

ORIGINAL ARTICLE

## The cost of cytoreductive surgery and perioperative intraperitoneal chemotherapy in the treatment of peritoneal malignancy in one Greek institute

A.A. Tentes<sup>1</sup>, N. Pallas<sup>1</sup>, O. Korakianitis<sup>2</sup>, C. Mavroudis<sup>2</sup>, A. Spiridonidou<sup>2</sup>, G. Zorbas<sup>1</sup>, S. Popidis<sup>1</sup>, N. Papadoniou<sup>1</sup>, V. Darladima<sup>1</sup>, A. Smyrnis<sup>1</sup>, C. Siopis<sup>1</sup>

<sup>1</sup>Department of Surgery, <sup>2</sup>Department of Anesthesiology, Didimotichon General Hospital, Didimotichon, Greece

### Summary

**Purpose:** Cytoreductive surgery and perioperative intraperitoneal chemotherapy in the treatment of patients with peritoneal malignancy is expensive. The purpose of this study was to estimate the current cost of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy and identify the most significant related parameters in one center in Greece.

**Methods:** A retrospective economic study was carried out on 105 patients that underwent 108 cytoreductive operations and hyperthermic intraoperative peritoneal chemotherapy (HIPEC) from 2006-2011 for peritoneal malignancy. The economic cost included the daily cost of hospital bed occupancy, the daily cost of occupancy in the intensive care unit (ICU), the expenditures (materials and drugs), and the pre-

operative, intraoperative, and postoperative examinations.

**Results:** The mean length of stay in the ICU and the mean hospitalization time was 5 and 23 days, respectively. The hospital mortality and morbidity was 5.6% (6 patients) and 48.1% respectively. The mean cost of treatment was 15677.3±11910.6 euros (range=4258,47-95990,87) per patient. Morbidity ( $p=0.009$ ), and prolonged stay in the ICU ( $p<0.001$ ) were the parameters that influenced independently the cost of treatment.

**Conclusion:** Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is an expensive treatment. The economic cost is largely influenced by morbidity and the length of stay in the ICU.

**Key words:** cost, HIPEC, perioperative intraperitoneal chemotherapy, peritoneal surface malignancy

### Introduction

Four decades ago peritoneal surface malignancy was considered a lethal disease with short survival and poor quality of life [1, 2]. The implementation of cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancy has improved survival in properly selected patients [3-9]. This novel technique has been used in the last decade in peritoneal malignancy centers in the USA, Europe, Asia, and Australia for peritoneal malignancy of gynecologic and gastrointestinal origin with low mortality and high morbidity rate [10-13]. The economic cost of this treatment is high because expenditures (drugs and materials) are expensive, the reimbursement rate is low, and morbidity is high. Patients presenting with complications usually require

prolonged stay in the ICU [14,15]. A preliminary report from two institutes in Greece has shown that the cost of this treatment is not as high as has been reported by others [16].

The purpose of maximal cytoreductive surgery using standard peritonectomy procedures is the resection of all the macroscopically visible cancer if possible. Multi-visceral resection is frequently required for this purpose [17]. The aim of intraperitoneal chemotherapy is eradication of residual microscopic disease. Expensive drugs and materials, high technology, and closed monitoring in the ICU are required. As a consequence the economic cost is obviously raised above the usual cost that is estimated for procedures characterized as major surgical operations.

Patients with peritoneal malignancy are categorized using the diagnosis-related group of classification

in which cytoreductive surgery and perioperative intraperitoneal chemotherapy is not included. This methodology is used in most European countries. According to current diagnosis-related groups of classification the high cost of this treatment has been shown to produce a significant financial deficit in the hospitals [14,18].

The number of publications focused on the economic cost of this treatment is limited. The purpose of this study was the estimation of the economic cost of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy in one Greek institute after 6-year experience in the treatment of patients with peritoneal malignancy.

## Methods

From 2006-2011, the files of patients with peritoneal surface malignancy that had undergone cytoreductive surgery with perioperative intraperitoneal chemotherapy were retrospectively reviewed.

Perioperative intraperitoneal chemotherapy is either HIPEC or early normothermic postoperative intraperitoneal chemotherapy (EPIC).

All patients were preoperatively assessed for the extent of prior surgery using prior surgical score (PSS). Patients that had not undergone any previous surgery were assessed as PSS-0. Patients that had undergone biopsy or surgery in one abdominopelvic region were assessed as PSS-1, those that had undergone surgery in 2-5 abdominopelvic regions were assessed as PSS-2, and those that had undergone surgery in more than 5 abdominopelvic regions were assessed as PSS-3. Patients were also assessed for their Karnofsky performance status and the extent of peritoneal dissemination using the peritoneal cancer index (PCI). Patients that were able to undergo major surgery and complete or near-complete cytoreduction were eligible for treatment. Those patients that had distant and unresectable metastatic disease were excluded.

### Treatments

#### Surgery

A midline incision was always used for maximal exposure of the abdominal cavity. The extent of peritoneal malignancy was assessed using the PCI after lysis of the adhesions. After tumor resection the completeness of cytoreduction was assessed using the CC-score [19]. Maximal cytoreductive surgery was possible using standard peritonectomy procedures: 1) epigastric peritonectomy procedure; 2) right subdiaphragmatic; 3) left subdiaphragmatic; 4) greater omentectomy+splenectomy; 5) lesser omentectomy; 6) pelvic peritonectomy; 7) right parietal peritonectomy; 8) left parietal peritonectomy; 9) antrectomy, subtotal gastrectomy, or total gastrectomy; 10) colectomy other than low anterior resection; 11) segmental intestinal resection.

#### HIPEC

The number of peritonectomy procedures was recorded in all patients. HIPEC was administered after tumor resection and before the reconstruction of the alimentary tract. The open abdominal technique (Coliseum) was used for HIPEC. HIPEC was possible

with a continuous extracorporeal circuit of four drains (two inflow and two outflow), one heat exchanger, and one or two roller pumps (depending on the type of the device) at 42.5-43° C for 60-90 min, depending on the cytotoxic drug.

Mitomycin-C (20 mg/m<sup>2</sup>) was used for the treatment of colorectal cancer and pseudomyxoma peritonei. Cisplatin (50 mg/m<sup>2</sup>) plus doxorubicin (15 mg/m<sup>2</sup>) were used for the treatment of ovarian cancer, sarcomatosis, and peritoneal mesothelioma. Gemcitabine (1000 mg/m<sup>2</sup>) or mitomycin-C (20 mg/m<sup>2</sup>) were used for the treatment of recurrent ovarian cancer. Mitomycin-C (10 mg/m<sup>2</sup>) plus cisplatin (50 mg/m<sup>2</sup>) were used in gastric and pancreatic cancer. The cytotoxic drugs were diluted in 2-3 lit of Ringer's lactate solution. Early postoperative intraperitoneal chemotherapy (EPIC) was used in a few cases of incomplete cytoreduction. Patients older than 70 years or those that had previously been treated with chemotherapy or radiotherapy were given intraperitoneal chemotherapy at a dose reduced by 30%.

#### EPIC

EPIC was used in a few cases of incomplete cytoreduction. Patients older than 70 years or those that had previously been treated with chemotherapy or radiotherapy were given intraperitoneal chemotherapy at a dose reduced by 30%.

EPIC was possible through a Tenckhoff catheter during the first 5 postoperative days. Rapid infusion of 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup>/day diluted in 1-1.5 lit of 1.5% dextrose was used for EPIC [20].

All patients remained in the ICU for at least 24 h after surgery. EPIC was always performed in the ICU. Therefore, patients that received EPIC remained in the ICU for at least 5 days.

#### Assessment of complications

Postoperative complications were recorded and assessed according to the following criteria: the uncomplicated patients were characterized as having grade 0 complications. Patients requiring minor intervention such as oral antibiotics, bowel rest, or basic monitoring were characterized as having grade 1 complications. Grade 2 complications were those that required moderate intervention such as IV antibiotics, prolonged tube feeding, or chest drainage. Grade 3 complications were those that required hospital re-admission, surgical or radiological intervention. Grade 4 complications were those that produced chronic disability, organ resection, or bowel diversion. Grade 5 complications were those that resulted in death.

#### Economic cost of treatment

The economic cost of treatment was the summation of the daily cost of hospital bed occupancy, the daily cost of occupancy in the ICU, the cost of materials and drugs, and the preoperative, intraoperative, and postoperative examinations.

#### Statistical analysis

Statistical analysis was possible using the SPSS (Statistical Package for Social Sciences-version 17). The proportions of patients with a given characteristic were compared by chi-square analysis or by Pearson's test. Differences in the means of continuous measurement were tested by the Student's t-test. Logistic regression analysis was used to identify the factors that were related to the cost of treatment. A two-tailed p value < 0.05 was considered statistically significant.

The cost of treatment was correlated to patients' age, gender, and anatomic distribution of the tumor, morbidity, mortality, and extent of prior surgery, extent of peritoneal malignancy, use of HIPEC, length of stay in the ICU, and length of hospitalization.

## Results

From 2006 to 2011, 105 patients, mean age 56.9±13 years (range 16-82), underwent 108 cytoreductions with HIPEC. The general characteristics of the patients are listed in Table 1.

The mean PCI of the patients was 14 and the mean number of the performed peritonectomy procedures was 5. Complete or near-complete cytoreductive operations were performed in 90 (83.3%) patients. Thirteen patients (12%) that underwent CC-1 or CC-2 surgery received HIPEC and EPIC. Ten patients that underwent CC-3 surgery received HIPEC for palliation of resistant ascites.

The mean length of stay in the ICU was 5 days (range 1-31) and the mean hospitalization time was 23 days (range 15-95). The number of uncomplicated patients was 56 (51.9%). Grade 1 morbidity was recorded in 10 (9.3%) patients, grade 2 in 9 (8.3%), grade 3 in 11 (10.2%), and grade 4 in 16 (14.8%) patients. The in-hospital mortality rate was 5.6% (6 patients).

**Table 1.** General patient and tumor characteristics

Characteristics	N	%
Gender		
Male	16	14.8
Female	92	85.2
Origin of the tumor		
Colorectal	18	16.7
Gastric	4	3.7
Ovarian	75	69.4
Sarcomatosis	3	2.8
Peritoneal mesothelioma	6	5.6
Pseudomyxoma peritonei	1	0.9
Pancreas	1	0.9
PSS		
0	40	37
1	9	8.3
2	36	33.3
3	23	21.3
CC		
0	69	63.9
1	21	19.4
2	8	7.4
3	10	9.3
Intraperitoneal chemotherapy		
HIPEC	95	88
HIPEC+EPIC	13	12

PSS: prior surgical score, CC: completeness of cytoreduction, HIPEC: hyperthermic intraperitoneal chemotherapy, EPIC: early postoperative intraperitoneal chemotherapy

The daily cost of hospital bed occupancy was 73.37 euros. The daily cost of the ICU was 187.82 euros. The mean cost of treatment was 15677,3±11910,6 euros (range 4258,47-95990,87) per patient. Univariate analysis showed that morbidity, completeness of cytoreduction, extent of peritoneal malignancy, advanced age (>65 years), prolonged stay in the ICU (>5 days), the number of peritonectomy procedures, and prolonged hospitalization (>16 days) were significantly related with the cost of treatment (Table 2). Multivariate analysis revealed that morbidity (p=0.009, HR=6.851, 95% CI 1.14-2.488), and prolonged stay in the ICU (p<0.001, HR=16.577, 95% CI 3.499-35.791) were the parameters that influenced independently the cost of treatment (Table 3).

## Discussion

Cytoreductive surgery is a combination of various surgical procedures. Complete or near-complete cytoreduction is frequently possible by multi-visceral resection in addition to standard peritonectomy procedures.

Based on 25 cases of pseudomyxoma peritonei, Sugarbaker et al. estimated that the mean cost of this treatment per patient was 166922 US dollars [21]. In France the cost of cytoreductive surgery and HIPEC in 75 patients treated between 2002 and 2003 was estimated in 39358 euros per patient. In that analysis the cost of HIPEC drugs was 3135 euros per patient, but was not included in the total amount because it was covered by

**Table 2.** Univariate analysis of cost of treatment

Parameters	p-value
Morbidity	<0.001
Gender	0.588
Tumor anatomic distribution	0.475
In-hospital mortality	0.093
Completeness of cytoreduction	0.003
EPIC	0.193
Length of ICU stay	<0.001
Prior surgical score	0.181
Number of peritonectomy procedures	0.006
Peritoneal cancer index	<0.001
Length of hospital stay	<0.001
Age	0.002

**Table 3.** Multivariate analysis of cost of treatment

Parameters	p-value	HR	95% CI
Morbidity	0.009	6.851	1.14-2.488
ICU stay	<0.001	16.577	3.499-35.791

HR: hazard ratio, CI: confidence interval

the pharmaceutical company in a research project [15]. The mean cost of treatment in the National Cancer Institute of Milan (Italy) on 382 consecutive patients treated between 1995 and 2008 was 36015.89 euros per patient [14]. In Australia it was estimated at 42946 euros per patient [22]. In the United Kingdom the cost of treatment per patient is 75000 pounds. However, the British National Health Service covers the outpatient assessment, follow-up, and research for every patient with peritoneal malignancy in addition to surgical treatment [23].

It is obvious that the estimations of the cost differ largely from country to country and are not comparable. In Italy and France the costs are assessed according to the methodology of activity-based costing [24-26]. The total cost is the summation of the cost of the preoperative investigations, the medications, the operating theatre occupation, the fees of the personnel, and the cost of the disposal material, the equipment amortization, the HIPEC device disposal, the HIPEC drugs, the cost of blood products, the ICU stay, the preoperative and postoperative stay, and the postoperative care [14].

In Greece the operating theatre occupation, the fees of the personnel, the equipment amortization, the cost of the blood products, the cost of follow-up, and research are not included in the estimation of the cost. It has been shown that those variables related to the operating theatre occupancy (PCI, number of the performed peritonectomy procedures, and completeness of cytoreduction) are strongly related to the cost of treatment. Additional costs related to cytoreductive surgery and HIPEC such as delayed complications requiring additional hospitalization, stoma closure, recurrence treated with additional systemic chemotherapy are not included in the cost estimation.

Nevertheless, it is obvious that cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is a highly expensive treatment requiring specialized personnel, high technology, expensive and reliable materials.

The estimation of the economic cost is based on the disease-related groups' classification which has been recently implemented in Greece but cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is not included in the estimation of the economic cost. Italian and French studies have shown that the extent of surgical activities is one of the most significant factors that increase the cost [14,15]. In contrast, in Greece the extent of surgical activities is not taken into account and, as a consequence, it appears that the cost of treatment is not equally expensive. The number of peritonectomy procedures is one among the factors that reflects the extent of surgical activities. Another significant factor is the operating theatre occupancy

which is not estimated in the cost. As a consequence, the length of stay in the ICU, and morbidity are obviously the parameters regulating the economic cost.

It has been definitely established that complications and the need of prolonged mechanical ventilation result to prolongation of stay in the ICU. Prolonged stay in the ICU increases the diagnostic procedures, invasive monitoring, and the amount of drugs and blood products. Eventually all these parameters increase the daily cost per patient [27,28].

Preliminary results from two Greek centers estimated that the cost of cytoreductive surgery and HIPEC was approximately 8500-9000 euros but in this study only the expenditures were included (drugs, medications, disposal material) in the estimation of the total cost of treatment [16]. Differences in regard to the estimation of the cost between Italy-France and Greece do not allow a reliable comparison. After 6 years of treatment of patients with peritoneal malignancy it has been shown that the real cost is higher than the cost that has been previously reported.

## Conclusions

Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy is an expensive treatment. Morbidity and the length of stay in the ICU largely influence the economic cost.

## References

1. Teo M, Foo KF, Koo WH et al. Lessons learned from initial experience with peritonectomy and intraperitoneal chemotherapy infusion. *World J Surg* 2006; 30: 2132-2135.
2. Sugarbaker PH. Peritoneum as the first line of defense in carcinomatosis. *J Surg Oncol* 2007; 95: 93-96.
3. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FAN. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg* 2007; 245: 104-109.
4. van Leeuwen BL, Graf W, Pahlman L, Mahteme H. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. *Ann Surg Oncol* 2008; 15: 745-753.
5. Munoz-Casares FC, Rufian S, Rubio MJ et al. The role of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal carcinomatosis in recurrent ovarian cancer. *Clin Transl Oncol* 2009; 11: 753-759.
6. Tentes AA, Kakolyris S, Kyziridis D, Karamveri C. Cytoreductive surgery combined with hyperthermic intraoperative intraperitoneal chemotherapy in the treatment of advanced epithelial ovarian cancer. *J Oncol* doi 10.1155/2012/358341.
7. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy.

- nant peritoneal mesothelioma. *Ann Oncol* 2007; 18: 827-834.
8. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; 15: 2426-2432.
  9. Elias D, Lefevre JH, Chevalier J et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27: 681-685.
  10. Glehen O, Kwiakowski F, Sugarbaker PH et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; 22: 3284-3292.
  11. Sugarbaker PH, Jablonski KA. Prognostic factors of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 1995; 221: 124-132.
  12. Stephens AD, Alderman R, Chang D et al. Morbidity and mortality of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the Coliseum technique. *Ann Surg Oncol* 1999; 6: 790-796.
  13. Saxena A, Yan TD, Chua TC, Morris DL. Critical assessment of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol* 2010; 17: 1291-1301.
  14. Baratti D, Scivales A, Balestra MR et al. Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *EJSO* 2010; 36: 463-469.
  15. Bonastre J, Jan P, Pouvourville G, Pocard M, Estpfan G, Elias D. Cost of an intraperitoneal chemohyperthermia (IPCH) related to cytoreductive surgery. *Ann Chir* 2005; 130: 553-561.
  16. Spiliotis J, Tentes AA, Vaxevanidou A et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of peritoneal carcinomatosis. Preliminary results and cost from two centers in Greece. *J BUON* 2008; 13: 205-210.
  17. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221: 29-42.
  18. Bonastre J, Chevalier J, Elias D et al. Cost-effectiveness of intraperitoneal chemohyperthermia in the treatment of peritoneal carcinomatosis from colorectal cancer. *Health Value* 2008; 11: 347-353.
  19. Jaquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH (Ed): *Peritoneal Carcinomatosis: Principles of Management*. Kluwer Academic Publ, Boston, 1996, pp 359-374.
  20. Sugarbaker PH (Ed): *Technical Handbook for the Integration of Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy into the Surgical Management of Gastrointestinal and Gynaecologic Malignancy (4th Edn)*. Ludann Co, Grand Rapids, Michigan, 2005, pp 12-24.
  21. Sugarbaker PH, Ronnett BM, Archer A et al. Pseudomyxoma peritonei syndrome. *Adv Surg* 1996; 30: 233-280.
  22. Chua TC, Martin S, Saxena A et al. Evaluation of cytoreductive surgery (peritonectomy) and hyperthermic intraperitoneal chemotherapy at the St George Hospital peritoneal surface malignancy program. *Ann Surg* 2010; 251: 323-329.
  23. Moran BJ. Establishment of a peritoneal malignancy treatment centre in the United Kingdom. *EJSO* 2006; 32: 614-618.
  24. Rossi CR, Foletto M, Mocellin S et al. Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis. *Cancer* 2002; 94: 492-499.
  25. Baker JJ. Activity-based costing for integrated delivery systems. *J Health Care Finance* 1995; 22: 57-61.
  26. Sullivan K. On the "efficiency" of managed care plans. *Int J Health Serv* 2001; 31: 55-65.
  27. Teres D, Rapoport J, Lemeshow S, Kim S, Akhras K. Effects of severity of illness on resource use by survivors and nonsurvivors of severe sepsis at intensive care unit admission. *Crit Care Med* 2002; 30: 2413-2419.
  28. Moerer O, Plock E, Mgbor U et al. A German national prevalence study on the cost of intensive care: an evaluation of 51 intensive care units. *Crit Care* 2007; 11: 1-10 doi: 10.1186/cc5952.