The surgical and clinicopathological characteristics of primary mucinous ovarian cancer: a single institution 30-year retrospective analysis

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Abstract

Objective: To evaluate the clinicopathological characteristics of primary mucinous ovarian carcinoma (MOC) and define oncologic outcomes.

Material and Methods: This retrospective study reviewed patients diagnosed with primary MOC at a single institution and underwent primary treatment between 1990 and 2019. The clinicopathological factors affecting oncological outcomes and treatment response were evaluated. The Kaplan-Meier method was used to evaluate survival outcomes. Survival curves were compared using the log-rank test.

Results: The cohort's (n=92) median (range) age was 48 (15-82) years. Seventy-five (81.5%) patients were in the International Federation of Gynecology and Obstetrics stage I-II. Forty patients received platinum-based adjuvant chemotherapy. The 5-year progression-free survival was 98% in stage I-II and 17% for stage III-IV ($p<0.001$). In multivariate analysis, the only independent risk factor for disease failure was stage (hazard ratio: 6.838, 95% confidence interval: 1,358-34,415; $p=0.020$).

Conclusion: Advanced stage was an independent poor prognostic factor for recurrence in patient with MOC. (J Turk Ger Gynecol Assoc 2023; 24: 252-60)

Keywords: Mucinous ovarian carcinoma, platinum-based chemotherapy, stage, survival, treatment response

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Introduction

Epithelial ovarian carcinoma (EOC) is the most common cause of death among gynecological cancers and it consists of several histologic subtypes, including serous, endometrioid, mucinous, and clear cell, each of which has distinct molecular, genetic, clinicopathological, and oncologic characteristics and outcomes (1-3). Therefore, identifying the histological subtype is critical for the assessment of the prognosis and treatment responses of EOCs (4).

Mucinous ovarian carcinoma (MOC) is a rare histological subtype that accounts for approximately 3% of all EOCs and has distinct clinical, histological and molecular features compared to other histological subtypes; the origin of the MOC has long been controversial (5). MOC has several clinical features that differ from those of the serous ovarian carcinomas (SOC) in terms of age at diagnosis, response to chemotherapy, prognosis, and tumor growth pattern. Although MOC is typically more placid and associated with significantly more favorable clinical outcomes than SOC in its early phases, it has a poorer

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prognosis in its more advanced stages (4-7). Despite these differences, MOC receive similar standard adjuvant therapy to other EOC subtypes. Studies have demonstrated that MOC is less susceptible to conventional chemotherapy in the neoadjuvant, adjuvant, and recurrence settings than the more prevalent high-grade SOCs (5,6,8-13). Due to the rarity and heterogeneity of MOC, adjuvant treatment options, management and risk factors for prognosis remain unclear.

Consequently, the primary objective of this research was to identify the clinicopathologic characteristics, survival rate, and prognosis of MOC, as well as the other related variables. Additional aims were to determine the efficiency of adjuvant platinum-based chemotherapy responses in MOC.

Material and Methods

Patients

This observational study was conducted at a tertiary research hospital. The University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital Research Ethics Committee confirmed that no ethical approval was required (approval number: 90057706-799/May). A retrospective analysis of patients diagnosed with primary MOC and treated at our gynecologic oncology clinic between 1990 and 2019 was conducted. The clinical, surgical, and pathological data of the patients were extracted from the gynecologic oncology department's computerized database system, and the patients' files, pathological reports, and operation notes were all evaluated. Patients with insufficient clinical data or follow-up, synchronized tumors, mixed type tumors or metastatic MOC were excluded from the study.

Pathology

The distinction between primary MOC and metastatic MOC was made according to a combination of clinical and pathological features. Once a diagnosis of MOC had been made, we employed a multidisciplinary approach to differentiate this condition, which was not solely dependent on pathology. To clarify this distinction, preoperative imaging, laboratory results, intraoperative findings (macroscopic features, frozen pathology), postoperative imaging upon suspicion, and endoscopy-colonoscopy, if necessary, were performed. To define the tumors morphology, correlations between macroscopic, microscopic and immunohistochemical features were investigated. Overall, an immunohistochemistry panel containing CK20, CK7, PAX8, ER, SATB2, CDX2, p16, and/or p53 helped the expert pathologists distinguish between primary and metastatic MOC, if needed. Eventually, all findings were correlated, followed by a final decision on primary versus metastatic MOC was made.

Surgery

The International Federation of Gynecology and Obstetrics (FIGO) staging criteria from 2014 were used. Surgical and pathologic evaluations were applied to adapt the FIGO 2014 staging method for use prior to 2014.

In our clinic, standard ovarian carcinoma staging included evaluation of the abdomen, peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic retroperitoneal lymphadenectomy and omentectomy. Systematic retroperitoneal lymphadenectomy was performed as complete pelvic plus paraaortic lymphadenectomy up to the level of the left renal vein. However, in some cases a lymphadenectomy was not performed according to the decision of the senior surgeon, based on the risk of high co-morbidity or adverse conditions during surgery. In intraoperative observation, if a macroscopic pathology was present, cytoreductive surgery techniques were used to target maximal cytoreduction in addition to staging surgery. Maximal cytoreduction was defined as the absence of visible disease after surgery; optimal cytoreduction was defined as 1 cm of macroscopic residual tumor after surgery; and suboptimal cytoreduction was defined as >1 cm of macroscopic residual tumor after surgery. The fertility-sparing approach was preferred for patients in the reproductive age group who desired fertility. The fertility-sparing method was described as conserving the uterus and at least a portion of at least one ovary. All surgical procedures were conducted by gynecological oncology specialists. The gynecologic oncology tumor council determined the choices for adjuvant treatment based on existing guidelines.

Chemotherapy and clinical response

Patients receiving chemotherapy were evaluated according to RECIST 1.1 criteria for chemotherapy response (14). Clinical response was defined as follows: (1) Complete clinical response, specifically complete disappearance of all target and non-target lesions, and absence of new lesions; (2) partial clinical response defined as at least a 30% decrease in the total size of all the target lesions or the presence of one or more non-target lesions and/or a tumor marker level that stays above the normal range; (3) progressive disease, defined as ≥20% increase in the maximum diameter of the target lesion, the appearance of ≥1 cm new lesion, or the progression of any non-target lesions; (4) stable disease, defined as lesions that are neither in the partial clinical response group nor in the progressive disease group, based on the smallest sum diameters while under study, as determined at the first-month post-treatment.

The clinical response of the patients was evaluated one month after the initial treatment (surgery + adjuvant therapy). The patients were evaluated using clinical, laboratory parameters

(CA-125 levels), and imaging techniques [magnetic resonance imaging (MRI) or computed tomography (CT)]. Recurrence was defined as the reappearance of disease during the follow-up of patients whose routine examinations had revealed the absence of the condition one month after initial treatment (complete clinical response). The advancement of disease during first-line adjuvant treatment is referred to as "refractory disease". After initial treatment, refractory disease and recurrence were considered "disease failure".

Survival

Progression-free survival (PFS) was defined as the amount of time between the initial surgery and the appearance of clinical or radiological signs of disease progression. In addition, PFS was defined as the time between the initial surgery and the final contact with a patient who had no disease-related symptoms. The time between the start of treatment and death from any cause or last contact was determined as overall survival (OS).

Patients were checked at three-month, six-month, and annual intervals after surgery. At each follow-up, a gynecological examination, CA125 measurement and abdominal ultrasonography were routinely conducted. Chest X-ray was utilized annually. CT, positron emission tomography-CT and MRI were used when needed.

Statistical analysis

For statistical analysis, SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA) software was used. For continuous data, descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum), and for categorical variables, as a number/percentage. Estimates of PFS and OS were determined using the Kaplan-Meier method. Using the log-rank test, survival curves were compared. Using the Cox proportional hazards model, a multivariate analysis was conducted to evaluate independent determinants influencing survival.

Results

Patients' characteristics

There were a total of 121 patients who received a diagnosis of primary MOC. Among these patients, 22 were excluded due to insufficient clinical data or follow-up, six were excluded due to synchronized tumors, and one was excluded because of a mixed-type tumor. The study involved the participation of the remaining 92 patients. The median (range) age was 48 (15-82) years, of which 23 (32%) were younger than 40 years of age. The median tumor size was 20 cm (range; 4-50 cm). Of the patients, 65 (71%) had a grade 1 tumor, 16 (17%) had a grade 2 tumor, and one (1%) had a grade 3 tumor. In total, 89 (96.7%) patients underwent primary cytoreduction, while three (3.3%) received neoadjuvant chemotherapy. The surgical outcome was identified as maximal, optimal, and suboptimal cytoreduction in 83 (90.2%), 2 (2.2%), and 7 (7.6%) patients, respectively. Seventy-five (81.5%) patients had stage I-II disease, whereas 17 (18.5%) had stage III-IV disease. Only 12 individuals with stage IA and a median age of 22 (15-38) years had fertility-sparing surgery.

Overall, 79 (85.9%) patients underwent a lymphadenectomy and 7 (8.9%) had nodal involvement. The median number of extracted lymph nodes was 35 (2-110). The median preoperative CA-125 level was 71 (2-1476) IU/mL. Ascites was present in 40 (56.5%) patients, and cytology was positive in 16 (17.4%). Omental metastasis was detected in 13 (14.1%). Appendectomy was performed in 77 (83.7%) patients, and appendiceal involvement was observed in 5 (6.5%). Table 1 summarizes the clinical, surgical, and pathological features.

Of the enrolled patients, 40 (43.5%) received postoperative adjuvant therapy. In accordance with current guidelines, in-clinic councils set the adjuvant therapy regimens for all patients. In our cohort, the regimens of adjuvant therapy for all patients were platinum-based therapies, although those included different combinations. Twenty-four (60%) patients received taxane plus platinum, 14 (35%) received cyclophosphamide + fluorouracil + cisplatin and two received other platinum-based chemotherapy regimens. Twenty-three patients receiving adjuvant treatment were in stages I-II, while 17 were in stages III-IV. Twenty-six (65%) patients received six cycles of chemotherapy, 12 (30%) fewer than six cycles and 2 (5%) received nine cycles.

Survival analysis

The median follow-up was 62 (2-140) months. After treatment, a complete clinical response was seen in 29 of 40 (72.5%) who received adjuvant chemotherapy. Refractory disease was observed in 11 (27.5%) patients after adjuvant therapy. In the follow-up, recurrence developed in 5 (17.2%) of 29 patients with complete clinical response to adjuvant chemotherapy. Fifty-two patients who did not receive adjuvant chemotherapy had a full clinical response and no recurrence. In the final analysis, 16 (17%) of 92 patients had disease failure (Figure 1).

All patients who underwent fertility-sparing surgery were at stage IA, and none of them received adjuvant chemotherapy. The median follow-up in this group was 96 (24-156) months. Additionally, no recurrence or death was observed during the follow-up period.

Subgroup analysis was also performed for advanced stage (stage III-IV) patients, and it was observed that 82% of these patients had primary cytoreductive surgery and 18% had interval cytoreductive surgery. Of the patients, 47% obtained maximal cytoreduction following surgery. All patients with advanced stages received adjuvant chemotherapy.

Table 1. Patients' characteristics

Characteristics			**Mean ± SD**	**Median (range)**
Age			46±15	48 (15-82)
Tumor size (cm)			19±8	20 (4-50)
CA-125 (IU/mL)			112±182	71 (2-1476)
CA-19-9 (IU/mL)			966±5039	83 (3-33904)
CEA (IU/mL)			20±15	2.8 (0-300)
Number of removed lymph nodes			40±28	35 (2-110)
Number of metastatic lymph nodes			9±9.3	3 (1-24)
			n	**(%)**
FIGO 2014 stage	Stage I-II		75	81.5
	Stage III-IV		17	18.5
Outcome of cytoreductive surgery	Suboptimal (residue tumor >1 cm)		7	7.6
	Optimal (residue tumor ≤1 cm)		2	2.2
	Maximal (no residue tumor)		83	90.2
Ascites	Present		40	56.5
	Absent		52	43.5
Peritoneal cytology	Positive		16	17.4
	Negative		70	76.1
	Not reported		6	6.5
Grade	1		65	71
	2		16	17
	3		1	1
	Unknown		10	11
Ovarian tumor laterality	Bilaterally		15	16.3
	Unilaterally	Left	50	54.3
		Right	25	27.2
	Not reported		2	2.2
Omental involvement	Present		13	14.1
	Absent		79	85.9
Appendiceal involvement[1]	Present		5	6.5
	Absent		72	93.5
Peritoneal involvement	Present		11	12
	Absent		81	88
Lymphadenectomy	Performed		79	85.9
	Not performed		13	14.1
Lymph node metastases[2]	Present		7	8.9
	Absent		72	91.1
Site of metastatic lymph node	Only pelvic		3	3.3
	Only para-aortic		1	1.1
	Pelvic and para-aortic		3	3.3
Adjuvant therapy	Not received		52	56.5
	Received		40	43.5
Chemotherapy regimen	Taxane[3] + platin[4]		24	60
	CFP[5]		14	35
	Others[6]		2	5

Table 1. Continued

Characteristics		Mean ± SD	Median (range)
Clinical response after adjuvant chemotherapy[7]	Complete clinical response	29	72.5
	Refractory disease	11	27.5
Recurrence[8]	Negative	76	93.8
	Positive	5	6.2

[1]: The 77 patients underwent appendectomy, [2]The 79 patients underwent lymphadenectomy, [3]Paclitaxel or docetaxel, [4]Carboplatin or cisplatin, [5]Cyclophosphamide + fluorouracil + cisplatin, [6]Platin-based other chemotherapy protocols, [7]Clinical response after adjuvant chemotherapy in 40 patients received adjuvant chemotherapy was evaluated, [8]Recurrence was evaluated in 81 patients with complete clinical response. SD: Standard deviation, CA-125: Cancer antigen-125, CEA: Carcinoembryonic antigen, FIGO: International Federation of Gynecology and Obstetrics, CFP: Cyclophosphamide + fluorouracil + cisplatin

After initial treatment (surgery + adjuvant therapy), a complete clinical response could not be obtained in one of the early-stage patients who received chemotherapy. A complete clinical response was achieved in 22 (95.7%) of the 23 patients who received adjuvant chemotherapy in stage I-II, whereas a complete clinical response was obtained in 7 (41.2%) of 17 patients who received adjuvant chemotherapy in stage III-IV ($p<0.001$). After initial treatment (surgery + adjuvant therapy), the complete clinical response rate of advanced-stage (stage III-IV) patients was 62.5% in those who achieved maximal cytoreduction after surgery and 22.2% in those who had residual disease after surgery. No significant difference was found in terms of overall clinical response between the groups with and without residual disease after surgery in the advanced MOC patients ($p=0.153$). The characteristics of patients with stages III-IV are given in Table 2.

OS could not be evaluated in the study cohort because the number of deaths (n=4) was insufficient. The five-year PFS percentage for the total cohort was 84%. In univariate analysis, stage (I-II vs. II-IV), tumor size (≥20 cm vs. <20 cm); the presence of ascites, omental metastasis, lymph node metastasis and outcome of cytoreductive surgery (maximal vs. optimal and suboptimal) were significant for PFS (Table 3). In addition, 5-year PFS was 100% in those not receiving adjuvant therapy and 63% in those who received adjuvant therapy ($p<0.001$). However, all patients who did not receive adjuvant therapy were stage IA patients.

The correlation test was applied to the factors that the univariate analysis had identified as significant. Since lymph node and omental involvement were substantially connected with the stage, they were omitted from the multivariate analysis despite their significance in the univariate analysis. The multivariate analysis model included stage, presence of ascites, tumor size and outcome of cytoreductive surgery (Table 3). In this model, stage was revealed as an independent risk factor for recurrence. Disease failure was approximately 7 times higher in stages III-IV (hazard ratio: 6,838, 95% confidence interval: 1,358-34,415; $p=0.020$). The estimated 5-year PFS for stages I-II was 98%, however, it was 17% for stages III-IV ($p<0.001$) (Figure 2).

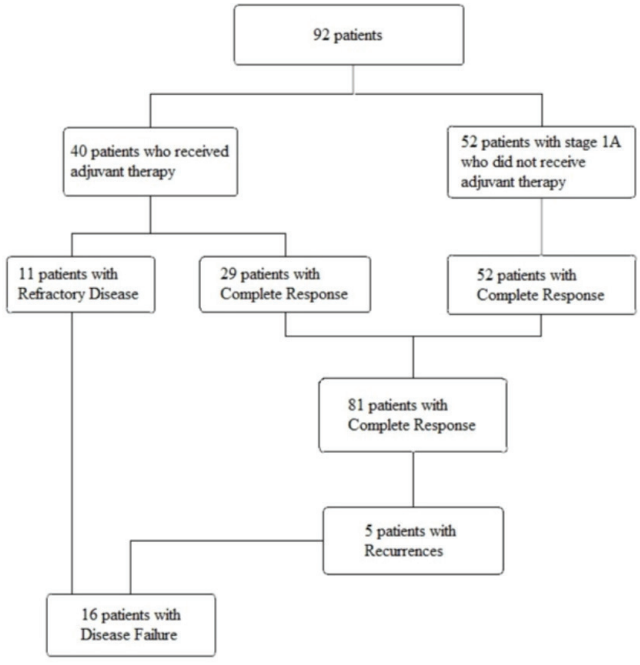

Figure 1. Flow chart of the treatment response of the patients

Table 2. The characteristics of patients with stage III-IV (n=17)

Characteristics		n	%
Outcomes of cytoreductive surgery	Suboptimal (residue tumor >1 cm)	7	41.1
	Optimal (residue tumor ≤1 cm)	2	11.7
	Maximal (no residue tumor)	8	47.2
Chemotherapy regimens	Taxane[1] + platin[2]	13	76.6
	CFP[3]	2	11.7
	Others[4]	2	11.7
Treatment response	Refractory disease	10	58.8
	Complete response	7	41.2
Recurrences	Negative	14	82.3
	Positive	3	17.7

[1]: Paclitaxel or docetaxel, [2]: Carboplatin or cisplatin, [3]: Cyclophosphamide + fluorouracil + cisplatin, [4]: Platin-based other chemotherapy protocols, CFP: Cyclophosphamide + fluorouracil + cisplatin

Table 3. Factors predicting the progression-free survival

Factors	Univariate analysis		Multivariate analysis			
	5-year progression-free survival		Risk of failure			
		Percentage	p-value	Hazard ratio	95% CI	p-value
Age[1]	≤48 years	88	0.212			
	>48 years	85				
FIGO 2014 stage	I-II	98	**<0.001**	1 (reference)	1.358-34.415	0.020
	III-IV	17		6.838		
Preoperative CA-125 level	≤35 IU/mL	88	0.065			
	>35 IU/mL	77				
Ascites	Absent	93	**0.001**	1 (reference)	0.231-18.733	0.514
	Present	72		2.080		
Ascites volume[1]	≤225 cc	73	0.998			
	>225 cc	70				
Tumor size[1]	≤20 cm	75	**0.002**	1 (reference)	0.000-2.202E105	0.917
	>20 cm	100		Not calculated[5]		
Lymph node dissection	Do not underwent	69	0.095			
	Underwent	86				
Lymph node metastasis	Negative	91	**<0.001**			
	Positive	0				
Number of removed lymph node[1]	≤35	86	0.879			
	>35	86				
Omental metastasis	Negative	95	**<0.001**			
	Positive	15				
Outcome of cytoreductive surgery	Maximal	91	**<0.001**	1 (reference)	0.322-4.115	0.829
	Suboptimal and optimal	22		1.150		
Fertility sparing surgery	No	82	0.089			
	Yes	100				
Adjuvant chemotherapy combination	Taxane[2] + platin[3]	52	0.566			
	CFP[4]	79				

[1]Median value, [2]: Paclitaxel or dosetaxel, [3]: Carboplatin or cisplatin, [4]: Cyclophosphamide + fluorouracil + cisplatin, [5]: No event in patients with tumor size more than 20 cm, CI: Confidence interval, FIGO: International Federation of Gynecology and Obstetrics, CA-125: Cancer antigen-125, CFP: Cyclophosphamide + fluorouracil + cisplatin

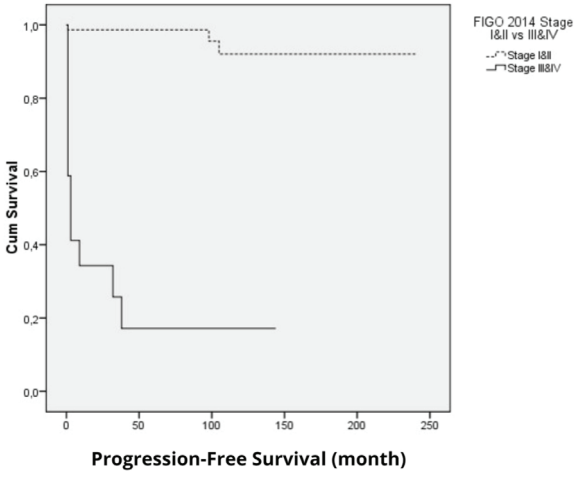

Figure 2. Relationship between progression-free survival and stage
FIGO: International Federation of Gynecology and Obstetrics

Discussion

Clinicopathologic characteristics that may influence the oncologic outcome in MOC were investigated. We observed that advanced FIGO stage was an independent risk factor for PFS. Complete clinical response was not associated with residual disease and was more prevalent in the early stages than in the advanced stages.

MOC is an uncommon histologic subtype of EOC and has different epidemiological, clinical, and molecular features, distinct from other EOCs (5). With advances in histopathological methods and innovations in tumor biology and genetics, the incidence of true primary MOC has declined over the years (6). MOC is generally a unilateral, large ovarian tumor, and more likely to emerge at a younger age, mostly between 36-50 years of age (15). In the current study, 32% of the patients were

younger than 40 years and most of the tumors were unilateral. In contrast to SOCs, MOCs are more often diagnosed at an early stage, which is characterized by a better prognosis for survival. However, at advanced stages, the prognosis is worse compared to other subtypes. It has been found that the mucinous type is a separate risk factor for a poor prognosis in advanced stages (5-8,16-18). In our study, most of the patients were at stage I-II (57% of them at stage IA) and had a better PFS and complete clinical response rate after chemotherapy than stage III-IV. During the follow-up period, no recurrence was observed among 12 patients with stage IA who had undergone fertility-preserving surgery. Young cancer patients in an early stage who desire fertility may be candidates for fertility-preserving surgery (5,6,19).

In the current study, the univariate analysis found that FIGO stage and maximal cytoreduction were identified as the prognostic factors for PFS. In the multivariate analysis, however, FIGO stage was the sole independent prognostic factor for PFS and disease failure was approximately 7 times higher for stages III-IV. Similar results were reported in an earlier study that investigate risk factors for recurrence, where stage and maximal cytoreduction were identified as prognostic factors for PFS in univariate analysis, while in multivariate analysis only stage was associated with PFS (20). In our study, five-year PFS was found to be 84% in the entire cohort, which is consistent with previous reports (17,20,21). We report a 5-year PFS of 17% in stages III-IV similar to the study by Mueller et al. (17).

As with other EOCs, surgical cytoreduction and removing all macroscopic disease are essential for the management of MOCs and survival is associated with the outcome of primary cytoreductive surgery (12,13,22-24). Other studies have reported OS and event-free survival to be significantly affected by residual disease and optimal cytoreduction for advanced MOC to be an important prognostic factor for survival (12,22,24). In our study, univariate analysis revealed that the 5-year PFS for maximal cytoreduction and suboptimal and optimal group was 91% and 22% ($p<0.001$), respectively, and for the stage I-II, and stage III-IV group it was 98% and 17% ($p<0.001$), respectively. However, multivariate analysis demonstrated that only stage was independently associated with PFS. Similar results were reported by Hollis et al. (20). However, Simons et al. (25) observed that optimal/complete debulking as opposed to suboptimal debulking did not increase OS in advanced-stage MOC. This was attributed to the presence of metastases in advanced-stage MOC (25).

Several publications have highlighted the resistance of this subtype to conventional chemotherapy (9-12). Hess et al. (9) reported the response rate to standard chemotherapy to be 26% in advanced stage MOC and 65% in serous ovarian cancer. Furthermore, Pectasides et al. (10), Pisano et al. (11) and Karabuk et al. (12) found the response rates to platinum-based chemotherapy to be 38.5%, 42%, and 57.9%, respectively, in stages III-IV. In the current study, the response rate in patients who received adjuvant chemotherapy at stages 3 and 4 was 41.2%. All these findings imply that advanced stages are associated with poor prognosis and has a restricted chemotherapy response to standard regimens as utilized in SOCs.

Previous research demonstrated that cytoreduction improves the efficacy of chemotherapy by implying that ovarian cancer cells are intrinsically receptive to chemotherapy, thereby increasing patient survival (23,26). Although complete cytoreduction is associated with enhanced survival in women with ovarian cancer histologic subtypes that have a poor response to chemotherapy, it cannot prevent the development of chemotherapy resistance in cells that are already resistant (23). These results indicate that the relationship between cytoreduction and survival may be mediated by a mechanism distinct from chemoresistance. In our study, although maximal cytoreduction was achieved in 47% of patients in stages III-IV, we found that the presence of residual disease at advanced disease was not associated with a higher chemotherapy complete response rate ($p=0.153$). Although there was no statistically significant difference, there was a clinically significant difference (62.5% vs. 22.2%). The absence of a statistically significant difference may be due to the limited number of patients in this group. Low sensitivity to chemotherapy affects the prognosis overall, and patients with advanced-stage MOC derive less benefit from treatment therapies (5,6).

Although MOCs have different tumorigenic, clinical, and molecular characteristics than SOCs, many physicians continue to use the same treatment strategy and criteria as SOCs because there is no clear consensus regarding the optimal treatment regimen for patients with MOC. Current guidelines for gynecologic (carboplatin and paclitaxel) and gastrointestinal (oxaliplatin, 5-fluorouracil) chemotherapy protocols are acceptable options (19). Although the GOG 241 study ended with a small number of patients, no difference was found in PFS between the two regimens (27). In our cohort, all patients received platinum-based regimens. Therefore, we were unable to make comparisons between regimens. With the improvements in genomic and molecular understanding of MOC, histology based targeted therapies could improve oncologic outcomes.

Study Limitations

The main limitations of this study were its retrospective design and that it covers a wide period between 1990 and 2019, so it includes heterogeneities in the adjuvant therapy regimens. Furthermore, there is a lack of central pathology review.

However extensive study periods are required to collect these rare tumors. In addition, the current study has a large cohort for a single center and has provided sufficient information regarding the oncological outcome and treatment response of patients in early and advanced stages.

Conclusion

In conclusion, stage is the most important factor in determining the prognosis in terms of PFS. The presence of an advanced stage was associated with a poor prognosis and a diminished response to chemotherapy. Residual disease was also a risk factor for disease progression, but it had no effect on chemotherapy response rates in the advanced stages. New molecular and genetic markers should be identified and used to personalize the histology-based treatment for MOC, and additional prospective multicenter trials should be developed for the treatment of advanced stages.

Ethics Committee Approval: *The University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital Research Ethics Committee has confirmed that no ethical approval is required (approval number: 90057706-799/May).*

Informed Consent: *Retrospective study.*

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