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Peritoneal Cancer Index and Completeness Cytoreduction Score are Needed to Better Define Stage and Results of Treatment in Advanced Epithelial Ovarian Carcinoma. An Observational Cohort Study

*Lozano P[1], Vásquez W[1], Salinas J[2], Mendizabal E[3], Palencia N[1], Martínez C[1], Martín L[1], Garciafilia L[1], Fernández ML[1] and González Bayón L[1]**

[1]Department of General Surgery, Gregorio Maranon Hospital, Spain

[2]Department of General Surgery, La Paz University Hospital, Spain

[3]Department of Gynecology Oncology, Gregorio Maranon Hospital, Spain

Abstract

Objective: This study aims to assess how peritoneal cancer index and completeness cytoreduction score help in defining stages and results of treatment in advanced ovarian carcinoma.

Methods: Newly diagnosed advanced epithelial ovarian cancer patients (FIGO stage IIIC/IV) at our Institution are treated by the Gynecologic Oncology Unit (Department of Gynecology) and by the Peritoneal Surgery Unit (Department of Surgery). After approval by the corresponding Multidisciplinary Committee (MDC), patients were treated with upfront CRS and adjuvant systemic chemotherapy in the Gynecologic Oncology Unit (cytoreductive surgery group), or with neoadjuvant chemotherapy followed by interval Cytoreductive surgery and HIPEC-cisplatin in the Peritoneal Surgery Unit (cytoreductive surgery + HIPEC group). Peritoneal cancer index and completeness cytoreductive score were systematically recorded.

Results: Since 2010 to 2017, 123 patients newly diagnosed of FIGO stage IIIC/IV were treated at our Institution. 54 patients in the cytoreductive surgery group and 69 at the cytoreductive surgery + HIPEC group. A significant correlation between peritoneal cancer index, completeness cytoreductive surgery and overall survival was observed in the whole cohort.

Conclusion: Epithelial ovarian cancer FIGO stages III/IV needs to be sub-staged by peritoneal extension and residual disease after cytoreductive surgery in order to precise results of treatments. Recording peritoneal cancer index and completeness cytoreductive score may help to define sub-stages and select treatment alternatives.

Keywords: Epithelial ovarian cancer; Cytoreduction surgery; Hyperthermic Intraperitoneal Intraoperative Chemotherapy (HIPEC); Peritoneal cancer index; Completeness cytoreduction score

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Correspondence:
Luis González Bayón, Department of General Surgery, Peritoneal Surgery Unit, Gregorio Maranon Hospital, C/ Doctor Esquerdo 44.28007 Madrid, Spain, Tel: 34-630-61-23-08; E-mail: lgbayon@salud.madrid.org

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Introduction

A new treatment strategy for Peritoneal Surface Malignancies has been developed based on complete cytoreductive surgery followed by the administration of Hyperthermic Intraperitoneal Intraoperative Chemotherapy (HIPEC) [1]. This approach has obtained the best results when dealing with peritoneal carcinomatosis originated from appendiceal mucinous tumors [2], malignant peritoneal mesothelioma [3] and colorectal cancer carcinomatosis [4,5]. Recently, cytoreductive surgery + HIPEC-cisplatin has demonstrated significant benefits in disease free survival and overall survival as interval surgery of stage III epithelial ovarian carcinoma after neoadjuvant chemotherapy compared to cytoreductive surgery + systemic chemotherapy, in a phase III trial [6]. This strategy combines the 2 most important elements in the treatment of epithelial ovarian cancer: Maximal effort cytoreductive surgery and intraperitoneal component in adjuvant chemotherapy [7].

Gynecologic oncologists use FIGO stage for staging epithelial ovarian cancer. FIGO stage IIIC brings together patients with one peritoneal implant located outside of the pelvis, >2 cm in size and patients with a 20 cm × 10 cm omental cake with a thick layer surrounding the liver. However,

though belonging to the same disease stage, it seems important to discriminate between them given that different amounts of peritoneal disease have impact on overall survival and disease-free survival, and therefore, it would help to adjust the best treatment strategy.

Peritoneal cancer index and completeness cytoreduction score described by Sugarbaker are intraoperative prognostic indicators in peritoneal surface malignancy that measure the extension of disease in the peritoneum at the beginning of the operation [8] and the macroscopic residual disease at the end of cytoreduction. These scores allow us comparing patients and outcomes between groups working in this field. Peritoneal cancer index gives two main pieces of information: First, about peritoneal disease extension, as a precise score of disease which presents correlation with survival in most peritoneal surface malignancy pathologies. Secondly, peritoneal cancer index can predict the feasibility of achieving a complete cytoreduction and if the effort is worth it, helping on intraoperative decision making [9,10]. Furthermore, it can be applied on CT scan helping on preoperative decision making [11].

Several authors have studied its significance in staging [12-14] and in determining probability of optimal cytoreduction in patients with advanced epithelial ovarian cancer [15].

The aim of this study was to assess the value of both, peritoneal cancer index and completeness cytoreduction score as prognostic independent indicators in patients with epithelial ovarian cancer FIGO stage IIIC -with or without pleural effusion (FIGO stage IVA), managed with two different treatment strategies and to evaluate whether they define different prognostic groups.

Patients and Methods

An observational study of patients newly diagnosed of epithelial ovarian cancer FIGO stage IIIC/IV treated at our institution during the study period from January 2010 to December 2017. Data were collected in a prospective database, and a retrospective analysis was carried out. The study was reviewed and approved by the Clinical Research Ethics Committee and all patients were evaluated in a Multidisciplinary Committee. All patients CT of the chest, abdomen and pelvis to assess the size, location and extension of the disease. CT/PET imaging was used when there was any doubt of extra-abdominal disease extension. All cases with disease limited to the pelvis, or with abdominal extrapelvic disease <2 cm were excluded as well as those with metastatic disease out of the peritoneal compartment save for cases with pleural effusion.

There were two groups of patients: Cytoreductive surgery group was evaluated by the Gynecology Committee and treated by primary cytoreductive surgery followed by adjuvant chemotherapy and the cytoreductive surgery + HIPEC group that was treated with neoadjuvant chemotherapy followed by cytoreductive surgery + HIPEC-cisplatin and adjuvant chemotherapy. This group was assessed by the multidisciplinary committee, those cases stage IIIC or IV with worse case scenarios were initially considered to be non-resectable by the surgeons were generally treated with neoadjuvant chemotherapy followed by interval cytoreductive surgery + HIPEC intraoperative peritoneal cancer index and completeness cytoreduction score were systematically record.

Peritoneal Cancer Index is an intraoperative quantification of the peritoneal disease and it is calculated once the abdomen is opened and all adhesions have been eliminated. A score is assigned to each area according to the diameter of the greatest lesion using the following scale: 0- no tumor, 1- tumor up to 5 mm, 2-tumor up to 5 cm, 3- tumor more than 5 cm o confluence lesions. The primary tumor is excluded of lesion size assessment. The final score refers to the sum of the 13 areas.

Completeness of cytoreduction score refers to the final assessment once cytoreduction is complete. The abdominal cavity is reviewed in search for residual lesions. In this case, the score depends on the size of any remaining tumor (CC0= no residual tumor present, CC1= residual tumor present <2.5 mm, CC2= residual tumor <2.5 cm, CC3= residual tumor >2.5 cm).

All patients underwent surgery with or without HIPEC performed by a senior peritoneal surgeon or by a senior gynecologic oncologist. The HIPEC protocol used was cisplatin 100 mg/m^2 during 60 min (dose reduction was used in cases of previous renal injury or advanced age >65 y).

The follow-up began on the day of ovarian cancer diagnosis and was routinely performed at outpatient clinics until August 2018.

The goal of the study was to evaluate the correlation between both scores and overall survival and whether Peritoneal Cancer Index may define different prognostic groups within the stage IIIB of EOC.

Statistical analysis

Unless otherwise stated, data was expressed as mean (standard deviation) or number (%). When data was normally distributed (based on the Kolmogorov-Smirnov test) variables were compared using the student-t test. The qualitative variables and risk measurement were analyzed using the chi-square test. To assess the impact of the risk score on survival, Kaplan-Meier survival curve analysis was performed, and the results were compared using Log-rank test. The collected data was entered into a database created in SPSS version 20 for Mac (SPSS, Inc., Chicago, Illinois, USA).

Results

Patients and tumor characteristics

A total of 123 patients who underwent treatment during the period of January 2010 to December 2017, were included in the study: Out of which 54 patients were in the cytoreductive surgery group and 69 patients in the cytoreductive surgery + HIPEC. Demographic baseline characteristics, and surgical and treatment information are shown in Table 1.

Overall survival and local recurrence

For all study cohorts of 123 patients, an inverse relationship between PCI and OS was observed (Figure 1, 2 and Table 2).

A direct statistically significant relation was observed between completeness cytoreduction score and overall survival, regardless of the treatment received (Figure 3). This confirms that PCI and CCS are prognostic indicators in EOC in the same way it has been reported in other PSM pathologies reported.

After a median follow up of 32 months, the median overall survival was 79 months in the CR + HIPEC group and 52 months in the CR group (p=0.1) though not reaching statistical signification, a clear trend in favor for CRS + HIPEC group was observed.

In the multivariate analysis Peritoneal Cancer Index (PCI<20 *vs.* PCI>20) (HR=2.79, 95% CI (1.43-5.43), p=0.01) and completeness cytoreduction (CC0-CC1 *vs.* CC2-CC3) (HR=0.28, 95% CI (0.19-0.59), p=0.01) were found to be independent OS prognostic factors

Table 1: Demographic and baseline characteristic.

Variables	Patients (n=123)	Percentage (%)
Age (years) ASA	**Median 56.00 ± 11.73**	
I	22	17
II	76	61.7
III	25	20.3
Status Performance		
Total activity	90	73.2
Restricted activity	33	26.8
Histological Type		
Serose	98	79.7
Mucinose	10	8.1
Endometroid	3	2.4
Celulas Claras	7	5.7
Others	5	4.1
Tumoral Grade		
Low	26	21.1
Moderate	18	14.6
High	79	64.2
FIGO stage		
IIIC	96	78
IV	27	22
Neoadjuvant CT		
No	44	35.8
Yes	79	64.2
Adjuvant CT		
No	13	10.6
Yes	105	85.4
Peritoneal Cancer Index	**Median 10.00 ± 9.083**	
PCI <10	62	50.4
PCI 10-20	38	30.9
PCI 20-30	17	13.8
PCI >30	6	4.9
Number of peritonectomies	**Median 2.00 ± 2.01**	
Number of anastomosis	**Median 0.45 ± 0.63**	
Number of visceral resections	**Median 3.00 ± 1.58**	
Linfadenectomy		
Yes	55	44.7
No	68	55.3
Complication CTCAE		
No	103	83.7
Yes (3,4)	20	16.3
Surgical treatment		
Cytoreductive Surgery R	54	43.9
Cytoreductive Surgery+HIPEC	69	56.1
Cytoreduction Grade (CCS)		
CCO-1	105	85.3
CC2-3	17	14.7

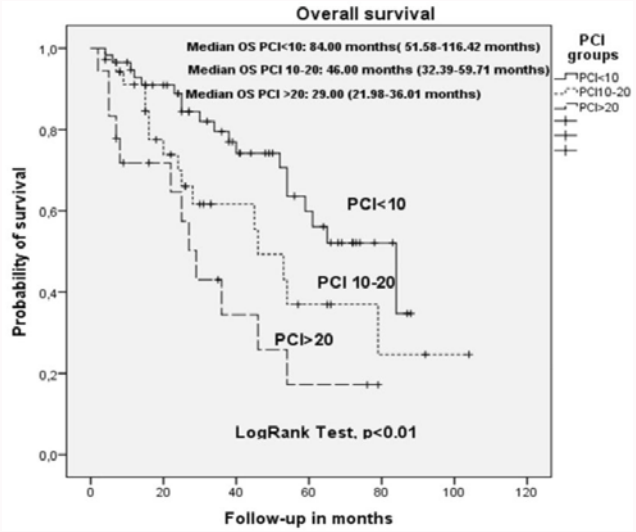

Figure 1: Overall survival for Peritoneal Cancer Index (PCI). Three different prognostic groups.

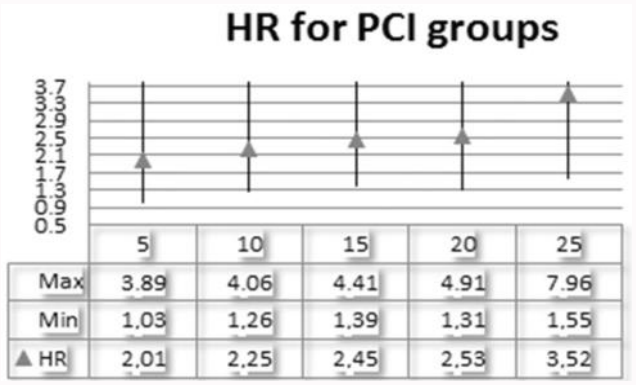

Figure 2: Hazard ratio for Peritoneal Cancer Index (PCI) groups. Max: Maximum; Min: Minimum; 5: PCI >5, HR 2.01; 10: PCI>10, HR 2.25; 15: PCI>15, HR 2.45; 20: PCI>20, HR 2.53; 25: PCI >25, HR 3.52

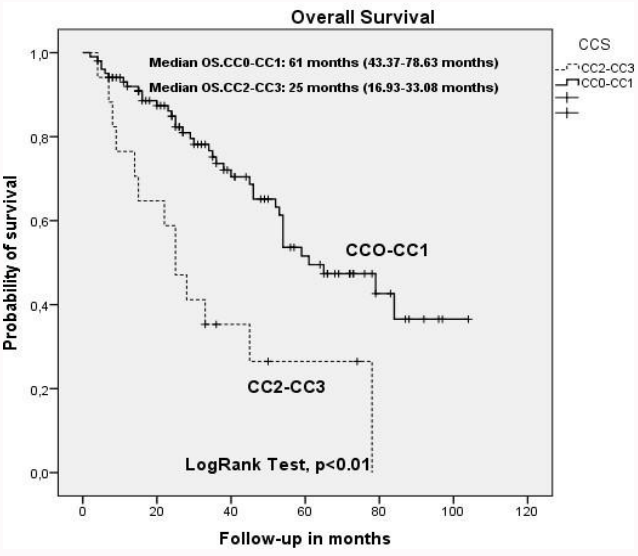

Figure 3: Overall survival for Completeness Cytoreductive Surgery (CCS). Two prognostic groups based on CCS.

Table 2: Univariate and multivariate COX regression overall survival.

Variables	Univariate COX regression			Multivariate COX regression		
	β	Relative Risk (95% CI)	p	β	Relative Risk (95% CI)	p
Age (years)	0.99	(0.97-1.02)	0.81			
Status Performances (total activity/Restricted activity)	1.16	(0.63-2.75)	0.63			
FIGO (IIIC/IV)	1.4	(0.68-2.85)	0.35			
Neoadjuvant CT (No/Yes)	1.44	(0.85-2.48)	0.19			
Adjuvant CT (No/Yes)	1.01	(0.43-2.39)	0.97			
Peritoneal Cancer Index (PCI>20/PCI>20)	**2.5**	**(1.31-4.91)**	**0**	**2.8**	**(1.43-5.43)**	**0.01**
Cytoreduction Grade (CC0-1/CC2- 3)	**0.3**	**(0.17-0.63)**	**0**	**0.3**	**(0.19-0.59)**	**0.01**
Treatment (CRS/CRS + HIPEC)	1.58	(0.91-2.75)	0.1			
Complication CTKAE (Yes/No)	1.03	(0.48-2.19)	0.93			

reaching statistic signification (Table 2).

Discussion

Peritoneal surgery based on cytoreductive surgery + HIPEC was initially developed to treat digestive malignancies with dissemination to the peritoneum. Common prognostic indicators in peritoneal surgery, mainly constituted by peritoneal cancer index and completeness cytoreduction score, support intraoperative decision regarding disease resectability and overall survival, and also allow the comparison of results across different working groups.

The recently NEJM paper published by van Driel et al. [6] raises again the debate on which treatment strategy offers the best long-term results. The authors conclude that intensification of intraperitoneal treatment with HIPEC achieved better results than the standard protocol of CRS + adjuvant chemotherapy. Previous important papers have shown that when part of the adjuvant CT is administered using the intraperitoneal route, better results are obtained when compared to standard treatments [16-18]. However, these alternative treatment protocols have not been widely accepted throughout the oncology community [7,19].

Van Driel et al. [6] try to quantify the disease peritoneal extension using the simplified peritoneal cancer index [20], but they over-simplified it by distinguishing 2 groups according to the number of abdominal regions involved: 0 to 5 and 6 to 8 regions involved (despite SPCI only counts with 7 abdominal regions). As a result, there is no precise information about the degree of peritoneal disease extension. Stage III patients include those with retroperitoneal lymphatic extension (IIIA1), microscopic peritoneal extension (IIIA2) and macroscopic peritoneal implants outside of the pelvis (<2 cm - IIIB, >2 cm -IIIC).

However, all the scoring systems available to evaluate the degree of peritoneal disease extension only take into account macroscopic peritoneal lesions (applied to FIGO IIIB and IIIC).

Scoring peritoneal extension beyond the preoperative FIGO staging criteria, at the beginning of the surgical procedure allows for more precise comparison of treatment results across different working groups. Peritoneal cancer index may be considered the most accurate score because it evaluates the disease by direct visualization of the 13 abdominal areas [11]. Our study shows a clear relationship between peritoneal cancer index and overall survival, making it possible to distinguish three different prognostic groups based on PCI value (PCI<10, PCI 10 to 20 and PCI>20). Therefore, in order to compare the results of different treatments across homogeneous groups in diseases with peritoneal extension, it is of paramount importance to accurately describe the tumor burden in the peritoneum.

Residual disease scoring at the end of cytoreduction is a known prognostic factor given the strong association between residual disease and overall survival [21]. In our study, the robust correlation found between completeness cytoreduction score and overall survival highly supports the use of this intraoperative assessment. Lampe et al. [12] described peritoneal cancer index to be an indicator of resectability on the basis of the good correlation observed between peritoneal cancer index and completeness cytoreduction score. Chereau et al. [13] described that a peritoneal cancer index <10 was associated with more complete resections. Tentes et al. [14] described peritoneal cancer index in epithelial ovarian cancer a significant prognostic factor of survival with a cut-off point in </> 10. Later on, these same authors described a 5-year survival rate of 70% in cases of peritoneal cancer index <15 [22]. We observed no overall survival benefit in patients with peritoneal cancer index >20 treated with interval Cytoreductive Surgery + HIPEC when compared with those who received cytoreductive surgery + CT. These results highlight the importance of intraoperative scoring, which should be considered in the decision-making process when indicating treatment with cytoreductive surgery ± HIPEC.

Peritoneal Cancer Index is an objective descriptor of the extension of peritoneal dissemination of the disease, with a survival association in most peritoneal surface malignancy as well as in advanced epithelial ovarian cancer. It aids the surgeon in the evaluation of the feasibility of the resection of the whole amount of disease as well as in the surgical planning. Residual disease after surgery in advanced EOC has a direct association with survival. Therefore, completeness cytoreduction score should be systematically included in cytoreductive surgery procedure for epithelial ovarian cancer to report information about residual disease.

References

1. Mohamed F, Cecil T, Moran B, Sugarbaker P. A new standard of care for the management of peritoneal surface malignancy. Curr Oncol. 2011;18(2):e84-96.

2. Yan TD, Bijelic L, Sugarbaker PH. Critical analysis of treatment failure following complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal neoplasms. Ann Surg Oncol. 2007;14(8):2289-99.

3. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: Multi-institutional experience. J

Clin Oncol. 2009;27(36):6237-42.

4. 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):63-8.
5. Nadler A, McCart JA, Govindarajan A. Peritoneal carcinomatosis from colon cancer: A systematic review of the data for cytoreduction and intraperitoneal chemotherapy. Clin Colon Rectal Surg. 2015;28(4):234-46.
6. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230-40.
7. Tewari D, Java JJ, Salani R, Armstrong DK, Markman M, Herzog T, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: A gynecologic oncology group study. J Clin Oncol. 2015;33(13):1460-6.
8. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359-74.
9. Berthet B, Sugarbaker TA, Chang D, Sugarbaker PH. Quantitative methodologies for selection of patients with recurrent abdominopelvic sarcoma for treatment. Eur J Cancer. 1999;35(3):413-9.
10. 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;22(9):2958-64.
11. Mazzei MA, Khader L, Cirigliano A, Cioffi Squitieri N, Guerrini S, Forzoni B, et al. Accuracy of MDCT in the preoperative definition of Peritoneal Cancer Index (PCI) in patients with advanced ovarian cancer who underwent peritonectomy and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Abdom Imaging. 2013;38(6):1422-30.
12. Lampe B, Kroll N, Piso P, Forner DM, Mallmann P. Prognostic significance of Sugarbaker's peritoneal cancer index for the operability of ovarian carcinoma. Int J Gynecol Cancer. 2015;25(1):135-44.
13. Chereau E, Ballester M, Selle F, Cortez A, Daraï E, Rouzier R. Comparison of peritoneal carcinomatosis scoring methods in predicting resect ability and prognosis in advanced ovarian cancer. Am J Obstet Gynecol. 2010;202(2):178.e1-10.
14. Tentes AA, Tripsiannis G, Markakidis SK, Karanikiotis CN, Tzegas G, Georgiadis G, et al. Peritoneal cancer index: A prognostic indicator of survival in advanced ovarian cancer. Eur J Surg Oncol. 2003;29(1):69-73.
15. Elzarkaa AA, Shaalan W, Elemam D, Mansour H, Melis M, Malik E, et al. Peritoneal cancer index as a predictor of survival in advanced stage serous epithelial ovarian cancer: A prospective study. J Gynecol Oncol. 2018;29(4):e47.
16. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335(26):1950-5.
17. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynaecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19(4):1001-7.
18. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354(1):34-43.
19. Vergote I, Harter P, Chiva L. Is there a role for intraperitoneal chemotherapy, including HIPEC, in the management of ovarian cancer? J Clin Oncol. 2019;37(27):2420-3.
20. Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FAN. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg. 2004;91(6):739-46.
21. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol. 2002;20(5):1248-59.
22. Tentes AA, Kakolyris S, Kyziridis D, Karamveri C. Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy in the treatment of advanced epithelial ovarian cancer. J Oncol. 2012;2012:358341.