections, 3 bone narrow suppression of I–II degree, 1 case of diarrhea with biliary sepsis, 1 case of delayed gastric empting, 1 transient hyponatremia, 1 deep venous thrombosis, 1 small bowel obstruction, and 1 case of dehydration.[4,7–10,12,13] The patient with biliary sepsis had a pancreatic cancer that had required a biliary stent.[8] Nine of the 13 minor complications were observed in the group of patients in whom laparoscopic HIPEC was carried out to palliate malignant ascites.[7,9,12,13]

DISCUSSION

Peritoneal carcinomatosis represents a common event in the terminal stage of different cancers, with a very poor prognosis and a high mortality rate within few months.[1,2] In the past 20 years, many reports have demonstrated that HIPEC associated with cytoreductive surgery could improve survival in patients with peritoneal carcinomatosis.[14–16] The rationale of HIPEC is to treat the residual microscopic disease after cytoreductive surgery by administrating a high concentration of chemotherapy into the peritoneal cavity.[7,17] This allows the abdominal cavity to be directly and constantly exposed to a high concentration of chemotherapeutic drugs, thus avoiding its massive administration in the systemic circulation, with less collateral effects.[7,18] The use of hyperthermia can potentiate the effects of local chemotherapy by improving the drug penetration, as shown by several studies, both in vivo and in vitro.[17,19] A direct cytotoxic effect of heat has also been reported.[18] Unfortunately, HIPEC, particularly if associated with extended cytoreductive surgery, is an aggressive procedure, requiring large laparotomy and a long operative time with nonnegligible morbidity and mortality rates.[2,18] The major factors of morbidity and mortality of HIPEC are the extent of cytoreduction, the number of intestinal anastomoses, the peritonectomy

procedure, and the lengthy operative time.[20,21] Laparoscopic access, when there is no need of cytoreduction or if only a limited resection is needed, can result in a less aggressive procedure.[9,10] Moreover, the use of laparoscopy to perform HIPEC may improve the effectiveness of intraperitoneal chemotherapy administration.[7,13] As reported in some experimental studies, laparoscopy should increase the intra-abdominal pressure during HIPEC, thus facilitating the chemotherapy penetration with advantageous changes in drug pharmacokinetics, as may occur in HIPEC performed with the closed technique.[22,23] To date, only 8 series encompassing a total of 183 patients showing the feasibility of laparoscopic HIPEC have been published.[4,7–13] Interestingly, no deaths related to the procedure were recorded, and a rate of only 7.1 % of minor complications was reported. The role of laparoscopic HIPEC used with adjuvant or neoadjuvant purpose is not well established in the literature. Too few series have been published so far, and none compares the laparoscopic technique to the open technique in terms of improvement of survival. Laparoscopic HIPEC has been proposed with neoadjuvant, adjuvant, and palliative aims.[4,7–13] Chang et al. report the only 5 cases of laparoscopic HIPEC with neoadjuvant purpose.[8] All the patients had surgically resectable pancreatic or gastric cancer without evidence of peritoneal dissemination, and laparoscopic HIPEC was performed with a preventive neoadjuvant purpose. The authors concluded that laparoscopic approach allows HIPEC to be performed at the time of staging in selected patients with resectable gastrointestinal cancer at a high risk for peritoneal recurrence with little morbidity and a short hospital stay.[8]

Esquivel et al. [4] describe 10 procedures of cytoreduction followed by HIPEC entirely performed laparoscopically for limited and resectable carcinomatosis. The authors recognize that HIPEC can be performed by laparoscopy only in highly selected cases, with a shorter hospital stay but with a higher morbidity compared to an open procedure.[4]

In 76 patients, laparoscopic HIPEC was performed to treat refractory malignant ascites, defined as unresponsive to noninvasive medical treatments, with a 95 % rate of success.[7–9,12,13] Palliation of malignant ascites seems to be the best indication for laparoscopic HIPEC, as we have previously proposed.[9] Because the therapeutic goal in these patients is not an increase in the length of survival but rather an improvement in quality of life, no extended cytoreduction is required. This allows a less technically demanding procedure to be performed, which may result in reduced surgical trauma and in shorter recovery time.[9] The etiology of malignant ascites is complex; it is caused by the combined effects of both tumor-produced specific proteins and mechanical obstructions to normal fluid drainage.[24] The use of conventional treatments such as administration of diuretics, repeated paracenteses, and systemic chemotherapy, even if initially useful, usually lose their efficacy over time.[25,26] On the other hand, the reduction of intra-abdominal fluid in symptomatic patients may result in longer survival and better quality of life.[9,25] Patients who mainly benefit from improvement of quality of life after HIPEC are those affected by malignant ascites because of the resolution or reduction normally observed after this procedure.[27] However, none of the studies reporting the use of laparoscopic HIPEC appraised the quality of life in the treated patients, even when the procedure was performed with the specific goal to treat uncomfortable refractory ascites. Even though HIPEC represents an important tool to treat malignant ascites, morbidity and mortality linked to the procedure do not represent a negligible problem when proposed as a palliative treatment in patients with cancer at an advanced state and a short life expectancy.[9,12] The use of laparoscopy to perform HIPEC may represent a good option by conjugating the effectiveness on ascites palliation with a minimally invasive approach.[9,12,26] The major factors of morbidity and mortality of HIPEC are the extent of cytoreduction, the number of intestinal anastomoses, the peritonectomy procedure, and the lengthy operative time.[20,21] All these factors are not present when HIPEC is performed as a palliative procedure.[9,26] Moreover, because no technically challenging act is usually necessary, laparoscopy can be often proposed as a feasible and safe approach, resulting in reduced surgical trauma and a more rapid recovery.[9,26]

Interestingly, all the published series report a very low morbidity rate and no deaths even if the number of the patients included is too small to draw major conclusions.[4,7–13] The small number of patients included in the series published so far represent a shortcoming of the present review. This constitutes and important element of evaluation for a procedure that, at our actual state of knowledge, must still be considered in the investigative stage.[4] Undoubtedly, laparoscopic HIPEC with a neoadjuvant or adjuvant aim cannot be routinely recommended for wide application because of the lack of data on its real effectiveness. Moreover, it does not seem like a good option to use the laparoscopic approach to perform cytoreduction in order to minimize the surgical trauma because in many case the tissue damage of intra-abdominal resections could be more important than that eventually derived from a laparoscopic incision. Furthermore, in such a case, the loss of tactile sensation, which is fundamental to the cytoreductive surgery, should represent an important limit.

The use of laparoscopic HIPEC as an effective tool for the palliation of malignant ascites refractory to other treatments seems to be an interesting option with a very low morbidity rate.

In conclusion, laparoscopic HIPEC appears to be a safe procedure, the effectiveness of which should be evaluated

in relationship to the indication. Its present role seems to be limited to the palliation of malignant ascites when other means have failed to provide relief to symptomatic patients. Because this procedure appears safe and effective when performed for this indication, we can hypothesize its increasing use for the treatment of patients in the terminal stage of cancer. However, further studies are necessary to evaluate this procedure's role as a neoadjuvant or adjuvant procedure.

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