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ORIGINAL RESEARCH ARTICLE

Investigating the effect of optimal cytoreduction in the context of platinum sensitivity in high-grade serous ovarian cancer

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Abstract

Introduction: The survival benefits of surgical cytoreduction in ovarian cancer are well-established. However, the surgical outcome has never been assessed while controlling for the efficacy of chemotherapy. This leaves the possibility that cytoreduction may not be beneficial for patients whose cancer does not respond well to adjuvant treatment. We sought to answer whether surgical cytoreduction independently improves overall survival when controlling for chemotherapy outcome.

Material and Methods: We performed a retrospective case–control study using our institution's ovarian cancer database to evaluate the effect of optimal cytoreduction on advanced stage, high-grade serous ovarian cancer. Patients' characteristics were compared using both univariate and multivariate regression modeling to assess for independent predictors of overall survival.

Results: A total of 470 patients were assessed for inclusion; 234 responders to chemotherapy and 98 nonresponders. Significant survival characteristics were identified and included in the multivariate analysis. Independent predictors of survival in the multivariate analysis were age, responder status, optimal cytoreduction, neoadjuvant chemotherapy, and number of chemotherapy cycles. Kaplan–Meier survival curves showed improved survival for both patients who responded to chemotherapy and for those undergoing optimal cytoreduction ($p < 0.001$). We also demonstrated improved survival for patients receiving optimal cytoreduction among both nonresponders and responders ($p < 0.001$).

Conclusions: Our analysis shows that patients who undergo optimal cytoreduction have an overall survival benefit regardless of their response to chemotherapy. Therefore, cytoreduction should be considered in all patients, even in those with advanced disease, if an optimal result can be achieved. This study was underpowered to assess patients who received neoadjuvant chemotherapy as a separate subgroup, but the order of treatment was controlled for in the overall analysis.

Abbreviations: CI, confidence intervals; CRS, cytoreductive surgery; HR, hazard ratio.

KEYWORDS
cytoreduction, ovarian cancer, overall survival, platinum-resistant, platinum-sensitive

1 | INTRODUCTION

Ovarian cancer is the deadliest gynecologic malignancy and the fifth leading cause of cancer deaths in women in the USA.[1] The majority of cases are diagnosed at an advanced stage (stage III or IV). The standard treatment regimen for advanced-stage ovarian cancer involves a combination of cytoreductive surgery (CRS) and chemotherapy. Chemotherapy consists of a platinum-based doublet, usually paired with paclitaxel.[2] In our study, disease that recurred within 6 months of completing treatment was considered platinum resistant. If the disease-free interval was greater than 6 months, the disease was considered platinum sensitive. Platinum-based chemotherapy is consistently the strongest predictor of overall survival (OS) in patients with ovarian cancer.[3–5]

The second-most important predictor of survival is the amount of disease remaining at the conclusion of CRS.[3] Traditionally, the objective of CRS has been to have no residual lesions greater than 1 cm in size at the conclusion of surgery, termed an optimal cytoreduction. This has been the standard for the analysis of cytoreductive outcomes since the 1990s. More recently, it has been shown that patients with no visible residual disease after surgery (complete cytoreduction) have longer OS than patients with disease less than 1 cm in size (optimal cytoreduction) or residual disease greater than 1 cm (suboptimal cytoreduction).[6–10]

If disease burden is such that optimal or complete cytoreduction is likely, upfront CRS is preferred.[11] However, if the surgeon believes that suboptimal cytoreduction is likely based on the patient's disease distribution or that the risk of extensive surgery is too great based on the patient's comorbidities, then administering 3–6 cycles of neoadjuvant chemotherapy followed by an interval CRS is undertaken without compromising OS.[12–15]

While the benefits of chemotherapy response and optimal CRS have been validated repeatedly, the effect of optimal CRS in the context of response to chemotherapy has only recently been evaluated.[16] Showing an OS benefit completely independent of chemotherapy response is important to establish that it is the physical removal of tumor that is beneficial and that optimal surgery is not simply a consequence of a less aggressive tumor biology.

We performed a retrospective, single-institution, cohort study comparing OS in patients with advanced, high-grade serous ovarian cancer, using multivariate analysis to identify independent predictors of OS. We hypothesized that optimal cytoreduction would result in improved OS, even when adjusting for chemotherapy response.

Key message

Surgical cytoreduction is a mainstay of treatment in ovarian cancer. However, its impact on survival has not been assessed in the context of chemo-sensitivity. We establish that optimal cytoreductive surgery improves overall survival regardless of the cancer's response to chemotherapy.

2 | MATERIAL AND METHODS

We performed a retrospective cohort study of patients with stage III or IV high-grade serous tubo-ovarian or primary peritoneal cancer at our institution. Optimal cytoreduction was defined as residual disease less than 1 cm and was determined at the conclusion of the case by the primary surgeon. Disease-free interval was calculated starting at the conclusion of treatment. Patients who had a disease-free interval greater than 6 months from the conclusion of their primary treatment were termed "responders". Patients who had persistent disease or a recurrence within 6 months of completing primary treatment were termed "nonresponders". These terms were used because we were unable to separate patients with platinum-refractory disease from those with platinum-resistant disease because of the small number of patients with refractory disease. At the completion of treatment, patients were followed with cancer antigen-125 (CA-125) and clinical examination every 3 months. Elevated CA-125 or new-onset symptoms prompted imaging evaluation at the primary physician's discretion. To be included for assessment, patients must have had at least 6 months of follow-up data following their primary treatment. We excluded patients with low-grade, stage I or II, or non-serous histology.

Patients were identified through the University of Iowa Ovarian Cancer Dataset (University of Iowa IRB-01: #201804817), which contains patient data from 1990 to 2015. Clinical data regarding surgical complexity,[17] outcome, functional status, and chemotherapy were collected. The responder and nonresponder groups were compared using Student's *t*-test for continuous variables and chi-squared tests for dichotomous variables ($p < 0.05$) (Table 1). All variables were then evaluated for their association with survival using the same tests. Variables deemed significant in the univariate analysis ($p < 0.05$) were then evaluated in a multivariate logistic regression to determine each variable's significance when controlling for other covariates. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for all variables. A backward elimination technique based on Akaike information criterion was used to further refine the model.

TABLE 1 Comparison of clinical data between responders and nonresponders. Clinical data were culled and univariate analysis with logistic regression was used to compare responders and nonresponders. Responders and nonresponders differed in 10/14 criteria

	Responders	Nonresponders	
	N = 234	*N* = 98	*p*-value
Age	59	62	0.035
Charlson Comorbidity Index			
1–3	45	12	0.078
4–6	158	68	
>6	25	15	
Stage			
3	193	70	0.023
4	41	28	
Disease in upper abdomen (other than omentum) by imaging			
Yes			
Large bowel (*N* = 17)	167	81	0.033
Spleen (*N* = 5)			
Porta - hepatis (*N* = 32)			
Mesenteric mets (*N* = 21)			
Other (*N* = 115)			
No	67	17	
Disease in the chest by imaging			
Yes			
Chest (*N* = 26)	30	18	0.192
Pleural effusion (*N* = 47)			
No	204	80	
Grade			
2	22	17	0.045
3	196	75	
Residual disease after surgery			
R0	60	4	<0.001
R1	117	52	
R2	57	42	
Surgery in pelvic lymph node			
Yes	57	13	0.026
No	177	85	
Surgical complexity			
Low (1–3)	112	60	0.239
Intermediate (4–7)	118	35	
High (≥8)	4	3	
Surgery in para-aortic lymph node			
Yes	51	13	0.075
No	186	85	
Neoadjuvant chemotherapy			
Yes	10	13	0.004
No	219	81	
Number of cycles delivered			
<6	7	7	0.296
≥6	227	89	

(Continues)

TABLE 1 (Continued)

	Responders	Nonresponders	
	N = 234	*N* = 98	*p*-value
Treatment			
Optimal (optimal surgery and ≥6 cycles)	165	49	<0.001
Suboptimal	69	49	
Dose-dense chemotherapy			
Yes	30	4	0.023
No	204	94	

Note: R0: No macroscopic disease; R1: residual disease ≤1 cm; R2: residual disease >1 cm. Using modern classification, all grade 2 specimens were high grade.

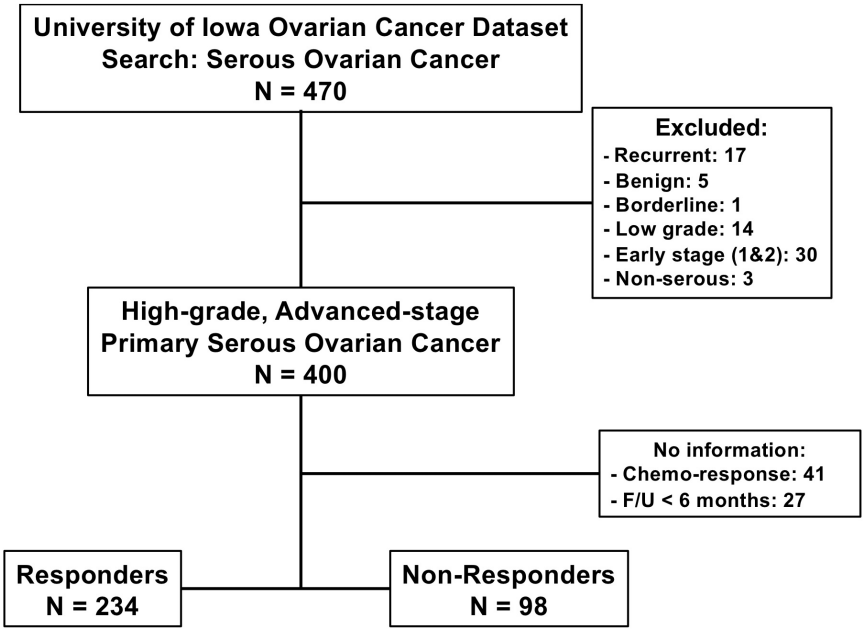


FIGURE 1 Flow of included patients. Of 470 patients within our database, 332 met our inclusion criteria. Of these, 234 (70.5%) were considered responders and 98 were nonresponders, which is consistent with historical percentages for platinum sensitivity. F/U, follow-up.

Kaplan–Meier curves were constructed to compare responders and non-responders and optimal vs suboptimal CRS. Median survival was calculated for all groups, and *p*-values and 95% CIs are reported. A final Kaplan–Meier curve was constructed combining both variables to represent four groups of patients based on responder status and surgery outcome.

3 | ETHICAL APPROVAL

This study was approved by the University of Iowa IRB-01 #201804817 on September 5, 2018, and complied with all guidelines regarding human subject research.

4 | RESULTS

In total, 470 patients were identified in our cancer database as having serous ovarian cancer. Of these, 332 met our inclusion criteria: 234 responders and 98 nonresponders (Figure 1). This rate of 70% responders is consistent with the known rate of platinum sensitivity in ovarian cancer.

Responders and nonresponders differed in several criteria, including the number undergoing neoadjuvant chemotherapy, upper abdominal disease, stage, residual disease after surgery, and age (Table 1).

The univariate analysis revealed significant differences in survival in 12 of 14 clinical factors (Table 2). The multivariate survival analysis was designed to adjust for all these patient characteristics. Five criteria were found to be significant after the multivariate analysis: age (HR 1.02; 95% CI 1.01–1.03; $p = 0.002$), response to chemotherapy (HR 0.27; 95% CI 0.20–0.35; $p < 0.001$), optimal surgery (HR 0.73; 95% CI 0.55–0.96; $p = 0.023$), number of cycles of chemotherapy (HR 0.84; 95% CI 0.72–0.99; $p = 0.038$), and receipt of neoadjuvant chemotherapy (HR 2.84; 95% CI 1.73–4.66; $p < 0.001$) (Table 2; Figure 2).

Kaplan–Meier curves demonstrating survival for responders and nonresponders and optimal and suboptimal surgical outcomes

TABLE 2 Univariate survival analysis: all factors assessed in the cox proportional hazard model

		Hazard ratio	95% CI	*p*-value
Age	**(years)**	**1.03**	**1.02–1.04**	**<0.001**
Charlson Comorbidity Index	**Low**	**ref**		
	Medium	**2.04**	**1.13–2.20**	**0.001**
	High	**1.58**	**1.34–3.11**	**0.007**
Stage		**1.37**	**1.06–1.76**	**0.015**
Grade		0.82	0.61–1.10	0.191
Imaging: Upper abdominal involvement	**(ref: No)**	**1.31**	**1.01–1.71**	**0.044**
Imaging: Chest involvement	(ref: No)	1.11	0.80–1.53	0.528
Surgical complexity score	**(by units)**	**0.91**	**0.84–0.97**	**0.008**
Optimal surgery	**(ref: Yes)**	**1.59**	**1.26–2.00**	**<0.001**
Pelvic lymphadenectomy	**(ref: Yes)**	**1.81**	**1.33–2.47**	**<0.001**
Para-aortic Lymphadenectomy	**(ref: Yes)**	**2.22**	**1.58–3.12**	**<0.001**
Cycles of chemotherapy	**(# cycles)**	**0.65**	**0.59–0.71**	**<0.001**
Neoadjuvant	**(ref: No)**	**2.25**	**1.50–3.38**	**<0.001**
Dose-dense chemotherapy	**(ref: No)**	**0.42**	**0.26–0.69**	**0.001**
Response to chemotherapy	**(ref: Responder)**	**4.04**	**3.08–5.29**	**<0.001**

Note: Bolded factors indicate significance within our univariate analysis. Factors that were significant predictors of survival within the final multivariate analysis were age, optimal surgery, cycles of chemotherapy, neoadjuvant chemotherapy, and response to chemotherapy.

Abbreviation: CI, confidence interval.

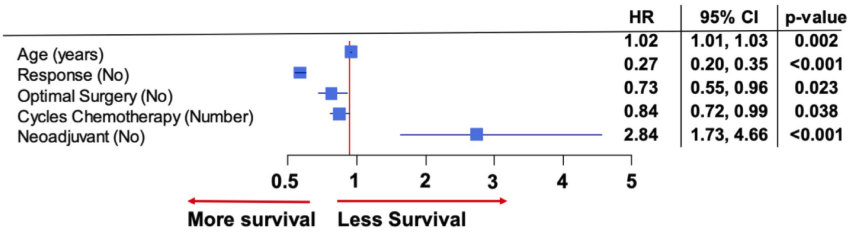


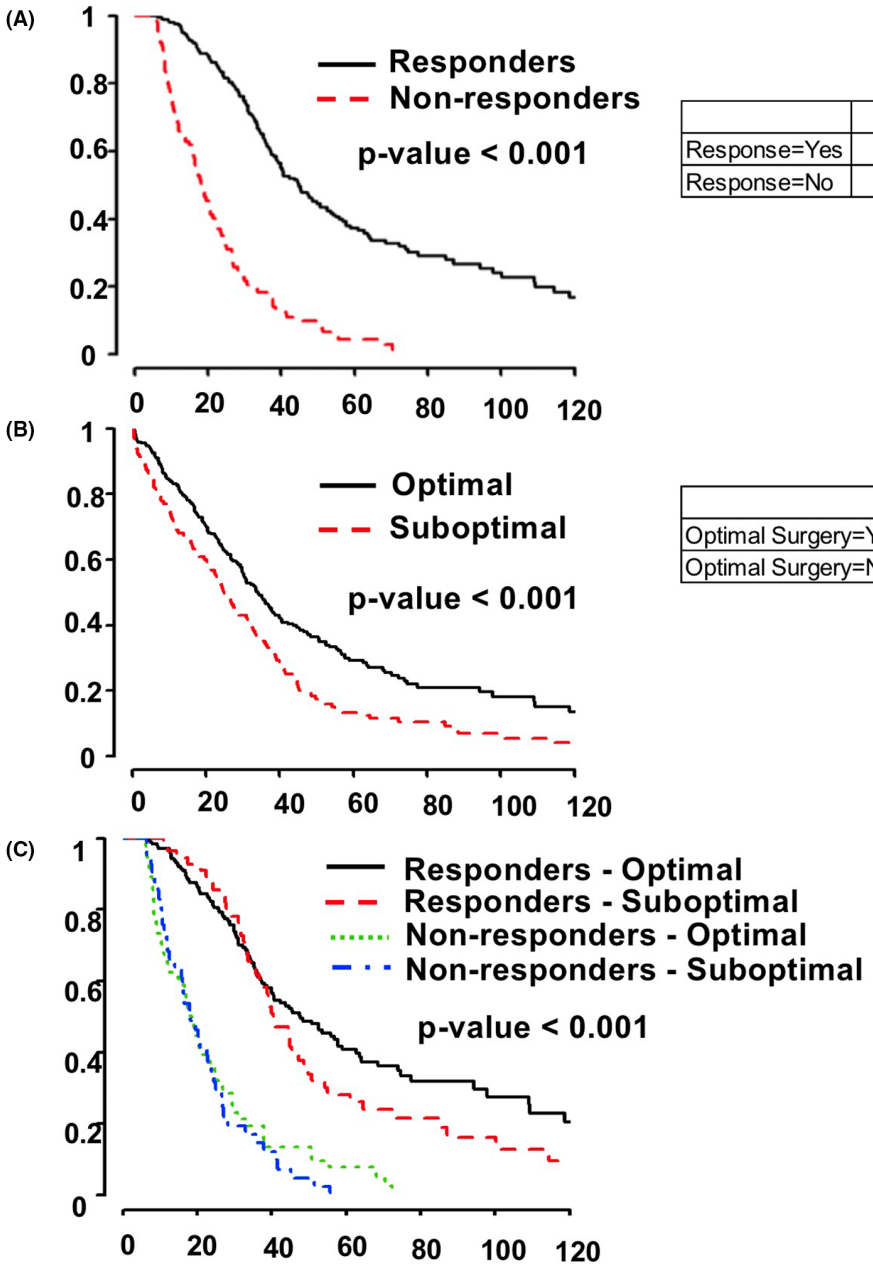
FIGURE 2 Multivariate cox proportional hazard model survival analysis. Significant variables in the survival univariate analysis ($p < 0.05$) were introduced in the multivariate analysis. The complexity index score was used to synthesize all surgical procedures in a single score. Figures in parentheses are reference values for the variables, eg the older the patient, the less survival. Patients who had suboptimal surgery and did not respond to chemotherapy had shorteer survival. Patients with more cycles of chemotherapy (up to six) had longer survival. CI, confidence interval; HR, hazard ratio.

were constructed (Figure 3). OS was 44.8 months for responders, 18.1 months for nonresponders ($p < 0.001$), 34.2 months for patients receiving optimal CRS, and 24.8 months for those receiving suboptimal CRS ($p < 0.001$). The survival curves for the combination of these two variables are depicted in Figure 3C.

5 | DISCUSSION

We observed, with thorough clinical data and follow-up, five independent predictors of OS in patients with advanced-stage, high-grade serous ovarian cancer. These data come from a single institution with a surgically aggressive philosophy and a preference for primary CRS when feasible. From our analysis, the strongest predictor of OS was the patient's response to chemotherapy. Patients with a disease-free interval greater than 6 months had, by far, the longest survival. This is consistent with previously published literature and lends credence to the validity of that assertion, as well as to our data.[3–5]

The survival benefit of CRS, especially complete cytoreduction, is well-established. However, the effect of surgery in the context of a patient's response to chemotherapy has only recently been a topic for investigation. In our study, by controlling for chemo-sensitivity, we further assert that surgical resection contributes to OS and is not simply a reflection of a disease process that is more amenable to treatment. In Figure 3B, the effect of optimal cytoreduction is clear. Ideally, we would have been able to also establish this fact within the nonresponder subgroup (Figure 3C), but our numbers did not allow us to make this conclusion. The survival curves within the nonresponder group in Figure 3C seem to overlap, but we must be cautious in saying there is no benefit because of the very small number of events in this cohort. Therefore, we can only draw conclusions



	n	events	median	95% CI
Response=Yes	233	157	44.8	39.9, 52.6
Response=No	98	95	18.1	16.1, 22.7

	n	events	median	95% CI
Optimal Surgery=Yes	268	193	34.2	30.1, 38.8
Optimal Surgery=No	128	117	24.8	21, 32.5

FIGURE 3 Survival curves for response to chemotherapy and optimal cytoreduction. Kaplan–Meier survival curves representing overall survival in responders vs nonresponders (A), optimal CRS vs suboptimal CRS (B), and the two groups combined (C). Overall survival was significantly improved by both response to chemotherapy and optimal CRS. In (C), the *p*-value demonstrating the overall effect of optimal CRS on survival was significant, with $p < 0.001$. However, with only 18 events in the subgroup analysis of nonresponders, we were unable to perform an adequate assessment of whether or not the benefit holds in this subgroup. CI, confidence interval; CRS, cytoreductive surgery.

from the study cohort as a whole and say that optimal cytoreduction improves OS independent of chemotherapy response. We believe that this was an important point to establish within the cytoreductive literature, especially in the context of someday being able to predict a patient's response to chemotherapy upon initial diagnosis. Should that ability be realized, the predicted response to chemotherapy would not prohibit proceeding with surgical cytoreduction.

A recent retrospective study by Liu et al. presented data regarding patients who received neoadjuvant chemotherapy but did not then undergo interval CRS.[18] In this cohort, the primary reason given for 39% of the patients to not undergo CRS was inadequate response to chemotherapy. The type of response to chemotherapy within these patients included platinum-refractory disease, stable or mixed response, and a positive response to chemotherapy that was still inadequate for CRS. It was reported that the burden of disease was considered too great to proceed with CRS in these patients. If this is the case, then proceeding with suboptimal debulking likely does not benefit the patient. However, if an optimal or complete cytoreduction is possible, even if the patient had a poor response to chemotherapy, then CRS should

be undertaken as it is independently beneficial for OS. In practice, we are aware that patients are not always offered CRS if their response to chemotherapy is poor, based on an assumption that CRS does not benefit these nonresponders. In a post-hoc analysis of ICON8, the objective response to chemotherapy in patients with advanced ovarian cancer was assessed using RECIST 1.1 criteria and then compared with cytoreduction rates. There was no correlation between the response to chemotherapy and the ability to predict an optimal or complete cytoreduction.[16] Additionally, a retrospective analysis assessing the effect of optimal or complete cytoreduction in patients with stable or progressive disease after neoadjuvant chemotherapy concluded that the amount of residual disease at the conclusion of surgery was correlated with OS.[19] Our study was underpowered to investigate the specific subgroup of neoadjuvant chemotherapy, but the benefit of cytoreduction was independent of neoadjuvant status. It should also be noted that platinum sensitivity and an interval radiologic response to chemotherapy are different outcomes, as one can only be assessed in retrospect. However, given the dearth of data on this topic, it is useful as a potential correlary. Therefore, based on this information and our results, an optimal surgery seems to be beneficial regardless of chemotherapy response. If a patient does not respond well to platinum-based chemotherapy, then the strongest improvement in their survival will be obtained via an optimal CRS, if feasible.

The other three factors identified within our analysis were of varying levels of significance. Age has long been known to be negatively correlated with OS, though the strength of its association was weak in our analysis. It is also a nonmodifiable risk factor, which is clouded by the increased comorbidities within an elderly population and alterations in treatment regimens based on patient age. Patients who received at least 6 cycles of chemotherapy had an improved OS compared with those who received fewer than 6 cycles. However, only seven patients received fewer than 6 cycles in both the optimal and the suboptimal groups, providing little power for such a conclusion. Lastly, the patients who received neoadjuvant chemotherapy had a significantly poorer OS, but this is almost certainly due to selection bias in a retrospective cohort study, reflecting a greater disease burden or poorer functional status in these patients. Multiple randomized, prospective trials have confirmed that neoadjuvant chemotherapy does not present inferior outcomes to post-CRS chemotherapy.[13–15]

The strengths of our study are that we assessed a large cohort of patients at a single institution with a consistent, aggressive surgical approach. Thorough clinical data with at least 6 months of follow-up were available for all patients. The dataset was large enough to perform a multivariate analysis, isolating each variable to assess the independent impact on survival.

The greatest weakness of this study is its retrospective nature. As such, it suffers from selection bias, which is likely the reason neoadjuvant chemotherapy showed such a strong correlation with poorer OS. Patients selected for neoadjuvant chemotherapy typically have poorer functional status and greater overall disease burden. Additionally, 17% of patients undergoing surgery at our institution for advanced-stage, high-grade serous carcinoma had inadequate follow-up data and were excluded from our analysis. It is possible that this inadequate follow-up was because of a poorer outcome and therefore skewed our data. We were also unable to stratify optimal CRS by residual disease volume (R1 vs R0) because of the long timeframe over which patient data were collected. R0 has only recently increased in importance within high-grade serous carcinoma literature, so it was inconsistently documented in our cohort. Additionally, the introduction of novel therapeutics such as poly (ADP-ribose) polymerase (PARP) inhibitors, especially for patients with *BRCA* mutations and homologous recombination deficiency have changed the treatment paradigms in recent years. During the data collection period for this study, germline *BRCA* testing was not necessarily routine and PARP inhibitors were not a part of treatment. It is unclear how this may have affected our results, but the absence of this information in this study is notable in the context of the modern literature landscape.

Lastly, as mentioned, our study was underpowered to determine a difference in patients who received neoadjuvant chemotherapy followed by optimal or suboptimal CRS because of our institution's preference for primary cytoreduction. This specific subpopulation was better investigated in the retrospective analysis by Nitecki et al., who showed an improvement in OS with decreasing postoperative disease burden.[19] Future studies should isolate this group to more thoroughly assess the impact of cytoreduction.

6 | CONCLUSION

Patients derive significant benefit from optimal or complete CRS. This is true regardless of their response to chemotherapy. Therefore, the decision to proceed with CRS should be based solely on the ability to achieve complete or optimal cytoreduction and a patient's fitness for planned procedures. A patient's observed or predicted response to chemotherapy should not be a factor. Future studies should focus on the population of patients who receive neoadjuvant chemotherapy with a poor radiologic response to clearly determine whether there is a benefit for CRS in these patients.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this manuscript. In addition, JG-B was the principal investigator, providing conceptualization, supervision, methodology, and analysis. Funding was acquired by JG-B and MG. ED contributed to the methodology and supervision. MG contributed to supervision.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Howlader N, Noone A, Krapcho M. SEER Cancer Statistics Review 1975–2016. 2019
2. Ovarian Cancer [updated Version 2.2020; cited 2021 November 15]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pd
3. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol*. 2002;20:1248-1259.
4. Hunter RW, Alexander ND, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis? *Am J Obstet Gynecol*. 1992;166:504-511.
5. Venesmaa P. Epithelial ovarian cancer: impact of surgery and chemotherapy on survival during 1977–1990. *Obstet Gynecol*. 1994;84:8-11.
6. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. *Gynecol Oncol*. 2013;130:493-498.
7. Rodriguez N, Miller A, Richard SD, et al. Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of gynecologic oncology group (GOG) 182. *Gynecol Oncol*. 2013;130:487-492.
8. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol*. 2006;103:1083-1090.
9. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol*. 1994;170:974-979. discussion 79-80.
10. Winter WE 3rd, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*. 2008;26:83-89.
11. Angeles MA, Cabarrou B, Gil-Moreno A, et al. Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer. *J Gynecol Oncol*. 2021;32:e78.
12. Wright AA, Bohlke K, Armstrong DK, 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;34:3460-3473.
13. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet*. 2015;386:249-257.
14. Fagotti A, Ferrandina G, Vizzielli G, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59:22-33.
15. Vergote I, Coens C, Nankivell M, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *Lancet Oncol*. 2018;19:1680-1687.
16. Morgan RD, McNeish IA, Cook AD, et al. Objective responses to first-line neoadjuvant carboplatin-paclitaxel regimens for ovarian, fallopian tube, or primary peritoneal carcinoma (ICON8): post-hoc exploratory analysis of a randomised, phase 3 trial. *Lancet Oncol*. 2021;22:277-288.
17. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol*. 2007;197(676):e1-e7.
18. Liu YL, Filippova OT, Zhou Q, et al. Characteristics and survival of ovarian cancer patients treated with neoadjuvant chemotherapy but not undergoing interval debulking surgery. *J Gynecol Oncol*. 2020;31:e17.
19. Nitecki R, Fleming N, Fellman B, et al. Partial response or stable disease after neoadjuvant chemotherapy for advanced ovarian cancer: time for surgery or more chemotherapy? *Gynecol Oncol*. 2021;162:S54.

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