

***Cytoreductive Surgery followed by Intra Peritoneal Hyperthermic
Perfusion in the treatment of recurrent epithelial ovarian cancer: a
Phase II clinical study***

Marcello Deraco¹, Carlo R. Rossi², Elisabetta Pennacchioli¹, Stefano Guadagni³, Danielle Carlier Somers¹, Nicola Santoro¹, Francesco Raspagliesi¹, Shigeki Kusamura¹ and Maurizio Vaglini†

¹ Dpt. of Surgery - National Cancer Institute of Milan, Italy

² Dpt. of Surgery - University of Padua, Italy

³ Dpt. of Surgery - University of L'Aquila

Running Head: CRS and IPHP in recurrent ovarian cancer

Acknowledgements: this study was partially financed by the AIRC (Italian Association of Cancer Research)

To whom correspondence should be addressed: Dr. Marcello Deraco, Unità Operativa Chirurgia Muscolo Scheletrica e Terapie Integrate Loco-Regionali, Istituto Nazionale per lo Studio e la Cura dei Tumori, via Venezian, 1 - 20133 Milano (Italy). Phone number: * 39 2 2390 2362; Fax number: * 39 2 2390 2404. E-mail: marcelloderaco@hotmail.com

Abstract

Aims and Background: The optimal salvage therapy for recurrent ovarian carcinoma has not been clearly established. Response to second-line chemotherapy is low with a short median survival (8.8-15 months). We investigated the effect of an aggressive approach consisting of surgery followed by intra peritoneal drug delivery and local hyperthermia.

Patients and Methods: In a phase II clinical study, 27 patients with advanced/recurrent ovarian carcinoma were treated with cytoreductive surgery (CRS) and intra peritoneal hyperthermic perfusion (IPHP). Median patient age was 53 years (30-67) and mean follow-up was 17.4 months (0.3-36.0). Patients had been surgically staged and heavily pre-treated with cisplatin based, taxol based or taxol/platinum containing regimens. Nineteen (70%) patients were cytoreduced to minimal residual disease < 2.5mm. The IPHP was performed with the closed abdomen technique, using a preheated polysaline perfusate containing Cisplatin (25mg/m²/l) + Mitomycin-C (3.3mg/m²/l) through a heart-lung pump (mean flow of 700 ml/min) for 60 minutes in the hyperthermic phase (42.5°C).

Results: Two-year overall survival was 55%. Median times to overall progression and local progression were 16 months and 21.8 months, respectively. Variables that affected the overall survival or time to progression were as follows: - residual disease (p=0.00025), patient age (p=0.04), and lag-time between diagnosis and CRS+IPHP (p=0.04). Treatment-related morbidity, mortality and acute toxicity (grade II-III) rates were 11%, 4% and 11%, respectively. Eight (89%) out of 9 patients had ascites resolution.

Conclusion: Our results suggest that CRS+IPHP is a well- tolerated, feasible and promising alternative in the management of selected patients with recurrent ovarian cancer, but further randomised controlled studies are needed in order to confirm our findings.

Key words: Ovarian Cancer, Peritoneal Carcinomatosis, Cytoreductive Surgery, Intra Peritoneal Hyperthermic Perfusion.

Introduction

Ovarian cancer remains the most lethal of all gynaecological malignancies ^[1], being responsible for about 50% of all deaths for female genital tract cancer ^[2]. It ranks high as a cause of female deaths in Canada, New Zealand, Israel and Northern Europe. Tumors of epithelial origin account for 80-90% of ovarian malignancies and approximately 75% of cases are diagnosed at advanced stage III or IV ^[2-4].

The conventional clinical approach for advanced ovarian cancer is based on debulking surgery followed by systemic chemotherapy. In spite of its being a highly chemosensitive tumor with 70-80% response rates to first-line chemotherapy, the majority of patients relapse and respond poorly to salvage chemotherapy ^[2].

Ovarian cancer dissemination most frequently occurs intraperitoneally. The disease remains in the cavity for most of its natural history ^[5,6], and this biological behaviour provides the opportunity for increasing drug concentration selectively in the tumor area by direct intraperitoneal instillation ^[7,8] in order to overcome intrinsic or acquired drug resistance and simultaneously reduce systemic side-effects.

However, this approach is still controversial, since most clinical trials have failed to show a substantial impact on disease-free and overall survival when therapeutic results were compared to those obtained using standard intravenous antineoplastic treatment ^[9-11]. This may be due to several reasons such as limited drug absorption into the tumor tissue in normothermic conditions or uncompleted drug distribution due to the abdominal postoperative adhesion ^[12].

In an attempt to overcome these drawbacks, intraperitoneal chemotherapy in hyperthermic conditions has become an area of growing interest supported by experimental observations. In fact, at 40-42°C, neoplastic cells become more chemosensitive due to an increase in the

intracellular concentration of drugs and in their activation process, especially for alkylating agents, and to alterations in the DNA repair process ^[13,14]. Moreover, it has been shown that these events have a greater intensity in cisplatin-resistant rather than cisplatin-sensitive ovarian cancer cell lines. Formation of platinum-DNA adducts after cisplatin exposure is enhanced and/or adduct removal is increased in heated cells, resulting in a relatively higher DNA damage ^[15].

The IPHP treatment was initially conceived for the treatment of advanced gastric cancer and peritoneal carcinomatosis ^[16,19] following surgical intervention, and a slight increase in morbidity in patients treated by this locoregional approach has been reported ^[20]. Recently, it has also been considered as a potentially effective second-line and salvage therapy in Phase I/II clinical studies in the management of advanced ovarian cancer ^[21,24].

In the present paper we report the preliminary results of a Phase II clinical trial in which patients with advanced epithelial ovarian cancer were treated by Cytoreductive Surgery (CRS) and Intra Peritoneal Hyperthermic Perfusion (IPHP). The endpoints were toxicity, morbidity, quality of life, disease control and impact on patient survival.

Patients and Methods

Patients

The study was conducted on 27 patients with histologically confirmed advanced epithelial ovarian cancer who were treated with cytoreductive surgery and IPHP.

All the patients had recurrent or progressive disease following primary surgical staging associated with adjuvant chemotherapy.

Median patient age was 53 years (range: 30-67 years) and mean follow-up was 17.4 months (range: 0.3-36.0 months).

Disease staging was carried out according to the FIGO criteria, with 1 (4%) patient classified at stage II, 23 (85%) at stage III, and 1 (4%) at stage IV. This information was not available for two patients. Nine out of 27 (33%) patients presented malignant ascites.

Hystologic classification was performed according to the WHO criteria. Serous tumors were the most frequent type and were observed in 23 (85%) patients; 3 (11%) patients had mucinous tumors and 1 (4%) patient had an undifferentiated lesion.

Of the 27 patients who entered this study, all but one had received previous surgery and 23 patients had undergone adjuvant systemic chemotherapy, 2 salvage intraperitoneal chemotherapy, 1 immunotherapy and 1 radiotherapy. Of the 23 patients which had received adjuvant chemotherapy, 13 (48.1%) had been given a taxol/cisplatin combination, 2 (7%) a taxol-based regimen, and 8 (30%) a platinum-based regimen. All pre-treated patients had received a mean of 3 chemotherapy lines before entering the present study.

All patients presented a ≥ 70 Karnofsky performance status; no severe cardiac dysfunction; and normal haematological, biochemical liver function, and creatinine clearance tests. Written informed consent, as defined by the guidelines of the Ethical Committee of the National Cancer Institute of Milan, was obtained from each patient.

Cytoreductive surgery

Patients were put in a supine position with gluteal folds advanced to the break on the operating table to allow full access to the perineum during the surgical procedure. This position is essential to avoid intraoperative skin or muscle necrosis.

A 3-way bladder catheter was placed in order to permit a cold lavage during hyperthermia and to avoid mucosal damage. A large-bore silastic nasogastric tube was used.

The abdomen was opened from xyphoid to pubis. Generous abdominal exposure was achieved through the use of a Thompson self-Retaining Retractor. A ball-tip electro-surgical handpiece was used to dissect the tumor on peritoneal surfaces from normal tissue.

The peritoneal carcinomatosis (PC) was classified in: PC1 = dissemination into pelvic localised peritoneum; PC2 = slight dissemination into remote peritoneum; PC3 = marked dissemination into remote peritoneum such as used for other peritoneal disseminating disease^[25]. Four (15%), 6 (22%) and 17 (63%) patients had PC1, PC2 and PC3 extension, respectively.

Cytoreductive surgery was performed in 18 (67%) patients, and included partial peritonectomy in 6 cases, single intestinal resection in 7 cases, multiple intestinal resection in 2 cases and omentectomy in 5 cases. Minor surgical procedures, such as sample biopsy, were carried out in 7 patients. The mean duration of CRS+IPHP procedure was 371 minutes (range: 240-600). The completeness of cytoreductive was defined according to Sugarbaker criteria in 4 classes^[26]: CC-0 - no residual disease, CC-1 - minimal residual disease <2.5 mm, CC-2: residual disease 2.5mm-2.5 cm, CC-3: residual disease >2.5 cm.

IPHP technique

After CRS, 4 silicone catheters were placed in the abdominal cavity. Two inflow catheters were placed in the right subphrenic cavity and at deep pelvic level, respectively; and two further catheters were placed in the left subphrenic cavity and in the superficial pelvic site.

During IPHP, continuous peritoneal temperature monitoring was performed by 6 thermocouples placed in the abdominal cavity, peritoneal site and rinopharing for central temperature. After abdominal skin closure, the catheters were connected to the extra-corporeal circuit. This technique was used for all patients. The preheated polysaline perfusate containing Cis-Platin (CDDP) (25mg/m²/l of perfusate) and Mitomycin (MMC) (3.3mg/m²/l of perfusate) was instilled in the peritoneal cavity using a heart-lung pump at a mean flow of 600 ml/min for 60 minutes from the true hyperthermic phase (42.5°C).

Following perfusion, the perfusate was quickly drained and the abdomen closed after careful intraperitoneal inspection.

Follow-up

In the postoperative period, patients were assisted in an Intensive Care Unit for at least 72 hours. They were evaluated with daily laboratory exams. Physical examination, haematological parameters, tumor marker (Ca125, CEA, CA19.9) determinations, creatinine clearance test, and thoracic and abdominal CT scans were performed every 3 months in the first year and every 6 months, thereafter. A further laparotomy was performed in 4 patients to assess tumor response or disease relapse. Analysis of chemotherapy-related toxicity was performed according to the World Health Organisation criteria. Survival was calculated from the date of surgery to date of death or time of last follow-up.

Statistical analysis

Estimated survival curve distribution was calculated by the Kaplan-Meier method. The Log-rank test was used to assess the significance of survival distributions.

Results

Clinical outcome

After salvage surgery, according to criteria previously described, 15 (55%) patients presented CC-0; 4 (15%) patients, CC-1; 3 (11%) patients, CC-2; and 5 (19%) patients, CC-3 residual disease.

Three months after CRS+IPHP treatment, complete response, defined on the basis of criteria previously described, was reached in 16 (59%) out of the 27 patients (15 with CC-0 and 1 CC-1). Resolution of ascites was observed in 8 out of 9 (89%) patients.

As regards recurrences, 4 (15%) patients presented distant metastases (liver n = 2, distant lymph nodes n = 1, lung n = 1), 5 (19%) patients showed locoregional relapse, and 4 (15%) patients had both local and distant metastases.

Two-year overall survival (OS) for the whole series of patients was 55%. (Fig. 1A) Progression-free survival (PFS) and local progression-free survival (LPFS) for the same period were 21% and 44%, respectively. (Fig. 1B, 1C)

Moreover, median time to progression (MTP) for the whole series of patients was 21.8 months, whereas median times to local progression (MTLP) were 16 months for the overall series and 27 months for the subset of patients with complete response to treatment.

Variables that affected outcome in terms of OS, and/or MTP and/or MTLP were: completeness of cytoreduction, extension of carcinomatosis, patient age and interval time between diagnosis and CRS+IPHP treatment.

The volume of residual disease significantly influenced the OS ($p=0.00025$). Patients with microscopic or minimal residual disease (CC-0/1) had a 77% probability of survival at 2 years with a MTP of 20.3 months, whereas all patients with residual disease $> 2.5\text{mm}$ (CC-2/3) died within 20.3 months and showed a MTP of 4.3 months. (Fig. 2A)

Moreover, patients with CP1/CP2 extension of carcinomatosis prior to the salvage surgery showed only a trend of higher survival probability as compared to patients with CP3 dissemination (2-year OS 63% vs. 50%, $p=0.09$). (Fig. 2B)

Another factor that was correlated with OS was patient age. Patients older than 53 years of age presented 67% 2-year OS while younger patients showed 40% 2-years OS ($p=0.04$) (Fig. 2C).

Finally, patients who were treated with CRS+IPHP within 18 months of diagnosis had a statistically significant advantage in terms of 2-year OS compared to those treated after the same period (71% vs.43%, $p=0.04$) (Fig.2D).

Toxicity, morbidity, and mortality

The acute toxicity (grade II-III) rate was 11% after CRS+IPHP treatment. Two (7%) patients presented renal toxicity grade II. There was 1 (4%) case of grade III haematological toxicity (hemoglobin=6,5; leucocytes=1.800; platelet=25.000) detected in the 10th day after the procedure. The event resolved spontaneously after 3 weeks, without further clinical complications. Thirteen (48%) patients presented microscopic hematuria. One patient presented chronic toxicity with an persistently elevated serum amilase level, with no related symptoms, until the end of her follow-up (6.1 months). One patient died of intravascular disseminated coagulopathy (IDC) one week after treatment, producing a treatment-related mortality rate of 4%. The resultant treatment-related morbidity was 11%. There were only two patients who presented minor surgical complications: one developed fever in the post-operative period and the other presented post-operative abdominal bleeding that resolved spontaneously.

Discussion

Clinical studies have shown that cisplatin- or taxol-based first-line chemotherapy achieves the highest response rates (around 70-80%), with a high proportion of complete responses, in patients with epithelial ovarian cancers. ^[27,28] However, negative second-look laparotomy, which is achievable in only 20-40% of cases ^[29-35], does not necessarily mean the patient is cured. Up to 47% of these patients relapse within 5 years; disease-free survival does not generally exceed 18 months, and 5-year survival ranges from 42 to 80%. ^[36-38]

Moreover, when previous effective drug combinations fail, there is virtually no chance of inducing a significant response with second-line treatment. A partial response and control of malignant effusions can be achieved occasionally and are usually associated with a short survival. ^[2]

Several groups of investigators have studied innovative forms of second-line or salvage therapy, such as new drugs or high-dose chemotherapy with autologous bone marrow support or intraperitoneal chemotherapy. Available data (Table 1) shows a somewhat higher response rate to carboplatin+ifosfamide and intraperitoneal chemotherapy in platinum-sensitive patients compared to platinum-resistant ones. According to different studies ^[39-46], the response rate to salvage therapies in the latter subgroup never exceeds 22%, and median survival ranges from 8.8 months to 15 months.

Following high-dose chemotherapy, a fairly high response rate has been observed that, however, did not reflect in a higher median survival, at least in the one study performed on an adequate series of patients. ^[42] Conversely, in resistant patients treated by intraperitoneal chemotherapy, a low response rate was observed, whereas the median survival was about two-three times longer than that observed following any other treatment.

Cytoreduction is one of the essential components of combined therapy currently investigated as it increases tumour perfusion and growth fraction, removes phenotypically-resistant clones, and thereby improves response to chemotherapy. Unfortunately, the benefits from secondary cytoreductive surgery for persistent or recurrent ovarian cancer have not been clearly established since there are no randomised controlled clinical trials to date that have addressed this issue. However, a review of 5 retrospective studies and 1 prospective study ^[47-52] has shown a statistically significant benefit for patients optimally debulked for recurrent ovarian cancer. In addition, this benefit is correlated with residual tumor volume and with the duration of complete clinical remission after primary therapy.

In our experience, the amount of residual disease was significantly associated with overall survival and time to progression. The extension of carcinomatosis had only a slight impact on outcome.

Our findings suggest that, regardless of the peritoneal carcinomatosis extension, a maximum surgical effort remains an important step in the treatment of advanced ovarian cancer, even in a salvage setting. Moreover, our treatment-related morbidity rate was 11%, i.e. lower than the median of 35% reported in literature ^[47-52]. Therefore, we are of the opinion that every attempt to resect the tumor tissue as much as is technically feasible may have a positive impact on survival and time to progression, without compromising the safety of the therapy.

Another interesting result in our case series is that the lag-time between diagnosis and CRS+IPHP treatment performance negatively influenced overall survival. This finding could be explained by the higher probability of developing resistant clones as the number of cell divisions increase, according to the Goldie-Coldman model. ^[53]

IPHP is the natural evolution of intraperitoneal chemotherapy that has been increasingly used over the last 2 decades, and still represents an intriguing area of clinical research. The peritoneal barrier, consisting of sub-mesothelial tissue and the capillary basement membrane,

limits the reabsorption of hydrophilic and high molecular weight drugs such as MMC and CDDP, permitting a longer drug exposure within the peritoneal cavity. ^[54] Moreover, IPHP increases tumor drug penetration with respect to normothermic conditions, and favours the drug diffusion into the peritoneal cavity and the elimination of microscopic cancer residues by circuit filters. ^[55]

The relatively low toxicity, morbidity and mortality rates, as well as the improvement in quality of life as a result of the ascites resolution observed in 8 (89%) out of 9 patients, suggest that CRS+IPHP is a safe, feasible and palliative alternative for the treatment of recurrent ovarian cancer. Furthermore, the results from our study are also promising both in terms of progression-free survival and overall survival.

However, it must be emphasised that cytoreductive surgery followed by intraperitoneal hyperthermic perfusion is a complex procedure that requires an approximately twelve-hour operation by a skilled surgical team and the subsequent support of an Intensive Care Unit.

Therefore, it is important to identify patients who can really benefit from this treatment. Whilst the search for prognostic and predictive biologic markers remains an important issue and must be pursued, the results from our study indicate that the most appropriate candidates for IPHP treatment are those with minimal residual disease after CRS, or those with a short clinical history of disease.

On the basis of these findings, a randomised controlled clinical trial has recently been activated to determine the real effect of CRS-IPHP, not only as salvage therapy in heavily pre-treated patients, but also as a second-line option for earlier stages of disease in patients with positive second-look laparotomy.

References

1. American Cancer Society. Cancer facts and Figures 1995. Atlanta: American Cancer Society, 6, 1995.
2. DiSaia PJ, Creasman WT: Clinical Gynecologic Oncology. Mosby-Year Book, Inc, pp 282-350, St. Louis, Missouri, 1997.
3. Mant JWF& Vessey MP: Ovarian and endometrial cancers. Cancer Surveys Trends in Cancer Incidence and Mortality, vol. 9:287-307, 1994.
4. Yancik R: Ovarian cancer: age contrasts in incidence, histology, disease stage at diagnosis, and mortality. Cancer, 71:517-523, 1993.
5. Longo DL, Young RC: The natural history and treatment of ovarian cancer. Review. Annu. Ver Med, 32:475-490, 1981.
6. Deraco M, Santoro N, Carraro O, Inglese MG, Rebuffoni G, Guadagni S, Carlier Somers D, Vaglini M: Peritoneal Carcinomatosis: Features of dissemination. Review. Tumori, 85:1-5, 1999.
7. Markman M: Intraperitoneal cisplatin and carboplatin in the management of ovarian cancer. [Review]. Semin Oncol, 21(2 supp.2):17-19, quiz 20, 58, 1994.
8. Sugarbaker PH, Graves T, De Bruijn EA, Cunliffe WJ, Mullins RE, Hull WE, Oliff L, Schlag P: Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis form gastrointestinal cancer: pharmacological studies. Cancer Res, 50:5790, 1990.

9. Alberts DS, Liu PY, Hannigan EV: Phase III study of intraperitoneal (IP) cisplatin (CDDP)/intravenous (IV) cyclophosphamide (CPA) in patients with optimal disease stage III ovarian cancer: A AWOOG-GOG-ECOG intergroup study. Proc ASCO, 14:273 [Abstract], 1995.
10. Howell SB, Kirmai S, McClay EF, Kim S, Braly P, Plaxe S: Intraperitoneal cisplatin based chemotherapy for ovarian carcinoma. Semin Oncol, 18 (1 suppl. 3):5-10, 1991.
11. Howell SB, Zimm S, Markman M, Abramson IS, Clearly S, Lucas WE, Weiss RJ: Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. J Clin Oncol, 5:1607-1612, 1987.
12. Markman M: Intraperitoneal Chemotherapy. Semin Oncol, 18:248-254, 1991.
13. Engelhardt R: Hyperthermia and drugs. Recent Results Cancer. Res., 104:136-203, 1987.
14. Teicher BA, Kowal CD, Kennedy KA, Sartorelli AC: Enhancement by hyperthermia of the in vitro cytotoxicity of mitomycin C toward hypoxic tumor cells. Cancer Res, 41:1096-1099, 1981.
15. Hettinga JVE, Lemstra W, Meijer C, Dam WA, Uges DRA, Konings AWT, Vries EGE, Kampinge H: Mechanism of hyperthermic potentiation of cisplatin action in cisplatin-sensitive and -resistant tumor cells. Br J Cancer, 75:1735-1743, 1997.
16. Bozzetti F, Vaglini M, Deraco M: Intraperitoneal hyperthermic chemotherapy in gastric cancer: rationale for a new approach. Tumori, 84:483-488, 1998.
17. Gomes Portilla A, Deraco M, Sugarbaker PH: Clinical Pathway for Peritoneal Carcinomatosis from Colon and Rectal Cancer: Guidelines for Current Practice. Tumori, 83:725-728, 1997.

18. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T: Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with MMC. *Cancer*, 61:232-237, 1988.
19. Yonemura Y, Fujimura T, Fushida S, Takegawa S, Kamata T, Katayama K, Kosaka T, Yamaguchi A, Miwa K, Miyazaki I: Hyperthermia-chemotherapy combined with cytoreductive surgery for the treatment of gastric cancer with peritoneal dissemination. *World J Surg*, 15:530-536, 1991.
20. Deraco M, Vaglini M, Santinami M, Santoro N, Inglese MG, Spatti GB: Intraperitoneal hyperthermic perfusion (IPHP): Analysis of morbidity and toxicity. *Oncol Rep*, 3:1103-1106, 1996.
21. Kober F, Heiss A, Roka R: Diffuse and gross peritoneal carcinomatosis treated by intraperitoneal hyperthermic chemoperfusion. *Cancer Treat Res*, 82:211-219, 1996.
22. Salle B, Gilly FN, Carry PY, Sayag A, Brachet A, Braillon G: Intraperitoneal chemo-hyperthermia in the treatment of peritoneal carcinomatosis of ovarian origin. Initial cases, physiopathologic data. *J Gynecol Obstet Biol Reprod, (Paris)* 22:369-371, 1993.
23. Steller MA, Egorin MJ, Trimble EL, Bartlett DL, Zuhowski EG, Alexander HR, Dedrick RL: A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. *Cancer Chemother Pharmacol*, 43:106-114, 1999.
24. Vaart PJM, Vange N, Zoetmulder FAN, Goethem AR, Telling O, ten Bokkel Huinink WW, Beijnen JH, Bartelink H, Begg AC: Intraperitoneal Cisplatin with Regional Hyperthermia in Advanced Ovarian Cancer: Pharmacokinetics and Cisplatin-DNA Adduct Formation in patients and Ovarian Cancer Cell Lines. *Eur J Cancer*, 34:148-154, 1998.

25. Japanese Research Society for Gastric Cancer (1981): The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg*, 11:127-139, 1981.
26. Jacquet P, Sugarbaker PH: Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res*, 15:49-58, 1996.
27. McGuire WP, Hoskin WJ, Brady MF, Kucera PR, Patridge EE, Look KY, Clarke-Pearson DL, Davidson M: Cyclophosphamide and Cisplatin compared with Paclitaxel and cisplatin in Patients with Stage III and IV Ovarian Cancer. *N Engl J Med*, 334:1-6, 1996.
28. Ozols RF, Young RC: Ovarian Cancer. *Curr. Probl. Cancer*, 11:57-122, 1988.
29. Dauplat J, Ferriere JP, Gorbinet M, Legros M, Chollet P, Gikaud B, Plagne R: Second look laparotomy in managing epithelial ovarian carcinoma. *Cancer*, 57:1627-1631, 1986.
30. De Gramont A, Drolet Y, Lavoie A, Painchaud M, Blouin R, Tessier C, Ouellet P: Adriamycin and cis-platinum in advanced ovarian cancer. *Eur J Cancer Clin Oncol*, 21:665-669, 1985.
31. Louie KG, Ozols RF, Myers CE, Ostchega Y, Jenkins J, Howser D, Young RC: Long-term results of a cisplatin-containing combination chemotherapy regimen for the treatment of advanced ovarian carcinoma. *J Clin Oncol*, 4:1579-1585, 1986.
32. Neijt JP, ten Bokkel Huinink WW, Van der Burg ME, van Oosterom AT, Willemse PH, Heintz AP, van Lent M, Trimbos JB, Bouma J, Vermoken JB: Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs. CHAP-5) in advanced ovarian carcinoma. *J Clin Oncol*, 5:1157-1168, 1987.
33. Pasmantier MW, Coleman M, Silver RT, Perry Ballard W: Six-drug chemotherapy (hexamethylmelamine, doxorubicin, cisplatin, cyclophosphamide, methotrexate, and 5-FU; CHAMP-5) for ovarian carcinoma: alternating sequences of combination regimens. *Cancer Treat Rep*, 69:689-693, 1985.

34. Steiner M, Rubinov R, Borovik R, Cohen Y, Robinson E: Multimodal approach (surgery, chemotherapy and radiotherapy) in the treatment of advanced ovarian carcinoma. *Cancer*, 55:2748-2752, 1985.
35. Wils J, Blijham G, Naus A, Belder C, Boschma F, Bron H, Ceelen T, Eekhout A, von Erp J, Geelen P, Geuns HV, Hoest J, Hoogland H, Huiskes J, de Koning Gans H, Kornman J, Kruyerer G, Lalisang F, Meulen JVD, Moorman P, de Pree N, Stoot J, Tushuizen P, Vreeswijk J, Wals J, Wetzels L, Willebrand D: Primary or delayed debulking surgery and chemotherapy consisting of cisplatin, doxorubicin, and cyclophosphamide in stage III-IV epithelial ovarian carcinoma. *J Clin Oncol*, 4:1068-1073, 1986.
36. De Gramont A, Drolet Y, Varette C, Louvet C, Gonzalez-Canall G, Krulik M, Cady J, Pigne A, Marpeau L, Barrat J, Gallot D, Malafosse M, Debray J: Survival after second-look laparotomy in advanced ovarian epithelial cancer. Study of 86 patients. *Eur J Cancer Clin Oncol*, 25:451-457, 1989.
37. Gershenson DM, Copeland LJ, Wharton JT, Atkinson EN, Sneige N, Edwards CL, Rutledge FN: Prognosis of surgically determined complete responders in advanced ovarian cancer. *Cancer*, 5:1129-1135, 1985.
38. Neijt JP, ten Bokkel Huinik WW, Van der burg MEL, Van Oosterrom AT: Complete remission at laparotomy: still a gold standard in ovarian cancer? *Lancet*, 1 (8488):1028, 1986.
39. Look KY, Muss HM, Blessing JÁ, Morris M: A phase II trial of 5-fluorouracil and high-dose leucovorin in recurrent epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Am J of Clinical Oncol*, 18:19-22, 1995.
40. Lorusso V, Catino A, Leone B, Rabinovich M, Gargano G, Paradiso A, De Lena M: Carboplatin plus ifosfamide as salvage treatment of epithelial ovarian cancer: a pilot study. *J of Clin Oncol*, 11:1952-1956, 1995.

41. Markman M, Reichman B, Hakes T, Jones W, Lewis JL Jr, Rubin S, Almadronesi L, Hoskins W: Responses to second line cisplatin based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. *J Clin Oncol*, 9:1801-1805, 1991.
42. Piver MS, Recio FO, Baker TR, Driscoll D: Evaluation of survival after Second-Line Intraperitoneal Cisplatin-Based Chemotherapy for Advanced Ovarian. *Cancer*, 73:1693-1698, 1994.
43. Stiff PJ, Bayer R, Kerger C, Potkul RK, Malhotra D, Peace DJ, Smith D, Fisher SG: High-dose chemotherapy with autologous transplantation for persistent /relapsed ovarian cancer: a multivariate analysis of survival for 100 consecutively treated patients. *J Clin Oncol*, 15:1309-1317, 1997.
44. ten Bokkel Huinink WW, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, Broom C, Scarabelli C, Dawidson N, Spanczynski M, Bolis G, Malmstrom H, Coleman R, Fields SC, Heron JF: Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*, 15:2183-2193, 1997.
45. Trimble EL, Adams JD, Vena D, Hawinks MJ, Friedman MA, Fisherman JS, Christian MC, Canetta R, Onetto N, Hayn R: Paclitaxel for platinum refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Referral center 9103. *J Clin Oncol*, 11:2405-2410, 1993.
46. Vergote I, Himmelmann A, Frankendal B, Scheistroen M, Vlachos K, Trope C: Hexamethylmelamine as second-line therapy in platin-resistant ovarian cancer. *Gynecol Oncol*, 47:282-286, 1992.
47. Berek JS, Hacker NF, Lagasse LD, Nieberg RK, Elashoff RM: Survival of patients following secondary cytoreductive surgery in ovarian cancer. *Obstet Gynecol*, 61:189-193, 1983.

48. Eisenkop SM, Friedman RL, Wang H: Secondary cytoreductive for recurrent ovarian cancer. A prospective study. *Cancer*, 76:1606-1614, 1995.
49. Janicke F, Holscher M, Kuhn W, von Hugo R, Pache L, Siewert JR, Graeff H: Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. *Cancer*, 70:2129-2136, 1992.
50. Morris M, Gershenson DM, Wharton JT, Copeland LJ, Edwards CL, Stringer CA: Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. *Gynecol Oncol*, 34:334-338, 1989.
51. Segna RA, Dottino PR, Mandeli JP, Konsker K, Cohen CJ: Secondary cytoreduction for ovarian cancer following cisplatin therapy. *J Clin Oncol* 11:434-439, 1993.
52. Vaccarello L, Rubin SC, Vlamis V, Wong G, Jones WB, Lewis JL, Hoskins WJ: Cytoreductive surgery in ovarian carcinoma patients with documented previously complete surgical response. *Gynecol Oncol*, 57:61-65, 1995.
53. Goldie JH, Coldman JA: A mathematics model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep.*, 63:1727-1733, 1979.
54. Jacquet P, Sugarbaker PH: Peritoneal-plasma barrier. In: Sugarbaker Ph (ed). *Peritoneal Carcinomatosis: Principles of management*. Boston, Kluwer Academic Publishers, pp:53-63, 1966.
55. Deraco M, Vaglini M, Santinami M, Costagli V, Di Re F, Inglese MG, Mascotti G, Persiani L, Santoro N, Sequeira C, Carlier-Somers D: Razionale per un trattamento chemioipertermico della carcinosi peritoneale. *Argomenti di Oncologia*, 16:149-159, 1995.

Fig.1A

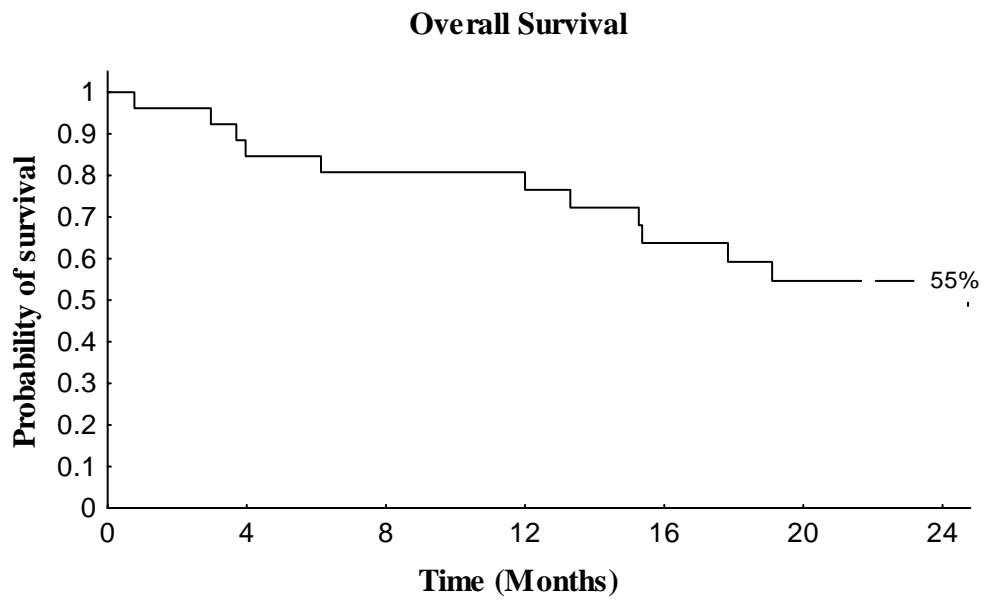


Fig.1B

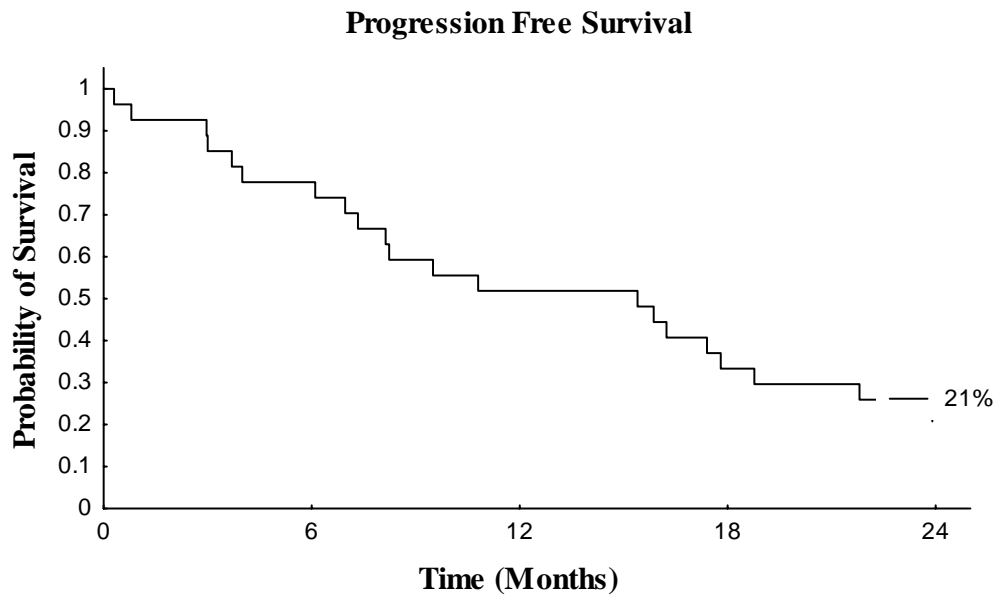


Fig.1C

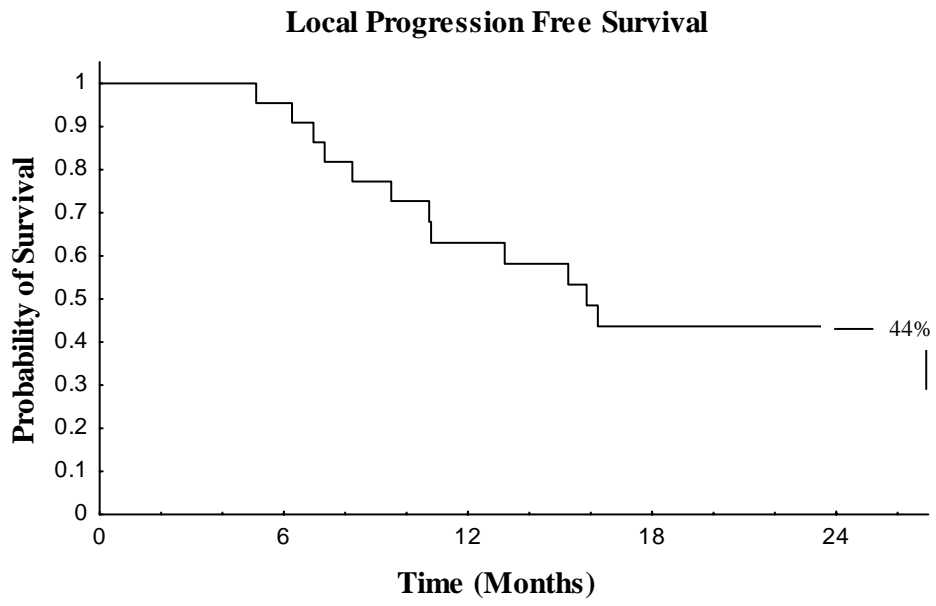


Fig.2A

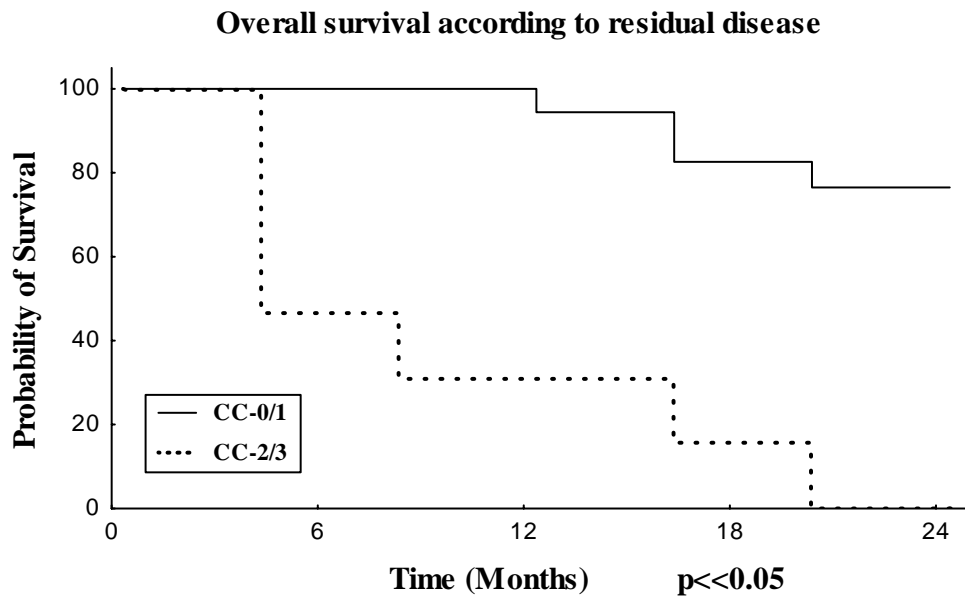


Fig.2B

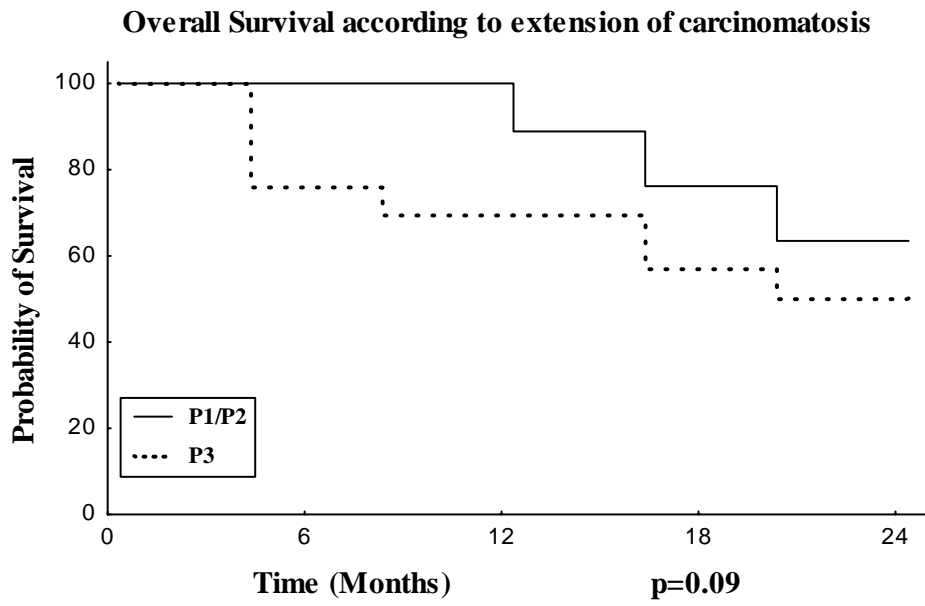


Fig.2C

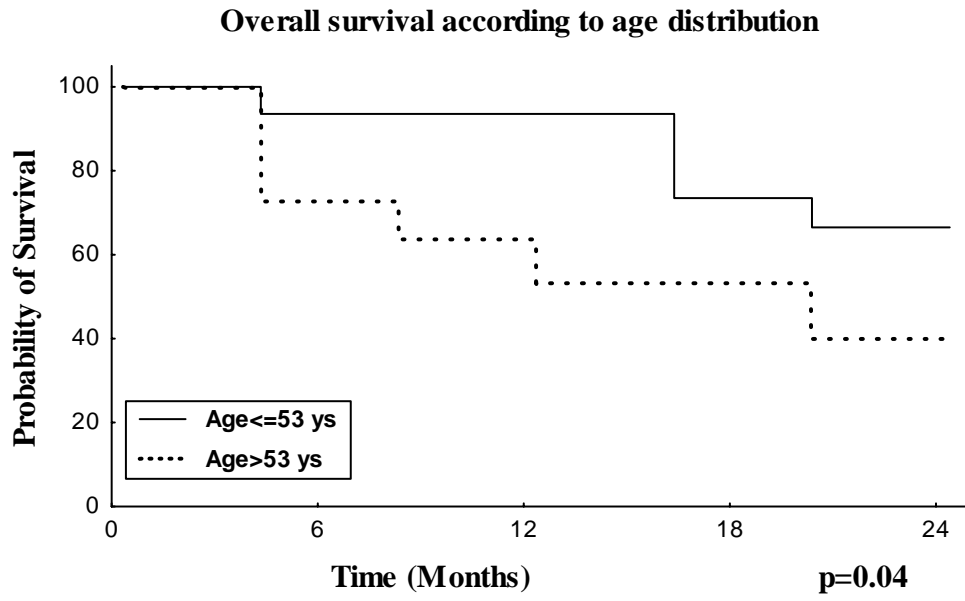


Fig.2D

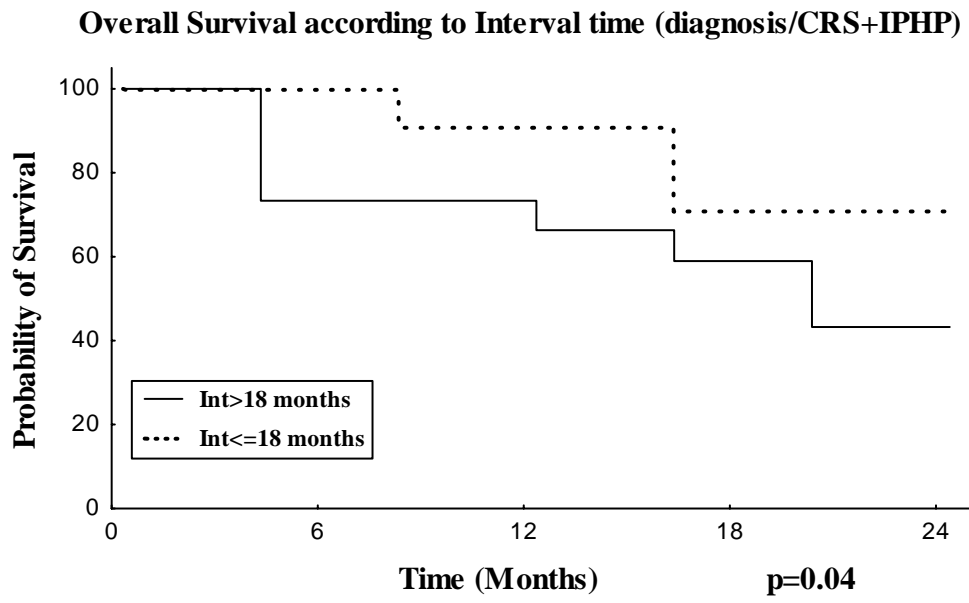


Table 1. Effect of salvage therapies as a function of first-line platinum response.

	Therapy	No. of Patients	Response Rate (%)		Median Survival (months)
			<i>Resistant</i>	<i>Sensitive</i>	
Lorusso et al.[28]	Carboplatin+ ifosfamide	35	0	56	-
Trimble et al. [49]	Paclitaxel	1000	22	-	8.8
Vergote et al.[52]	Hexamethylmelamine	61	14	-	9*
Look et al. [27]	5-FU	49	6.6	17.2	-
Huinink et al.[48]	Topotecan	112	13.3	28.8	15
Stiff et al. [45]	High-dose Chemotherapy	100	81	94	13
Piver et al.[40]	Intraperitoneal	63	7	50	29
Markman et al. [33]	Chemotherapy**	89	11	56	-

*Responders; **Cisplatin-Based Regimen