Published online 2022 October 20 **Original Article**

Clinical Characteristics and 8-year Survival Rate in Advanced Ovarian Cancer Following Neoadjuvant Chemotherapy: A Single Center Experience

Azamsadat Mousavi[1], Setareh Akhavan[1], Shahrzad Sheikhhasani[1], Narges Zamani[1], Elahe Rezayof[2] and Arezoo Esmailzadeh[1,*]

[1] Gynecology Oncology Department, Vali-E-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran

* ***Corresponding author:*** Arezoo Esmailzadeh, Gynecology Oncology Department, Vali-E-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran. Email: dr.a.esmailzadeh@gmail.com

Received 2021 May 14; **Revised** 2022 June 18; **Accepted** 2022 October 06.

Abstract

Background: More than 75% of epithelial ovarian cancer (EOC) cases are diagnosed in advanced stages, which is associated with tumor recurrence and chemotherapy resistance. So far, to the best of our knowledge, a similar study has not been conducted in Iran to investigate the clinical characteristics and survival rate of these patients treated with neoadjuvant chemotherapy (NACT).

Objectives: This study aimed to evaluate the clinical characteristics and survival of patients treated with NACT followed by cytoreductive surgery and the factors affecting survival.

Methods: This retrospective cohort study was conducted on 147 advanced ovarian cancer cases who were treated with NACT referring to the Gynecology Oncology Department of Imam Khomeini Hospital in Tehran, Iran, between 2011 and 2021 and met the inclusion criteria for this study. The survival curve and Cox regression method were used to analyze the data.

Results: The results revealed that 8.9% of advanced EOC (147/1,650) were treated with NACT and the average number of NACT courses was 4.12 periods. The survival rates of 1, 3, 5, and 8 years were 85.31%, 44.05%, 18.35%, and 13.77%, respectively. The mean and median of survival time were 47.7 and 36 months, respectively. Nearly 80% of the patients had stages 3C and 4A before receiving NACT. Based on the results of the adjusted Cox regression model, tumor marker level showed a significant relationship with survival rate (P=0.008), and also peritoneum involvement had a clinically significant impact on survival with a hazard ratio of 2.88.

Conclusion: The results suggested that 8.9% of ovarian cancer cases were treated with NACT. It was also revealed that the average number of NACT courses was 4.12 periods and the 8-year survival rate was 13.77%. CA125 tumor marker level showed a significant relationship with survival rate, and peritoneum involvement had a clinically significant impact on survival.

Keywords: Advanced ovarian cancer, Epithelial ovarian cancer, Neoadjuvant chemotherapy, Survival rate

1. Background

Cancer is one of the leading causes of death and an effective health outcome in life expectancy in any country of the world (1). In 2019, the World Health Organization (WHO) classified cancer as the first or second leading cause of death before the age of 70 in 112 of 183 countries (1, 2). Like most cancers, gynecologic cancers have been on the rise in recent decades (3), and according to GLOBOCAN 2020, among women, breast cancer, cervical cancer, ovarian cancer, and uterine cancer are among the 10 most common cancers worldwide (1).

Based on the international agency for research on cancer data in 2020 (4) and GLOBOCAN (1), the number of new cases and deaths due to ovarian cancer in the world were 313,959 and 207,252, respectively, and the age-standardized incidence and mortality rates were 6.6 and 4.2 per 100,000 cases, respectively. The highest incidence was in central and eastern Europe (10.7 per 100,000 cases) and the lowest was in central Africa (4.4 per 100,000 cases). The disability-adjusted life year attributed to ovarian cancer in 2019 was 5,359,740 (3).

Ovarian cancer accounts for 2.5% of cancers in women, with 5% of deaths in this group (5, 6). One of the important reasons for this difference is that more than 75% of epithelial ovarian cancer (EOC) cases are diagnosed in advanced stages that are related to tumor recurrence and chemotherapy resistance (6-9). Ovarian cancer is one of the most sensitive tumors to chemotherapy and cytotoxic drugs, and adjuvant chemotherapy is prescribed for most of these patients. In recent decades, neoadjuvant chemotherapy (NACT) has been used for patients with advanced ovarian cancer, and the results of studies have shown improved survival following NACT administration (10, 11).

The choice treatment for ovarian cancer in most patients is surgery. Surgery often needs to be completed with chemotherapy; some patients may not even have the condition to have complete resection of the mass at first and may be candidates for NACT and then have surgery again after chemotherapy. As mentioned, the most effective treatment for early-stage ovarian cancer is surgery, and for advanced disease, it involves reducing the tumor burden through surgery along with six cycles of intravenous chemotherapy with carboplatin and paclitaxel. On the other hand, if necessary,

cytoreduction surgery is performed after three cycles of chemotherapy (12-16).

Primary cytoreduction surgery (PCS) followed by chemotherapy has been the standard treatment; however, in recent years, several studies have been performed to compare standard treatment with NACT followed by cytoreduction surgery and subsequent adjuvant chemotherapy in advanced ovarian cancer. The results of these trials showed that NACT acts like PCS in terms of outcomes, such as overall survival (OS) and reduced treatment-induced mortality (15, 17).

To the best of our knowledge, no study has been conducted in Iran so far to investigate the clinical characteristics and survival rate of these patients treated with NACT. This issue shows the necessity of conducting this study. Moreover, in the studies conducted in other centers, the results obtained have been contradictory and these results might have been influenced by the experience of the medical centers and their facilities, the stages of disease diagnosis, and the epidemiological characteristics of the patients.

2. Objectives

Given that no similar study has been conducted in Iran and the results of previous studies have been diverse in different countries and also since the choice of appropriate treatment in this group of women is controversial, this study aimed to evaluate the clinical characteristics of patients treated with NACT and assess the overall 8-year survival rate and the factors affecting it.

3. Methods

3.1. Study design

This retrospective cohort study was conducted on all patients with a diagnosis of ovarian cancer who referred to Valiasr Hospital of Imam Khomeini Hospital in Tehran, Iran, between 2011 and 2021 and met the inclusion criteria were examined. Totally, during the study period, the total number of EOCs referred to our hospital was 1,650, of which 147 patients underwent NACT and were included in the analysis. The required information of the patients was extracted from their medical records and in cases where the required information in the medical records was incomplete, such as information about patient survival, it was collected by telephone.

3.2. Participants

All ovarian cancer patients treated with NACT were included in this analysis. Eligible cases were all patients having positive pathology indicating primary ovarian cancer referring during the study period, candidate for NACT treatment, and having the consent to participate in the study. On the other hand, the exclusion criteria were incomplete data recorded in the file and a history of previous surgery on the tumor.

3.3. Measurements

In this study, the most important outcome was the OS of patients, which was extracted using the information in the patients' files and their telephone follow-up. To calculate the survival rate, the time of cancer diagnosis was considered the initial event and the time of death due to ovarian cancer was regarded as the endpoint event. Cases were censored at the time of their last follow-up, which is, due to the inability to patients follow, death due to causes other than ovarian cancer, or November 2021 (end of the study), whichever came first.

Patients' performance status was assessed in this study. Performance status is a standard scale to assess the patient's daily activities while living with cancer, and in this study, to assess the patients' performance status, WHO Performance status (18) was used. In this scale, Performance status is determined from a score of 0 to 5 (6 states), where a score of 0 indicates that the patient is active and has no restrictions, while a score of 5 indicates the death of the patient.

3.4. Ethical considerations

The required information of patients was extracted from their files, and patients' information was kept and reported confidentially. In cases required for a telephone call, the objectives of the research were first explained to the respondents and, if desired, they answered the questions. Other ethical considerations were observed in accordance with the Helsinki Declaration. The proposal of this research was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, with the code IR.TUMS.IKHC.REC.1399.378 on 2020-12-29.

3.5. Potential confounders

In addition to survival data, age, gravidity, chief complaints, CA125 tumor marker, one-sided/bilateral tumor, ultrasound and magnetic resonance imaging (MRI) findings before receiving NACT, FIGO stage in imaging before NACT, pathobiological results of the biopsy of omentum, ascites, and ovary, the types of drugs used in the NACT, permanent tumor pathology, FIGO stage during surgery, CA125 tumor marker in patient follow-up, the interval between recurrence to surgery, and the interval between recurrence and adjuvant therapy were assessed as potential confounders.

3.6. Statistical Analysis

Mean ± standard deviation, median (interquartile range [IQR]), count, and percentage indices were used to describe the data. The survival curve was used to show the survival rate over time. To investigate the relationship between predictor variables and survival

rate, the Cox regression model was used which was both an unadjusted and adjusted Cox model (for possible confounding variables). One of the important assumptions of using the Cox regression model is to establish the proportionality of hazard. The hazard ratio (HR) and their 95% confidence interval (CI) were reported as effect size intrests. This assumption was tested in this study using the Schoenfeld residuals method. The results showed that there was no significant deviation from this assumption. All analyzes were performed using Stata software version 13 (Stata Corp, College Station, TX, USA). A p-value of less than 0.05 was considered significant.

4. Results

The total number of EOCs referring to our hospital was 1,650, of which 147 (8.9%) patients underwent the NACT regimen (95% CI: 7.6-10.4%). The mean scores of participants' age and gravidity were 54.9±11.1 years and 4.36±2.92, respectively. According to the chief complaint, 27.2%, 72.1%, 5.1%, and 13.2% of the subjects had abdominal pain, abdomen swelling (ascites), gastrointestinal symptoms (vomiting), and others (vaginal bleeding and asthma), respectively. The median of the CA125 tumor marker was 632 (U/mL) (interquartile range: 356-1578) before NACT. In 64 (45.07%) and 43 (30.28%) participants, the mass was unilateral and bilateral, respectively.

The clinical characteristics of patients are presented in Table 1. The results showed that based on ultrasound and MRI findings, 96.6% of the cases had ascites, 78.9% had omental

Table 1. Clinical characteristics of patients

Variables		Count	Percent
Ultrasound and MRI findings	Ascites	142	96.6
	Omentum	116	78.91
	Lymph nodes	40	27.21
	Peritoneum	104	70.75
	Mesenteric intestine	8	5.44
	Liver-spleen	14	9.52
	Carcinomatosis	7	4.76
	Subdiaphragmatic	5	3.4
Positive lung imaging		4	2.72
Pleural effusion		25	17.01
FIGO stage in imaging before NACT	3	8	6.06
	3A	1	0.76
	3B	15	11.36
	3C	88	66.67
	4	15	11.36
	4A	1	0.76
	4B	3	2.27
Pathobiology biopsy	Omentum	26	17.69
	Ascites	61	41.5
	Ovary	40	27.2
Types of drugs used in the NACT	Taxol	138	95.17
	Carboplatin	138	95.17
	Gemzar	0	0
	Others	2	1.38
Permanent tumor pathology	High grade serous	120	93.02
	Low grade serous	2	1.55
	Mucinous	1	0.78
	Endometrioid	0	0
	Metastatic carcinoma	1	0.78
	undifferentiated	2	1.55
	Free of tumor	1	0.78
	Small cell of ovarian	1	0.78
	Epithelioid sarcoma	1	0.78
FIGO stage in imaging at the interval surgery time	3	7	6.86
	3A	1	0.98
	3B	11	10.78
	3C	72	70.59
	4	5	4.90
	4A	2	1.96
	4B	2	1.96
	1C	1	0.98
Types of drugs used in the adjutant chemotherapy	Taxol	106	76.27
	Carboplatin	116	83.45
	Gemzar	21	15.11
	Others	7	5.04

MRI: Magnetic resonance imaging; FIGO: International Federation of Gynecology and Obstetrics; NACT: Neoadjuvant chemotherapy

Table 2. One-8-year survival rates in patients with ovarian cancer treated with NACT

Survival time	Survival rate (%)	SD	95% CI
1 year	85.31	0.04	75.02-91.59
2 years	65.92	0.05	53.76-76.02
3 years	44.05	0.06	30.66-56.64
4 years	25.17	0.06	12.39-92.46
5 years	18.35	0.06	7.32-69.61
6 years	18.35	0.06	7.32-69.61
7 years	13.77	0.06	4.28-40.40
8 years	13.77	0.06	4.28-40.40

SD: Standard deviation; CI: Confidence interval

involvement, and 70.75% had peritoneal involvement. Pleural effusion was reported in 25 (17.01%) subjects. Before NACT, stage 3C was the most common stage (66.67%), followed by stages 3B and 4, each 11.36%. Before surgery, paclitaxel (175 mg/m2) was prescribed for 138 (95.17%) cases, and carboplatin (AUC 5) for 138 (95.17%) cases with a three-week interval. Based on the results, the average number of NACT courses was 4.12±1.6 cycles (range: 1 to 11). After surgery, carboplatin was prescribed for 116 cases, paclitaxel for106 cases, and gemcitabine for 21 cases. During surgery, stage 3C was the most common stage (70.59%), followed by stage 3B (10.78%). At the onset of NACT, patients' performance status was 0-2.

According to the results, the mean tumor marker at the time of follow-up of patients was 212.5±305.1 (median: 89, IQR: 16-295) and the mean time interval between recurrence to surgery and recurrence to the start of adjuvant treatment were 10.4±9.7 and 7.4±8.5 months, respectively. One to eight-year survival rates in patients with ovarian cancer treated with NACT are shown in Table 2 and Figure 1. The mean follow-up time was 26.3 months (min: 3 and max: 96 months). The mean and median of survival time were 47.7 and 36 months, respectively.

The results of the Cox regression model are shown in Table 3. Based on the results, older age (P=0.049), higher gravidity (P=0.047), higher tumor markers (P=0.044), and peritoneal involvement (P=0.025) were significantly associated with increased ovarian cancer survival. Unilateral ovarian involvement was associated with a higher survival rate of ovarian cancer (P=0.056). The association between the omentum and lymph nodes involvement was not significant.

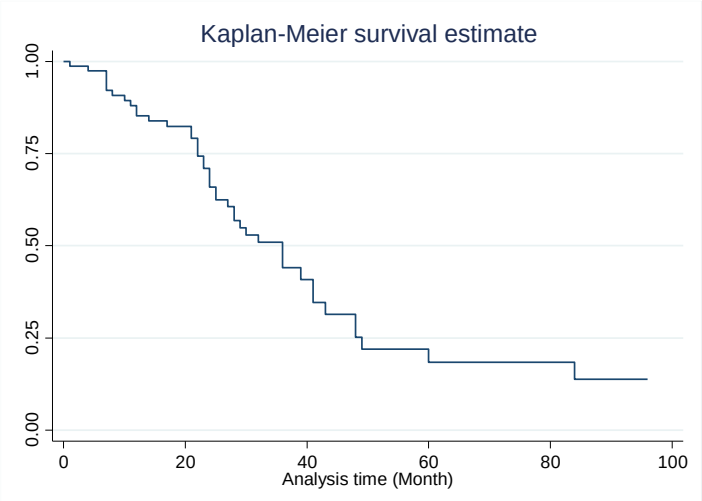

Figure 1. Survival curve in patients with ovarian cancer treated with NACT

Table 3. Estimation of crude and adjusted hazard ratios for demographic and clinical variables

Predictors	Un-adjusted analysis			Adjusted analysis		
	HR	P	95% CI	HR	P	95% CI
Age (year)	1.03	0.049	1.0001-1.06	1.047	0.062	0.99-1.10
Gravity	1.11	0.047	1.001-1.24	1.012	0.877	0.86-1.18
CA-125 (per 100) (U/mL)	1.004	0.044	1.0001-1.007	1.005	0.008	1.001-1.01
One-sided involvement	0.53	0.056	0.27-1.01	0.50	0.087	0.23-1.10
Omentum involvement	1.96	0.106	0.86-4.46	1.34	0.607	0.43-4.13
Lymph node involvement	0.58	0.124	0.29-1.15	0.690	0.338	0.32-1.47
Peritoneal involvement	3.25	0.025	1.16-9.13	2.88	0.085	0.86-9.63

CI: Confidence interval; HR: Hazard ratio

In the univariate Cox regression model (Table 3), first, the relationship between all predictors with ovarian cancer survival was investigated and the predictors that had a significant relationship with survival rate or were tended to be significant (p-value less than 0.10) were included in the adjusted model. The results of the adjusted model suggested that tumor marker level had a significant relationship with survival rate (P=0.008). However, the involvement of the peritoneum with HR = 2.88 was clinically significant and statistically tended to be significant (P=0.085).

5. Discussion

This cohort study aimed to evaluate the clinical characteristics of patients undergoing NACT and assess the overall 8-year survival rate and the factors affecting it. The main results revealed that of all patients referring with the diagnosis of EOC, 8.9% were treated with NACT and the average number of NACT courses was 4.12 periods. Based on the results, the survival rates of 1, 3, and 8 years were 85.31%, 44.05%, and 13.77%, respectively. Nearly 80% of patients had stages 3C and 4A before receiving NACT. According to the results of the Cox model, older age, higher gravidity, higher tumor marker, and peritoneal involvement were significantly associated with decreased ovarian cancer survival. In our study, the mean scores of participants' age and gravidity were 54.9 years and 4.3, respectively, while the peak incidence of EOC was at 60 years; therefore, it can be concluded that the age of ovarian invasive epithelial cancer in Iran is slightly lower (19). Ovarian cancer is also associated with infertility and low parity; nevertheless, in our data, it was present in women with an average of 4 deliveries (19).

Unilateral ovarian involvement was associated with a higher survival rate of ovarian cancer. After controlling for confounding variables, tumor marker level showed a significant relationship with survival rate (P=0.008), and peritoneum involvement with HR = 2.88 had a clinically significant impact on survival.

The rate of NACT use has been increasing in recent years. Matsuo et al. (20) in their study revealed that 29.1% of women underwent the NACT regimen before receiving interval cytoreductive surgery. Although the tendency to select NACT has been rising in recent years, the standard treatment for advanced EOC is primary surgery (20, 21). In the United States, this rate increased from 8.6% to 22.6% between 2004 and 2013 (22) and changed from 17.6% to 45.1% between 2006 and 2016 (23), this is while in our study this rate was 8.9%.

In our center, the mean number of NACT courses was 4.12 periods and its median was 3. In a study conducted by Nakamura et al. (24), the median of NACT courses in both groups of patients with non-residual and residual tumors after interval debulking surgery (IDS) was 6. In a study performed by Liu et al. (25) on 199 newly diagnosed women with ovarian cancer, who were candidates for NACT, the median number of courses was reported to be 4. Therefore, the median number of courses in our study was significantly less than that in the study by Nakamura et al., however, similar to that in the research by Liu et al.

In our study, approximately, 80% of patients had advanced stages (3C and 4A) before receiving NACT. The findings of similar studies have shown that more than 75% of ovarian cancers are diagnosed in advanced stages. In the study by Nakamura et al. (24), 68% of included patients were at stage 3C at the time of cancer diagnosis. In our study, approximately 67% of the cases were diagnosed with stage 3C. Therefore, it can be concluded that most cases of ovarian cancer are diagnosed in advanced stages; this is because the symptoms of ovarian cancer are one of the most common complaints among women, and these symptoms are usually nonspecific and do not have a clear diagnostic pattern and screening test (26). The diagnostic method of EOC for staging before NACT is laparoscopic or clinical (20, 27). We selected the clinical method for staging since imaging findings, such as computed tomography scan, are confirmed by biopsy under the imaging guide.

Rauh-Hain et al. (28), in their study on stage 3C and 4 EOC (during 2003-2011 in the US), concluded that the 5- and 10-year survival rates were 25.3% and 12.2% in the NACT-treated group, respectively. A comparison of the two studies shows that the 5-year survival rate at our center was slightly lower than that in the United States (18.35% vs 25.3%).

In different studies, OS is similar in both NACT and PDS groups, while surgical complications and mortality are less in the NACT group (20, 21, 27, 29, 30). This has led to the tendency to NACT in the advanced serous EOC; however, the main issue is the correct selection of patients for achieving similar results. As we can observe in the Scorpion study, OS was equal to 47 months and in CHOROUS and EORTC trials was 27 months, due to younger patients and better performance status, compared with the CHOROUS and EORTC trials (27). In a study by Liu et al. (31) conducted on 224 women with advanced ovarian cancer (stages 3 and 4) who received NACT, a one-year survival rate of 86.1% was reported. In our study, the one-year survival rate was 85.31%, which was consistent with the results of previous studies.

The findings of a study by Zeng et al. (32), which was conducted on advanced-stage EOC after IDS, showed that CA125 was one of the most reliable prognosticators for predicting cancer survival. In another study, conducted on patients with stage 3B-IV EOC treated with cytoreductive surgery, the results showed that a decrease in CA125 was associated with a decrease in disease-specific mortality (33). Normalization of CA-125 levels before

IDS is associated with survival improvement after debulking surgery and is also considered a prognostic factor (21, 30). The results of the adjusted Cox regression model suggested that CA-125 tumor marker level had a significant relationship with survival rate and the involvement of the peritoneum with HR = 2.88 was clinically significant.

Among the strengths of this study were that it was the first report on the survival rate of patients with ovarian cancer under NACT and in this study, patients were followed for 10 years and the 8-year survival rate was calculated. One of the limitations of this study was the incomplete follow-up of all patients, which in some cases occurred due to not refereeing to the hospital or changing the phone number. It is recommended that disease-free survival and mortality be calculated in future studies. In addition, a multicenter study with a larger sample size is recommended to achieve more accurate results.

6. Conclusion

In our center, 8.9% of ovarian cancer cases were treated with NACT during 2011-2021. The average number of NACT courses was 4.12 periods, and the survival rates of 1, 3, 5, and 8 years were 85.31%, 44.05%, 18.35%, and 13.77%, respectively. Almost 80% of the patients had stages 3C and 4A before receiving NACT. CA125 tumor marker level showed a significant relationship with survival rate, and peritoneum involvement with HR = 2.88 had a clinically significant impact on survival. However, although the exact criteria for selecting patients who benefit from NACT before debulking surgery are not very clear, the ultimate goal for a decision on NACT should be the achievement of complete cytoreductive surgery without residual disease remains.

Acknowledgments

The authors would like to thank the Vice Chancellor for the Research of Tehran University of Medical Sciences for their financial and scientific support.

Footnotes

Conflicts of Interest: All authors declared no conflict of interest.

Ethical considerations: All participants or their legal guardians provided verbal informed consent. All stages of research were conducted following the Declaration of Helsinki and the Ethical Statements of the Ethics Committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.IKHC.REC.1399.378).

Consent for publication: Not applicable. Availability of data and material

All data generated or analyzed during this study were included in this published article.

Funding: This study was funded by the Tehran University of Medical Sciences. The funder had no role in the study design, data collection, analyses, interpretation of the results, or decision to submit results.

Authors' contributions: Study conception and design: AM, SA, SS, NZ, ER, and AE. Data collection, statistical expertise, and analysis and interpretation of data: AM, SA, SS, NZ, ER, and AE. Manuscript preparation, supervision, administrative support, and critical revision of the paper: AM, SA, SS, and AE. All authors read and approved the final manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;**71**(3):209-49. doi: 10.3322/caac.21660. [PubMed: 33538338].
2. WHO. Global health estimates 2020: deaths by cause, age, sex, by country and by region, 2000-2019. 2020. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.
3. Yi M, Li T, Niu M, Luo S, Chu Q, Wu K. Epidemiological trends of women's cancers from 1990 to 2019 at the global, regional, and national levels: a population-based study. *Biomark Res.* 2021;**9**(1):1-12.
4. IARC. Ovary: Globocan 2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/25-Ovary-fact-sheet.pdf.
5. Howlader N, Noone A, Krapcho M, Garshell J, Miller D, Altekruse S, et al. SEER cancer statistics review, 1975–2012. National Cancer Institute; 2014.
6. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin.* 2018;**68**(4):284-96. doi: 10.3322/caac.21456. [PubMed: 29809280].
7. Wu SG, Wang J, Sun JY, He ZY, Zhang WW, Zhou J. Real-world impact of survival by period of diagnosis in epithelial ovarian cancer between 1990 and 2014. *Front Oncol*. 2019;**9**:1-10. doi: 10.3389/fonc.2019.00639. [PubMed: 31448220].
8. Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. *Ther Adv Med Oncol.* 2014;**6**(6):293-304. doi: 10.1177/1758834014544891. [PubMed: 25364394].
9. Gao Y, Li Y, Zhang C, Han J, Liang H, Zhang K, et al. Evaluating the benefits of neoadjuvant chemotherapy for advanced epithelial ovarian cancer: a retrospective study. *J Ovarian Res*. 2019;**12**(1):1-8. doi: 10.1186/s13048-019-0562-9. [PubMed: 31519183].
10. Batra S, Nayak H, Dave KS. Role of neoadjuvant chemotherapy (NACT) followed by surgical cytoreduction in advanced epithelial ovarian cancer. *J Obstet Gynaecol India.* 2012; **62**(5):541-5. doi: 10.1007/s13224-011-0106-8. [PubMed: 24082555].
11. Mazzeo F, Berlière M, Kerger J, Squifflet J, Duck L, D'Hondt V, et al. Neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy in patients with primarily unresectable, advanced-stage ovarian cancer. *Gynecol Oncol*. 2003;**90**(1):163-9. doi: 10.1016/s0090-8258(03)00249-x. [PubMed: 12821358].
12. Bijelic L, Jonson A, Sugarbaker P. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. *Ann Oncol.* 2007;**18**(12):1943-50. doi: 10.1093/annonc/mdm137. [PubMed: 17496308].
13. Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G,

Rubin SC, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med.* 2004;**351**(24):2489-97. doi: 10.1056/NEJMoa041125. [PubMed: 15590951].
14. van der Burg ME, van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *N Engl J Med*. 1995;**332**(10):629-34. doi: 10.1056/NEJM199503093321002. [PubMed: 7845426].
15. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010; **363**(10):943-53. doi: 10.1056/NEJMoa0908806. [PubMed: 20818904].
16. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;**34**(28):3460-73. doi: 10.1200/JCO.2016.68.6907. [PubMed: 27502591].
17. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet*. 2015;**386**(9990):249-57. doi: 10.1016/S0140-6736(14)62223-6. [PubMed: 26002111].
18. Picot J, Cooper K, Bryant J, Clegg A. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. *Health Technol Assess.* 2011;**15**(41):1-204. doi: 10.3310/hta15410. [PubMed: 22146234].
19. Berek JS. Berek & Novak's gynecology. Lippincott Williams & Wilkins; 2019.
20. Matsuo K, Matsuzaki S, Nusbaum DJ, Maoz A, Oda K, Klar M, et al. Possible candidate population for neoadjuvant chemotherapy in women with advanced ovarian cancer. *Gynecol Oncol.* 2021;**160**(1):32-9. doi: 10.1016/j.ygyno.2020.10.027. [PubMed: 33196436].
21. Moschetta M, Boussios S, Rassy E, Samartzis EP, Funingana G, Uccello M. Neoadjuvant treatment for newly diagnosed advanced ovarian cancer: where do we stand and where are we going? *Ann Transl Med.* 2020;**8**(24):1-9. doi: 10.21037/atm-20-1683. [PubMed: 33490222].
22. Melamed A, Hinchcliff EM, Clemmer JT, Bregar AJ, Uppal S, Bostock I, et al. Trends in the use of neoadjuvant chemotherapy for advanced ovarian cancer in the United States. *Gynecol Oncol.* 2016;**143**(2):236-40. doi: 10.1016/j.ygyno.2016.09.002. [PubMed: 27612977].
23. Knisely AT, Clair CMS, Hou JY, Collado FK, Hershman DL, Wright JD, et al. Trends in primary treatment and median survival among women with advanced-stage epithelial ovarian cancer in the US from 2004 to 2016. *JAMA Netw Open*. 2020;**3**(9):e2017517.
24. Nakamura K, Kitahara Y, Nishimura T, Yamashita S, Kigure K, Ito I, et al. Nadir CA-125 serum levels during neoadjuvant chemotherapy and no residual tumor at interval debulking surgery predict prognosis in advanced stage ovarian cancer. *World J Surg Onco*l. 2020;**18**(1):1-9. doi: 10.1186/s12957-020-01978-6. [PubMed: 32791996].
25. Liu YL, Zhou QC, Iasonos A, Chi DS, Zivanovic O, Sonoda Y, et al. Pre-operative neoadjuvant chemotherapy cycles and survival in newly diagnosed ovarian cancer: what is the optimal number? A memorial sloan kettering cancer center team ovary study. *Int J Gynecol Cancer*. 2020;**30**(12):1915-21. doi: 10.1136/ijgc-2020-001641. [PubMed: 33106271].
26. Jayde V, White K, Blomfield P. Symptoms and diagnostic delay in ovarian cancer: a summary of the literature. *Contemp Nurse.* 2010;**34**(1):55-65. doi: 10.5172/conu.2009.34.1.055. [PubMed: 20230172].
27. Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). *Int J Gynecol Cancer.* 2020;**30**(11):1657-64. doi: 10.1136/ijgc-2020-001640. [PubMed: 33028623].
28. Rauh-Hain JA, Melamed A, Wright A, Gockley A, Clemmer JT, Schorge JO, et al. Overall survival following neoadjuvant chemotherapy vs primary cytoreductive surgery in women with epithelial ovarian cancer: analysis of the National Cancer Database. *JAMA Oncol*. 2017;**3**(1):76-82. doi: 10.1001/jamaoncol.2016.4411. [PubMed: 27892998].
29. Feng Z, Wen H, Li R, Liu S, Fu Y, Chen X, et al. Comparison of survival between primary debulking surgery versus neoadjuvant chemotherapy for ovarian cancers in a personalized treatment cohort. *Front Oncol.* 2021;**10**:1-6. doi: 10.3389/fonc.2020.632195. [PubMed: 33643924].
30. Fleming ND, Westin SN, Rauh-Hain JA, Soliman PT, Fellman BM, Coleman RL, et al. Factors associated with response to neoadjuvant chemotherapy in advanced stage ovarian cancer. *Gynecol Oncol.* 2021;**162**(1):65-71. doi: 10.1016/j.ygyno.2021.04.002. [PubMed: 33838925].
31. Liu YL, Filippova OT, Zhou Q, Iasonos A, Chi DS, Zivanovic O, et al. Characteristics and survival of ovarian cancer patients treated with neoadjuvant chemotherapy but not undergoing interval debulking surgery. *J Gynecol Oncol.* 2020;**31**(1):1-12. doi: 10.3802/jgo.2020.31.e17. [PubMed: 31833259].
32. Zeng J, Huang H, Shan Y, Li Y, Jin Y, Pan L. The effect of CA125 nadir level on survival of advanced-stage epithelial ovarian carcinoma after interval debulking surgery. *J Cancer.* 2017;**8**(17):3410-15. doi: 10.7150/jca.21362. [PubMed: 29151924].
33. Zwakman N, van de Laar R, van Gorp T, Zusterzeel PL, Snijders MP, Ferreira I, et al. Perioperative changes in serum CA125 levels: a prognostic factor for disease-specific survival in patients with ovarian cancer. *J Gynecol Oncol.* 2017;**28**(1):1-12. doi: 10.3802/jgo.2017.28.e7. [PubMed: 27670261].