

The St Constantin Hospital's initial experience with CRS-HIPEC

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ABSTRACT

Introduction: Cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) is a spreading technique for the treatment of peritoneal carcinomatosis, a technique that is associated with high morbidity and mortality rates. We report retrospectively the experience of St Constantin Hospital Brasov, underlining the good results obtained in terms of both reduction of complications and oncologic outcome.

Methods: Between June 2013 and October 2015, 32 patients with a median age of 55.6 years, underwent 34 CRS-HIPEC combined procedures.

Results: CCR-0 resection was achieved in 19/34 of patients, CCR-1 in 8/34 of patients and CCR-2 in 7/34 of patients, with a median operative time of 560 minutes (range 400-620 minutes). Median hospital stay was 9 days (4 days in laparoscopic HIPEC-20 days). Total morbidity rate was 40%, with WHO grade 3 and 4 morbidity rate 0 and the 30 days mortality was 0. With a median follow up of 11.8 months, the overall survival (OS) rate was 62%. Gastrointestinal (GI) origin in contrast with ovarian origin and peritoneal cancer index (PCI) higher than 19 showed a worst prognosis in terms of both OS and Progression Free Survival (PFS).

Conclusions. In a referral surgical oncology centre, CRS-HIPEC related perioperative mortality and morbidity can be reduced with a multidisciplinary patient management and a correct patient selection for this procedure. Our single centre retrospective series confirm the advantage in PFS and OS of the combined treatment CRS-HIPEC in the management of peritoneal carcinomatosis.

Key words: HIPEC, cytoreductive surgery

INTRODUCTION

Regional progression of several primitive peritoneal tumours such as Pseudomixoma Peritonei and Malignant Peritoneal Mesothelioma, and of several secondary peritoneal tumours deriving from gastrointestinal and ovarian tumors, results in Peritoneal Carcinomatosis (PC), a condition that is characterized by multiple peritoneal nodules of different measures and localization inside the peritoneal cavity (1-3). The causes of PC are still studied and debated. As for primary peritoneal cancers, in many solid tumor we can

observe a peritoneal spreading mainly due to a transcelomatic diffusion of cancer cells, that it is favoured by serosal surface invasion of the primary tumour, by tumour spontaneous or hyatrogenic rupture and by biological malignant cells characteristics (4). PC often causes a rapid worsening of quality of life due to pain, ascites and bowel obstruction. These conditions are caused by the progressive involvement of the peritoneum, due to cancer nodule growing that can cause bowel compression and volvolus. PC was considered as a systemic diffusion, treated with systemic chemotherapy and supportive care, while surgery in the past was only considered to palliate symptoms. PC is associated with a poor prognosis with a median survival of 6 months (2, 5-6). Primary peritoneal malignancies are characterized by a progression with an high incidence of regional recurrence after surgical debulking, with a very low incidence of distant metastasis, which usually occur late in the natural history of PC. In secondary PC, in many cases peritoneum is the only metastatic site (35%), allowing the development of more aggressive therapies. Considering peritoneum as an organ, the setting of therapy changed from a systemic to a loco-regional prospective. Intraperitoneal chemotherapy showed higher efficacy in comparison with systemic chemotherapy, and this efficacy is increased sinergically by hyperthermia. Pharmacokinetic and pharmacodynamic studies demonstrated that regional chemotherapy is quite unuseful if it is not associated with a surgical debulking. The association of cytoreductive surgery (CRS), usually very aggressive to obtain an optimal cytoreduction, with Intraperitoneal Hyperthermic Chemotherapy (HIPEC), showed to increase survival when peritoneum is the only metastatic site (7-9). The survival benefit is associated with a high morbidity, ranging 27-56% and mortality ranging 0-11% (10). This rates are optimized only in referral centres. At the St Constantin Hospital Brasov, a multidisciplinary team with a great experience in oncological surgery and locoregional therapies, take care of patients affected by PC.

MATERIALS AND METHODS

In our Hospital every patient suitable for a CRS-HIPEC procedure is evaluated by a multidisciplinary group, analyzing patient's medical history, clinical examination and imaging. Only patients with performance status (PS) < 2, in according with Eastern Cooperative Oncology Group (ECOG) (11) with primary PC (pseudomixoma peritonei and

mesothelioma) and secondary (from ovarian, GI and selected cases of sarcoma origin), with possible complete cytoreduction and without extraperitoneal disease are selected to undergo CRS-HIPEC. Surgical and anaesthesiological procedures have been well assessed and standardized (12, 13).

Patients

Between June 2013 and September 2015, n. 34 CRS-HIPEC procedures were performed on n. 32 patients, after an exhaustive explanation of CRS-HIPEC procedure an informed consent was signed by every patient. All procedures were performed under general anaesthesia. During the day before surgery a central venous catheter and a peridural catheter were placed, and intestinal toilet was obtained with Macrogol, 4000 69,6 gr per os.

Cytoreductive surgery (CRS)

A xifo-pubic laparotomy was performed in every patient. The first surgical step was a complete lyses of adhesions, if present, followed by Peritoneal Cancer Index (PCI) calculation, in order to assess definitively staging PC and the feasibility of CS, and by obtaining also a complete exposures of peritoneal surface to HIPEC. Only when an optimal cytoreduction was feasible, the HIPEC procedure was performed. Selective peritonectomy according to the Sugarbaker technique (14) was performed and in particular peritonectomy of sub-diaphragmatic surfaces, of the Glisson capsule with colecistectomy, Morrison sac, abdominal wall, pelvic peritoneum, epatoduodenal ligament and lesser omentum. Every procedure needed to obtain a complete cytoreduction was performed and in particular posterior pelvectomy by Hudson, rectal anterior resection and/or sigmoid resection, splenectomy, ileal, colonic and gastric resections, when indicated. The completeness of cytoreduction was classified following Glehen scale: CCR-0 in case of complete cytoreduction, CCR-1 with peritoneal nodules less than 5 mm in diameter and CCR-2 with nodules of 5 mm or more in diameter. HIPEC was indicated only in case of CCR-0 or CCR-1 resection, because of 5 mm power of penetration of chemotherapeutic agents also in hyperthermic conditions.

Hyperthermic intra-peritoneal chemotherapy (HIPEC)

Typical components of the device used for treating peritoneal cavity carcinomatosis are: 1) a heater or a heat exchanger; 2) a pumping system, including one or two peristaltic pumps; 3) a reservoir to contain the

whole perfusion solution; 3) a circuit for carrying the drugs and the heated fluid to the patient peritoneal cavity. In 1999 an Italian Biomedical Company (Rand Biotech srl, Medolla, Italy) firstly developed an HIPEC dedicated device that is typically used to treat by hyperthermic perfusion the peritoneal cavity, as it is illustrated in *figure 1*. The outmost peculiarity of this device (Performer™), is the easy portability and adaptability to different purpose, since it may be used also for isolated anatomical districts or organ perfusion such as for isolated limb treatment and for isolated liver or lung perfusion. The components of the Performer™ as illustrated in *figure 1*, a and b, are an heat exchanger, a line of extracorporeal circuit consisting in inflow catheters directed to the peritoneum, outflow catheters coming from the peritoneum, two roller pumps to maintain a constant flow of perfusing solution, allowing a flow rate from 100 to 2000 ml/min, a filter to eliminate or decrease the circulation of cell fragments, debris or clusters of biological materials circulating in the outflow line, up to 8 thermometer lines connected to temperature probes, to check the temperature in various areas of the peritoneal cavity, and measuring the tempera-

tures from 28°C to 46°C. In our patients, HIPEC was performed through four 28 French catheters, two for inflow (1 sub-diaphragmatic and 1 pelvic) and two for outflow (1 sub-diaphragmatic and 1 pelvic). Two temperature probes were placed in the pelvis and in the sovramesocolic space, to monitor the intra-abdominal temperatures. All the procedures were performed with closed abdomen technique, with a temporary cutaneous running suture to close the abdominal wall. The perfusion machine (Performer-LRTTM, Rand SrL, Medolla, Italy), was connected to the circuit and 3 to 4 liters of warm saline solution was circulated into the abdomen. Once reached the optimal perfusion flow rate (> 800 ml/min) and 40° C intra-peritoneal temperature, citotoxic drugs were added. We used Cisplatin (43 mg/L of solution/m²) and Doxorubicin (15 mg/L of solution) for ovarian cancer PC; for Peritoneal Mesothelioma and for peritoneal sarcomatosis, we used Cisplatin (25 mg/L of solution/m²) and Mytomicin C (3,3 mg/L of solution/m²) for Pseudomixoma Peritonei and PC of colonic origin. Mean intra-abdominal temperature was 41,3° C (range 40-43° C) and the duration of chemoperfusion was 60 or 90 minutes. At the end of HIPEC, the abdomen was

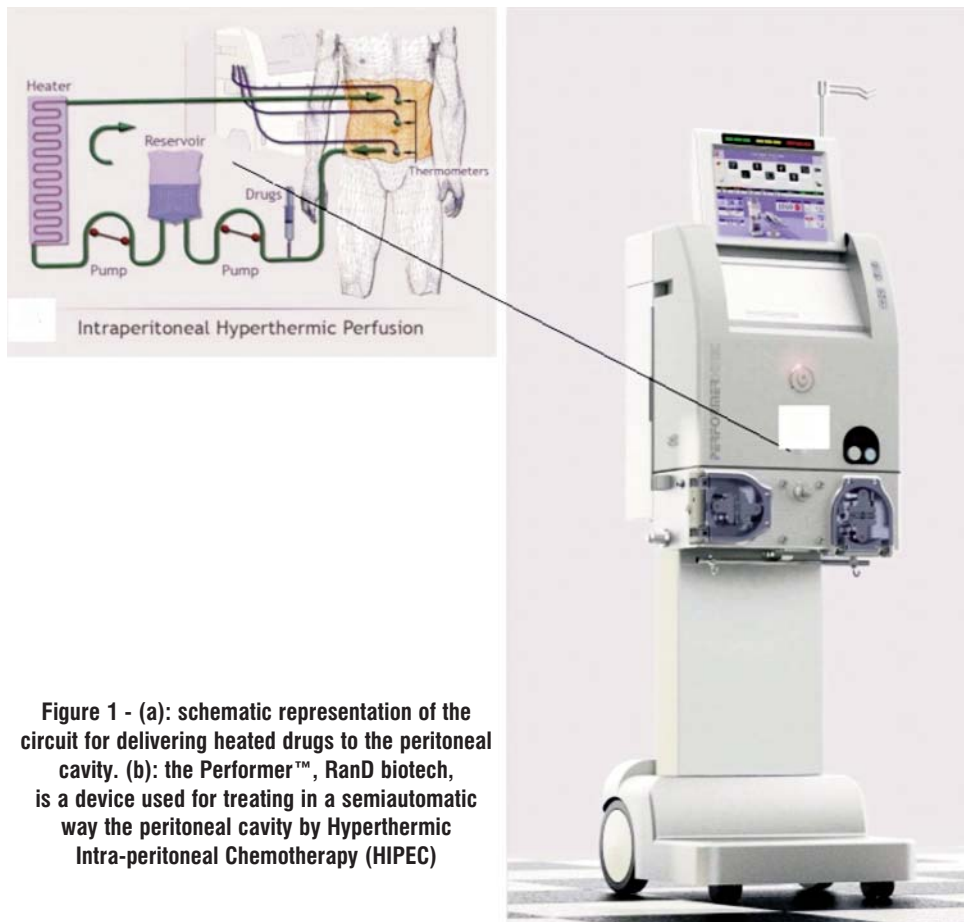


Figure 1 - (a): schematic representation of the circuit for delivering heated drugs to the peritoneal cavity. (b): the Performer™, RanD biotech, is a device used for treating in a semiautomatic way the peritoneal cavity by Hyperthermic Intra-peritoneal Chemotherapy (HIPEC)

irrigated with 3 litres of saline solution, the laparotomy was re-opened and anastomosis were performed when needed. After haemostatic control, the median laparotomy was definitively closed.

Post-operative management

After surgery, patient was transferred to intensive care unit for monitoring, if required. Naso-gastric tube was placed intra-operatively and maintained until return of bowel function, drains were placed to recognize any signs of bleeding or anastomosis leaking. Parenteral nutrition was provided, starting 24-48 hours after surgery and was maintained until sufficient oral calories intake was possible. Patients characteristics were resumed in *table 1*.

Statistical analysis

Overall survival (OS) was defined from the time of CRS-HIPEC procedure to the date of death, due to any cause or to the time of last contact. Recurrence-free survival (RFS) was defined as the time from CRS-HIPEC procedure to the date of regional or distant recurrence, second primary cancer, and/or death without evidence of disease.

RESULTS

Patient demographics

From 2013 to 2015, 32 patients, 7 males and 25 females, underwent 34 combined CRS-HIPEC treatment at our Hospital. Median age was 55.6 years (range 34-78 years). Patients were affected by GI tract tumors, pseudomixoma peritonei, epithelial ovarian cancer, malignant peritoneal mesothelioma. Median time between diagnosis and treatment with CRS-HIPEC was 12 months (range 2-48 months). Patients characteristics are resumed in *table 1*.

Surgical procedures

30 patients underwent a single CRS-HIPEC while 2 patient underwent two procedures for progression of the disease. There was no staging laparoscopy, in all patients a laparotomy was directly performed. Median PCI was 14 (range 1-30). In all patients we performed peritonectomies with other debulking procedures: 6 colonic resections, 4 small bowel resections, 10 anterior resections, 6 splenectomies, 1 partial gastrectomy, 8 liver resections(1 anatomic left lobectomy/ 7 atypical resections & in situ destructions), 1 urethral resection with implantation, 1 major vascular resection& reconstruction as reported in detail in *table 2*. In 14 patients a temporary colostomy was performed to protect a

Table 1 - Patient's demographics

	N.	%
Male	6	18.7
Female	25	81.3
Age (years)		
<40	3	
40-49	8	
50-59	9	
60-69	11	
>70	3	
Median age (range)	55.6(34-78)	
Time from diagnosis to CRS-HIPEC (months)	12	
Median Time from diagnosis to CRS-HIPEC (range)	2-24	
Operative time (minutes)	560	
Median Operative time (range)	400-620	
No. Surgical Procedures in the same patient		
≤1	30	
>1	2	
No. of Anastomoses		
≤1	17	
>1	1	
PCI index		
<9	10	
≥9	24	
Primary Tumor type:		
Gastrointestinal	8	
Ovary	22	
Uterine	2	
PMP	1	
MP	1	

Table - Surgical procedures

Procedures	N.	%
Splenectomy	4	12
Partial gastrectomy	2	6
Liver resection	8	24
Colecistectomy	28	82
Histerectomy and/or salpingo-oophorectomy	8	24
Partial cistectomy	6	18
Small bowel resection	4	12
Colorectal resections	16	47
Urethral resection & implantation	1	3
Iliac vein resection+reconstruction	1	3
Internal iliac artery resection	1	3
Diaphragmatic resection & phrenoraphy	9	26

colorectal anastomosis. Middle operative time was 560 minutes (range 420-620 minutes). CCR-0, CCR-1 and CCR-2 resections was achieved respectively in 19/34, 8/34 and 7/34 of patients.

Morbidity and mortality

Median hospitalization time was 9 days. Morbidity

Table 3 - Major morbidity

Major morbidity	N.	%
Reintervention	0	-
Anastomotic leakage	0	-
Sepsis	0	-
Wound infection	6	18%
Acute Pancreatitis	0	-
Acute Renal Insufficiency	0	-
Anemia (G 3/4)	31	91%

occurred in 13 patients (40%). There were no major complications (adverse events of grade 3-4) in our series, with no anastomotic leakage, no re-interventions and 0 cases of sepsis (*table 3*). No perioperative and 30 days deaths occurred.

Survival

Median follow up was 11.8 months (range 2–26 months) and overall survival was 62%(21/34). Median Time to Recurrence was 12.8 months (range 10 –18 months) and Median Time to Death was 5.6 months (range 2-14 months). Overall survival (OS) was influenced by tumoral histology with a better prognosis for ovarian carcinomatosis than GI origin and non-GI non-ovarian carcinomatosis, as well as the PCI level (low), the CCO status and the chemosensibility.

DISCUSSION

CRS-HIPEC represents a therapeutic option for patients affected by peritoneal carcinomatosis deriving from primitive peritoneal tumours or as secundarism, from epithelial ovarian cancer, GI tract tumors such as appendiceal, colo-rectal or gastric. Several monocentric retrospective studies, phase I and II trials (18-25), one multicentric retrospective series (26) and one randomized prospective clinical trial, showed an improvement of OS with this combined technique, in comparison to standard therapies, i.e. systemic chemotherapy, either neoadjuvant or adjuvant, and surgery. CRS-HIPEC is an effective treatment but it is affected by an high morbidity and mortality rate (27-29), due to the extension of the time for radical surgery, necessary to obtain an optimal cytoreduction.

The principal objective of this study was to confirm the CRS-HIPEC efficacy, by showing that in a referral center with a dedicated equipe experienced in oncological surgery, the morbidity and mortality rates can be reduced. The most common surgical complication is anastomotic leakage, as reported in the literature (20, 30-31). The presence of neoplastic cells near the

anastomosis, as well as the heat and the cytotoxic drug effects on tissues could favour an anastomotic leakage. Thus, our equipe routinely performs either anastomosis protected by lateral colostomy or terminal colostomy in Hartman manner taking into account the patient status and the recurrence risk.

We haven't experience any haemathologic adverse events of grade 3 and 4 due to the HIPEC in our group of patients, but we used blood transfusion in 31/34 procedures (mean 2.8 units of erythrocytes concentrates) to compensate the blood loss during the surgery and in the early postoperative phase. (28, 30-32).

Data from the literature suggest that the extent of cytoreduction and the number of anastomosis were strictly related to grade 3 and 4 adverse event rates (25, 28, 30, 32-34). While in all the published series of patients, the morbidity remains elevated, mortality was significantly reduced in high volume oncologic centers, than in non-dedicated centres, where morbidity and mortality were higher ranging 9-12% (24, 28, 35-39).

CRS-HIPEC requires specific competences and an adequate learning curve, strongly indicating the necessity to perform such a treatment only in referral centre with a well trained team in abdominal oncology surgery. Another important element that is a key point to obtain not only an improvement in OS and in quality of life, but also a morbidity and mortality rate reduction was a correct and an appropriate patient selection. The first selection criteria is the Eastern Cooperative Oncology Group (ECOG) performance status, that is directly related to an increasing in adverse events rate, when the score is poor. An important selection criteria for the patient outcome is the extension of the carcinomatosis, whose evaluation is standardized as peritoneal cancer index (PCI). PCI is not only directly related to the oncological outcome in terms of both OS and PFS, but also with severe adverse events incidence. Besides, recently a PCI > 17-19 was indicated as a relative contraindication for CRS-HIPEC, making it very difficult to obtain an optimal debulking (40, 41).

CONCLUSION

Our series of patients, by showing results analogues to those already present in the literature, confirmed the efficacy of CRS-HIPEC to treat peritoneal carcinomatosis, with an improvement of OS in comparison with traditional therapies, in a selected patient population. When performed in abdominal surgical oncology units, the mortality after CRS-HIPEC treatments can be reduced, otherwise remaining a not negligible morbidity rate.

The paper focuses on our initial experience with implementing cytoreductive surgery and HIPEC. Considerable efforts are needed for CRS-HIPEC nationwide implementation, at least within oncologic institutes and regional hospitals. Moreover, there are high hopes for the introduction of preemptive HIPEC in the high-risk categories of peritoneal recurrence: abdominal cancers with positive cytology (ovary, colon, appendix, stomach, pancreas), colorectal cancer penetrating surrounding tissues, occlusive colorectal cancer, T3 signet ring cells mucinous cancer, the presence of ovarian metastases. Ideally these cases should be known subsequent to pre-surgery evaluation, and HIPEC should be performed together with primary surgery. Cases with high peritoneal recurrence risk that have already been subject to surgery can benefit from routine second look and HIPEC, after the adjuvant chemotherapy.

REFERENCES

- Blair SL, Chu DZ, Schwarz RE. Outcome of palliative operations for malignant bowel obstruction in patients with peritoneal carcinomatosis from non-gynecological cancer. *Ann Surg Oncol*. 2001 Sep;8(8):632-7.
- Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg*. 2002 Dec;89(12):1545-50.
- Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer*. 2000 Jan 15;88(2):358-63.
- Jacquet P, Vidal-Jove J, Zhu BW, Sugarbaker PH. Peritoneal carcinomatosis from intra-abdominal malignancy: Natural history and new prospects for management. *Acta Chir Belg*. 1994 Jul-Aug;94(4):191-7.
- Al-Shammaa HA1, Li Y, Yonemura Y. Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *World J Gastroenterol*. 2008 Feb 28;14(8):1159-66.
- Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer*. 1989 Jan 15;63(2):364-7.
- Moran BJ, Meade B, Murphy E. Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for peritoneal carcinomatosis of colorectal origin: a novel treatment strategy with promising results in selected patients. *Colorectal Dis*. 2006 Sep;8(7):544-50.
- Knorr C, Reingruber B, Meyer T, Hohenberger W, Stremmel C. Peritoneal carcinomatosis of colo-rectal cancer: incidence, prognosis, and treatment modalities. *Int J Colorectal Dis*. 2004 May;19(3):181-7. Epub 2003 Aug 29.
- Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg*. 2006 Feb;243(2):212-22.
- Stewart JH, Shen P, Levine EA. Intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: current status and future directions. *Ann Surg Oncol*. 2005 Oct;12(10):765-77. Epub 2005 Aug 18.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-55.
- Deraco M, Baratti D, Cabras AD, Zaffaroni N, Perrone F, Villa R, et al. Experience with peritoneal mesothelioma at the Milan National Cancer Institute. *World J Gastrointest Oncol*. 2010 Feb 15;2(2):76-84.
- Baratti D, Pennacchioli E, Kusamura S, Fiore M, Balestra MR, Colombo C, et al. Peritoneal sarcomatosis: is there a subset of patients who may benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy? *Ann Surg Oncol*. 2010 Dec;17(12):3220-8.
- Sugarbaker PH. Peritonectomy procedures. *Surg Oncol Clin N Am*. 2003 Jul;12(3):703-27, xiii.
- Kaplan EL, Meier P. Non parametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53: 457-481.
- Sharp S, Sterne J. Meta-analysis. *Stat Tech Bull* 1997; 38: 9-14.
- Cox DR. Regression model and life tables. *J Royal Stat Soc B* 1972; 34: 187-220.
- Bartlett DL, Buell JF, Libutti SK, Reed E, Lee KB, Figg WD, et al. A phase I trial of continuous hyper-thermic peritoneal perfusion with tumor necrosis factor and cisplatin in the treatment of peritoneal carcinomatosis. *Cancer*. 1998 Sep 15;83(6):1251-61.
- Feldman AL, Libutti SK, Pingpank JF, Bartlett DL, Beresnev TH, Mavroukakis SM, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol*. 2003 Dec 15;21(24):4560-7.
- Gilly FN, Beaujard A, Glehen O, Grandclement E, Caillet JL, Francois Y, et al. Peritonectomy combined with intraperitoneal chemohyperthermia in abdominal cancer with peritoneal carcinomatosis: phase I-II study. *Anticancer Res*. 1999 May-Jun;19(3B):2317-21.
- Glehen O, Mithieux F, Osinsky D, Beaujard AC, Freyer G, Guertsch P, et al. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. *J Clin Oncol*. 2003 Mar 1;21(5):799-806.
- Shen P, Levine EA, Hall J, Case D, Russell G, Fleming R, et al. Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. *Arch Surg*. 2003 Jan;138(1):26-33.
- Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, Gavazzi C, et al. Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. *Ann Surg Oncol*. 2004 Apr;11(4):393-8.
- Elias D, Blot F, El Otmány A, Antoun S, Lasser P, Boige V, et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer*. 2001 Jul 1;92(1):71-6.
- Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surg*. 2000 Jun;66(6):561-8.
- Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, 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 Aug 15; 22(16):3284-92.
- Moran BJ, Meade B, Murphy E. Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for peritoneal carcinomatosis of colorectal origin: a novel treatment strategy with promising results in selected patients. *Colorectal Dis*. 2006 Sep;8(7):544-50.
- Shen P, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA, et al. Cytoreductive surgery and intra-peritoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from non-appendiceal colorectal carcinoma. *Ann Surg Oncol*. 2004 Feb;11(2):178-86.
- Ahmad SA, Kim J, Sussman JJ, Soldano DA, Pennington LJ, James LE, et al. Reduced morbidity following cyto-reductive surgery and intraperitoneal hyperthermic chemoperfusion. *Ann Surg Oncol*. 2004 Apr;11(4):387-92.
- Glehen O, Osinsky D, Cotte E, Kwiatkowski F, Freyer G, Isaac S, et al. 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*. 2003 Oct;10(8):863-9.
- Elias D, Goere D, Blot F, Billard V, Pocard M, Kohneh-Shahri N, et al. Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after complete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. *Ann Surg Oncol*. 2007 Jun;14(6):1818-24. Epub 2007 Mar 14.
- Verwaal VJ, van Ruth S, de Bree E, et al. 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* 2003; 21: 3737-43.
- Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G,

- et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol*. 1999 Dec;6(8):790-6.
34. Smeenk RM, Verwaal VJ, Zoetmulder FAN. Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei—a report of 103 procedures. *Eur J Surg Oncol*. 2006 Mar;32(2):186-90. Epub 2005 Nov 21.
 35. Kusamura S, Younan R, Baratti D, Costanzo P, Favaro M, Gavazzi C, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. *Cancer*. 2006 Mar 1;106(5):1144-53.
 36. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intra-peritoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. *Ann Surg Oncol*. 2006 May;13(5):635-44. Epub 2006 Mar 10.
 37. Butterworth SA, Panton ON, Klaassen DJ, Shah AM, McGregor GI. Morbidity and mortality associated with intraperitoneal chemotherapy for pseudomyxoma peritonei. *Am J Surg*. 2002 May;183(5):529-32.
 38. Cavaliere F, Perri P, Di Filippo F, Giannarelli D, Botti C, Cosimelli M, et al. Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol*. 2000 May;74(1):41-4.
 39. Scuderi S, Costamagna D, Vaira M, et al. Treatment of pseudomyxoma peritonei using cytoreduction and intraperitoneal hyperthermic chemotherapy. *J Surg Oncol* 2003; 89(4 Suppl): 43–5.
 40. Elias D , Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol*. 2010;28(1): 63-68.
 41. Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. *Ann Surg Oncol*. 2015 Sep;22(9):2958-64.