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Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

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ABSTRACT

Background. The current treatment of ovarian cancer consists of cytoreductive surgery (CRS) and systemic chemotherapy. The aim of this study was to examine if hyperthermic intraperitoneal chemotherapy (HIPEC) is an alternative modality to treat this category of patients along with a second attempt of surgical resection and second- or third-line systemic chemotherapy afterward.

Methods. In an 8-year period (2006–2013), 120 women with advanced ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] III_c and IV) who experienced disease recurrence after initial treatment with conservative or debulking surgery and systemic chemotherapy were randomized into two groups. Group A comprised 60 patients treated with CRS followed by HIPEC and then systemic chemotherapy. Group B comprised 60 patients treated with CRS only and systemic chemotherapy.

Results. The mean survival for group A was 26.7 versus 13.4 months in group B ($p < 0.006$). Three-year survival was 75 % for group A versus 18 % for group B ($p < 0.01$). In the HIPEC group, the mean survival was not different between patients with platinum-resistant disease versus platinum-sensitive disease (26.6 vs. 26.8 months). On the other hand, in the non-HIPEC group, there was a statistically significant difference between platinum-sensitive versus platinum-resistant disease (15.2 vs. 10.2 months, $p < 0.002$). Complete cytoreduction was associated with longer survival. Patients with a peritoneal cancer index score of <15 appeared also to have longer survival.

Conclusions. The use of HIPEC along with the extent of the disease and the extent of cytoreduction play an important role in the survival of patients with recurrence in an initially advanced ovarian cancer.

The most common cause of primary ovarian malignancy is epithelial carcinoma, accounting for 95 % of ovarian neoplasia. Its exact cause has not yet been identified; however, many several pathophysiologic mechanisms have been suggested, including the dedifferentiation of ovarian surface epithelium or the attachment of distal fallopian tube cells to the ovary during ovulation.[1]

The lifetime risk of epithelial ovarian cancer (EOC) is 1 of 70 women; it is the leading cause of death related to gynecologic malignancy.[2,3] As a result of its indolent clinical course, EOC tends to be diagnosed at an advanced stage, often resulting in unfavorable outcomes because disease stage at diagnosis is the most significant prognostic factor.[4]

EOC metastasizes locally or via blood vessels and lymphatics. Nonetheless, one of its most distinct features is the tendency to disseminate into the peritoneal cavity, causing peritoneal carcinomatosis, indicative of advanced stage disease.

So far the standard of care for ovarian cancer has been surgery followed by systemic chemotherapy. However, treatment with cytoreductive surgery (CRS), as described by Sugarbaker, and hyperthermic intraperitoneal chemotherapy (HIPEC) is another approach, showing promising

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TABLE 1 Characteristics of 120 patients

Characteristic	HIPEC	Non-HIPEC
n	60	60
Mean age, years	58.3	58.1
Mean no. of cycles of adjuvant chemotherapy	5	5
Mean preoperative CA-125 value (U/ml)	83.7	80.5

Characteristic	HIPEC		Non-HIPEC	
	n	%	*n*	%
Stage				
III_c	41	68.3	35	58.3
IV	19	31.7	25	41.7
Platinum responsiveness				
Sensitive	38	63.3	36	60
Resistant	22	36.7	24	40
Ascites				
Yes	18	30	16	26.7
No	42	70	44	73.3
Optimal cytoreduction at primary surgery	51	85	46	76.6
PCI				
PCI < 5	7	11.7	8	13.3
5 ≤ PCI < 10	24	40	22	36.7
PCI ≥ 10	29	48.3	30	50
CC				
CC-0	39	65	33	55
CC-1	12	20	20	33.3
CC-2	9	15	7	11.7

HIPEC hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal carcinomatosis index, *CC* completeness of cytoreduction

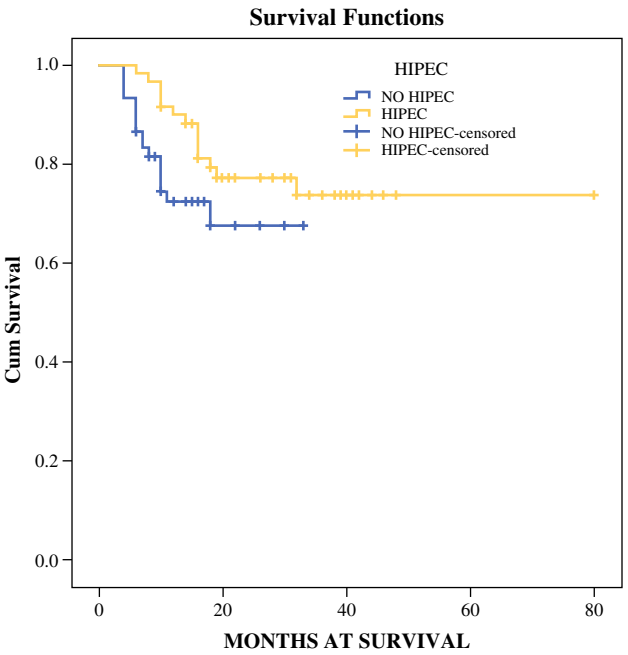

FIG. 1 Kaplan–Meier survival plot, HIPEC versus no HIPEC, $p = 0.006$

results.[5] CRS consists of peritonectomy procedures and visceral resections aimed at the complete removal of tumor from the abdominal cavity. The most common chemotherapeutic agents used in HIPEC for EOC are cisplatin, doxorubicin, and paclitaxel.

Here we present a series of patients diagnosed with advanced EOC (stages III_c and IV), randomized for the application of HIPEC, and patient outcomes in terms of survival and recurrence.

PATIENTS AND METHODS

Over a period of 8 years (2006–2013), our team has treated 120 women with stage III_c and IV EOC who experienced disease recurrence after initial treatment with CRS or debulking surgery and systemic chemotherapy. Using online statistic tools (GraphPad Software), the patients were randomized preoperatively into two groups with similar demographic, clinical, and therapeutic features (Table 1). Randomization was performed by a member of the Department of Statistical Analysis who did not have any information regarding patient characteristics or medical records. Power analysis yielded a minimum of 33 patients, and the accrual goal was met. The exclusion criteria were as follows: Gynecologic Oncology Group (GOG) performance status 3 or 4; evidence of pleural disease or lung metastasis; more than three sites of bowel obstruction; and evidence of bulking disease in retroperitoneal area or on the mesentery. The inclusion criteria were as follows: women aged between 18 and 70 years with recurrent ovarian cancer; GOG performance status 1 or 2; no evidence of disease beyond the abdomen; and no splanchnic metastasis.

In the first group of patients (group A, $n = 60$), CRS was followed by the administration of HIPEC and subsequent systemic chemotherapy. Specifically, the HIPEC protocols used were as follows: for platinum-sensitive disease ($n = 34$): cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 delivered for 60 min at 42.5 °C; for platinum-resistant disease ($n = 26$): doxorubicin 35 mg/m^2 and (paclitaxel 175 mg/m^2 or mitomycin 15 mg/m^2) delivered for 60 min at 42.5 °C. In 40 of these patients, HIPEC was performed using the open (coliseum) technique, while on the remaining 20 the closed technique was performed.

The second group of patients (group B, $n = 60$) underwent CRS followed by systemic chemotherapy.

All patients were operated on by the same surgical team. Each patient was informed about inclusion onto the study and the possible surgical complications, and each signed a consent form approved by the ethics committee of the hospital. Each case was presented at the hospital's multidisciplinary team and was discussed before surgical management.

Study outcome was mean overall survival (OS) depending on disease stage, platinum responsiveness, completeness of cytoreduction (CC score), peritoneal cancer index (PCI), and treatment with HIPEC.

Statistical analysis was performed by SPSS software, version 17 (IBM).

RESULTS

Mean OS in the HIPEC group was 26.7 versus 13.4 months in the non-HIPEC group, yielding a statistically significant difference ($p = 0.006$) (Fig. 1).

HIPEC versus No HIPEC

In stage III_c disease, survival was 26.9 months in the HIPEC group versus 14.2 months in the non-HIPEC group. In stage IV disease, survival was 26.4 months in the HIPEC group versus 11.9 months in the non-HIPEC group (Table 2). In platinum-sensitive disease, survival was significantly higher in the HIPEC group (26.8 vs. 15.2 months in the non-HIPEC group, $p = 0.035$) (Fig. 2a). In platinum-resistant disease, no such difference was observed (26.6 months in the HIPEC group vs. 10.2 months in the non-HIPEC group, NS) (Fig. 2b).

TABLE 2 Survival by disease stage

Mean survival	Stage III_c survival (months)	Stage IV survival (months)
HIPEC	26.9	26.4
Non-HIPEC	14.2	11.9

HIPEC hyperthermic intraperitoneal chemotherapy

HIPEC Group

In the HIPEC group, survival was 26.9 months for stage III_c disease versus 26.4 months for stage IV disease. Also, when examined per responsiveness to platinum-based chemotherapy, patients with both platinum-sensitive and platinum-resistant disease had similar mean OS after HIPEC administration (26.6 months for platinum-resistant and 26.8 months for platinum-sensitive disease, $p = 0.287$).

When the HIPEC patients were examined separately according to platinum responsiveness and disease stage, no statistically significant differences in survival were identified. In particular, in stage III_c disease, the survival was similar between platinum-sensitive (27.28 months) and platinum-resistant (26.08 months) disease. Respectively, in stage IV disease, no difference was detected in the survival of those with platinum-sensitive (25.4 months) versus platinum-resistant (27 months) disease. Accordingly, patients with platinum-resistant disease had similar survival, irrespective of the disease stage (26.8 months for stage III_c vs. 27 months for stage IV disease). The results were similar for patients with platinum-sensitive disease (27.28 months for stage III_c vs. 25.4 months for stage IV disease) (Table 3).

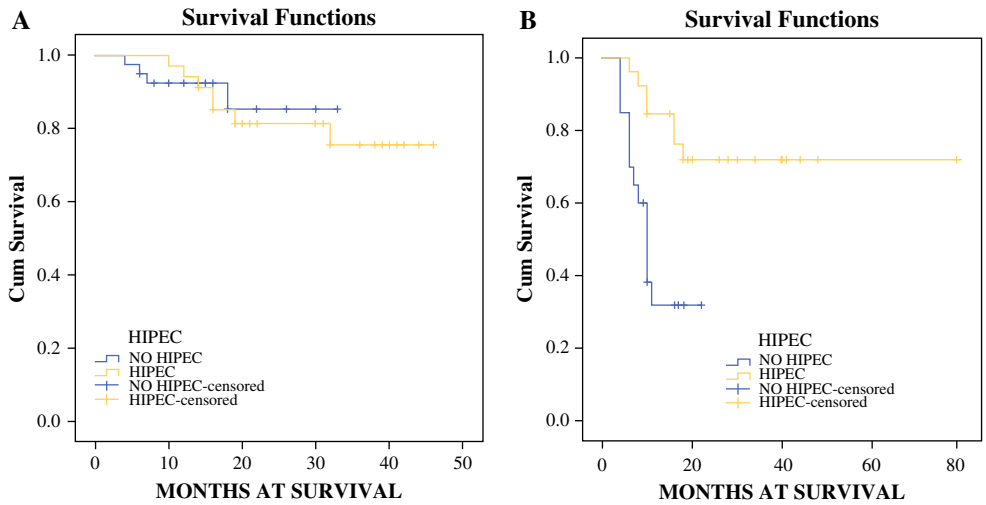

FIG. 2 **a** Kaplan–Meier survival plot, platinum-sensitive disease, HIPEC versus no HIPEC, $p = 0.035$. **b** Kaplan–Meier survival plot, platinum-resistant disease, HIPEC versus no HIPEC

TABLE 3 Survival by stage and platinum responsiveness by HIPEC group

Mean survival	Stage III_c survival (months)	Stage IV survival (months)
HIPEC group		
Platinum sensitive	27.28	25.4
Platinum resistant	26.08	27
Non-HIPEC group		
Platinum sensitive	15.7	13.5
Platinum resistant	10.7	9.37

HIPEC hyperthermic intraperitoneal chemotherapy

Non-HIPEC Group

Mean survival in the non-HIPEC group was 14.2 months for III_c stage disease and 11.9 months for stage IV disease. Patients with platinum-resistant disease had a mean survival of 10.2 months, while patients with platinum-sensitive disease had a mean survival of 15.2 months ($p = 0.002$). This statistically significant difference was not present in the HIPEC group.

When the second group of patients was studied separately according to platinum responsiveness and disease stage, no statistically significant differences were observed. In stage III_c disease, patients with platinum-sensitive disease had a survival of 15.7 months versus 10.7 months in patients with platinum-resistant disease (NS). In stage IV disease, similarly, no statistically significant differences were detected (13.5 months for platinum-sensitive vs. 9.37 months for platinum-resistant disease). In platinum-resistant disease, no statistically significant differences were observed between the two stages (10.7 months for stage III_c disease vs. 9.37 months for stage IV disease). Respectively, survival was similar between stage III_c (15.7 months) and stage IV (13.5 months) disease in patients with platinum-sensitive disease (Table 3).

CC Score

Survival in the HIPEC group versus the non-HIPEC group was as follows. In the HIPEC group, survival was 30.9 months when a CC score of zero (CC-0) was achieved, 23.9 months for CC-1, and 12.1 months for CC-2. In the non-HIPEC group, in CC-0 survival was 16.1 months, in CC-1 it was 11 months, and in CC-2 survival was 6.7 months. In CC-0 cytoreduction, survival was significantly higher in the HIPEC group (30.9 months vs. 16.9 months in the non-HIPEC group, $p = 0.038$). Moreover, in the non-HIPEC group, survival was significantly prolonged when the score was CC-0 (16.1 months in CC-0 vs. 6.7 months in CC-2, $p = 0.002$).

Peritoneal Cancer Index

In the HIPEC group, survival for PCI ≤ 15 was 30.4 months, while in PCI > 15 it was 21.5 months. In the non-HIPEC group, survival was 15.4 months for PCI ≤ 15 and 9.2 months for PCI > 15 ($p = 0.012$). Survival in the HIPEC versus the non-HIPEC group was significantly higher, both in PCI ≤ 15 ($p = 0.031$) and PCI > 15 ($p = 0.049$).

DISCUSSION

The need for randomized studies of the implementation of CRS and HIPEC has been often reported. To our knowledge, this is the first randomized study to identify the role of HIPEC in recurrent EOC (REOC). HIPEC appears to hold a significant position in the management of REOC: in our study population, it significantly prolonged OS (26.7 vs. 13.4 months in the non-HIPEC group, $p = 0.006$).

EOC is the most common cause of primary ovarian malignancy; it is also the leading cause of death from gynecologic malignancy.[2,3] With its indolent clinical course, EOC is often (60 %) diagnosed at an advanced stage, and it characteristically tends to disseminate intraperitoneally.[4] Moreover, 60 % of advanced EOC patients will experience recurrence in the first 3 years after diagnosis and treatment.[6]

CRS and HIPEC has been implemented at several time points in the course of the disease, making the timing of HIPEC in the disease course a most important issue.[7,8] CRS and HIPEC have shown maximum efficacy when applied either after neoadjuvant chemotherapy without previous resection (interval HIPEC) or after initial CRS and a full course of adjuvant chemotherapy in patients with a clinically complete response (consolidation HIPEC).[9]

In a recent review of recurrent EOC patient series, median OS and median disease-free survival after CRS and HIPEC and subsequent adjuvant chemotherapy were 15–57 months and 3–48 months, respectively, while 5-year OS and 5-year disease-free survival were 18–57 % and 0–12.5 % respectively. When a complete cytoreduction was achieved, median OS was 97.4 months and 5-year OS was 63–67 %.[8] Our results of 26.7 months for OS are in accordance with previous experience.

Two phase III trials have attempted to determine whether interval CRS after adjuvant chemotherapy adds a survival benefit, with conflicting results. The European Organisation for Research and Treatment of Cancer

(EORTC) trial identified a 6-month survival advantage in patients reexplored after three cycles of chemotherapy, while GOG reported no such benefit, pointing out the importance of initial cytoreduction.[10,11]

The extent of cytoreduction is one of the most crucial prognostic factors, greatly improving OS, in all disease stages, when HIPEC follows a complete cytoreduction (CC-0 or CC-1).[12] Many series have reported a relationship between survival and surgical outcome, indicating completeness of cytoreduction as the strongest predictor of survival.[13] This prognostic effect has been reported in many patient series, such as the HYPER-O registry, which also identified it as a prognostic factor in multivariate analysis.[9] Our results confirm previous reports: we found that the effect of HIPEC is maximized when a complete cytoreduction is achieved, leading to statistically significantly prolonged survival.

Regarding the choice of the intraperitoneal chemotherapeutic drug used in recurrent ovarian cancer, there has been no consensus.[9,14–16] Our team used cisplatin and paclitaxel in platinum-sensitive disease, and doxorubicin and paclitaxel or mitomycin in platinum-resistant disease.

For the subsequent systemic therapy, single-agent therapy seems to be an important option in the therapeutic plan of platinum-resistant patients, taking into consideration the cumulative toxicity from previous treatment. Numerous agents are available, such as gemcitabine, pegylated liposomal doxorubicin (PLD), topotecan, paclitaxel, docetaxel, oral etoposide, and hormonal agents.[13]

One of the significant findings of our study is that in the HIPEC group, similar survival was observed both in platinum-sensitive and platinum-resistant disease, which is not the case in the non-HIPEC group. This observation can be attributed to several reasons.

First, the role of hyperthermia needs to be evaluated. One possible explanation is that the increased temperature leads to the activation of heat-shock proteins, which in turn modify multiple cellular functions through their interference with protein folding. It is known that neoplastic cells express higher amounts of heat-shock proteins, therefore becoming more susceptible to the effect of hyperthermia.[17]

Another possible interpretation is that the administration of doxorubicin intraperitoneally modifies the response of remaining neoplastic cells to systematic chemotherapy. This effect of anthracycline use remains to be identified.

Moreover, one probable effect of hyperthermic chemoperfusion is epigenetic alterations.[18] These modifications are another mechanism that may explain the effect of HIPEC in altering responsiveness to platinum-based chemotherapy.

Finally, intraperitoneal administration provided immediately after surgery, before the formation of adhesions, and the pharmacokinetic advantages of intraperitoneal versus intravenous chemotherapy may contribute to this phenomenon.

Bakrin et al. have reported similar results.[14,19] In a multicenter French study including 474 REOC patients, patients with platinum-resistant and platinum-sensitive disease treated with optimal cytoreduction had a similar survival of 51.6 and 47.2 months, respectively (NS).[19] In our study accordingly, survival was 26.6 months in platinum-sensitive and 26.8 months in platinum-resistant disease (NS).

Several recent studies have been attempting to identify the role of CRS and HIPEC in recurrent EOC.

Our team has previously reported a series of 28 recurrent EOC patients, in 14 of whom CRS was followed by HIPEC and systemic chemotherapy, while in the remaining 14 CRS was followed only by systemic chemotherapy. The results were significantly better in the HIPEC group, with a 1- and 3-year OS of 90 and 30 %, respectively.[20]

A case–control study by Fagotti et al. compared survival data in 30 platinum-sensitive EOC patients undergoing secondary CRS and HIPEC versus 37 patients who did not undergo HIPEC. Statistically significant results were reported in favor of the HIPEC group regarding the rates of secondary recurrence, the duration of secondary response, and mortality, with a disease-free survival of 26 months in the HIPEC group versus 15 months in the non-HIPEC group.[21]

So far, the management of REOC is based up systemic chemotherapy. However, the need for an alternative treatment modality has been pointed out by Stathopoulos et al., who state that multiple chemotherapy lines (3–9 lines) do not offer a survival benefit versus 1 or 2 lines.[22]

The need for appropriate surgical management of recurrent EOC has been shown in a study by Fotopoulou et al., describing tertiary CRS in the course of treatment of patients with multiple relapses.[23]

As in previously reported series, our study confirms the importance of complete cytoreduction. EOC follows a pattern of intraperitoneal dissemination and presents as a locoregional disease. The effort to minimize remnant disease aims to improve chemotherapeutic penetration in neoplastic tissue and also acts protectively against chemoresistance, given that less disease burden requires fewer cycles of systemic chemotherapy.[24]

CONCLUSIONS

CRS and HIPEC offer a significant survival benefit to patients with recurrent EOC. This observation applies to both platinum-sensitive and platinum-resistant disease. Maximum efficacy of HIPEC is noted when complete cytoreduction is achieved.

DISCLOSURE None.

REFERENCES

1. Kurman RJ, Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. *Hum Pathol.* 2011;42:918–31.
2. Surveillance, Epidemiology, and End Results (SEER). National Cancer Institute. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed Aug 2014.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013;63:11–30.
4. Slomovitz B, Soliman P, Wolf J. Gynecologic Cancers. In: Feig B, Berger D, Fuhrman G, editors. The MD Anderson surgical oncology handbook. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2006.
5. Sugarbaker PH. Peritonectomy procedures. *Cancer Treat Res.* 1996;82:235–53.
6. Spiliotis J, Halkia E, Roukos DH. Ovarian cancer screening and peritoneal carcinomatosis: standards, "omics" and miRNAs for personalized management. *Expert Rev Mol Diagn.* 2011;11:465–7.
7. Gonzalez Bayon L, Steiner MA, Vasquez Jimenez W, Asencio JM, Alvarez de Sierra P, Atahualpa Arenas F, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of advanced epithelial ovarian carcinoma: upfront therapy, at first recurrence, or later? *Eur J Surg Oncol.* 2013;39:1109–15.
8. Mulier S, Claes JP, Dierieck V, Amiel JO, Pahaut JP, Marcelis L, et al. Survival benefit of adding hyperthermic intraperitoneal chemotherapy (HIPEC) at the different time-points of treatment of ovarian cancer: review of evidence. *Curr Pharm Des.* 2012;18:3793–803.
9. Helm CW, Richard SD, Pan J, Bartlett D, Goodman MD, Hoefer R, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. *Int J Gynecol Cancer.* 2010;20:61–9.
10. van der Burg ME, van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med.* 1995;332:629–34.
11. Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med.* 2004;351:2489–97.
12. Schorge JO, Garrett LA, Goodman A. Cytoreductive surgery for advanced ovarian cancer: quo vadis? *Oncology.* 2011;25:928–34.
13. Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and management of peritoneal metastases from ovarian cancer. *Gastroenterol Res Pract.* 2012;2012:541842.
14. Bakrin N, Cotte E, Golfier F, Gilly FN, Freyer G, Helm W, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. *Ann Surg Oncol.* 2012;19:4052–8.
15. Cotte E, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F, et al. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. *World J Surg.* 2007;31:1813–20.
16. Raspagliesi F, Kusamura S, Campos Torres JC, de Souza GA, Ditto A, Zanaboni F, et al. Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: the experience of National Cancer Institute of Milan. *Eur J Surg Oncol.* 2006;32:671–5.
17. Didelot C, Lanneau D, Brunet M, Joly AL, De Thonel A, Chiosis G, et al. Anti-cancer therapeutic approaches based on intracellular and extracellular heat shock proteins. *Curr Med Chem.* 2007;14:2839–47.
18. Hegyi G, Szigeti GP, Szasz A. Hyperthermia versus oncothermia: cellular effects in complementary cancer therapy. *Evid Based Complement Altern Med.* 2013;2013:672873.
19. Bakrin N, Bereder JM, Decullier E, Classe JM, Msika S, Lorimier G, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. *Eur J Surg Oncol.* 2013;39:1435–43.
20. Spiliotis J, Vaxevanidou A, Sergouniotis F, Lambropoulou E, Datsis A, Christopoulou A. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study. *J BUON.* 2011;16:74–9.
21. Fagotti A, Costantini B, Petrillo M, Vizzielli G, Fanfani F, Margariti PA, et al. Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: a case-control study on survival in patients with two year follow-up. *Gynecol Oncol.* 2012;127:502–5.
22. Stathopoulos GP, Papadimitriou C, Aravantinos G, Rigatos SK, Malamos N, Stathopoulos JG, et al. Maintenance chemotherapy or not in ovarian cancer stages IIIA, B, C, and IV after disease recurrence. *J BUON.* 2012;17:735–9.
23. Fotopoulou C, Savvatis K, Kosian P, Braicu IE, Papanikolaou G, Pietzner K, et al. Quaternary cytoreductive surgery in ovarian cancer: does surgical effort still matter? *Br J Cancer.* 2013;108:32–8.
24. Fagotti A, Gallotta V, Romano F, Fanfani F, Rossitto C, Naldini A, et al. Peritoneal carcinosis of ovarian origin. *World J Gastrointest Oncol.* 2010;2:102–8.