Published in final edited form as:

JAMA Oncol. 2017 January 01; 3(1): 76–82. doi:10.1001/jamaoncol.2016.4411.

Neoadjuvant Chemotherapy Compared with Primary Cytoreductive Surgery in Women with Epithelial Ovarian Cancer: Analysis of the National Cancer Database

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Abstract

Importance—Uncertainty remains about the relative benefits of primary cytoreductive surgery (PCS) versus neoadjuvant chemotherapy (NACT) for advanced-stage epithelial ovarian cancer (EOC).

Purpose—Compare overall survival of PCS versus NACT in a large national population of women with advanced-stage EOC.

Design—Retrospective cohort study.

Setting—Hospitals across the United States reporting to the National Cancer Data Base who cared for patients with advanced-stage EOC diagnosed between 2003–2011.

Participants—We identified women with stage IIIC and IV EOC diagnosed between 2003–2011. We focused on patients aged ≥ 70 years with a Charlson comorbidity index=0 who were likely candidates for either treatment.

Exposure—Initial treatment approach of PCS vs. NACT, examined using an intent-to-treat analysis.

Main Outcome—Overall survival, defined as months from cancer diagnosis to death or date of the last contact. We used propensity score matching to compare similar women who underwent PCS and NACT. The association of treatment approach with overall survival was assessed using the Kaplan-Meier method and the log-rank test. We assessed whether the findings were influenced

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Disclosure of Interests: The authors declare that there are no conflicts of interest.

by differences in the prevalence of an unobserved confounder, such as limited performance status [Eastern Cooperative Oncology Group (ECOG) 1–2], pre-operative disease burden, and BRCA status.

Results—Among 22,962 patients, 19,836 (86.4%) received PCS and 3,126 (13.6%) underwent NACT. We matched 2,935 patients treated with NACT with similar patients who received PCS. Among propensity-score matched groups, the median overall survival was 37.3 (95% CI, 35.2–38.7) months in the PCS group and 32.1 (95% CI, 30.8–34.1) months in the NACT group ($P<0.001$). However, if the NACT group had a higher proportion of women with performance statuses of 1–2 compared with PCS (60% vs. 50%), the association of PCS and improved survival would not be statistically significant.

Conclusions and Relevance—PCS was associated with improved survival compared with NACT in healthy women aged ≥ 70 years. The lower survival in women who received NACT could be explained by a higher prevalence of limited performance status in women undergoing NACT.

Introduction

Epithelial ovarian cancer (EOC) is associated with the highest case-fatality ratio of all gynecologic cancers. Primary cytoreductive surgery (PCS) followed by chemotherapy consisting of carboplatin and paclitaxel is the traditional treatment regimen for women with advanced EOC.[1] Neoadjuvant chemotherapy with interval cytoreductive surgery (NACT) and post-operative chemotherapy is an alternative approach,[2–3] often used to treat patients with large tumor burdens, multiple comorbidities, or stage IV disease.[4–5]

The role of NACT in the treatment of EOC remains controversial. Several retrospective studies have suggested that PCS with optimal cytoreduction is more effective than NACT for women with advanced-stage EOC, with improved progression-free and overall survival.[6–10] However, two phase III randomized clinical trials have demonstrated that NACT is non-inferior to PCS for women with stages IIIC and IV EOC with high disease burdens.[2–3] Both trials have been criticized because a high number of patients who received PCS had >1 cm of residual disease after surgery, the survival durations were shorter than expected, and a significant proportion of women received single agent carboplatin instead of the traditional platinum-based doublet.[11–12] Exploratory analyses of the Vergote et al. trial[2] revealed that patients with stage IIIC disease and <4.5 cm of disease had superior survival when treated with PCS, and patients with stage IV disease had better survival when treated with NACT.[13]

Despite the evidence supporting the non-inferiority of NACT, this approach is not accepted by some gynecologic oncologists in the United States.[11–12] The purpose of this study was to compare the overall survival of women with advanced-stage EOC who underwent PCS with those who received NACT in a large United States population. We restricted our study sample to women who were ≥ 70 years of age and without medical comorbidities to maximize the likelihood that patients would be eligible for either treatment and reduce bias related to the preferential use of NACT in elderly and frail women.

Materials and Methods

We identified women diagnosed with advanced-stage (stage IIIC and IV) EOC during 2003–2011 from the National Cancer Data Base (NCDB). The NCDB is a nationwide oncology cancer registry that includes information on approximately 70% of all incident cancers diagnosed in the United States and serves as a surveillance mechanism for more than 1,430 hospitals participating in the American College of Surgeons Commission on Cancer.[14] Because all data are de-identified, this study was deemed exempt by the Massachusetts General Hospital's Institutional Review Board.

To better compare NACT with PCS among patients who were likely candidates for either treatment, we studied women who were 70 years old with a Charlson comorbidity index of 0. The Charlson Comorbidity Index includes comorbidities likely to impact survival among hospitalized cancer patients; a score of zero means none of the Charlson comorbidities were present.[15–16] From 54,382 patients with incident stage IIIC or IV ovarian cancer diagnosed between 2003–2011, we excluded women whose ICD-O-3 histologic code did not correspond to a category of EOC (N=2,828), women with other cancers (N=6,321), those without microscopic confirmation (N=239), or unknown follow-up time (N=4). We next excluded women with Charlson scores 0 and/or age >70 years old (N=17,921), patients diagnosed with ovarian cancer at one institution but treated at another (N=550), those missing data on the timing of post-operative chemotherapy, women treated with palliative intent, and women with unknown surgical procedures (N=2,758). Finally, to identify primary (rather than salvage) therapy, we restricted the cohort to patients in whom chemotherapy or surgery was initiated within 3 months of diagnosis, resulting in a final study population of 22,962 women (Figure 1).

The exposure of interest was initial treatment approach of PCS vs. NACT. We performed an intent-to-treat analysis, in which patients who had initial PCS were included even if they never received chemotherapy, and those who had initial NACT were included even if they never received surgery. Receipt of treatment, including chemotherapy, in the NCDB has been documented to be reliable.[17–18] The primary outcome of interest was overall survival, defined as months from cancer diagnosis to death or date of the last contact.

Control variables included age at diagnosis, race/ethnicity, year of diagnosis, and geographic location of the treating facility. We documented median household income of the ZIP code of residence as estimated by the American Community Survey, categorized in quartiles (< \$38,000, \$38,000–\$47,999, \$47,000–\$62,999 and \$63,000). Insurance status was categorized as uninsured, private insurance, Medicare, or another type of government insurance. The treating facility was categorized according to the Commission on Cancer Accreditation program as a Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, or other.

Statistical Analysis

We compared categorical variables using χ^2 tests and continuous variables using independent sample t tests. Propensity score matching was undertaken to create a cohort in which subjects who underwent PCS and NACT were balanced on covariates that might

confound the effect of treatment approach on survival.[19] We fit logistic regression models to estimate the probability of receiving NACT; independent variables included age, year of diagnosis, race/ethnicity, treating facility type, insurance status, income, geographic region, rural/urban status, stage, histology, and grade. We then matched each woman who received NACT with a woman who underwent PCS who had the same propensity to undergo NACT using a caliper of 0.2.[20] We compared standardized differences of covariates in the propensity-matched cohort (eFigure 1).

We compared overall survival between women who underwent PCS versus NACT in the propensity score matched cohort using the Kaplan-Meier method and the log-rank test. Cox proportional hazards models were used to estimate Hazard Ratios (HRs) and 95% confidence intervals (CI) for the association of treatment with survival. We repeated analyses stratified by stage and period of diagnosis in the propensity matched groups; we also tested for the interaction of treatment approach by stage and treatment approach by period of diagnosis in separate models.

In sensitivity analyses, we repeated all analyses after excluding women who received chemotherapy without interval cytoreductive surgery from the NACT group because of a concern that these women may have been too sick to undergo surgery. Additionally, we restricted the analysis to high-volume centers, defined as hospitals that treated ≥ 20 ovarian cancer cases/year,[21–22] and women with high-grade serous cancer. For these analyses, we refit the propensity score models.

Although we adjusted for numerous observed characteristics using propensity score analyses, propensity scores cannot adjust for unmeasured confounders. Therefore, we tested the sensitivity of our associations between treatment group and survival to several potential unmeasured confounders.[23–24] To do this, we assumed that there were unmeasured factors, i.e. preoperative disease burden, performance status, and BRCA status, that were associated with both the treatment received and survival. We then updated our estimates of the differences in survival after adjusting for these additional unobserved variables using specific assumptions about differences in the prevalence of these characteristics in women receiving PCS vs. NACT and the confounder's association with survival. Based on the Gynecologic Oncology Group (GOG)–182 study estimate of the effects of preoperative disease burden on overall survival, we estimated that women with high preoperative disease burden have a HR of death of 1.33 compared with women with a moderate disease burden. [25] We instituted a range of assumptions about the prevalence of high disease burden, which is likely to have been more prevalent among women undergoing NACT. Similarly, the impact of performance status of 1 or 2, compared to a performance status of 0, in women with EOC is associated with a HR of time to death of 1.71.[26] We also assumed performance status of 1 or 2 was more prevalent among women undergoing NACT. Finally, the impact of BRCA status was also assessed. BRCA mutation is associated with a better prognosis in women with EOC, in a large series the HR of time to death was 0.72 in women with a BRCA mutations compared to those without the mutation.[27] We assumed BRCA mutations were more prevalent among the PCS group, assuming this group may be more likely to pursue aggressive treatment of their cancer with PCS.

Statistical tests were 2-sided and differences were considered statistically significant at $P<0.05$. All statistical analyses were performed using R 3.0.3 (*R Foundation for Statistical Computing, Vienna, Austria*).

Results

Among 22,962 included patients, 19,836 (86.4%) underwent PCS and 3,126 (13.6%) patients received NACT. Of those who underwent NACT, 813 (26.0%) never received interval cytoreductive surgery, while 2,925 (14.7%) of women treated with PCS did not receive chemotherapy within six months of surgery. Table 1 summarizes selected patient characteristics and eTable 1 summarizes additional demographic and clinical characteristics of the study population. Women who had NACT were significantly older and less likely to be diagnosed with stage IIIC disease.

In a multivariable model, factors associated with use of NACT included older age at diagnosis, more recent diagnosis, serous histology, and stage IV vs. IIIC disease (eTable 2). After stratifying by stage, associations were similar. Propensity score matching between the PCS and NACT groups yielded 2,935 matched pairs (93.9% of 3,126 patients) in the NACT group (Table 1, eTable 1). After propensity score matching, all characteristics were balanced in the two groups (eFigure 1).

The median follow-up was 56.5 months in the PCS group and 56.3 months in the NACT group in the propensity matched cohort (eFigure 2 shows Kaplan–Meier survival curves for the propensity-matched groups for the entire population). The median overall survival in the propensity-matched cohort was 37.3 months [95% Confidence Interval (CI)=35.2–38.7] for the PCS group and 32.1 months (95%CI=30.8–34.1) in the NACT group ($P<0.001$). Within the cohort, 30 and 60 day survival rates were 98.8% and 97.4% in the NACT group, respectively, and 97.4% and 94.7% in the PCS group. In addition, five and ten year survival rates were 25.3% and 12.2% in the NACT group, and 32.8% and 14.2% in women who underwent PCS.

Overall, women in the NACT group had an 18% increased hazard of death from all-causes compared with PCS [Hazard Ratio (HR)=1.18; 95%CI=1.11–1.26] (Table 2). When stratified by period of diagnosis, the association of treatment approach with survival was similar for each period (P for interaction of treatment approach by time period=0.7, data not shown) (Table 2). Results differed slightly after stratifying by stage; in women with stage IIIC the propensity-matched HR in women that received NACT compared to PCS was 1.24 (95%CI=1.11–1.37); and in stage IV the propensity-matched HR was 1.13 (95%CI=1.04–1.23); however, these differences were not statistically significant (P for interaction=0.3).

In sensitivity analyses, we assessed the association of treatment group with all-cause survival after excluding patients who only received chemotherapy. Among women who received either PCS or NACT followed by interval cytoreductive surgery, in the propensity score adjusted analysis, the median overall survival was 40.1 (95%CI=38.2–41.7) months in the women in the PCS group and 32.4 (95% CI=30.9–34.2) months in the NACT group ($P<0.001$); adjusted HR= 1.29, (95%CI=1.21–1.38) (eFigure 3 shows Kaplan–Meier

survival curves for the propensity-matched groups for this population). Among women who received treatment at high-volume centers, in the propensity score adjusted analysis, the median overall survival was 37.7 (95% CI=36.1–39.9) months in the women in PCS group and 32.0 (95% CI=30.7–34.0) months in the NACT group ($P<0.001$); adjusted HR=1.20, (95% CI=1.13–1.28). When patients with high-grade serous cancer were analyzed separately, in the propensity score adjusted analysis, the median overall survival was 44.0 (95% CI=41.6–46.6) months in the women in PCS group and 35.6 (95% CI=33.9–38.0) months in the NACT group ($P<0.001$); adjusted HR=1.28, (95% CI=1.16–1.41).

In analyses assessing the sensitivity of our findings to potential unmeasured confounders, we tested whether differences in the burden of disease, performance status, or BRCA status[25–27] could explain our findings. Our findings were robust to rather large differences in the prevalence of high disease burden and BRCA status (eTable 3). For example, given prior evidence that a high pre-operative disease burden is associated with higher mortality (HR=1.33) compared with moderate disease burden, if 95% of women receiving NACT had high disease burden compared with 60% of women in the PCS group, the association of PCS with better survival would still be statistically significant. The findings were less robust for potential moderate sized differences in performance status. For example, given prior evidence that a limited performance status [Eastern Cooperative Oncology Group (ECOG) 1–2] is associated with higher mortality (HR=1.71) compared with a performance status of 0, if 60% of women receiving NACT had an ECOG of 1–2 compared with 50% in the PCS group, then the association of PCS and improved survival would no longer be statistically significant.

Discussion

In this large national study examining primary treatment for healthy women aged 70 with advanced-stage EOC, PCS was associated with improved survival of approximately 5 months compared with NACT. PCS was associated with improved survival even when we restricted our analyses to patients who received NACT without interval cytoreductive surgery, patients with high-grade serous cancers, or those treated at high-volume centers. The findings were robust to large differences in two potential unobserved confounders, high pre-operative disease burden and BRCA status, but not large differences in the prevalence of limited performance status.

Two clinical trials showed non-inferior survival in women randomized to NACT, compared with PCS. However, these trials have significant shortcomings. The Vergote et al. trial[2] is limited by the short overall survival and low proportion of patient who were optimally cytoreduced to <1 cm of residual disease (41.6%). The median overall survival of patients randomized to PCS was only 29 months and 30 months in the NACT group. Similarly, in the CHemotherapy OR Upfront Surgery (CHORUS) trial[3] the median overall survival of patients randomized to PCS was 23 months vs. 24 months in the NACT group, and only 41% of the patients in the PCS arm were optimally cytoreduced to <1cm of residual disease.

Prior retrospective studies and a meta-analysis have demonstrated improved overall survival in women who received PCS.[6–10,28] However, observational studies do not provide the

same level of evidence as randomized controlled trials. In observational studies, women who receive NACT are usually older, have more comorbid conditions, have higher pre-operative tumor burdens, and likely more limited performance status. These factors can result in large differences in the distribution of prognostic factors between women receiving NACT or PCS.

In the current investigation we restricted the population to healthy women ≥ 70 years old to identify women who were likely candidates for either treatment. Additionally, we used propensity score matching to adjust for many variables that have traditionally been associated with treatment approach. We also tested the robustness of our estimates to potential unobserved confounders. These analyses suggest that our finding of lower survival with NACT was robust to differences in the prevalence of high pre-operative disease burden and BRCA mutation status. On the other hand, the lower survival in women who received NACT could be explained by a higher prevalence of limited performance status in women undergoing NACT, if the prevalence of performance status ECOG of 1–2 is higher in the NACT vs. PCS group (i.e., 60% vs. 50%).

Remarkably nearly 15% of women never initiated chemotherapy after PCS while approximately 26% of the women treated with NACT did not undergo surgery. Similar to our findings, a study of women with stage III and IV EOC diagnosed between 1995 and 2008 using the Surveillance, Epidemiology, and End Results–Medicare data showed that 15% of women underwent surgery alone.[29] Similarly, Wright et al.[30] noted that 19% of older patients with stage II–IV ovarian cancer who underwent primary surgery never received post-operative chemotherapy and 66% of women treated with initial chemotherapy never underwent surgery. In comparison, in the study by Vergote et al.[2] 12% of the patients in the NACT arm did not receive surgery. The decision not to perform surgery in a significant number of patients after NACT may be related to the existence of platinum-resistant disease, or other unobserved clinical factors (e.g., limited performance status). Although our inclusion of patients treated with chemotherapy only in the NACT cohort could bias survival estimates in the primary intent-to-treat analysis, when patients receiving chemotherapy alone were removed, NACT remained associated with lower survival compared with PCS.

In this study PCS was associated with improved survival in women with both stage IIIC and IV disease. Although the estimate of the effect of treatment approach on survival was larger in patients with stage IIIC, the interaction term was not statistically significant, suggesting there was no significant difference in our findings by stage. Similarly, when we performed an analysis stratified by period of diagnosis (because the types of patients undergoing NACT may have changed after the publication of the study by Vergote et al.) [2,31–32], we found no differences.

One of the strengths of this study is that it includes information on nearly 70% of the women diagnosed with ovarian cancer in the United States. Nevertheless, it is important to note several limitations. We lacked information about the extent of post-operative residual disease and specific chemotherapy regimens and doses. The differences in survival between treatment approaches could be attributed to other unmeasured factors, such as a more

aggressive tumor biology in women who received NACT. In addition, we had no information on how treatment decisions were made, which are often based upon the likelihood of cure and perceptions of how specific interventions will impact patients' quality of life. The results of the present study are limited to healthy women ≥ 70 years, and should not be extrapolated to other populations. Finally, if most surgeons in the United States considered PCS superior to NACT during the study period, then the patients who underwent NACT, even though relatively young and healthy, may have been even more different than they appeared.

In conclusion, we found that PCS is associated with improved survival compared with NACT in healthy women ≥ 70 years. This difference was robust to large differences in two potential unobserved confounders, high disease burden and BRCA status; however, the lower survival in women who received NACT could be explained by differences in another unobserved confounder, limited performance status, if the rates are higher in patients who underwent NACT vs. PCS. Such information will be important to collect for future observational studies. Future research should focus on which patients benefit most from PCS or NACT to tailor the treatment of women with advanced stage EOC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by The Deborah Kelly Center for Outcomes Research, Massachusetts General Hospital. This work is supported by R25CA092203 from the National Cancer Institute at the National Institutes of Health. Dr. Wright is supported by K07 CA166210 and Dr. Keating is supported by K24CA181510 from the National Cancer Institute.

J. Alejandro Rauh-Hain, MD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This work was supported by The Deborah Kelly Center for Outcomes Research, Massachusetts General Hospital. This work is supported by R25CA092203 from the National Cancer Institute at the National Institutes of Health. Dr. Wright is supported by K07 CA166210 and Dr. Keating is supported by K24CA181510 from the National Cancer Institute. Support from The Deborah Kelly Center for Outcomes Research assisted in the design and conduct of the study; collection, management, analysis, and interpretation of the data. Support from the National Cancer Institute assisted in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript.

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Figure 1.

Flow diagram of the study population and propensity matched cohort. Exclusion criteria are described on right hand side. Utilizing an optimal algorithm to perform 1:1 propensity score matching.

Table 1

Demographic and clinical selected characteristics of the study population before and after propensity score matching.

	NACT	PCS	P	NACT	PCS	P
Number	3,126 (13.61%)	19,836 (86.39%)		2,935 (50.00%)	2,935 (50.00%)	
Age (Years)			<0.001			0.9
< 41	125 (4.0%)	1,212 (6.1%)		124 (4.2%)	118 (4.0%)	
41–50	464 (14.8%)	4,309 (21.7%)		456 (15.5%)	469 (16.0%)	
51–60	1,125 (36.0%)	7,188 (36.2%)		1,061 (36.1%)	1,074 (36.6%)	
61–70	1,412 (45.2%)	7,127 (35.9%)		1,294 (44.1%)	1,274 (43.4%)	
Grade			<0.001			0.9
1	56 (1.8%)	745 (3.8%)		56 (1.9%)	56 (1.9%)	
2	209 (6.7%)	2,538 (12.8%)		209 (7.1%)	212 (7.2%)	
3	1,833 (58.6%)	13,972 (70.4%)		1,827 (62.2%)	1,821 (62.0%)	
Unknown	1,028 (32.9%)	2,581 (13.0%)		843 (28.7%)	846 (28.8%)	
Histology			<0.001			0.7
Serous	2,074 (66.3%)	14,944 (75.3%)		2,063 (70.3%)	2,056 (70.1%)	
Clear Cell	72 (2.3%)	807 (4.1%)		72 (2.5%)	85 (2.9%)	
Endometrioid	57 (1.8%)	1,093 (5.5%)		57 (1.9%)	58 (2.0%)	
Mucinous	44 (1.4%)	540 (2.7%)		44 (1.5%)	34 (1.2%)	
Carcinosarcoma	69 (2.2%)	603 (3.0%)		69 (2.4%)	74 (2.5%)	
Other	810 (25.9%)	1,849 (9.3%)		630 (21.5%)	628 (21.4%)	
Stage			<0.001			0.1
IIIC	1,199 (38.4%)	14,459 (72.9%)		1,199 (40.9%)	1,262 (43.0%)	
IV	1,927 (61.6%)	5,377 (27.1%)		1,736 (59.1%)	1,673 (57.0%)	

NACT: Neoadjuvant chemotherapy; PCS: Primary Cytoreductive Surgery

Table 2

Median Overall Survival of Patients Receiving NACT vs. PCS in the propensity matched groups, overall and stratified by period of diagnosis and stage.

	Median Overall Survival PCS [months (95% CI)]	Median Overall Survival NACT [months (95% CI)]	Hazard Ratio (95% CI)
Overall (NACT)	37.3 (35.2–38.7)	32.1 (30.8–34.1)	1.18 (1.11–1.26)
Period of Diagnosis			
2003–2005	34.2 (31.5–37.1)	28.7 (25.7–30.9)	1.19 (1.07–1.33)
2006–2009	37.3 (34.9–39.3)	34.1 (31.2–36.7)	1.15 (1.05–1.27)
2010–2011	42.1 (41.1–44.3)	33.1 (31.3–35.3)	1.24 (1.06–1.46)
Stage			
IIIC	46.5 (41.9–51.0)	37.8 (35.9–40.8)	1.24 (1.11–1.37)
IV	31.4 (29.7–33.3)	28.1 (26.3–30.3)	1.13 (1.04–1.23)

PCS: Primary cytoreductive surgery. NACT: Neoadjuvant chemotherapy.