RESEARCH ARTICLE

Tertiary Cytoreduction for Recurrent Epithelial Ovarian Cancer: a Multicenter Study in Turkey

Macit Arvas[1], Yavuz Salihoglu[2], Veysel Sal[1], Tayfun Gungor[3], Hamdullah Sozen[2], Ilker Kahramanoglu[1]*, Samet Topuz[2], Fuat Demirkiran[1], Cem Iyibozkurt[2], Tugan Bese[1], Burcin Salman Ozgu[3], Dogan Vatansever[2], Nedim Tokgozoglu[1], Sinan Berkman[2], Hasan Turan[1], Ergin Bengisu[2], Nigar Sofiyeva[1], Irem Demiral[2], Mutlu Meydanli[3]

Abstract

Background: The purpose of this study was to determine the benefit of tertiary cytoreductive surgery (TC) for secondary recurrent epithelial ovarian cancer (EOC), focusing on whether optimal cytoreduction has an impact on disease-free survival, and whether certain patient characteristics could identify ideal candidates for TC. Materials and Methods: Retrospective analysis of secondary recurrent EOC patients undergoing TC at three Turkish tertiary institutions from May 1997 to July 2014 was performed. All patients had previously received primary cytoreduction followed by intravenous platinum-based chemotherapy and secondary cytoreduction for first recurrence. Clinical and pathological data were obtained from the patients' medical records. Survival analysis was caried out using the Kaplan Meier method. Actuarial curves were compared by the two tailed Logrank test with a statistical significance level of 0.05. Results: Median age of the patients was 49.6 years (range, 30-67) and thirty-eight (72%) had stage III–IV disease at initial diagnosis. Twenty six (49%) had optimal and 27 (51%) suboptimal cytoreduction during tertiary debulking surgery . Optimal initial cytoreduction, time to first recurrence, optimal secondary cytoreduction, time interval between secondary cytoreduction and secondary recurrence, size of recurrence, disease status at last follow-up were found to be significant risk factors to predict optimal TC. Optimal cytoreduction in initial and tertiary surgery and serum CA-125 level prior to TC were independent prognostic factors on univariate analysis. Conclusions: Our results and a literature review clearly showed that maximal surgical effort should be made in TC, since patients undergoing optimal TC have a better survival. Thus, patients with secondary recurrent EOC in whom optimal cytoreduction can be achieved should be actively selected.

Keywords: Ovarian cancer - recurrence - cytoreduction - surgery - survival.

Asian Pac J Cancer Prev, **17 (4)**, 1909-1915

Introduction

The role of surgical cytoreduction in newly diagnosed epithelial ovarian cancer (EOC) has been widely accepted while an improvement in survival was shown in cases in whom residual disease was less than 0.5 cm or who had no residual disease, in particular (Bristow et al., 2002; Chi et al., 2006; Arikan et al., 2014). The role of secondary cytoreduction in recurrent EOC is less clear. Almost all studies in this area are retrospective in nature (Sehouli et al., 2010; Eisenkop et al., 2000; Zang et al., 2004; Harter et al., 2006). A recent Cochrane review concluded that complete cytoreduction is associated with improvement in survival in patients with platinum-sensitive EOC (Al Rawahi et al., 2013). The benefits of secondary cytoreduction and definiton of patients who most likely to benefit are expected to be better determined after the results of three ongoing prospective clinical trials, DESKTOP III (ClinicalTrials.gov number NCT01166737), GOG 213 (ClinicalTrials.gov number NCT00565851), and SOCceR (Netherlands Trial Register number NTR3337).

The chances of developing recurrent disease after a second clinical remission is nearly 100 percent (Shih et al., 2010). Hitherto data regarding tertiary cytoreduction are limited with a few retrospective studies.

All of the previous 8 studies conclude mainly that TC may have a survival benefit in a highly select group of

*[1]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Cerrahpasa Faculty of Medicine, [2]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, [3]Dr Zekai Tahir Burak Womens Health Research and Education Hospital, Ankara, Turkey *For correspondence: ilkerkahramanoglu@hotmail.com*

secondary recurrent EOC patients, especially in whom an optimal cytoreduction can be achieved (Shih et al., 2010; Leitao et al., 2004; Karam et al., 2007; Gultekin et al., 2008; Fotopoulou et al., 2011; Hızlı et al., 2012; Tang et al., 2013; Fotopoulou et al., 2013).

The objective of this study was to determine the benefit of TC in secondary recurrent EOC, whether optimal cytoreduction had an impact on disease-free survival (DFS), and whether certain patient characteristics could identify ideal candidates for TC.

Materials and Methods

After obtaining approval from the Institutional Review Board at Istanbul University Cerrahpasa School of Medicine (Date: 02.06.2015/Number: A-07), retrospective analysis of secondary recurrent EOC patients underwent TC at three Turkish tertiary institutions from May 1997 to July 2014 was performed. The data were collected from the medical records. Patients' age at initial diagnosis, EOC histologic subtype, stage and tumor grade at initial diagnosis, outcomes of initial, secondary and TC (optimal vs suboptimal), time to first recurrence, time from secondary cytoreduction, number of lines of chemotherapy prior to TC, platinum sensitivity, serum CA-125 level prior to TC, size of the largest recurrence, sites of recurrence (single vs multiple), status at last follow-up and length of survival from TC were captured. All patients had previously undergone primary cytoreduction followed by intravenous platinum-based chemotherapy and secondary cytoreduction for first recurrence. Staging was performed according to the FIGO guidelines (Benedet et al., 2000). Patients were considered eligible for tertiary cytoreduction if they fulfill the following criteria: good performance status (PS 0-1 ECOG), no extra-abdominal metastasis and/or unresectable intra-abdominal tumors (peritoneal carcinomatosis, multiple liver metastasis, involvement of porta hepatis, pancreatic head, abdominal wall or para-aortic lymph nodes above renal vein) and/or ascites at diagnostic preoperative instrumental procedures. All surgeries were performed via midline laparotomy by gynecologic oncologists.

Optimal cytoreduction was defined as residual disease of less than 1 cm for initial cytoreduction and 0.5 cm for secondary and tertiary cytoreduction. Patients with a platinum-free interval of six months or longer and less than six months were considered to have platinum-sensitive and platinum-resistant disease, respectively.

Outcomes of interest were overall survival (OS) and disease-spesific survival (DSS). OS was defined as the time from initial diagnosis to death or last follow-up. DSS was defined as the time from tertiary surgical cytoreduction to death or last follow-up.

Statistical analyses were performed using the SAS statistical software (version 9.1.3; The SAS Institute, Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant. Survival analysis was caried out using Kaplan Meier method. Acturial curves compared by the two tailed Logrank test with a statistical significance level of 0.05. Among the single factor analysis results, the independent variables of P<0.2 (to rule confounding more effectively, we used liberal criterion p <0.2 for inclusion of covariates in the model (Maldonado et al., 1993)) were selected as the potential predictors of the survival timeafter TC, then the multivariate proportional hazards regression model described by Cox was performed. The estimates of the models are given as adjusted hazard ration with 95 % confidence interval.

Results

The clinicopathologic characteristics of the patients and comparison of patients with regard to outcome of TC were presented in Table 1. Median age of the patients was 49.6 years (range, 30–67) and thirty-eight patients (72%) had stage III–IV disease at initial diagnosis. Seven patients had grade I (13.2%), sixteen patients had grade II (30.2%) and thirty patients had grade III disease (56.6%). Thirty-five patients (66%) had serous histology, five patients had mucinous (9%), five patients had endometrioid (9%), one patient had clear cell histology (2%) and the remaining seven patients had mixed tumor histologies (14%). Time interval for the appearance of first recurrence after the initial surgery was ≤32 months in 31 patients (58%) and >32 months for the remaining 22 patients (42%). Secondary cytoreductive surgery for the initial recurrent disease was optimal (≤0.5 cm) in 32 patients (60%) and

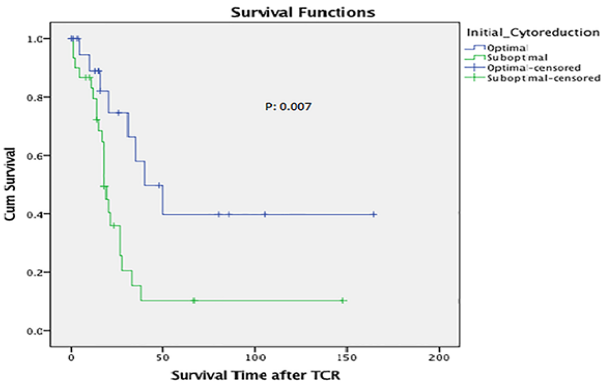

Figure 1. The Cumulative Survival Rates of Patients with Optimal Initial Cytoreduction and Patients with Suboptimal Cytoreduction

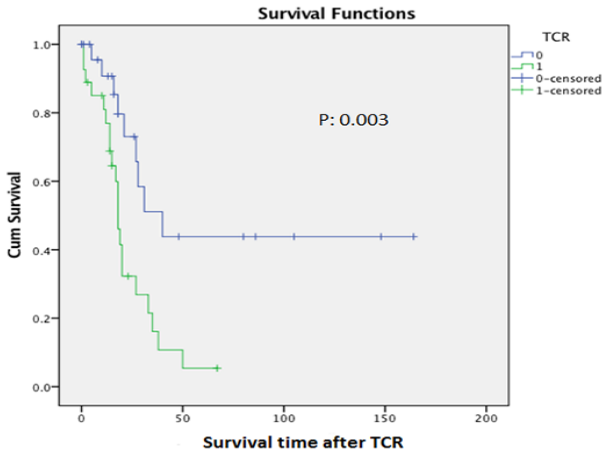

Figure 2. The Cumulative Survival Rates by TC (TC≤0.5 cm (0) Versus TC>0.5 cm(1))

Table 1. Comparison of Patients with Respect to Cytoreductive Outcome of Tertiary Cytoreduction

Variable	Optimal n (%)	Suboptimal n (%)	P
Age at initial diagnosis			0.449**
≤50 years	18 (53)	16 (47)	
>50 years	8 (42)	11 (58)	
Histology			0.313*
Serous	17 (48.6)	18 (51.4)	
Endometrioid	4 (80)	1 (20)	
Mucinous	1 (20)	4 (80)	
Clear cell	0	1 (100)	
Mixed	4 (57.1)	3 (42.9)	
Stage at initial diagnosis			0.598*
I	3 (37.5)	5 (62.5)	
II	5 (71.4)	2 (28.6)	
III	17 (47.2)	19 (52.8)	
IV	1 (50)	1 (50)	
Tumor grade			0.496**
1	2 (28.6)	5 (71.4)	
2	8 (50)	8 (50)	
3	16 (53.3)	14 (46.7)	
Initial cytoreduction			0.002**
Optimal (≤1 cm)	17 (73.9)	6 (26.1)	
Suboptimal (>1 cm)	9 (30)	21 (70)	
Time to first recurrence			0.019**
≤32 months	11 (35.5)	20 (64.5)	
>32 months	15 (68.2)	7 (31.8)	
Secondary cytoreduction			0.016 **
Optimal (≤0.5 cm)	20 (62.5)	12 (37.5)	
Suboptimal (> 0.5 cm)	6 (28.6)	15 (71.4)	
Age at TC			0.865**
≤ 55 years	16 (50)	16 (50)	
> 55 years	10 (47.6)	11 (52.4)	
Time from Secondary cytoreduction			0.003**
≤25 months	12 (34.3)	23 (65.7)	
>25 months	14 (77.8)	4 (22.2)	
Number of lines of chemotherapy regimens prior to TC			0.609*
≤3	23 (47.9)	25 (52.1)	
>3	3 (60)	2 (40)	
Treatment-free interval after Secondary cytoreduction			0.697**
≤20	17 (47)	19 (53)	
>20	9 (53)	8 (47)	
Platinum sensitivity			0.0704**
Sensitive	22 (56.4)	17 (43.6)	
Resistant	4 (28.6)	10 (71.4)	
CA125 levels atTC			0.058**
≤190	18 (56.3)	14 (43.7)	
>190	8 (38.1)	13 (61.9)	
Size of largest recurrence			0.024*
≤8 cm	23 (56.1)	18 (43.9)	
>8cm	3 (25)	9 (75)	
Sites of recurrence			0.206**
Single	17 (56.7)	13 (43.3)	
Multiple	9 (39.1)	14 (60.9)	
Status at last follow-up			0.003**
NED	8 (88.9)	1 (11.1)	
AWD	9 (64.3)	5 (35.7)	
DOD	9 (30)	21 (70)	

TC: Tertiary Cytoreduction, NED = no evidence of disease, AWD = alive with disease, DOD = dead of disease; *P- values from Fisher's Exact Test **P-values from Chi-square test

suboptimal in the remaining 21 patients (40%). Median age at the time of TC was 55 years (range, 31–72). The median time from secondary to TC was 25.1 months (range, 4-84 months). It was ≤25 months in 35 patients

Table 2. Disease Specific Survival after Tertiary Cytoreduction

Variable	N	Median (95% CI)	p-value[1]	p-value[2]	Adjusted HR (95% CI)[3]
Overall group	53	27.0 (18.3-35.7)			
Age at TC					
≤ 55 years	32	20.0 (10.6-29.4)	0.789		
>55 years	21	33.0 (12.0-54.0)			
Stage at Initial Diagnosis					
I-II	15	31.0 (9.3-52.7)	0.872		
III-IV	38	21.0 (13.4-28.6)			
Initial Cytoreduction					
Optimal (≤1 cm)	23	40.0 (17.6-62.3)	0.007	0.187	0.50 (0.179-1.399)
Suboptimal (>1 cm)	30	18.0 (16.1-19.9)			1.0
Time to first reccurence					
≤32 months	31	20.0 (16.7-23.3)	0.177	0.573	1.291 (0.573-2.908)
>32 months	22	33.0 (14.8-51.1)			1.0
Secondary cytoreduction					
Optimal (≤0.5 cm)	32	27.0 (16.8-37.2)	0.234		
Suboptimal(>0.5cm)	21	18.0 (13.9-22.1)			
Time from secondary cytoreduction					
≤25 months	35	21.0 (12.5-29.5)	0.813		
>25 months	18	27.0 (18.4-35.6)			
Treatment free interval after secondary cytoreduction					
≤20 months	36	21.0 (11.3-30.7)	0.969		
>20	17	27.0 (6.4-47.5)			
Tertiary cytoreduction					
Optimal (≤0.5 cm)	26	40.0 (19.1-60.9)	0.003	0.093	0.458 (0.184-1.140)
Suboptimal (>0.5 cm)	27	18.0 (15.8-20.2)			1.0
Platinium sensitivity					
Sensitive	39	27.0 (14.1-39.9)	0.485		
Resistant	14	21.0 (8.9-33.0)			
CA125 level at TC					
≤190	32	33.0 (14.8-51.3)	0.023	0.311	0.616 (0.241-1.572)
>190	21	18.0 (17.0-19.1)			1.0
Size of largest reccurence					
≤8 cm	41	27.0 (15.1-38.9)	0.680		
>8 cm	12	18.0 (6.3-29.7)			
Sites of reccurence					
Single	30	27.0 (12.9-41.1)	0.406		
Multiple	23	20.0 (10.6-29.4)			

[1] P-values from Log-Rank Test (Univariate); [2] P-values from Cox Regression Model (Multivariate); [3] HR from Cox Regression Model

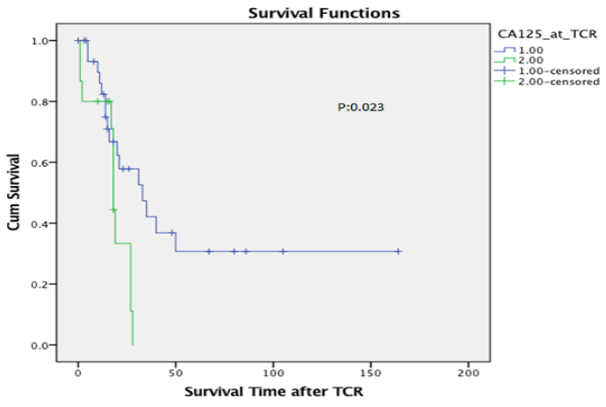

Figure 3. The Cumulative Survival Rates by CA125 Level at TC (≤190 (1) Versus >190 (2))

(66%) and >25 months in the remaining 18 patients (34%). Thirty-six (68%) had ≤20 months treatment free interval (TFI) and seventeen patients (32%) patients had >20 months TFI before the tertiary cytoreduction. Number of lines of chemotherapy regimens prior to TC was ≤3 in 48 patients (90%) and platinum sensitivity was observed in 39 patients (73%). CA125 level at TC was ≤190 IU/L in 32 patients (60%) and >190 IU/L in 21 patients (40%). Largest size of recurrent disease was ≤8 cm in 41 patients (77%) and >8cm in 12 patients (23%). Twenty six patients (49%) had optimal cytoreduction during tertiary debulking surgery while twenty seven had suboptimal cytoreduction (51%). Optimal initial cytoreduction, time to first recurrence, optimal secondary cytoreduction, time interval between secondary cytoreduction and secondary

Table 3. All Studies[a] Regarding Tertiary Cytoreduction for Ovarian Cancer

Author, year	Number of patients	Median follow-up after TC (months)	Disease-free survival (DFS) (mo) (optimal / suboptimal TC)	Complete tumor resection (%)	Independent prognostic factors in univariate analysis	Independent prognostic factors in multivariate analysis	Multiple site recurrence rate (%)	Platinum sensitivity (%)	Predictors of complete tumor resection
Karam AK et al, 2007	47	NR	24/16 (p=0.03)	64	Presence of diffuse disease, microscopic residual disease	Presence of diffuse disease	NA	0	Size of the largest tumor <5 cm
Gultekin M al, 2008	20	15	32/6 (p= 0.2)	35	Cytoreductive outcome of primary and secondary cytoreductive surgeries	None	50	0	Not found
Shih KK et al, 2010	77	28-Sep	60/13 (p<0.001)	72	Time from secondary cytoreduction, time to second recurrence, TFI, platinum sensitivity, optimal tertiary cytoreduction	Optimal tertiary cytoreduction	62	28	Single site of recurrence
Hizli D et al, 2012	23	13	14b/0b (p= 0.018)	65	Optimal tertiary cytoreduction	NA	83	0	Not found
Fotopoulou et al, 2013	406	14	49c/12c (p<0.001)	54	NR	High grade histology, tumor residuals at second and third surgery, interval to second relapse, ascites, distant metastasis, tumor involvement of upper abdomen, platinum third-line chemotherapy	NA	38	Platinum-resistant status, tumor residuals at second surgery, peritoneal carcinomatosis, tumor involvement of upper abdomen, lymph node dissection performed at TC
Tang J, 2013	83	16	33/14.9 (p=0.001)	41	Complete tumor clearance	Complete tumor clearance	NA	NA	Carcinomatosis, tumor sites in the middle and upper abdomen
Present study	53	27-Jun	40/18 (p=0.003)	49	Optimal initial cytoreduction, optimal TC, CA-125 level prior to TC,	None	43	73	Optimal initial cytoreduction, time to first recurrence, optimal secondary cytoreduction, time interval between SC and TC, size of the largest recurrence, status at last follow-up

TC: Tertiary cytoredution. TFI: Treatment-free interval. NR: Not reported. NA: Not available; [a]Two retrospective studies authored by Leitao MM et al. 2004(9) and Fotopoulou et al. 2011(12) were excluded from the table while patients in those studies included in the following studies authored by Shih KK et al. 2010(8) and Fotopoulou et al. 2013 (15), respectively.; [b]Treatment-free survival, instead of DFS; [c]Overall survival, instead of DFS.

recurrence, size of recurrence, disease status at last follow-up were found to be significant risk factors to predict optimal TC (Table 1).

With a median follow up of 27.6 months after TC, disease specific survival (DSS) was 27 months (Table 2). It seems that probability of survival beyond 40 months is less than 0.3. In univariate analysis, outcomes of initial and tertiary cytoreduction (Figure 1, 2), time to first recurrence and serum CA-125 level prior to TC (Figure 3) were found to be significant prognostic factors. However, when we adjust for other factors in multivariate analysis, none of the variables were significant (Table 2).

Discussion

The role of TC in patients with recurrent EOC was first assessed in 2004 by Leitao et al and great benefit in patients who had undergone optimal TC and with a treatment free interval longer than 12 months was reported (Leitao et al., 2004). Following studies questioned about the best candidates for TC, prognostic effect of TC and the impact of residual disease after TC (Karam et al., 2007; Gultekin et al., 2008; Shih et al., 2010; Fotopoulou et al., 2011; Hızlı et al., 2012; Tang et al., 2013; Fotopoulou et al., 2013). Results of the literature review regarding TC are presented in Table 3. Only 8 retrospective studies were published to date with different results (Leitao et al., 2004; Karam et al., 2007; Gultekin et al., 2008; Shih et al., 2010; Fotopoulou et al., 2011; Hızlı et al., 2012; Tang et al., 2013; Fotopoulou et al., 2013). Therefore, the questions still remain unanswered.

In the first study in this area, Leitao et al. reported 26 patients with TC in 2004, from Memorial Sloan-Kettering Cancer Center (Leitao et al., 2004). In the following study from the same center, 77 patients who underwent TC were evaluated, including the 26 patients in their previous report (Shih et al., 2010). They suggested that TC for recurrence after secondary cytoreduction may be a very reasonable option especially in patients in whom an optimal (≤0.5 cm) cytoreduction, or preferably no gross residual disease, is thought to be feasible (Shih et al., 2010). In addition, single site recurrence was found to be the only predictor of complete tumor resection. Karam et al. similarly showed a survival benefit for patients who were able to undergo

optimal TC (Karam et al., 2007). However, their findings indicated that the advantage of TC is limited to those patients with limited disease. Size of the largest tumor (<5 cm) was determined as a significant predictor of optimal TC (Karam et al., 2007).

In the study of Gultekin M et al, including 20 patients with TC, optimal primary and secondary cytoreductive surgeries were found to have significant favorable effect on survival in univariate analysis (Gultekin et al., 2008). However, multivariate analysis did not reveal any significant prognostic factor. It has been suggested that TC may not be helpful for survival in patients with secondary recurrence of EOC (Gultekin et al., 2008). In a subsequent study, the most pessimistic results were found with treatment-free survival of 14 and 0 months after optimal and suboptimal TC, respectively (p=0.018) (Hızlı et al., 2012). They could not find any clinicopathologic factor associated with TC outcome (Hızlı et al., 2012).

In a retrospective study from China, 83 patients were evaluated and complete tumor clearance was found to be associated with better prognosis (Tang et al., 2013). It has been shown that patients with carcinomatosis or tumor sites in the middle and upper abdomen have lower chance to undergo optimal TC (Tang et al., 2013). They concluded that a prospective randomised study is needed to determine the role of TC in secondary recurrence of EOC (Tang et al., 2013).

The largest, unicenter report came from Charite´ University Medical Center Berlin in 2011 (Fotopoulou et al., 2011). Unlike other studies, which patients who had undergone palliative surgery were excluded, Fotopoulou et al. evaluated all consecutive patients without any exclusion (Fotopoulou et al., 2011). Complete TC, serous papillary histology and 3 or more years interval to primary diagnosis were found to have significant positive effect on survival (Fotopoulou et al., 2011). Tumor involvement of the upper and middle abdomen and peritoneal carcinomatosis were the only two parameters affecting tumor resection (Fotopoulou et al., 2011).

A recent, international multicenter study including 406 patients showed that even in the last stage of the disease, complete macroscopic tumor clearance has a significant favorable impact on overall survival (Overall survival: 49 vs 12 months) (Fotopoulou et al., 2013). Unlike previous studies, they showed for the first time that after controlling for resiual status, benefit of complete TC is clear, overruling the presence of peritoneal carcinomatosis which no prognostic significance was found. In addition, postoperative systemic chemotherapy was shown for the first time to have a significant impact on overall survival. However, a selection bias was suspected while only those patients who were fit enough and able to tolerate chemotherapy had already more favorable prognosis than patients who were not able to tolerate or even so advanced that chemotherapy was not indicated (Fotopoulou et al., 2013). Progression-free interval was the most important survival determinant.

In the present analysis, we assessed the value of TC in recurrent EOC patients. Optimal cytoreduction was achieved in 26 out of 53 patients (49%). Optimal initial cytoreduction, time to first recurrence, optimal secondary cytoreduction, time interval between SC and TC, size of the largest recurrence, status at last follow-up were the most important predictors of the optimal TC. Optimal cytoreduction in initial and tertiary surgery and CA-125 level prior to TC were independent prognostic factors in univariate analysis.

Our study has some limitations, similar to previous studies. The main limitations are its retrospective design, the relatively small number of patients included and the lack of systemic evaluation of the indication for TC.

Including our data, the literature review clearly shows that maximal surgical effort should be made in TC, while patients underwent optimal TC have a better survival. Thus, to select the patients with secondary recurrent EOC in whom optimal cytoreduction can be achieved, comes into question. Prospective trials and further studies with larger patient populations are needed to provide an answer.

References

Al Rawahi T, Lopes AD, Bristow RE, et al (2013). Surgical cytoreduction for recurrent epithelial ovarian cancer. *Cochrane Database Syst Rev*, **2013**, 2.

Arikan SK, Kasap B, Yetimalar H, et al (2014). Impact of prognostic factors on survival rates in patients with ovarian carcinoma. *Asian Pac J Cancer Prev*, **15**, 6087-94.

Benedet JL, Bender H, Jones 3rd H, et al (2000). FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet*, **70**, 209-62.

Bristow RE, Tomacruz RS, Armstrong DK, et al (2002). Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol*, **20**, 1248-59.

Chi DS, Eisenhauer EL, Lang J, et al (2006). What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? *Gynecol Oncol*, **103**, 559-64.

Eisenkop SM, Friedman RL, Spirtos NM (2000). The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer*, **88**, 144-53.

Fotopoulou C, Richter R, Braicu IE, et al (2011). Clinical outcome of tertiary surgical cytoreduction in patients with recurrent epithelial ovarian cancer. *Ann Surg Oncol*, **18**, 49-57.

Fotopoulou C, Zang R, Gultekin M, et al (2013). Value of tertiary cytoreductive surgery in epithelial ovarian cancer: an international multicenter evaluation. *Ann Surg Oncol*, **20**, 1348-54.

Gultekin M, Velipasaoglu M, Aksan Guldeniz, et al (2008). A Third Evaluation of Tertiary Cytoreduction. *J Surgical Oncol*, **98**, 530-4.

Harter P, du Bois A, Hahmann M, et al (2006). Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. *Ann Surg Oncol*, **13**, 1702-10.

Hızlı D, Boran N, Yılmaz S, et al (2012). Best predictors of survival outcome after tertiary cytoreduction in patients with recurrent platinum-sensitive epithelial ovarian cancer. *Eur J Obstet Gynecol Reprod Biol*, **163**, 71-5.

Karam AK, Santillan A, Bristow RE, et al (2007). Tertiary cytoreductive surgery in recurrent ovarian cancer: Selection criteria and survival outcome. *Gynecol Oncol*, 104, 377-80.

Leitao MM, Kardos S, Barakat RR, et al (2004). Tertiary

cytoreduction in patients with recurrent ovarian carcinoma. *Gynecol Oncol*, **95**, 181-8.

Maldonado G, Greenland S (1993). Simulation study of confounder-selection strategies. *Am J Epidemiol*, **138**, 923-36.

Sehouli J, Richter R, Braicu EI, et al (2010). Role of secondary cytoreductive surgery in ovarian cancer relapse: who will benefit? A systematic analysis of 240 consecutive patients. *J Surg Oncol*, **102**, 656-62.

Shih KK, Chi DS, Barakat RR, et al (2010). Tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: an updated series. *Gynecol Oncol*, **117**, 330-5.

Tang J, Liu LD, Shu S, et al (2013). Outcomes and patterns of secondary relapse in platinum-sensitive ovarian cancer: Implications for tertiary cytoreductive surgery. *EJSO*, **39**, 786-91.

Zang RY, Li ZT, Tang J, et al (2004). Secondary cytoreductive surgery for patients with relapsed epithelial ovarian carcinoma: who benefits? *Cancer*, **100**, 1152-61.