Impact of residual disease at interval debulking surgery on platinum resistance and patterns of recurrence for advanced-stage ovarian cancer

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HIGHLIGHTS

- Size and distribution of residual disease after interval debulking surgery does not impact location of recurrence
- Multiple locations of 'optimal' disease after interval debulking surgery portend a short progression-free interval
- Patients with multiple locations of 'optimal' disease after interval debulking surgery have an elevated risk of platinum resistance

ABSTRACT

Objective To evaluate the impact of size and distribution of residual disease after interval debulking surgery on the timing and patterns of recurrence for patients with advanced-stage epithelial ovarian cancer.

Methods Patient demographics and data on disease treatment/recurrence were collected from medical records of patients with stage IIIC/IV epithelial ovarian cancer who were managed with neoadjuvant chemotherapy/interval debulking surgery between January 2010 and December 2014. Among patients without complete surgical resection but with ≤1 cm of residual disease, the number of anatomic sites (<1 cm single anatomic location vs <1 cm multiple anatomic locations) was used to describe the size and distribution of residual disease.

Results A total of 224 patients were included. Of these, 70.5% (n=158) had a complete surgical resection, 12.5% (n=28) had <1 cm single anatomic location, and 17.0% (n=38) had <1 cm multiple anatomic locations. Two-year progression-free survival for complete surgical resection, <1 cm single anatomic location, and <1 cm multiple anatomic locations was 22.2%, 17.9% and 7%, respectively (p=0.007). Size and distribution of residual disease after interval debulking surgery did not affect location of recurrence and most patients had recurrence at multiple sites (complete surgical resection: 64.7%, <1 cm single anatomic location: 55.6%, and <1 cm multiple anatomic locations: 71.4%). Controlling for additional factors that may influence platinum resistance and surgical complexity, the rate of platinum-resistant recurrence was similar for patients with complete surgical resection and <1 cm single anatomic location (OR=1.07, 95% CI 0.40 to 2.86; p=0.888), but women with <1 cm multiple anatomic locations had an increased risk of platinum resistance (OR=3.09, 95% CI 1.41 to 6.78 p=0.005).

Conclusions Despite current classification as 'optimal,' <1 cm multiple anatomic location at the time of interval debulking surgery is associated with a shorter progression-free survival and increased risk of platinum resistance.

INTRODUCTION

Epithelial ovarian cancer is the seventh most common diagnosis of cancer among women worldwide.[1] Most women with ovarian cancer are not diagnosed until it has reached an advanced stage. More than two-thirds of women with epithelial ovarian cancer present with at least stage III disease.[1] As a result, ovarian cancer is the most lethal gynecologic malignancy, with 13 770 deaths in 2021.[2]

Poor prognostic factors help to focus on potential targets for disease treatment. For ovarian cancer, many of the established poor prognostic factors (age, histology, and performance status) are non-modifiable.[3] Residual tumor volume at the time of debulking surgery is the only modifiable prognostic factor for ovarian cancer.[3] Complete surgical resection is associated with improved progression-free survival and overall survival, compared with residual macroscopic residual disease after debulking surgery.[3] As such, the goal of both primary and interval debulking surgery is complete surgical resection.[3 4]

However, when complete surgical resection cannot be achieved, minimal residual disease is also associated with improvement in overall survival for patients undergoing primary debulking surgery.[4] Chi et al showed an incremental improvement in overall survival with low-volume residual disease at the time of primary debulking surgery, as patients with complete surgical resection had median survival of 106 months compared with 66 months for those with <5 mm residual disease and 48 months for those with 6–10 mm of residual disease.[4] Manning-Geist et al built on this work to show that survival among patients deemed 'optimal' after primary debulking surgery can vary by the size and distribution of residual disease.[5] Small volume disease confined to a single anatomic location had improved survival

compared with multiple anatomic locations of small volume disease at the time of primary debulking surgery.[5]

Interval debulking surgery has been established as an alternative treatment for women with stage IIIC/IV disease thought to be at high risk of peri-operative morbidity and/or with low likelihood of achieving optimal residual disease if primary cytoreductive surgery were to be undertaken prior to initiation of chemotherapy.[6 7] Traditional surgical goals for interval debulking surgery were established from literature on goals for primary debulking surgery. Similar to primary debulking surgery, patients undergoing interval debulking surgery with complete surgical resection have better outcomes than patients with so-called optimal (<1 cm) residual disease following debulking.[8 9] Recent work from our group has suggested that the relationship between volume of residual disease and survival at the time of interval debulking surgery mirrors that of the relationship between volume of residual disease and survival found at primary debulking surgery,[10] as patients with complete surgical resection at interval debulking surgery had a 58-month overall survival compared with 37 months with <1 cm single location disease and 26 months with <1 cm multiple location disease.[10]

This investigation seeks to further elucidate these results by evaluating the impact of size and distribution of residual disease after interval debulking surgery with respect to timing and patterns of recurrence and rates of platinum resistance for patients with advanced stage epithelial ovarian cancer.

METHODS

After obtaining institutional review board approval, a retrospective chart review was conducted for all patients at Brigham and Women's Hospital and Massachusetts General Hospital undergoing interval surgery for advanced stage (FIGO stage IIIC/IV) epithelial ovarian/fallopian tube/primary peritoneal carcinomas between January 2010 and December 2014 with follow-up data collected through March 31, 2019. The study design, outcomes, and statistical methods for this work are similar to those previously published regarding the impact of volume of residual disease on overall survival.[10] Patients were excluded from this study if they underwent primary debulking surgery. They were also excluded if they had non-epithelial histology or low-grade serous histology, or if the location/volume of residual disease was not documented in their operative report, or their medical records were incomplete. We excluded suboptimally debulked patients given the difficulty of delineating the timing of progression/recurrence with disease that was resistant both to chemotherapy and to debulking surgery. Decision to undergo primary debulking surgery or interval debulking surgery was made by the primary surgeon after evaluation of disease burden and fitness for radical surgery. During the study period, diagnostic laparoscopy was not routinely used to evaluate disease burden. Rather, evaluation of the initial disease burden was based on physical examination and CT imaging of the chest, abdomen, and pelvis. Patients with multiple liver/lung metastases and/or who were felt to be at high risk of being suboptimally debulked with an attempt at primary debulking surgery were triaged to neoadjuvant chemotherapy. The primary surgeon ultimately determined if a patient was fit for radical surgery. Assessment was influenced by the patient's performance status and nutritional status. Neoadjuvant chemotherapeutic regimens were platinum- and taxane-based and administered according to standardized protocols during the study period. The intent of neoadjuvant treatment was three to four cycles of chemotherapy prior to interval debulking surgery. After completion of three to four cycles of chemotherapy, patients underwent imaging to determine the likelihood of resectability. If deemed unresectable, patients received additional cycles of upfront chemotherapy. All surgical procedures were performed with the goal of complete surgical resection or optimal debulking (<1 cm maximal diameter of largest residual tumor nodule) when complete surgical resection was not possible. Surgical procedures were assigned a complexity score reflecting the difficulty and number of procedures performed as described previously by Aletti et al.[11] The surgical complexity score was used as a proxy for the volume of disease on entry for interval debulking surgery. Post-operatively, patients were treated with at least three cycles of additional chemotherapy.

Patients were classified into three groups based on volume and distribution of residual disease at the completion of interval debulking surgery as previously described by Manning-Geist et al.[5 10] Patients with complete surgical resection of disease were classified as such. Those with remaining disease with maximal diameter of largest residual tumor nodule $\leq$1 cm were classified into two groups according to the number of anatomic locations of disease:<1 cm single location of disease and <1 cm multiple locations of disease. In cases where multiple tumor nodules involving a single anatomic location were present, this was coded as <1 cm single location given the difficulty defining a measurable volume of disease in this setting. For example, a patient with a single location of $\leq$1 cm disease on the bowel mesentery was coded as <1 cm single location. Similarly, a patient with multiple $\leq$1 cm nodules on the bowel mesentery was coded as <1 cm single location because the bowel mesentery was one of our predefined anatomic locations. Anatomic locations included diaphragm, upper abdomen (excluding the diaphragm), pelvis, bowel serosa, bowel mesentery, pelvic and/or para-aortic lymph nodes, and abdominal peritoneum.[5 10]

Patients were then followed up through March 31, 2019 for evidence of progression/recurrence or death. Recurrence/progression was defined as either physician documented evidence of recurrence or a rising CA125, and radiologist documented evidence of new disease on follow-up imaging. Imaging reports from the date of recurrence were reviewed, and the location of recurrence was documented with the same anatomic location categories as described above, with additional categories for liver, lungs, thorax, brain, ascites, and pleural effusion. Progression-free survival was defined as the number of months between the date of initiation of chemotherapy and either disease progression or death. Platinum resistance was defined as the diagnosis of recurrent disease less than 6 months after completion of the final cycle of chemotherapy. Overall survival was defined as the number of months between the date of initiation of chemotherapy and death from any cause. Patients alive and progression-free or alive with disease were censored for progression-free survival and overall survival, respectively, at the date of last follow-up.

Differences in clinical, surgical, and histopathologic factors among these three patient groups were examined with the X^2 test and Student's t-test, where appropriate. Two-year progression-free survival was calculated using the Kaplan-Meier method. Cox proportional hazards models were used to compare risks of

Table 1 Patient demographics and clinical characteristics

Characteristics	Complete surgical resection (n=158)	≤1 cm single location (n=28)	≤1 cm multiple locations (n=38)	P value
	Median (range)	Median (range)	Median (range)	
Age	64.5 (39–89)	66 (34–82)	66 (47–83)	0.918
Body mass index (BMI)	24.7 (17.3–45.2)	24.6 (16.9–42.5)	25.3 (16.1–39.8)	0.843
	Number (%)	Number (%)	Number (%)	
Ethnicity				0.683
Asian	6 (3.8)	0 (0)	1 (2.6)	
Black	3 (1.9)	1 (3.6)	0 (0)	
Hispanic	2 (1.3)	1 (3.6)	1 (2.6)	
Other	1 (0.6)	0 (0)	0 (0)	
Unknown	5 (3.2)	2 (7.1)	4 (10.5)	
White	141 (89.2)	24 (85.7)	32 (84.2)	
Charlson Comorbidity Index				0.59
Low (0–1)	17 (10.8)	4 (14.3)	2 (5.3)	
Intermediate (2–3)	79 (50)	12 (42.9)	23 (60.5)	
High (≥4)	62 (39.2)	12 (42.9)	13 (34.2)	
Stage				0.679
IIIC	91 (57.6)	14 (50)	23 (60.5)	
IV	67 (42.4)	14 (50)	15 (39.5)	
Histologic type				0.225
Serous	149 (94.3)	25 (89.3)	37 (97.4)	
Endometrioid	2 (1.3)	0 (0)	0 (0)	
Carcinosarcoma	3 (1.9)	0 (0)	1 (2.6)	
Clear cell	1 (0.6)	0 (0)	0 (0)	
Mixed	2 (1.3)	3 (10.7)	0 (0)	
Mucinous	1 (0.6)	0 (0)	0 (0)	
Histologic grade				0.631
1	0 (0)	0 (0)	0 (0)	
2	5 (3.2)	0 (0)	1 (2.6)	
3	153 (96.8)	28 (100)	37 (97.4)	

development of platinum resistance. Multivariate analysis models were built with development of platinum resistance as the outcome of interest. Factors included in the model were age, stage, number of pre-operative chemotherapy cycles, pre-operative CA125 >35, and platinum exposure. Multivariate analysis models also included surgical complexity score as a proxy for volume of disease encountered on entry to the abdomen. A p value <0.05 was considered statistically significant. The SPSS version 20.0 statistical package was used for all statistical analyses.

RESULTS

A total of 224 women with FIGO stage IIIC and IV epithelial ovarian cancer were managed with neoadjuvant chemotherapy followed by interval debulking surgery at either Brigham and Women's Hospital or Massachusetts General Hospital. Table 1 displays the patient demographics and clinical characteristics of the study population. The three volume of residual disease groups were similar with respect to age, BMI, race, Charlson Comorbidity Index, histology, and stage of disease at presentation. Table 2 displays peri-operative treatment characteristics. Residual disease groups were similar with respect to CA125 at diagnosis, number of pre-operative chemotherapy cycles, pre-operative CA125, and number of post-operative chemotherapy cycles. However, patients who achieved complete surgical resection were more likely to have a low surgical complexity score than those with <1 cm single location and <1 cm multiple locations (70.9% vs 46.4% vs 47.4%; p=0.002), implying that they may have had improved response to neoadjuvant chemotherapy and less disease on entry for interval debulking surgery.

As previously published,[12] the rate of optimal cytoreduction (≤1 cm of residual disease) during the study period was 94.1%. For the purpose of the current study, patients who were suboptimally debulked were excluded from analysis (please refer to Methods). A total of 158 (70.5%) patients were classified as having had complete surgical resection at the time of their interval debulking surgery. For patients with ≤1 cm of gross residual disease, the number of anatomic locations was used as a proxy for volume of residual disease. In this cohort, 28 patients (12.5%) had <1 cm single location disease and 38 (17.0%) had <1 cm multiple

Table 2 Treatment characteristics

Treatment characteristics	Complete surgical resection (n=158) Median (range)	≤1 cm single location (n=28) Median (range)	≤1 cm multiple locations (n=38) Median (range)	P value
CA125 at diagnosis	783.5 (14.8–17,000)	771 (56.3–83,220)	943 (63–17,200)	0.566
Number of pre-operative cycles (median)	3 (2–9)	3 (3–7)	3 (2–6)	0.784
Pre-operative CA125	39 (3.6–4273)	67 (6–28,298)	53.1 (7.3–633)	0.159
	Number (%)	**Number (%)**	**Number (%)**	
>3 Cycles of pre-operative chemotherapy	68 (43)	10 (35.7)	18 (47.4)	.637
Pre-operative CA125 >35	81/150 (54)	18/27 (66.7)	24/36 (66.7)	0.233
Surgical complexity score				0.002
Low (1–3)	112 (70.9)	13 (46.4)	18 (47.4)	
Moderate (4–7)	42 (26.6)	11 (39.3)	15 (39.5)	
High (>7)	4 (2.5)	4 (14.3)	5 (13.2)	
Number of post-operative cycles, median (range)	3 (0–6)	3 (0–4)	3 (2–10)	0.557

locations disease . As previously published,[12] the most common sites of residual disease among those with <1 cm single location disease were the diaphragm, the bowel mesentery, and the pelvis.

Table 3 summarizes patterns of recurrence based on the volume of residual disease at the conclusion of interval debulking surgery. Patients who achieved complete surgical resection were more

Table 3 Patterns of recurrence

	Complete surgical resection Number (%)	<1 cm single location Number (%)	<1 cm multiple locations Number (%)	P value
Timing of recurrence				0.005
<6 months	34 (21.5)	7 (25)	19 (50)	
6–12 months	61 (38.6)	13 (46.4)	12 (31.6)	
>12 months	63 (39.9)	8 (28.6)	7 (18.4)	
Site of recurrence				0.035
Upper abdomen	1 (0.7)	0 (0.0)	1 (2.9)	
Pelvis	4 (2.9)	2 (7.4)	0 (0.0)	
Bowel	4 (2.9)	0 (0.0)	1 (2.9)	
Nodal	16 (11.5)	3 (11.1)	3 (8.6)	
Bowel mesentery	0 (0.0)	2 (7.4)	0 (0)	
Abdominal peritoneum	14 (10.1)	2 (7.4)	3 (8.6)	
Multiple sites	90 (64.7)	15 (55.6)	25 (71.4)	
Liver	5 (3.6)	0 (0.0)	0 (0.0)	
Lungs	1 (0.7)	1 (3.7)	2 (5.7)	
Thorax	0 (0.0)	1 (3.7)	0 (0.0)	
Brain	4 (2.9)	1 (3.7)	0 (0.0)	
Site of recurrence (grouped)				0.405
Single abdominal/pelvic site	44 (31.7)	9 (33.3)	8 (22.9)	
Multiple sites	90 (64.7)	15 (55.6)	25 (71.4)	
Extra-abdominal	5 (3.6)	3 (11.1)	2 (5.7)	
Pleural effusion at recurrence	10 (7.2)	2 (7.4)	7 (20)	0.064
Ascites at recurrence	27 (19.4)	12 (44.4)	13 (37.1)	0.006

Table 4 Univariate and Multivariate analysis for platinum resistance

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age						
<65	Ref	Ref		Ref	Ref	
≥65	1.31	0.72 to 2.37	0.377	1.23	0.65 to 2.33	0.526
Stage						
3	Ref	Ref		Ref	Ref	
4	1.03	0.57 to 1.87	0.931	1.03	0.53 to 1.97	0.94
Pre-operative CA125 >35	1.57	0.84 to 2.93	0.162	1.48	0.76 to 2.88	0.246
Surgical Complexity Score						
Low (1–3)	Ref	Ref		Ref	Ref	
Moderate (4–7)	1.43	0.75 to 2.72		1.28	0.65 to 2.54	0.48
High (>7)	2	0.62 to 6.53		1.48	0.41 to 5.27	0.549
Residual disease						
Complete surgical resection	Ref	Ref		Ref	Ref	
<1 cm single location	1.22	0.48 to 3.10	0.682	1.07	0.40 to 2.86	0.888
<1 cm multiple locations	3.65	1.74 to7.63	0.001	3.09	1.41 to6.78	**0.005**

likely to be without recurrence after 12 months of follow-up than those with <1 cm single location and <1 cm multiple locations, with recurrence-free rates of 39.9%, 28.6% and 18.4% (p=0.005) in each group, respectively. In addition, patients with <1 cm multiple locations had the highest rate of platinum-resistant disease (50%), when compared with those with <1 cm single location (25%) and those with complete surgical resection (21.5%) (p=0.005). There were no significant differences in the number of sites of disease at the time of recurrence regardless of volume of disease left at the time of interval debulking surgery. Importantly, however, patients with complete surgical resection were less likely to recur with ascites than patients with <1 cm single location and <1 cm multiple locations at 19.4%, 44.4%, and 37.1% for each group (p=0.006). The 2-year progression-free survival for patients with complete surgical resection, <1 cm single location, and <1 cm multiple locations was 22.2%, 17.9%, and 7%, respectively (p=0.007).

On univariate analysis, the volume of residual disease influenced the risk of platinum resistance. Compared with complete surgical resection, <1 cm multiple locations was associated with an increased risk of platinum resistance (OR=3.65, 95% CI 1.74 to 7.63; p=0.001), although <1 cm single location was not associated with an increased risk (p=0.68) (Table 4). Multivariate analysis of factors related to platinum resistance was then conducted. Based on the assumption that response to presurgery chemotherapy would influence the risk of platinum resistance, surgical complexity was included in this model as a surrogate for remaining disease after presurgical chemotherapy. On multivariate analysis (controlling for age, stage, surgical complexity, and platinum exposure defined as the number of pre-operative cycles of chemotherapy), the volume of residual disease was the only factor associated with an increased risk of platinum resistance. Specifically, patients with <1 cm multiple locations were associated with a threefold increased risk of platinum resistance compared with complete surgical resection (OR=3.09, 95% CI 1.41 to 6.78; p=0.005) (Table 4).

DISCUSSION

Summary of Main Results

Groups with one location of <1 cm disease and multiple locations of <1 cm disease have traditionally been considered together as an optimally cytoreduced cohort, but this study demonstrates key differences between these groups both in recurrence and platinum resistance. Patients with multiple locations of optimally reduced disease have increased rates of platinum resistance, defined as tumor progression within 6 months of completion of prior platinum therapy, in comparison with patients with a single location of optimally reduced disease, for whom rates of platinum resistance resemble those of patients with no evidence of disease at the end of interval debulking surgery.[13]

Results in the Context of Published Literature

Platinum resistance indicates a short interval between treatment completion and recurrence and also implies more resistant and aggressive disease. Patients with platinum-resistant ovarian cancer have less than 15% likelihood of a meaningful response to subsequent chemotherapy and have a median survival of 9–12 months compared with 2 years for patients with platinum-sensitive ovarian cancer.[14] Genome wide mutations, alterations in P53, and epigenetic changes have all been identified as possible molecular pathways to platinum resistance.[15–17] Prior studies have also implicated advanced stage, poor differentiation, and elevated initial CA125 >1000 as clinical risk factors for platinum resistance.[18 19]

Given previously described risk factors, we conducted multivariate analysis of platinum resistance, controlling for age, stage, number of pre-operative chemotherapy cycles, pre-operative CA125 >35, and platinum exposure. Finally, we controlled for surgical complexity score as a proxy for volume of disease encountered on entry to the abdomen. We found a statistically significant association between platinum resistance and <1 cm multiple locations disease in comparison with complete surgical resection. In

contrast, patients with <1 cm single location and complete surgical resection had similar rates of platinum resistance. The findings in this study may provide an explanation for the previously described differences in overall survival after interval debulking surgery for patients with <1 cm multiple locations disease in comparison with <1 cm single location disease.[10] Importantly, despite implications for recurrence-free survival and platinum resistance, the size and distribution of residual disease after interval debulking surgery do not impact distribution of disease at the time of recurrence, with most patients recurring at multiple abdominal/pelvic sites regardless of volume of disease left at the time of interval debulking surgery.

Few of the previously described risk factors for platinum resistance—clinical or genetic—are modifiable with current treatments. This study suggests that the volume of disease left at the time of interval debulking surgery is a potentially modifiable risk factor that is independently associated with platinum resistance. These findings are consistent with recent data suggesting that the presence of positive washings after intravenous/intra-peritoneal chemotherapy increases platinum resistance, in acknowledgment that residual disease does affect rates of platinum resistance.[20] We propose that the volume of residual disease is an immediately modifiable risk factor for platinum resistance and should be considered in the development of treatment plans and surgical planning for patients with advanced-stage epithelial ovarian cancer.

Strengths and Weaknesses

The strengths of this study include a large sample size and long period of follow-up. However, the current study is not without limitations. Given the retrospective nature of this study, there is a reliance on complete and accurate medical records. This opens the possibility of inter-observer variability in reporting location and dimension of residual tumors. We dealt with this limitation by cross-validating rater scoring for volume and location of residual disease. In addition, complete description of the initial disease burden encountered on entry for interval debulking surgery varied in the operative report. Disease burden prior to interval debulking surgery is an important factor that has the potential to reflect response to presurgery chemotherapy and influence residual disease and survival. While the surgical complexity score was used as a proxy for disease burden encountered on entry for interval debulking surgery, the absence of a direct assessment of the initial disease burden has the potential to limit study conclusions.

We must also note that our sample size was not evenly distributed between groups. The sample sizes for the <1 cm single location and <1 cm multiple locations disease patient groups were small, so our study may have been underpowered to detect differences between these groups. Finally, the results of this study may not be generalizable to all patient populations because it was conducted at two large academic institutions, with a relatively homogeneous (87.9% white) patient population.

Implications for Practice and Future Research

The identified association of the <1 cm multiple locations with platinum resistance also identifies a population for further exploration of the molecular/genetic and clinical basis for platinum resistance. Further studies should explore potential differences between the <1 cm single location population and the <1 cm multiple locations population to identify additional risk factors for platinum resistance and examine whether a more aggressive surgical approach, with a higher percentage of patients achieving complete surgical resection or <1 cm single location, improves rates of platinum resistance and survival.

CONCLUSIONS

The volume of residual disease after interval debulking surgery may serve as a modifiable risk factor for platinum resistance. Increased rates of platinum resistance in the <1 cm multiple location population may help to explain the previously described survival benefit for the achievement of <1 cm single location disease in comparison with <1 cm multiple locations disease. This suggests that surgical effort should seek to achieve complete surgical resection. However, when complete surgical resection is not possible, every effort should be made to minimize the volume of residual disease as <1 cm multiple locations are associated with inferior survival and an increased risk of platinum resistance.

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