Comparison of Long-Term Survival Rates of Primary Surgery and Surgery After Neoadjuvant Chemotherapy in Ovarian Cancer

Over Kanserinde Neoadjuvan Kemoterapi Sonrası Cerrahi ile Primer Cerrahinin Uzun Dönem Sağkalımların Karşılaştırılması

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ABSTRACT

Introduction: To compare long-term survival of primary debulking surgery (PDS) and interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) in patients with advanced ovarian cancer.

Methods: Patients who underwent debulking surgery for ovarian cancer between 2001 and 2014 were included in the study.

Results: Of 378 patients, 191 (50.5%) underwent PDS and 187 (49.5%) underwent IDS. Compared with PDS group, IDS was associated with higher optimal surgical performance (residual <1 cm) (83% vs 65%, p<0.001), lower visible tumor rate in the upper abdomen during surgery (12% vs 46%, p<0.001), lower intraabdominal ascites rate (2% vs 64%, p<0.001), lower postoperative (within 30 days) mortality (0 vs 5) and lower bowel resection/colostomy rate (3% vs 11%, p=0.001). The median follow-up period was 43 (1-161) months. Overall survival (OS) was longer in the PDS group [56.8 months (95% CI: 48.2-65.4) vs 43.5 (95% CI: 38.1-48.8), log-rank test p=0.026]. PDS was superior in both residual subgroups, 64.9 vs 44.6 months (p=0.008) in ≤1 cm group and 41.6 vs 25.3 months (p=0.044) in >1 cm group. The 8-year OS was higher in the PDS group (31.8% vs 12.7%). According to multivariate Cox analysis, age, suboptimal debulking, IDS and presence of tumor in the upper abdomen were independent factors associated with shorter OS duration (hazard ratio: 1.013; 1.606; 1.456 and 1.495, respectively).

Conclusion: NAC in patients with FIGO 2010 stage 3 ovarian cancers is useful in reducing tumor spread, surgical morbidity and suboptimal surgery rates. However, long-term survival rates were shorter than the PDS group.

Keywords: Chemotherapy, cytoreduction, FIGO, ovarian carcinoma

ÖZ

Amaç: İleri evre over kanserli hastalarda primer debulking cerrahisi (PDS), neoadjuvan kemoterapi sonrası cerrahisi (NAC), aralıklı debulking cerrahinin (IDS) uzun dönem sağkalım açısından karşılaştırılması amaçlanmıştır.

Yöntemler: 2001-2014 yılları arasında yumurtalık kanseri nedeniyle opere edilen hastalardan evre 3 olanlar çalışmaya alındı.

Bulgular: Toplam 378 hasta, 191'i (%50,5) PDS, 187'si (%49,5) IDS olarak ayrıldı. PDS grubu ile karşılaştırıldığında, IDS grubunda optimal cerrahi (rezidüel <1 cm) performansı daha yüksek (%83-%65, p<0,001), ameliyat sırasında üst batında makroskopik tümör görülen hasta oranı daha az (%12-%46, p<0,001), 1 litreden fazla intraabdominal asit daha az (%2-%64, p<0,001), postoperatif (30 gün içinde) eksitus daha az (0-5), bağırsak rezeksiyonu/kolostomi oranı daha az (%3-%11, p=0,001) izlendi. Ortanca takip süresi 43 (1-161) aydı. Genel sağkalım (GS), PDS grupta daha uzundu [56,8 ay (%95 CI: 48,2-65,4) vs 43,5 (%95 CI: 38,1-48,8), log-rank testi p=0,026]. Rezidüel hastalık ≤1 cm ve >1 cm olan her iki alt grupta PDS üstündü (sırasıyla 64,9 ay vs 44,6, p=0,008; 41,6-25,3, p=0,044). 8 yıllık GS oranı, PDS hastalarında daha yüksekti (%31,8'e karşılık %12,7). Çok değişkenli Cox analizine göre, yaş, suboptimal cerrahi, IDS ve üst batın bölgesindeki tümör varlığı, kısa GS süresi ile ilişkili bağımsız faktörlerdi (sırasıyla tehlike oranı: 1,013; 1,606; 1,456 ve 1,495).

Sonuç: FIGO evre 3 over kanserli hastalarda neoadjuvant-kemoterapi, tümör yayılımını azaltmada, cerrahi morbiditeyi azaltmada ve optimal storedüksiyonun azaltılmasında yararlıdır. Ancak uzun dönem sağkalım oranları primer cerrahi grubuna göre daha kısa bulundu.

Anahtar Kelimeler: Kemoterapi, sitoredüksiyon, FIGO, yumurtalık karsinomu

Introduction

Three-quarters of patients with ovarian cancer are diagnosed with advanced-stage disease (FIGO 2010 stage 3/4) at presentation. Primary debulking surgery (PDS) followed by chemotherapy with paclitaxel and carboplatin, and neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) are two main treatment approaches (1,2). According to randomized controlled trials, survival is similar for both treatment approaches (3-5). These studies showed that postoperative complication rates were lower and the optimal surgery rate was higher in IDS after NAC. Therefore, over the past decade, the use of NAC has increased and PDS rates are showing a negative trend (6).

Recently, several studies have shown poorer survival in IDS compared to PDS (4,7-12).

In this study, we compared the outcomes of patients with advanced stage (FIGO stage 3) ovarian cancer treated with IDS after NAC or PDS.

Methods

The study included patients who underwent surgery for advanced stage ovarian, tubal, or peritoneal cancer at İstanbul University İstanbul Faculty of Medicine Hospital between 2001 and 2013. A total of 378 patients were evaluated retrospectively. Clinical data were obtained from medical records of the patients. Inclusion criterion was a diagnosis of advanced stage high grade (FIGO stage 3C) epithelial ovarian, tubal, or peritoneal cancer according to postoperative pathology reports. Patients were triaged to undergo PDS followed by adjuvant chemotherapy (PDS group) or to receive neoadjuvant chemotherapy with IDS (IDS group).

Patients

All patients were evaluated by a multidisciplinary team of gynaecologic oncologists, radiologists, gynaecopathologists, radiation oncologists and medical oncologists. For patient evaluation, we used magnetic resonance imaging and computerized tomography, tumor markers (CA-125, CA19-9, CEA) and computed tomography for lung examination. According to these evaluations, patients planned for primary surgery were directed to preoperative preparation. Patients planned for NAC were referred to the Department of Interventional Radiology for ascites cytology or tru-cut biopsy from tumoral tissue and directed to the NAC protocol after pathological confirmation. NAC consisted of carboplatin (area under the curve 5-6) and paclitaxel (135-175 mg/m^2) every 3 weeks. The number of planned chemotherapy cycles was 3-4 prior to surgery.

As a standard surgical procedure in both groups (IDS-NAC and PDS), bilateral salpingo-oophorectomy, hysterectomy, appendectomy, and omentectomy were performed, and all visible tumors were removed if possible. Pelvic/para-aortic lymphadenectomy or sampling was performed in some patients. The decision to perform pelvic/para-aortic lymphadenectomy was determined by the surgical team. Other surgical procedures, the most common of which were large/small bowel resection and splenectomy, were performed when necessary. Optimal surgery was defined as the absence of a tumor larger than 1 cm at the end of the surgical procedure. After surgery, all patients

were treated by the same team of medical oncologists and received the same regimen of chemotherapy (paclitaxel plus platinum-based chemotherapy).

Follow-up

All patients underwent a follow-up protocol after postoperative chemotherapy. The patients were evaluated with a gynecological examination and CA-125 markers every 3-4 months in the first two years. After two years, patients were evaluated every six months. If recurrent disease was suspected, patients were assessed by magnetic resonance imaging and by positron emission tomography, if necessary.

The overall survival (OS) was defined as the time from initial treatment to death or to the last follow-up examination. The primary endpoint of this study was OS.

The Statistical Package for the Social Sciences (SPSS) for Windows version 21 was used to perform all analyzes. Kaplan-Meier method was used for survival distributions and significance for survival duration was determined by the log-rank test. Differences between groups were analyzed using Fisher's exact and chi-square tests. P values less than 0.05 was considered significant.

Since this study is a retrospective review, the permission of the local ethics committee has not been obtained. However, all patients signed an informed consent for the use of their clinical data.

Results

A total of 378 patients, 191 in the PDS group and 187 in the IDS group, were analyzed. Clinical and survival features are presented in Table 1. During 43 months of median follow-up period, 128 (67%) patients from the PDS group and 137 (73%) patients from the IDS group died (p=0.185). The optimal surgery rate was higher in the IDS group (83% vs 65%, p<0.001). The mean age was higher in the PDS group (56.3±13.2 vs 59.7±10.5). In the PDS group, there was more tumor in the upper abdomen (46% vs 12%, p<0.001), intraabdominal ascites more than 1 liter (64% vs 2%, p<0.001), higher lymphadenectomy rate (53% vs 13%, p<0.001), higher bowel resection/colostomy rate (11% vs 3%, p=0.001), and higher postoperative mortality (within 30 days) (5 vs 0) (Table 1).

Survival Analysis

The PDS group had a higher median OS duration than the IDS group (56.8 vs 43.5 months, log-rank test p=0.026). 2-year OS rates were higher in the IDS group (85% vs 77%) and 3-year, 5-year, and 8-year OS rates were higher in the PDS group (64.3% vs 60.6%, 47.1% vs 36.6%, 31.8% vs 12.7%, respectively) (Figures 1-2).

Subgroup Analysis (Table 2)

Each group was subdivided in terms of optimal surgery. OS times of subgroups based on optimality are presented in Table 2. The best survival was in the PSD group with optimal surgery (64.9 months). The IDS group undergoing suboptimal surgery had the worst survival (25.3 months).
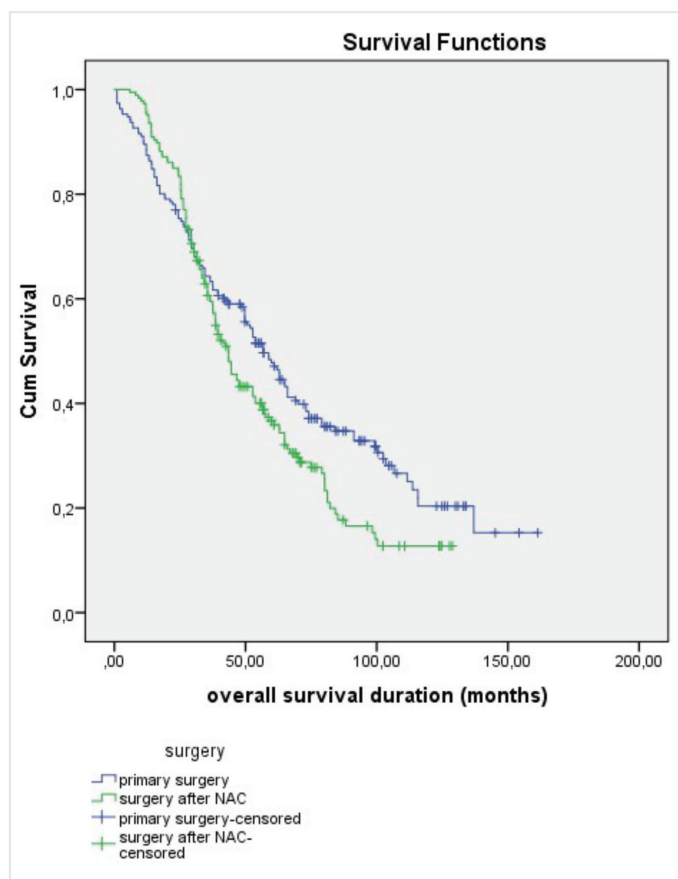
Figure 1. Overall survival of patients grouped according to neoadjuvant chemotherapy (log-rank test p=0.026)

NAC: neoadjuvant chemotherapy

Table 1. Clinical and survival results of patients based on PDS/IDS

Feature	Primary debulking surgery (n=191)	Interval debulking surgery (n=187)	p
Age, (years) mean ± SD	56.3±13.2	59.7±10.5	**0.007**
>60 years	72 (37.7%)	93 (49.7%)	
Performance of optimal surgery	124 (65%)	156 (83%)	**<0.001**
Presence of visible tumor at upper abdomen during surgery	88 (46%)	23 (12%)	**<0.001**
Ascites (more than 1 liter)	123 (64%)	5 (2%)	**<0.001**
Lymphadenectomy	102 (53%)	24 (13%)	**<0.001**
Bowel resection/colostomy	21 (11%)	6 (3%)	**0.001**
Total exitus	128 (67%)	137 (73%)	0.185
Postoperative (within 30 days)	5 (2.6%)	-	
Median overall survival	56.8	43.5	**0.026**
(months) 95% CI	48.2-65.4	38.1-48.8	
2-year survival rate	77.0%	85.0%	
3-year survival rate	64.3%	60.6%	
5-year overall survival rate	47.1%	36.6%	
8-year overall survival rate	31.8%	12.7%	

SD: standard deviation, CI: confidence interval, PDS: primary debulking surgery, IDS: interval debulking surgery

Cox regression analysis (Table 3)

Factors related to OS were analyzed by univariate and multivariate analyses (Table 3). The examined factors included age, optimal surgery, presence of tumor in the upper-abdomen, lymphadenectomy and treatment option (PDS or IDS). According to multivariate analysis, suboptimal surgery [hazard ratio (HR), 1.606; (95% CI, 1.184-2.177); p=0.002], presence of tumor in the upper-abdomen [HR, 1.495; (95% CI, 1.113-2.006); p=0.007], IDS [HR, 1.456; (95%CI, 1.076-1.970); p=0.015], and age [HR, 1.013; (95% CI, 1.002-1.024); p=0.025] were associated with shorter survival duration. Lymphadenectomy was associated with OS in univariate analysis, but not in multivariate analysis.

Discussion

The NAC-IDS approach has been undertaken for patients with advanced stage ovarian cancer over the last 25 years, as an alternative option to PDS. This approach is increasingly preferred and the use of PDS is decreasing in clinics (6,13). Comparative survey outcomes for PDS and IDS continue to be published. To date, more than 20 studies comparing survival have been published (Table 4). In some studies, NAC-IDS seems advantageous in terms of survival, whereas others have reported that the PDS approach is preferable (Table 4). However, there is consensus that IDS is superior to PDS in terms of performance of optimal debulking (12-14).

In this study, optimal debulking and absence of upper abdominal metastasis were independent positive prognostic factors according to multivariate analysis (Table 3). These factors were higher in the NAC group. Despite these good results in the NAC group, survival was lower (median OS duration was 43.5 vs 56.8 months, p=0.026) (Table 1). The survival advantage of PDS has become more prominent in the long-term survival analysis (Figures 1, 2). In addition, PDS was superior in terms of survival in subgroup analysis based on performance of optimal surgery (Table 2). Interestingly, patients with NAC have a shorter survival rate compared to patients with PDS, even though optimal surgery has been achieved. Similarly, in a recent study, Kessous et al. (15) reported that
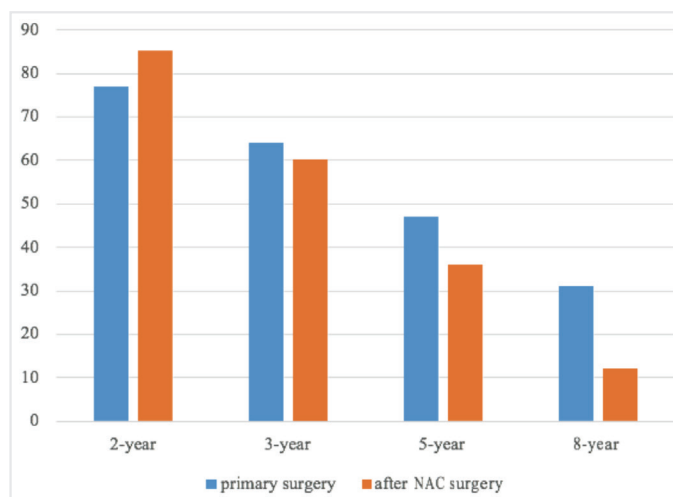

Figure 2. Comparison of overall survival rates (%) for IDS/PDS groups at 2, 3, 5 and 8th years

IDS: interval debulking surgery, PDS: primary debulking surgery

patients with PDS had better OS than with NAC-IDS (60 months vs 48 months, p=0.039). However, complete cytoreduction rates in the PDS group were lower than in the NAC-IDS group (65.9% vs 40.2%, p=0.001).

In another study, Rosen et al. (9) reported that optimal surgery rates in patients with PDS were lower than patients with NAC-IDS (64% vs 79%). However, long-term OS rates were significantly higher (seven-year survival rate 8.6% vs 41.1%; p<0.0001) in patients with PDS. In our study, 8-year OS rates were higher in the PDS group (31.8% vs 12.7%) (Table 1). In this study, 2-year OS rate in IDS seems to be better (not statistically significant) and 3-year and later survival was higher in PDS. The number of patients who died in the postoperative period was higher in the primary surgery arm (5 vs 0). This result causes the survival of the PDS to be short in the first year.

In a recent comparative study of two groups, May et al. (16) reported that 5-year survival was better for patients undergoing PDS than in patients who received NAC (39% vs 27%; p=0.02). However, the gross residual tm (>1 cm) ratio in the PDS group was higher in their study (28% vs 19%, p=0.02).

Many studies comparing the survival of the two groups are presented in Table 4. According to randomized controlled prospective trials, survival rates were similar in patients with advanced stage ovarian cancer who underwent NAC-IDS or PDS. Conversely, in retrospective studies, the survival of patients with PDS appears to be slightly better than that of patients with NAC-IDS (Table 4). However, optimal cytoreduction rates in PDS arms of randomized controlled trials were low. The reported rates were 42% in Vergote and 37.6% in Kehoe. This may be associated with

low survival in the PDS group. Additionally, a patient eligible for PDS may have received NAC due to the randomization procedure. The main limitation in these randomized trials is that the selection process, which significantly biases the results, is usually not known.

In a recent meta-analysis, Qin et al. (17) and colleagues analyzed 22 retrospective observational studies and reported that OS was longer in the PDS group than that in the NAC group, irrespective of the degree of residual disease. Additionally, the authors stated that patients with FIGO stage 3 [HR=1.43, (95% CI: 1.05-1.95)] and 4 [HR=1.14, (95% CI: 1.06-1.23)] diseases had a better survival with PDS.

Regarding the adverse effect of NAC, some authors suggest that chemotherapeutics given may facilitate the emergence of chemotherapy-resistant cancer cell clones in NAC-IDS patients (18,19). Another hypothesis is that the tumor implants, which are shrinking due to chemotherapy, cannot be seen during laparotomy.

There are probably a limited number of patients who are eligible for surgery after NAC, and the criteria for this group need to be clarified. In fact, the main limitation in our study and in other studies comparing NAC and IDS is the uncertainty of patient selection criteria.

Conclusion

NAC followed by IDS appears to be worse than PDS in patients with stage 3 ovarian cancer. With NAC, tumor spread and surgical morbidity are reduced and optimal cytoreduction rates are increased. However, these positive improvements do not reflect positively on the OS of the patients.

Table 2. Analysis of overall survival of subgroups according to neoadjuvant chemotherapy and optimal surgery

Optimality	Surgery	Median overall survival duration (months)				p
		Estimate	Standard error	95% CI		
				Lower bound	Upper bound	
Optimal	Primary surgery (n=124)	64.9	8.1	48.9	80.9	
	Surgery after NAC (n=156)	44.6	3.9	36.9	52.2	**0.008**
	Overall	56.8	4.4	48.0	65.5	
Suboptimal	Primary surgery (n=67)	41.6	7.6	26.7	56.5	
	Surgery after NAC (n=31)	25.3	1.6	22.0	28.6	**0.044**
	Overall	34.4	5.0	24.6	44.2	
Overall	Overall	49.7	3.2	43.3	56.0	

CI: confidence interval, NAC: neoadjuvant chemotherapy

Table 3. Survival related factors according to multivariate and univariate cox regression analysis

Reference variabl	Univariate analysis				Multivarite analysis			
	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.017	1.006	1.027	**0.002**	1.013	1.002	1.024	**0.025**
Suboptimal surgery	1.317	1.032	1.681	**0.027**	1.606	1.184	2.177	**0.002**
Presence of tumor at upper-abdomen	1.433	1.110	1.849	**0.006**	1.495	1.113	2.006	**0.007**
Absance of lymphadenectomy	1.707	1.302	2.237	**0.001**	1.766	0.938	1.736	**0.121**
IDS	1.317	1.032	1.681	**0.027**	1.456	1.076	1.970	**0.015**

CI: confidence interval, HR: hazard ratio, IDS: interval debulking surgery

Table 4. Results of studies comparing primary debulking surgery with interval debulking surgery after neoadjuvant chemotherapy in ovarian cancer

Trials/year	Design	n	Superior	Overall survival (months) IDS vs PDS	p
Vergote et al. (4) (EORTC/NCIC trial)	Randomized controlled	670	-	29.0 vs 30.0	NS
Kehoe et al. (20) (CHORUS)	Randomized controlled	550	IDS	24.1 vs 22.6	NS
Shimizu et al. (21)	Retrospective	165	IDS	31 vs 21	<0.05
Scwartz et al. (22)	Retrospective	265	PDS	12.8 vs 26.1	NS
Kuhn et al. (23)	Prospective, nonrandomized	63	IDS	42 vs 23	0.007
Kayıkçioglu et al. (24)	Retrospective	205	PDS	34.1 vs 37.9	NS
Morice et al. (25)	Retrospective	68	IDS	26 vs 22	NS
Hegazy et al. (26)	Prospective cohort	59	PDS	25 vs 28	NS
Loizzi et al. (27)	Retrospective	60	PDS	32 vs 40	NS
Inciura et al. (28)	Retrospective	574	PDS	23.7 vs 25.4	NS
Steed et al. (29)	Retrospective	116	PDS	29 vs 44	0.03
Hou et al. (30)	Retrospective	172	PDS	46 vs 47	NS
McLean et al. (31)	Retrospective	175	PDS+	29 vs 34	NS
Chi et al. (32)	Retrospective	316	PDS	37 vs 50	-
Rauh-Hain et al. (33)	Retrospective	242	IDS++	33 vs 29	NS
Glasgow et al. (34)	Retrospective	104	PDS€	25 vs 39	NS
Fago-Olsen et al. (8)	Retrospective	1677	PDS	29.4 vs 31.9	0.099
Rosen et al. (9)	Retrospective	326	PDS*	8.6% vs 41.1%	<0.001
Solmaz et al. (35)	Retrospective	292	PDS	48.2 vs 57.7	NS
Bian et al. (36)	Retrospective	339	-	25 vs 25	NS
Luo et al. (19)	Retrospective	341	PDS	41 vs 51	NS
Meyer et al. (13)	Multi-institutional observational	1538	PDS	33 vs 43 (IIIC) 31 vs 36 (IV)	>0.05 (in IIIC)
Kessous et al. (15)	Retrospective	263	PDS	48.8 vs 60.2	0.039
May et al. (16)	Retrospective	303	PDS**	27% vs 39%	0.02
Present study 2018	Retrospective	378	PDS	43 vs 56	0,026

*The authors reported a 7-year overall survival rate in each group, **5-year survival, +only patients older than 65 years analyzed, ++only stage IV patients analyzed, €only patients older than 70 years analyzed, IDS: interval debulking surgery, PDS: primary debulking surgery

Ethics Committee Approval: Since this study is a retrospective review, the permission of the local ethics committee has not been obtained.

Informed Consent: All patients signed an informed consent for the use of their clinical data.

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