

# Role of Explorative Laparoscopy to Evaluate Optimal Candidates for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Patients with Peritoneal Mesothelioma

BARBARA LATERZA<sup>1</sup>, SHIGEKI KUSAMURA<sup>1</sup>, DARIO BARATTI<sup>1</sup>,  
GRAZIA DANIELA OLIVA<sup>1,2</sup> and MARCELLO DERACO<sup>1</sup>

<sup>1</sup>Department of Surgery, National Cancer Institute, Milan;

<sup>2</sup>Department of Surgery, University of Messina, Messina, Italy

**Abstract.** *Background:* Prognosis of peritoneal mesothelioma (PM) treated by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is closely related to the completeness of the surgical cytoreduction. The reliability of explorative laparoscopy (EL) in selecting patients with PM amenable to optimal combined treatment has never been specifically assessed. *Patients and Methods:* Thirty-three patients with PM underwent EL before CRS and closed-abdomen HIPEC with cisplatin and doxorubicin. EL effectiveness in predicting complete cytoreduction (residual tumour nodules  $\leq 2.5$  mm) was analyzed. *Results:* At EL, peritoneal involvement was considered amenable to complete CRS in 30 out of 33 patients (91%). In this group, cytoreduction was complete in 29 patients and incomplete in one. Three patients were judged not amenable to complete CRS and subsequently were not able to undergo complete cytoreduction. *Conclusion:* EL findings can integrate clinical and radiological information in the selection process of patients with PM for combined treatment.

Peritoneal mesothelioma (PM) is a rare and rapidly fatal disease (1). Although different treatment approaches have been proposed, including surgery, systemic and locoregional chemotherapy, its median overall survival is 12 months (2). Recently, an innovative approach combining aggressive cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has obtained encouraging survival results in selected patients (3-6).

*Correspondence to:* Marcello Deraco, MD. Istituto Nazionale Tumori Milano, Via Venezian n.1 20133 Milano, Italy. Tel: +39 0223902362, Fax: +39 0223902404, e-mail: marcello.deraco@istitutotumori.mi.it

*Key Words:* Peritoneal mesothelioma, peritonectomy, hyperthermic intraperitoneal chemotherapy, explorative laparoscopy.

The completeness of cytoreduction is the dominant prognostic factor after combined treatment. Such a variable, however, is determined after the completion of the surgical phase, being of no use in preoperative patient selection. Recently, computed tomography (CT) scan criteria to identify the patients who can benefit from CRS and HIPEC (7) have been published. Nevertheless, CT has intrinsic limitations due to its low sensitivity in evaluating small-volume lesions (8).

Explorative laparoscopy (EL) has been used to predict the feasibility of complete cytoreduction in patients with peritoneal carcinomatosis, but its role in patients with PM has not been addressed.

This study aims to evaluate the reliability of EL in predicting the completeness of cytoreduction in patients with PM.

## Patients and Methods

From August 1995 to January 2007, seventy-four patients were submitted to CRS and HIPEC by the same surgical team at the Milan National Cancer Institute (Italy). Inclusion criteria were: confirmed histological diagnosis of PM; age  $\leq 75$  years; performance status (Eastern Cooperative Oncology Group)  $\leq 2$ ; no significant comorbidity; no extraperitoneal metastasis or peritoneal disease not amenable to potentially complete cytoreduction at pre-operative CT scan; informed written consent.

Thirty-three patients underwent EL for a better definition of peritoneal disease diffusion. Their mean age was 32 years (range 22-74 years). Histological subtype was epithelial (n=25), well-differentiated papillary (n=5), multicystic (n=1) and biphasic (n=2).

*Pre-operative explorative laparoscopy.* All the laparoscopic investigations were performed over a 12-year period by different surgical teams. However, the following procedures were respected for all the patients: under general anaesthesia, pneumoperitoneum was established with closed technique using the Verres needle or open technique using the Asson's trocar. The 0° or 30° laparoscope was introduced through a 10 mm umbilical port. One or two additional operative 5 mm trocars were positioned on the right and

Table I. Laparoscopic and surgical exploration findings in four patients who did not achieve complete cytoreduction.

Laparoscopic exploration findings				Surgical exploration findings			
Epigastric tumour >5 cm	Involvement of small bowel and its mesentery	PCI	Amenable to complete cytoreduction	Epigastric lesion >5 cm	Involvement of small bowel and its mesentery	PCI	CC
No	No	10	Yes	No	Yes	33	2
No	Yes	26	No	No	Yes	30	2
No	Yes	36	No	No	Yes	39	2
No	Yes	29	No	No	Yes	39	3

PCI: peritoneal cancer index; CC: completeness of cytoreduction.

left side of the optical trocar; parietal peritoneum, liver surfaces, bilateral diaphragm undersurfaces, epigastric region, hepatic hilum, greater omentum, pelvic region, small bowel and its mesentery were assessed; adhesiolysis was performed as necessary; multiple biopsies were carried out. Patients with incomplete laparoscopic evaluation were excluded. The mean operative time was 40 minutes (range 20-60 minutes). No complications were reported.

Final judgement of the possibility of obtaining a complete cytoreduction was made by the senior surgeon after careful examination of EL tapes. Disease involvement of critical areas such as the epigastric region and the small bowel and its mesentery was specifically assessed. The laparoscopic Peritoneal Cancer Index (PCI) was determined.

*Cytoreductive surgery and HIPEC.* CRS was performed with the aim of removing all the visible tumour, as described previously. Peritoneal carcinomatosis was quantified at surgical exploration according to the PCI (9). The CC was classified at the end of the cytoreduction according to Sugarbaker (9): CC-0, no residual disease; CC-1, residual disease ≤2.5 mm; CC-2, residual disease >2.5 to ≤25 mm; CC-3, residual disease >25 mm. CC- 0 to -1 indicates optimal cytoreduction and CC-2 to -3 indicates suboptimal cytoreduction.

HIPEC was performed according to the closed-abdomen technique with cisplatin (43 mg/l of perfusate) and doxorubicin (15.25 mg/l of perfusate) for 90 minutes at 42.5°C. Perfusate volume was 4-6 L with an average flow of 700 ml/min. An extracorporeal perfusion circuit [Performer LRT; RAND, Medolla (MO), Italy] was used.

*Statistics.* The primary studyend point was the effectiveness of laparoscopic exploration to predict the completeness of cytoreduction. Sensitivity was defined as the percentage of patients undergoing complete CRS who were deemed amenable to complete CRS at EL. Specificity was defined as the percentage of patients undergoing incomplete CRS who were deemed not amenable to complete CRS at EL. Positive predictive value was the percentage of patients who were deemed amenable to complete CRS at EL and underwent complete CRS. Negative predictive value was the percentage of patients who were deemed not amenable to complete CRS at EL and underwent incomplete CRS. Accuracy was the percentage of patients correctly diagnosed by EL.

Additionally, the reliability of EL in identifying a tumour mass >5 cm in the epigastric region and a massive involvement of the small bowel and its mesentery were assessed by comparison to laparotomy findings.

## Results

At EL, peritoneal involvement was considered amenable to complete CRS in 30 out of 33 patients (91%). In this group, cytoreduction was complete (CC- 0 to 1) in 29 patients and incomplete in one. Three patients were judged not amenable to complete CRS at EL and they all underwent suboptimal CRS (CC- 2 to -3) and HIPEC for palliation of intractable ascites. Overall, the completeness of cytoreduction was not predicted correctly in only one patient.

In the present series, sensitivity was 29/29 (100%), specificity 3/4 (75%), positive predictive value 29/30 (96.6%), negative predictive value 3/3 (100%) and accuracy 32/33 (96.9%).

Regarding the specific sites of disease involvement, no patients presented an epigastric lesion >5 cm diameter at both laparoscopic and surgical exploration. Massive involvement of the small bowel and its mesentery was apparent in three patients at EL, but at surgical exploration it was confirmed in four.

The characteristics of the four patients who did not receive a complete cytoreduction are shown in Table I. EL provided disease quantification comparable to surgical exploration.

## Discussion

Over the last decade, the combination of CRS and HIPEC has been associated with survival improvement, as compared to historical series of PM conventionally treated by palliative surgery and systemic/intraperitoneal chemotherapy. This innovative treatment approach is complex, expensive and related to high rates of morbidity and operative mortality. Accordingly, the selection of patients who may benefit from this combined procedure is an important issue.

Nowadays, CT scan represents the most reliable diagnostic study to assess the peritoneal diffusion of PM, although its low sensitivity towards small peritoneal nodules may result in unexpected findings of unresectable tumour deposits (10). In patients with inconclusive radiological evaluation, operative laparoscopy may visualize peritoneal surfaces and obviate the need to perform a surgical exploration. The

Table II. Literature and present study data on effectiveness of laparoscopic evaluation in predicting the completeness of cytoreduction.

Authors (ref.)	Year	No. of patients	Disease	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Pomel <i>et al.</i> (12)	2005	11	PM, ovarian and colorectal cancer PC	100	NA	91	87.5	NA
Valle and Garofalo (13)	2006	97	PM, PMP, GI and breast PC Sarcomas	100	NA	98	98	NA
Present study	2008	33	PM	100	75	97	97	100

PM: peritoneal mesothelioma; PMP: pseudomixoma peritonei; PC: peritoneal carcinomatosis; GI: gastrointestinal; NA: not available; PPV: positive predictive value; NPV: negative predictive value.

benefits of laparoscopic surgery are obvious in terms of less pain, shorter hospitalization and quicker time to recovery. Other advantages are low intra- and postoperative morbidity and sanitary costs. Although it has been demonstrated that laparoscopic staging may spare unnecessary laparotomies in a significant number of cases (11), the role of EL in patients with PM has never been addressed in the literature.

Several studies have evaluated the ability of explorative laparoscopic in assessing the extent of peritoneal dissemination in gastrointestinal and ovarian cancer (12, 13), and in selecting the candidates for CRS and HIPEC. Some of these publications involve a few cases of PM.

In 2005, Pomel *et al.* reported 11 patients as candidates for CRS and HIPEC for peritoneal carcinomatosis of different origins who underwent explorative laparoscopy. At laparoscopy, three patients were judged to have not resectable peritoneal carcinomatosis. The authors obtained agreement between laparoscopic and surgical exploration findings of 87.5% (12).

Recently Valle and Garofalo published a report regarding a series of 97 patients with peritoneal carcinomatosis (seven with PM). EL was not feasible in one patient and the disease was understaged in two (one with PM). The authors reported no major complications and no neoplastic infiltration at trocar sites. Reliable information on disease extent were obtained in 98% of patients (13).

Our results are comparable to those of the aforementioned (see Table II). Specificity and negative predictive value were reported only in our series since we also performed CRS and HIPEC in patients considered not cytoreducible at EL in order to palliate ascites not responsive to any medical treatment. Differently from previous studies, the present one included only patients with PM. Furthermore, we analysed two well-defined potential predictive factors of incomplete cytoreduction: massive involvement of the small bowel and its mesentery, and the presence of an epigastric lesion >5 cm.

The possible limitations of the present study are its retrospective nature and the fact that laparoscopic exploration was performed by different surgical teams. Nevertheless, all laparoscopic videos were re-evaluated by the same senior surgeon to assess the likelihood of obtaining a complete

cytoreduction. Furthermore, the high degree of agreement between laparoscopic and surgical findings demonstrates that pre-operative laparoscopic evaluation may give helpful information even if performed by general surgeons without specific experience with CRS and HIPEC. Nevertheless, it is clear that a standardized laparoscopic approach is needed in this clinical setting.

In the present series, no patients developed port trocar metastases after EL. Port trocar metastasis is a potential complication of explorative laparoscopy in patients with peritoneal malignancies. This event has an estimated hazard of occurrence ranging from 1.1% to 3.9% (14). It has been demonstrated that a careful laparoscopic procedure can minimize the formation of the port trocar tumour seeding (15).

In conclusion, explorative laparoscopy can reliably predict the completeness of cytoreduction in patients with PM for whom clinical and radiological information is not conclusive.

## References

- 1 Antman KH, Blum RH, Greenberger JS, Flowerdew G, Skarin AT and Canellos GP: Multimodality therapy for malignant mesothelioma based on a study of natural history. *Am J Med* 68: 356-362, 1980.
- 2 Eltabbakh GH, Piver MS, Hempling RE, Recio FO and Intengen ME: Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma. *J Surg Oncol* 70: 6-12, 1999.
- 3 Feldman AL, Libutti SK, Pingpank JF, Bartlett DL, Beresnev TH, Mavroukakis SM, Steinberg SM, Liewehr DJ, Kleiner DE and Alexander HR: Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol* 21: 4560-4567, 2003.
- 4 Deraco M, Nonaka D, Baratti D, Casali P, Rosai J, Younan R, Salvatore A, Cabras AD and Kusamura S: Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 13: 229-237, 2006.
- 5 Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR and Levine EA: Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg* 67: 999-1003, 2001.

- 6 Brigand C, Monneuse O, Mohamed F, Sayag-Beaujard AC, Isaac S, Gilly FN and Glehen O: Peritoneal mesothelioma treated by cytoreductive surgery and intraperitoneal hyperthermic chemotherapy: results of a prospective study. *Ann Surg Oncol* 13: 405-412, 2006.
- 7 Yan TD, Haveric N, Carmignani CP, Chang D and Sugarbaker PH: Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Cancer* 103: 839-849, 2005.
- 8 Jacquet P, Jelinek JS, Steves MA and Sugarbaker PH: Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 5: 1631-1636, 1993.
- 9 Jacquet P and Sugarbaker PH: Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res* 15: 49-58, 1996.
- 10 Deffieux X, Castaigne D and Pomel C: Role of laparoscopy to evaluate candidates for complete cytoreduction in advanced stages of epithelial ovarian cancer. *Int J Gynecol Cancer* 16(Suppl 1): 35-40, 2006.
- 11 Buyske J: Role of laparoscopic-assisted techniques in staging malignant diseases. *Surg Clin North Am* 80: 495-503, 2000.
- 12 Pomel C, Appleyard TL, Gouy S, Rouzier R and Elias D: The role of laparoscopy to evaluate candidates for complete cytoreduction of peritoneal carcinomatosis and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 31(5): 540-543, 2005.
- 13 Valle M and Garofalo A: Laparoscopic staging of peritoneal surface malignancies. *Eur J Surg Oncol* 32(6): 625-627, 2006.
- 14 Paolucci V, Schaeff B, Schneider M and Gutt C: Tumor seeding following laparoscopy: international survey. *World J Surg* 23(10): 989-997, 1999.
- 15 Lacy AM, Delgado S, Garcia-Valdecasas JC, Castells A, Piqué JM, Grande L, Fuster J, Targarona EM, Pera M and Visa J: Port site metastases and recurrence after laparoscopic colectomy. A randomized trial. *Surg Endosc* 12(8): 1039-1042, 1998.

*Received June 12, 2008*

*Revised August 8, 2008*

*Accepted August 19, 2008*