Short-term Outcome of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Preliminary Analysis of a Multicentre Study

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Abstract. *Aim: To assess the incidence of morbidity and mortality of Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy. Patients and Methods: A retrospective multicentric study was performed. Six hundred and eighty-three patients were recorded. Predictors of morbidity and mortality were evaluated with univariate and multivariate analysis. Results: In univariate analysis, older age, Eastern Cooperative Oncology Group score, a greater value of Peritoneal Cancer Index (PCI) and sub-optimal cytoreduction were correlated with higher mortality, while older age, presence of ascites, ovarian origin of carcinomatosis, closed technique, a greater value of PCI, longer operative time and sub-optimal cytoreduction were predictors of higher morbidity. In multivariate analysis, older age and a greater value of PCI were correlated with higher mortality; older age, ovarian origin of tumor, presence of ascites, closed technique and longer operative time were predictors of higher morbidity. Conclusion: Careful patient selection has to be performed to improve clinical outcomes.*

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Cytoreductive surgery (CRS) plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) represent a promising approach to treat peritoneal surface malignancies (PSM) (1-3). Actually, mortality and morbidity rates remain the most comprehensive measures used to assess short-term outcomes of a specific procedure. Surgical complications are frequently the main reason to modify patient treatment. Nevertheless, nowadays these two outcome measures remain hard to assess and identify by the surgical literature for the lack of standardization and under-reporting. For this reason, presently, in the surgical field, there is an absence of a clear system to classify complications. These considerations are valid also for CRS plus HIPEC. Furthermore, the issue is relatively complex because the appearance of postoperative complications related to surgery can be confounded with toxic side effects of the intraperitoneal chemotherapy.

To provide a substantial contribution to this field, we carried out a multicentre retrospective study. We report on the preliminary analysis of this experience.

Patients and Methods

A retrospective multicentre study from eight Italian Centres was performed. Six hundred and eighty-three patients submitted in

the November 2000 – January 2014 period to CRS-plus-HIPEC, were recorded.

Two centres recorded more than 100 cases, four centres between 50 to 100 and two centres less than 50. To satisfy the statistical criteria, only 507 patients were enrolled. Morbidity was evaluated in accordance with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Predictors age, gender, body-mass index (BMI), primary tumour site, Eastern Cooperative Oncology Group (ECOG) score, ascites, neoadjuvant chemotherapy (NACT), HIPEC technique, Peritoneal Cancer Index (PCI), operative time, Completeness of Cytoreduction score (CC-score) of morbidity and mortality were evaluated with univariate and multivariate analysis. *p*-Values <0.05 were considered statistically significant.

Results

The mean age of the patients was 56.6 years standard deviation (SD)±11.5; 83% were female. Four hundred and sixty-one (90.9%) patients had peritoneal carcinomatosis, 293 were of ovarian, 106 of colon and 62 of gastric origin; 46 (9.1%) patients had other peritoneal malignancies. The ECOG score was 0 for 193 patients (38.1 %), 1 for 150 (29.6%), 2 for 136 (26.8%) and 3 for 28 (5.5%). One hundred and seventy-four patients (50.7%) had preoperative ascites. Average BMI was 24.9 (±4.6). Ninety-three patients (18.3%) were submitted to NACT. The average PCI was 12 (±9.4). The closed abdomen technique was used in 396 cases (78.1%) and the Coliseum technique in 111 (21.9%). Three hundred and eighty-seven (76.3%) patients did not have visible residual disease (CC-0 score), 73 (14.4%) had residual disease ≤2.5 mm (CC-1 score), 29 (5.7%) had residual disease between 2.5 mm and 2.5 cm (CC-2 score) and 18 (3.6%) had residual disease >2.5 cm (CC-3 score). The average operative time was 504 min (±156,2) (Table I). The mean stay in the intensive care unit was 2.1 days (range=0-18 days). Mean hospital stay was 16.5 days (range=1-95 days). Grade 2-4 morbidity occurred in 280 patients (55.2%). Between the recorded complications (Table II), the most frequent were: pleural effusion (10.2%), anemia (9.8%), pancreatitis (9.4%), nausea (8%), postoperative ileus (7.6%), renal deficiency (6.9%), sepsis (5.3%), wound infections (4.9%) and intestinal perforations (4.3%). Overall re-operation percentage was 7.2% (intestinal leakage: 18 cases, haemoperitoneum: 14 cases, abdominal abscess: 3 cases and colostomy dehiscence: 2 cases). Mortality occurred in 18 cases (3.6%). The causes of death were: 1 Wernicke syndrome, 1 pulmonary embolism, 3 haemoperitoneum, 5 cardio-respiratory failure, and 8 multi-organ failure (5 correlated with an intestinal fistula, 2 determined by sepsis and 1 post-haemoperitoneum). In univariate analysis, the older age (p=0.027), the ECOG score 3 *vs*. 0 (p=0.016), a greater value of PCI (p=0.014) and CC-score 2 *vs*. 0 (p=0.044) were correlated with a higher mortality, while the older age (p<0.01), the presence of ascites (p<0.01), the ovarian origin of carcinomatosis (p<0.01), the closed abdomen technique (p=0.015), a greater value of PCI (p=0.014), longer operative time (p<0.01) and CC-score 1 *vs*. 0 (p=0.022) and 2 *vs*. 0 (p=0.043) were predictors of higher morbidity. In multivariate analysis the older age (p=0.047) and a greater value of PCI (p=0.026) were correlated with a higher mortality; the older age (p<0.01), the ovarian origin of tumour (p<0.01), the presence of ascites (p=0.011), the closed abdomen technique (p<0.01) and longer operative time (p<0.01) were predictors of higher morbidity (Tables III and IV).

Discussion

PSM has been regarded as inoperable condition and treated by systemic chemotherapy or palliative therapies. Based on the theory that PSM is a locoregional disease, CRS-plus-HIPEC have been applied in selected patients with these pathologies. Chua *et al*. (4) have showed that the morbidity and mortality of CRS and HIPEC were similar to other major gastrointestinal interventions. In literature, major morbidity rates have been reported ranging from 12% to 57% in high-volume centres (4-5), even if, in recent publications, the overall grade III-IV morbidity rates are shown to be between 7 and 41% (6-11). These results are due to the learning curve that has been demonstrated to be necessary to minimize mortality and morbidity after the procedure (12, 13). Instead, regarding the mortality, it is reported that it ranges from 0.9% to 11% (4, 14, 15).

Among the numerous classifications used to report morbidity, some investigators have preferred to use the Clavien system (16), others the Feldman or modified Clavien system (17), still others the Elias classification (18), the Bozzetti classification (19) or the CTCAE (20). This heterogeneity in the adopted systems impedes the comparison between treatment-related complication rates among the various reports. All these classification systems, beyond to be different from each other, are no intended, except CTCAE, to account for toxicities related to the use of chemotherapy during HIPEC. For this reason, Kusamura proposed to use the World Health Organization toxicity scale (6). Others authors, Elias (18), Smeenek (21) and Glehen (7), prefer to use the CTCAE version 3.0 (20) that, in 2006, during the 5th International Workshop on Peritoneal Surface Malignancy (22), was adopted by an international panel of experts as the definitive classification system for complications resulting from CRS plus HIPEC. In 2009, an updated version of CTCAE called version 4.0 was published (20).

There are many risk factors, as described in the literature, associated with the appearance of complications related to CRS plus HIPEC. However, it is not possible to make a comparison between the various series because of the

Table I. *Patients' characteristics*.

	N°
Patients	683
Enrolled patients	507
Mean age (range) (years)	56.6 (28-77)
Gender	
Male	97 (17%)
Female	412 (83%)
Average BMI	24.9±4.6
Peritoneal carcinomatosis	461 (90.9%)
Ovarian origin	293
Colon origin	106
Gastric origin	62
Peritoneal malignancies from other origins	46 (9.1%)
Performance status (ECOG)	
0	193 (38.1%)
1	150 (29.6%)
2	136 (26.8%)
3	28 (5.5%)
Ascites	174 (50.7%)
NACT	93 (18.3%)
Mean PCI (range)	12 (0-39)
Average operative time (min)	504 (SD±156.2)
HIPEC technique	
Closed abdomen	396 (78.1%)
Coliseum	111 (21.9%)
Postoperative residual disease (CC Score)	
0	387 (76.3%)
1	73 (14.4%)
2	29 (5.7%)
3	18 (3.6%)

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; NACT: NeoAdjuvant ChemoTherapy; Min: minutes; PCI: Peritoneal Cancer Index; HIPEC: Hyperthermic IntraPEritoneal Chemotherapy CC score: Completeness of Cytoreduction score.

Table II. *Complications schedule*.

Blood disorders
- o Anemia 50 pts.
- o Leukopenia 19 pts.
- o Trombocytopenia 18 pts.

Cardiac disorders
- o Arrhythmia 10 pts.
- o Myocardial infarction 4 pts.

Gastrointestinal disorders
- o Intestinal perforation 22 pts.
- o Haemoperitoneum 18 pts.
- o Anastomotic leakage 1 pts.
- o Pancreatic fistula 9 pts.
- o GI haemorrhage 5 pts.
- o Abdominal abscess 6 pts.

General disorders
- o Nausea 41 pts.
- o Emesis 7 pts.
- o Diarrhea 1 pt.
- o Postoperative ileus 39 pts.
- o Gastric stasis 1 pt.

Hepato-bilio-pancreatic disorders
- o Pancreatitis 48 pts.
- o Biliary complications 6 pts.

Infections
- o Sepsis 27 pts.

MOF
- o 8 pts.

Nervous system disorders
- o 7 pts.

Respiratory, thoracic and mediastinal disorders
- o Pleural effusion 52 pts.
- o PNX 21 pts.
- o Respiratory distress 4 pts.
- o Pulmonary oedema 5 pts.
- o Pulmonary embolism 11 pts.
- o Pneumonia 19 pts.
- o Diaphragmatic perforation 2 pts.

Renal and urinary disorders
- o Urinary infection 6 pts.
- o Renal deficiency 35 pts.
- o Urinary leakage 8 pts.

Skin and subcutaneous tissue disorders
- o Wound infection 25 pts.

Vascular disorders
- o DVT 6 pts.
- o DIC 6 pts.

Pts: Patients; GI: GatroIntestinal; MOF: multi organ failure; PNX: pneumothorax; DVT: deep venous thrombosis; DIC: disseminated intravascular coagulation.

numerous variables used by the different authors. Thus, we report the most representative series in this field: Kusamura *et al*. (6), in their report, by a univariate analysis, found that the following variables were proven to have a statistically significant correlation with major morbidity: male gender, ECOG score, no previous systemic chemotherapy, carcinomatosis extension, number of bowel anastomoses >2, duration of procedure, extent of cytoreduction and dose of CDDP >240 mg. In multivariate analysis, no previous systemic chemotherapy, extent of cytoreduction and fractionated dose of cisplatin (CDDP) >240 mg were independent risk factors for major morbidity. Glehen *et al*. (7) have carried out only a univariate analysis reporting that major morbidity was statistically linked with the carcinomatosis stage, duration of surgery and number of resections and of peritonectomy procedures. Hansson *et al*. (8), instead, in their multivariate analysis, have observed that morbidity was associated with stoma formation, duration of surgery, perioperative blood loss and PCI. Casado-Adam *et al*. (9), in their univariate analysis, have found a statistically significant correlation between morbidity, histological grade, PCI, small bowel resections, colorectal anastomosis and the number of anastomoses performed; their multivariate analysis shown that PCI was the only independent risk factor for gastrointestinal complications. Finally, Mizumoto *et al*. (10), in their univariate analysis, have showed that PCI greater than

Table III. *Univariate and multivariate analysis of risk factors for morbidity.*

	Univariate[a] *p*-Value	Multivariate[b] *p*-Value
Gender	0.122	
Age	<0.01	<0.01
BMI	0.248	
Primary tumour site		
Colon	0.021	
Stomach	0.541	<0.01
Ovary	<0.01	
ECOG		
1	0.543	
2	0.652	
3	0.708	
Ascites	0.003	0.011
NACT	0.216	
HIPEC technique	0.015	<0.01
PCI	0.014	
Operative time	<0.01	<0.01
CC score		
1	0.022	
2	0.004	
3	0.174	

[a]Chi square test or Fisher's exact test. [b]Logistic regression model with backward elimination method. BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; NACT: NeoAdjuvant ChemoTherapy; Min: minutes; PCI: Peritoneal Cancer Index; HIPEC: Hyperthermic IntraPEritoneal Chemotherapy; CC score: Completeness of Cytoreduction score.

Table IV. *Univariate and multivariate analysis of risk factors for mortality.*

	Univariate[a] *p*-Value	Multivariate[b] *p*-Value
Gender	0.524	
Age	0.027	0.047
BMI	0.643	
Primary tumour site		
Colon	1.000	
Stomach	0.473	
Ovary	0.478	
ECOG		
1	0.105	
2	0.232	
3	0.016	
Ascites	1.000	
NACT	0.755	
HIPEC technique	0.775	
PCI	0.014	0.026
Operative time	0.438	
CC score		
1	0.565	
2	0.044	
3	0.480	

[a]Chi square test or Fisher's exact test. [b]Logistic regression model with backward elimination method. BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; NACT: NeoAdjuvant ChemoTherapy; Min: minutes; PCI: Peritoneal Cancer Index; HIPEC: Hyperthermic IntraPEritoneal Chemotherapy; CC score: Completeness of Cytoreduction score.

20, operation time longer than 5 h and blood loss greater than 2.5 l were significant risk factors for the occurrence of postoperative complications. Multivariate analysis showed that PCI higher than 20 was the only significant factor which increased the occurrence of postoperative complications. A PCI greater than 20 was associated with 2.8-times increased risk of postoperative complications.

The analysis of our experience documented that mortality and morbidity rates of CRS-plus-HIPEC are acceptable and within the literature range. Morbidity was correlated with some predictive factors already documented in the literature (6, 9, 10), like PCI, operation time and extension of cytoreduction in univariate analysis, with the operative time being the predictive factor for the multivariate one. Instead, original results are represented by the statistical correlation, both on uni- and multivariate evaluation, between morbidity and the older age of patients, the presence of preoperative ascites, the ovarian origin of carcinomatosis and the closed abdomen technique used to perform the HIPEC.

While the presence of ascites, indirect index of diffuse disease, should be assimilable to the role of the PCI, statistically significant also in the multivariate analyses of Hasson (8), Casado-Adam (9) and Mizumoto (10), the older age (23, 24), the ovarian origin of tumor and HIPEC technique are not supported by the literature. We retain that the higher percentage of morbidity correlated with closed abdomen technique is particularly interesting, because this finding has never been reported in the literature. We think that further analyses are useful to understand if the lower complication rates correlated to the Coliseum technique are dependent on the technique or the two samples of patients have different characteristics.

Concerning mortality, we did not find any items against which to compare our results, therefore we believe that they can be considered a landmark in this topic. In particular, mortality was statistically correlated, in univariate analysis, with older age of patients, higher ECOG score, greater value of PCI and CC score 3 *vs*. 0 and, in multivariate one, only with older age and higher PCI.

In conclusion, in light of this preliminary analysis, we retain that, to improve short-term outcome of patients submitted to CRS-plus-HIPEC, an optimal selection is necessary, referring especially to PCI and age, with particular care to the performance status.

With respect to the higher morbidity and mortality correlated to an incomplete cytoreduction, we retain that it

is mandatory to carry-out the preoperative staging as accurately as possible, considering the possibility to include, in the diagnostic algorithm of doubtful cases, the exploratory laparoscopy approach.

Our intention is to subsequently provide more detailed evaluation of the role of the HIPEC technique after performing a more accurate assessment of the two groups of patients subjected to open or closed approach.

References

1 Macrì A: New approach to peritoneal surface malignancies. World J Gastrointest Oncol *2(1)*: 9-11, 2010.

2 Levine EA, Stewart JH 4th, Shen P and Russell GB, Loggie BL, Votanopoulos KI: Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. J Am Coll Surg *218(4)*: 573-585, 2014.

3 Macrì A, Maugeri I, Trimarchi G, Caminiti R, Saffioti MC, Incardona S, Sinardi A, Irato S, Altavilla G, Adamo V, Versaci A and Famulari C: Evaluation of quality of life of patients submitted to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinosis of gastrointestinal and ovarian origin and identification of factors influencing outcome. In Vivo *23(1)*: 147-150, 2009.

4 Chua TC, Yan TD, Saxena A and Morris DL: Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Annals of Surgery *249*: 900-907, 2009.

5 Stewart JH IV, Shen P and Levine EA: Intraperitoneal hyperthermic chemotherapy: an evolving paradigm for the treatment of peritoneal surface malignancies. Expert Rev Anticancer Ther *8*: 1809-1818, 2008.

6 Kusamura S, Younan R, Baratti D, Costanzo P, Favaro M, Gavazzi C and Deraco M: Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: Analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer *106*: 1144-1153, 2006.

7 Glehen O, Osinsky D, Cotte E , Kwiatkowski F, Freyer G, Isaac S, Trillet-Lenoir V, Sayag-Beaujard AC, François Y, Vignal J and Gilly FN: Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: Morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol *10*: 863-869, 2003.

8 Hansson J, Graf W, Pahlman L, Nygren P and Mahteme H: Postoperative adverse events and long-term survival after cytoreductive surgery and intraperitoneal chemotherapy. Eur J Surg Oncol *35*: 202-208, 2009.

9 Casado-Adam A, Alderman R, Stuart OA, Chang D and Sugarbaker PH: Gastrointestinal complications in 147 consecutive patients with peritoneal surface malignancy treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Int J Surg Oncol 2011. Article ID 468698, 10 pages. doi:10.1155/2011/468698.

10 Mizumoto A, Canbay E, Hirano M , Takao N, Matsuda T, Ichinose M and Yonemura Y: Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at a single institution in Japan. Gastroenterol Res Pract 2012:836425. doi: 10.1155/2012/836425.

11 Youssef H, Newman C, Chandrakumaran K, Mohamed F, Cecil TD and Moran BJ: Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin Dis Colon Rectum *54*: 293-299, 2011.

12 Smeenk RM, Verwaal VJ and Zoetmulder FA: Learning curve of combined modality treatment in peritoneal surface disease. Brit J Surg *94*: 1408-1414, 2007.

13 Kusamura S, Baratti D and Deraco M: Multidimensional analysis of the learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies. Ann Surg *255*: 348-356, 2012.

14 Feldman L, Barkun J, Barkun A, Sampalis J and Rosenberg L: Measuring postoperative complications in general surgery patients using an outcomes-based strategy: Comparison with complications presented at morbidity and mortality rounds. Surgery *122*: 711-719, 1997.

15 Verwaal, VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H and Zoetmulder FA: Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy *versus* systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol *21*: 3737-3743, 2003.

16 Clavien PA, Sanabria JR and Strasberg SM: Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery *111*: 518-526, 1992.

17 Elias D, Matsuhisa T, Sideris L, Liberale G, Drouard-Troalen L, Raynard B, Pocard M, Puizillou JM, Billard V, Bourget P and Ducreux M: Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: Pharmacokinetics, tissue distribution and tolerance. Ann Oncol *15*: 1558-1565, 2004.

18 Bozzetti F, Braga M, Gianotti L, Gavazzi C and Mariani L: Postoperative enteral *versus* parenteral nutrition in malnourished patients with gastrointestinal cancer: A randomised multicentre trial. Lancet *358*: 1487-1492, 2001.

19 Younan R, Kusamura S, Baratti D, Cloutier AS and Deraco M: Morbidity, toxicity, and mortality classification systems in the local regional treatment of peritoneal surface malignancy. J Surg Oncol *98*: 253-257, 2008.

20 https:ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

21 Smeenk RM, Verwaal VJ and Zoetmulder FA: Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei-A report of 103 procedures. Eur J Surg Oncol *32*: 186-190, 2006.

22 Baratti D, Kusamura S and Deraco M: The Fifth International Workshop on Peritoneal Surface Malignancy (Milan, Italy, December 4-6, 2006: methodology of disease-specific consensus. J Surg Oncol *98(4)*: 258-262, 2008.

23 Spiliotis JD, Halkia E, Boumis VA, Vassiliadou DT, Pagoulatou A and Efstathiou E: Cytoreductive surgery and HIPEC for peritoneal carcinomatosis in the elderly. Int J Surg Oncol 2014; 2014: 987475.

24 Macrì A, Saladino E, Trimarchi G, Bartolo V, Rossitto M, Cannaò A, Rizzo A and Famulari C: Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy in elderly patients. In Vivo *25(4)*: 687-690, 2011.

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