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Case series

Complete surgical resection of isolated recurrent high-grade epithelial ovarian cancer in highly selected patients without chemotherapy is associated with an excellent outcome

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ABSTRACT

The purpose of this study was to determine the outcome for patients with recurrent ovarian cancer treated with surgical resection alone. Consecutive patients were identified who had complete resection of a surgically isolated metastasis of recurrent high-grade ovarian cancer between 1/2006 and 1/2018 who did not receive adjuvant chemotherapy. Eight such patients were identified. The mean age was 54.4 yrs (range, 46.1–62.9 yrs). Six of the 8 patients (75%) had a complete resection at initial surgery and all but one (88%) were initially treated with intraperitoneal chemotherapy. The median time from completion of primary chemotherapy to recurrence was 38.7 mo (14.4–96.4 mo). Sites of recurrence included lymph nodes ($n = 2$), spleen ($n = 1$), and peritoneal cavity ($n = 5$). Minimally invasive surgical techniques were used in 7 of the 8 patients. Mean progression-free survival after secondary surgery was 19.8 mo (95% CI, 15.8-N.R.) and mean overall survival was 64.8 mo (95% CI, 54.6-N.R.). With a median follow-up of 65.2 months (23.3–84.6 mo) from the secondary resection, 4 of 8 patients remain without evidence of recurrence. Only 1 of the 5 patients with peritoneal recurrence remains disease-free. All 4 patients in remission have a post-resection time longer than the time from initial treatment to the surgery for recurrence. This study finds that it may be reasonable to omit chemotherapy in highly selected patients after complete secondary surgical resection. Resection of isolated recurrences can be accomplished with minimally invasive surgery, and these patients have an excellent prognosis. Non-peritoneal recurrences may have a better prognosis after secondary surgery.

1. Introduction

Epithelial ovarian cancer is the leading cause of death from gynecological malignancy. In 2018, there were approximately 22,240 new cases and 14,070 deaths from ovarian cancer in the United States (Siegel et al., 2018). When treated with a combination of surgery and chemotherapy, the majority of patients achieve a complete clinical remission. Although remissions can be permanent, the vast majority of patients ultimately develop recurrent disease and require additional treatment.

The role of secondary surgical resection is controversial, but some studies have shown a survival advantage to secondary cytoreductive surgery with complete resection in patients who recurred > 6 months after completing initial chemotherapy (Du Bois et al., 2017). Factors associated with successful secondary surgery include complete primary resection, lack of significant ascites, and good performance status (Harter et al., 2009; Harter et al., 2011).

In studies of secondary cytoreductive surgery, most patients are treated with adjuvant chemotherapy after secondary surgery, even in the absence of remaining disease. While the frequency of subsequent recurrence makes adjuvant therapy tempting, there are no data that demonstrate benefit of adjuvant therapy over active surveillance after complete surgical resection of recurrent cancer. To investigate this issue, we reviewed our experience in patients with a complete surgical resection who were not treated with chemotherapy.

2. Materials and methods

The purpose of this study was to determine the outcome for patients with isolated recurrent ovarian cancer who were treated with surgical resection alone. This retrospective study was conducted with IRB approval. The records of all patients who had surgery for ovarian cancer

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from 1/1/2006 to 1/1/2018 were reviewed. Patients were included if they had recurrent high grade epithelial ovarian cancer, had achieved a complete remission after primary surgery and chemotherapy, had a radiologically verified recurrence, underwent a surgery to remove the recurrent cancer in which the disease was completely resected, and did not receive chemotherapy following the surgery. Demographic information and clinical documentation were reviewed to help determine patient outcome. Progression-free survival (PFS) was the primary outcome. This was calculated from the date of secondary or tertiary surgical cytoreduction to the date of clinical or radiologically verified recurrence or last follow-up. Overall survival (OS) was calculated from the secondary or tertiary surgery to the date of death or last follow-up. Data were analyzed with JMP 14.0.0 (SAS Institute, Cary, NC) and survival curves were generated using the methods of Kaplan and Meier (1958).

3. Results

During the study period we identified 796 patients who had primary surgery for ovarian cancer. Overall, 56 patients of these patients underwent secondary surgery for recurrence. Secondary surgical cytoreduction was at the discretion of the attending surgeon and considered in patients who had platinum-sensitive recurrent ovarian cancer, minimal residual disease after primary surgery, no significant ascites on recurrence, and good performance status. Of the patients that had recurrent cancer, 8 were identified who had an isolated metastasis treated with surgical resection and did not receive chemotherapy following surgery. The mean age of these patients at diagnosis was 54.4 years (range, 46.1–62.9). Three patients (38%) had known deleterious germline mutations in *BRCA*. Six of the 8 patients (75%) had a complete surgical resection at the time of initial surgery, and all but one (88%) were treated with intraperitoneal (IP) chemotherapy in the upfront setting. Demographics are presented in Table 1. The decision to omit adjuvant chemotherapy was due to a surgical complication ($n = 1$), poor tolerance of upfront chemotherapy ($n = 1$), or preference for close follow-up instead of additional chemotherapy in the setting of a CA-125 that returned to baseline value and was < 10 U/ml ($n = 6$).

The median time between last chemotherapy treatment and recurrence prompting surgical resection was 38.7 months (range, 14.4–96.4). The site of recurrent disease included lymph nodes ($n = 2$), spleen ($n = 1$), and peritoneum ($n = 5$). This was the first recurrence in 6 of the 8 patients (75%) and the second recurrence in 2 of the 8 patients (25%). Secondary surgery included laparoscopy ($n = 6$), hand-port assisted surgery ($n = 1$) and laparotomy ($n = 1$). The mean PFS after secondary resection was 19.8 months (95% CI, 15.8-N.R.). The mean OS was 64.8 months (95% CI, 54.6-N.R.). With a median follow-up of 65.2 months from the secondary resection, 4 of 8 patients remain without evidence of recurrence (range, 23.3–84.6 months). In the 4 patients who did not recur after secondary surgery, the disease-free interval after secondary surgical resection was longer than the first disease-free interval. Only 1 of the 5 patients (20%) with a peritoneal recurrence remains disease-free. The mean PFS interval for the peritoneal recurrences was 18.8 months (95% CI, 15.8-N.R.), which was significantly shorter than that of the non-peritoneal recurrences ($P = 0.05$).

Six of the 8 patients had a CA-125 that was the same or lower than the initial nadir after surgery and returned to < 10 U/ml within eight weeks of surgery. Two patients had CA-125 levels that were higher after the secondary resection than the nadir value after the primary surgery. One of these patients had a CA-125 of 28 U/ml after a nadir of 17 U/ml with a peritoneal recurrence of a clear cell ovarian cancer. She declined therapy due to poor tolerance of primary chemotherapy and recurred at 7.3 months in the liver. The other patient had a nadir of 65 U/ml after surgery for a peritoneal recurrence of endometrioid ovarian cancer. Her surgery was complicated by a fascial dehiscence and she did not receive subsequent chemotherapy. She recurred in the peritoneal cavity in 15.7 months.

Table 1
Clinical parameters at the time of initial cancer diagnosis and treatment, tumor histology, details of recurrence, and patient outcomes ($n = 8$).

	FIGO Stage	Histology	Primary resection	Chemo type	BRCA germline status	CA125 at diagnosis	CA125 nadir	Recurr. site	Recurrence surgery	CA125 after surgery	Status	PFS (months)	OS (months)
1	IIIC	Serous	Complete	IP	Wild type	206	9	Nodal	Groin dissection	6	Disease free	84.6[a]	84.6[a]
2	IIA	Serous	Complete	IP	Wild type	362	4	Peritoneum	Laparoscopy	4	Disease free	23.3[a]	23.3[a]
3	IIC	Clear cell	Optimal[b]	IP	Wild type	1282	7	Peritoneum	Laparoscopy	7	Recurred	21.5	23.2[a]
4	IIIC	Serous	Optimal[b]	IP	Deleterious BRCA1	1470	7	Nodal	Laparoscopy	7	Disease free	71.2[a]	71.2[a]
5	IIB	Serous	Complete	IP	Deleterious BRCA1	168	14	Spleen	Laparoscopy	9	Disease free	59.1[a]	59.1[a]
6	IIIC	Serous	Complete	IV	Deleterious BRCA1			Peritoneum	Laparoscopy	7	Died of disease	15.9	67.4
7	IIIC	Endometrioid	Complete	IP	Wild type	941	12	Peritoneum	Hand port	67	Died of disease	15.8	54.6
8	IIC	Clear cell	Complete	IP	Wild type	48	17	Peritoneum	Laparotomy	28	Recurred	19.3	27.5[a]

FIGO = International Federation of Gynecology and Obstetrics, IV = Intravenous, IP = Intraperitoneal.
[a] Indicates censored value.
[b] Optimal as defined by greatest residual disease visible but < 1 cm in largest dimension.

4. Discussion

This case series demonstrates that carefully selected patients with recurrent high-grade ovarian cancer who have complete resection of an isolated metastasis can be followed after surgery with an excellent prognosis. Further, four of the patients in this series are still disease-free after a prolonged observation (23.3 to 84.6 months) and have a secondary remission that is longer than their initial remission. In this series, the mean PFS after secondary resection was 19.8 months, comparable to the 21.1-month median PFS in patients who had a complete surgical resection and were also treated with chemotherapy in the AGO DESKTOP III trial (Du Bois et al., 2017).

The role for secondary surgical cytoreduction in recurrent high-grade epithelial ovarian cancer has been controversial. It has been argued that secondary cytoreductive surgery should be performed in patients with a platinum-free interval of > 6 months, especially when the recurrent disease is limited (Chi et al., 2006). The AGO DESKTOP III trial prospectively tested secondary surgery in patients who were good candidates for surgery based on a previously validated scoring system (Du Bois et al., 2017). This trial included patients with a platinum-free interval of > 6 months, good performance status, no disease after initial surgery, and patients without significant ascites as a marker for peritoneal carcinomatosis. This randomized study assigned patients with recurrent ovarian cancer to either secondary surgery or treatment with chemotherapy alone. In the surgical group, a complete secondary resection was achieved in 72%. Secondary surgery improved the PFS by 5.6 months with a hazard ratio for recurrence of 0.66 (95% CI, 0.52–0.83). The PFS improvement was 7.2 months when secondary surgery was complete with no residual disease (HR = 0.56; 95% CI, 0.43–0.72), but there was no improvement in patients with any residual disease compared to no surgery (HR = 0.98; 95% CI, 0.71–1.35). GOG 213 is a similar trial but with different eligibility criteria (Coleman et al., 2018). This trial also included patients with a platinum-free interval of > 6 months, but patients only needed to be deemed good surgical candidates by the investigator. Complete resection was achieved in 67% of patients but surgery was not associated with a benefit in PFS (HR = 0.88; 95% CI 0.70–1.11) or OS (HR = 1.28; 95% CI 0.92–1.78). A PFS benefit was noted in patients in the surgical arm who had a complete resection compared to those patients who did not have surgery (HR = 0.68; 95% CI 0.51–0.90). However, this did not translate to an OS advantage (HR = 1.11; 95% CI 0.74–1.66) which was the primary endpoint of the trial. Almost all patients in both of these trials received post-surgical chemotherapy. However, only 20% of the patients in the DESKTOP III trial were treated with maintenance bevacizumab compared to 84% of patients in GOG 213.

The current series has identified a population that appears to benefit from secondary surgical resection. However, weaknesses in this study include its small size and the fact that these patients were highly selected which may not allow these results to be generalized to all patients with recurrent ovarian cancer. The majority of patients in this series were treated with IP chemotherapy, and this may have contributed to the favorable prognoses seen with extra-peritoneal recurrences. In addition, several of the patients in this series were *BRCA* (+), a group that is known to have an excellent prognosis after intraperitoneal chemotherapy (Naumann et al., 2018). Nonetheless, the results of this series are encouraging, with a mean survival that is comparable to other randomized clinical trials and four patients remaining progression-free after prolonged follow-up.

Isolated recurrent ovarian cancer amenable to surgical resection alone is relatively rare, demonstrated by the few patients identified over a 12-year period. While this is a limited series of patients, we hope that our results will encourage further research into the outcomes of secondary surgical resection without chemotherapy in broader patient populations. Additional studies are needed to further substantiate the merit of this treatment strategy and to delineate the groups of patients most likely to benefit.

To our knowledge, this case series is the first to report positive outcomes for patients with recurrent high-grade epithelial ovarian cancer treated with surgical resection alone. Notably, our patients had isolated metastatic lesions with negative resection margins and there was a high prevalence of BRCA germline mutation. It may be reasonable to consider an active surveillance option in similar patients with long platinum-free intervals, particularly in those with non-peritoneal recurrence and return of tumor markers to baseline in the postoperative period.

Conflicts of interest

Dr. Naumann has recieved consulting fees from Genetech, AstraZeneca, Clovis, SutroBio, Merck, OncoMed, Janssen, and Tesaro; research funding from Bristol-Myers-Squib, OncoMed, and Merck; and speaker fees from Genetech, outside of the submitted work.

Dr. Brown has recieved fees from Ethicon, Tesaro, Clovis, Genentech, Olympus, and Invitae, outside of the submitted work.

Mr. Boyles has no potential conflicts of interest to report.

Author contributions

Dr. Naumann generated the concept for the study, provided and collected data, provided statistical analysis, and was involved in the writing and revision of this manuscript.

Mr. Boyles collected data, analyzed data, and was involved in the writing and revision of this manuscript.

Dr. Brown provided data and was involved in the writing and revision of this manuscript.

All authors approve of the final manuscript.

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