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Case series

Chemotherapy alone may have equivalent survival as compared to suboptimal surgery in advanced endometrial cancer patients

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A B S T R A C T

Objective: To describe outcomes in patients with advanced endometrial cancer treated with chemotherapy only and compare them to patients treated with a combination of chemotherapy and surgery.

Methods: Retrospective chart review for all patients diagnosed with stage III and IV endometrial cancer from January 1, 2000 to December 31, 2015. We abstracted relevant demographic and clinical data. Kaplan-Meier analysis was used to create survival curves; Cox proportional hazards regression model was used to identify prognostic factors.

Results: Ninety-six patients met inclusion criteria; the median age was 64.5. Seventy patients were treated with combination therapy and 26 with chemotherapy alone. For the entire group, median overall survival (OS) was significantly different between groups (22.3 months surgery versus 9.8 months chemotherapy only, $p = 0.0002$). After multivariable analysis, having carcinosarcoma (HR 3.84 95% CI 2.64–5.03, $p = 0.03$), having grade 3 disease (HR 4.95 95% CI 3.70–6.18, $p = 0.01$), and having chemotherapy only (HR 4.13 95% CI 3.23–5.02, $p = 0.002$) were associated with increased mortality. When analysis was restricted to just patients who had a suboptimal debulking or chemotherapy alone, median OS was equivalent similar at 9.4 and 9.8 months ($p = 0.46$).

Conclusion: For advanced endometrial cancer patients, surgery in addition to chemotherapy confers a survival advantage except when optimal debulking cannot be achieved.

1. Introduction

Outcomes for advanced endometrial cancer patients are poor, with approximately 20% of patients with stage IV disease surviving to five years after receiving a diagnosis, regardless of histology (Lewin et al., 2010). Despite the limited survival for these patients, the general recommendation has traditionally been for upfront cytoreductive surgery unless the disease burden is felt to be unresectable (Network, 2017). Much of the research for these patients has focused on the demonstrated survival advantage of aggressive surgical debulking with a goal of no gross residual disease, but there has been less focus on those patients who may not be candidates for extensive surgical effort (Rauh-Hain et al., 2010; Shih et al., 2011; Patsavas et al., 2011; Memarzadeh et al., 2002; THOMAS et al., 2007). Indeed, it has been demonstrated in the ovarian cancer literature that more extended debulking procedures often require more complex surgery with increased risk of surgical morbidity (Chi et al., 2010). Surgical morbidity is an important consideration among advanced endometrial cancer patients given that they are often obese and frequently have obesity related co-morbid conditions (Setiawan et al., 2013; Nicholas et al., 2014). Surgical morbidity may outweigh any potential benefits in this subset of advanced endometrial cancer patients.

There are limited data to support recommendations for chemotherapy alone in the treatment of patients with advanced endometrial cancer and significant disease burden or poor functional status. However, there has been some description and study of chemotherapy alone in advanced ovarian cancer patients given that approximately 20% of these patients never undergo surgical debulking (Shalowitz et al., 2016; Marchetti et al., 2017). These studies have found that chemotherapy alone can achieve reasonable disease control and improved overall survival (OS) as compared to no treatment. While there is limited data on the management of advanced endometrial cancer with chemotherapy alone, it has been demonstrated that undergoing a suboptimal debulking results in a significant reduction in OS as compared to optimal debulking, and it is worth exploring if a suboptimal surgery improves outcomes at all as compared to systemic therapy alone (Shih et al., 2011; Patsavas et al., 2011).

Given the paucity of data on this topic for patients with endometrial cancer, and the focus of previous studies specifically on outcomes with aggressive cytoreductive surgery, further investigation into outcomes of chemotherapy only in advanced endometrial cancer patients is warranted. As such, we aimed to further characterize the outcomes for advanced endometrial cancer patients treated with chemotherapy alone as compared to those managed with cytoreductive surgery and

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chemotherapy, including all histologic subtypes and all patients regardless of baseline performance status or co-morbid conditions.

2. Methods

After receiving approval by the University of Virginia's (UVA) Institutional Review Board, we performed a retrospective chart review of all women (ages 18–89) evaluated for a diagnosis of stage IIII or IV endometrial cancer from January 1, 2000 to December 31, 2015. Patients were identified using UVA's tumor registry. We otherwise had no exclusion criteria and included all histologic subtypes. We abstracted relevant clinical and demographic information from the medical record, including age, race/ethnicity, medical co-morbidities, ECOG performance status at time of diagnosis, primary treatment modality (chemotherapy alone, neoadjuvant chemotherapy (NACT), or primary debulking surgery), histologic subtype, extent of surgery (none, simple hysterectomy +/− bilateral salpingo-oopohorectomy +/- pelvic and/or *para*-aortic lymph node dissection, or radical surgery), residual disease after surgery (suboptimal or > 1 cm, optimal or < 1 cm, no visible residual disease), type of chemotherapy, cycles of chemotherapy given in the upfront setting, any adjuvant radiation (none, brachytherapy alone, external beam +/− brachytherapy), site (s) of first recurrence, time to first recurrence, date of last follow-up and vital status at that time, and/or date of death.

The primary outcome of interest was overall survival. Progression free survival was the second outcome of interest. We employed standard univariable statistical analysis with Chi-square, Fisher's exact, and Wilcoxon rank sum tests where appropriate. Kaplan-Meier survival analysis with the log rank test was used to determine differences in OS and PFS. A Cox proportional hazards model was applied to evaluate the effect of relevant demographic and clinical characteristics on OS. Given the limited number of events, BMI and radiation treatment were ultimately excluded; the model was not significant affected by the inclusion or exclusion of any of the aforementioned co-variates. There were too few patients who were ever disease free to create a meaningful model for PFS. SAS 9.3 was used for all statistical analysis; a p-value of < 0.05 was considered significant.

3. Results

A total of 96 patients were included for analysis. 70 (72.9%) had surgery and chemotherapy and 26 (27.1%) had chemotherapy alone. The median age for the entire cohort was 64.5 years (range 30.0–81.0). Forty-four patients (45.8%) were stage III at diagnosis, and 52 (54.1%) were stage IV. The most common histologic subtypes were endometrioid (n = 34, 35.4%) and serous (n = 29, 30.2%). Almost half of all patients (n = 42, 43.8%) did not have an assigned ECOG performance assigned at diagnosis; among those who did (n = 46), most were assigned 0 or 1 (66.7%). Approximately 38.5% of patients in the cohort were never disease free despite treatment.

For patients treated with chemotherapy only, multiple reasons were enumerated for the omission of surgery. Most commonly, surgery was omitted due to bulk of disease (n = 11, 42.3%). Five patients (19.2%) were not deemed surgical candidates due to other medical co-morbidities. Six patients (23.1%) died before they could undergo surgery. For the remaining four patients (15.4%), the reason could not be determined from chart review. Among those treated with combination therapy, 12 patients (17.1%) had neoadjuvant (NACT) chemotherapy and 58 patients (82.9%) had upfront surgery. Seventy percent of patients had cytoreduction to no gross residual disease, 14.2% had optimal debulkings, and 12.9% had suboptimal debulkings; three of the nine patients who had suboptimal debulkings had received neoadjuvant chemotherapy.

When comparing patients based on primary treatment modality, there were few demographic differences. The groups were similar with regard to median age, race, BMI, insurance provider/status, and other medical co-morbidities. More patients in the surgery cohort had an ECOG performance status of 0 or 1 ($p = 0.006$). Patients treated with chemotherapy alone were more likely to have stage IV disease ($p = 0.02$). With regards to distribution of histology, the groups were unequal, with the chemotherapy group having more patients with mixed or undifferentiated tumor types and surgery group with more patients with carcinosarcoma ($p = 0.0012$). While patients in the chemotherapy group were more likely to be treated with any type of radiation ($p = 0.0052$), approximately 90% of patients in both groups were treated with platinum based chemotherapy for a median of 6 cycles. Of note, those in the neoadjuvant cohort had a median of three cycles of chemotherapy prior to interval debulking. After primary therapy, for patients treated with chemotherapy alone, one (3.8%) patient had a complete response, ten (38.5%) had a partial response, ten (11.5%) had stable disease, ten (38.5%) had progression, and two had unknown responses. Among those in the neoadjuvant cohort, one (8.3%) had a complete response, eight (66.7%) had a partial response, three (25.0%) had progression. For patients who had surgery upfront, 40 (69.0%) had a complete response, 17 (29.3% had a partial response), and one was unknown. Significantly more patients in the chemotherapy group were never disease free as compared to their counterparts who underwent surgery (84.6% versus 21.4%, $p < 0.0001$) (Table 1).

The median PFS was 6.4 months for the chemotherapy group and 12.7 months for the combined treatment group ($p = 0.05$). The median OS for the chemotherapy group was significantly less at 9.8 months as compared to 22.3 months for the surgery group ($p = 0.0002$).

When we restricted the analysis to only those patients who had received chemotherapy alone or had a suboptimal debulking in addition to chemotherapy, the median OS was not significantly different (9.8 months for chemotherapy vs 9.4 months suboptimal debulking, $p = 0.45$)

After multivariable analysis, neither age at diagnosis nor stage were predictive of overall survival. With regard to histology, only carcinosarcoma was associated with worse survival (HR 5.23 (95% CI 3.91–6.56), $p = 0.03$). Not surprisingly, grade 2 (HR 9.22 (95% CI 7.75–10.86), $p = 0.0008$) and 3 (HR 10.33 (95% CI 8.87–11.80), $p = 0.002$) were associated increased risk of death. ECOG performance status was not associated with worse survival. Receiving chemotherapy only was associated with worse survival as compared to those who received surgery as part of treatment (HR 4.37 (95% CI 3.35–5.38), $p = 0.005$) (Table 2).

For the entire cohort, 29 patients (30.2%) had cancer related deaths, 27 (28.1%) were lost to follow-up and died from unknown causes, 30 patients (31.6%) were alive at last follow-up; the remaining 10 patients (10.4%) died from other causes, including another cancer, PE, sepsis, and dementia. When comparing those who had chemotherapy alone to those who had surgery as part of treatment, 29 of the 30 patients alive at last follow-up had undergone surgical treatment (41.4% versus 3.8%). With regards to cancer-specific mortality, 27% of patients who had surgery died from their disease compared to 38% of patients who had received chemotherapy alone. Six patients (8.6%) who underwent surgery died of causes other than cancer as compared to 15.4% in the chemotherapy only group. Interestingly, all non-cancer related deaths in the chemotherapy alone group were secondary to sepsis (both treatment and non-treatment related), indicating that the omission of surgery as part of their treatment was likely due to early, unanticipated deaths.

4. Discussion

In this single institution, retrospective study of 96 advanced endometrial cancer patients, we found a significant difference in PFS and OS between those managed with chemotherapy alone as compared to those managed with a combination of surgery and chemotherapy. The median OS was 9.8 months for the chemotherapy alone group and 22.3 months for patients who had surgery and chemotherapy. However,

Table 1
Patient characteristics stratified by primary treatment.

	Chemotherapy only N = 26	Chemotherapy and surgery N = 70	P-Value
Age, median (Q1-Q3)	65.5 (57.0–72.0)	63.5 (58.0–68.0)	0.68
BMI, median (Q1-Q3)	31.4 (26.0–35.0)	32.3 (26.1–39.1)	0.90
Race			
White	22 (84.6)	60 (85.7)	
Black	3 (11.5)	7 (10.0)	
Other	1 (3.8)	3 (4.3)	0.97
Insurance			
Private	9 (34.6)	30 (42.8)	
Medicaid	2 (7.7)	1 (5.7)	
Medicare	13 (50.0)	33 (47.1)	
Uninsured/unknown	2 (7.7)	3 (4.2)	0.46
ECOG performance status			
0	3 (11.5)	14 (21.5)	
1	0 (0.0)	19 (29.2)	
2	3 (11.5)	7 (10.8)	
3	1 (3.9)	2 (3.1)	
Unknown	19 (73.1)	23 (35.4)	0.006
Pulmonary disease			
Yes	22 (84.6)	62 (88.6)	
No	4 (15.4)	8 (11.4)	0.60
Cardiac disease			
Yes	15 (57.7)	46 (65.7)	
No	11 (42.3)	24 (34.3)	0.47
Stage			
IIIA	0 (0.0)	12 (17.1)	
IIIB	0 (0.0)	4 (5.7)	
IIIC	5 (19.2)	23 (32.9)	
IVA	4 (15.3)	3 (4.3)	
IVB	17 (65.4)	28 (40.0)	0.02
Histology			
Endometrioid	7 (26.9)	27 (38.6)	
Serous	4 (15.4)	25 (35.7)	
Clear cell	1 (3.9)	3 (4.3)	
Carcinosarcoma	2 (7.7)	9 (12.9)	
Undifferentiated/ other	12 (46.2)	6 (8.6)	0.0012
Radiation			
None	15 (57.7)	36 (51.4)	
External beam	10 (38.4)	12 (17.1)	
Brachytherapy only	0 (0.0)	16 (22.9)	
External beam and brachytherapy	1 (3.9)	6 (8.6)	0.0052
Chemotherapy			
Platinum	23 (88.5)	65 (91.4)	
Clinical trial	3 (11.5)	2 (2.9)	
Other/none	0 (0.0)	4 (5.7)	0.24
Cycles of chemotherapy,			
median (Q1-Q3)	6.0 (2.0–6.0)	6.0 (4.0–6.0)	0.99
Site of Recurrence			
None	1 (3.9)	33 (47.1)	
Local	0 (0.0)	4 (5.7)	
Distant	1 (3.9)	13 (18.5)	
Local and distant	2 (7.7)	5 (7.1)	
Never disease free	22 (84.6)	15 (21.4)	< 0.0001
Total Follow-up time (m),			
median (Q1-Q3)	9.5 (3.0–15.5)	24.4 (12.0–48.1)	< 0.0001

when we examined only those patients who were suboptimally debulked, the median overall survival was 9.4 months, essentially the same as patients who received chemotherapy alone. After multivariable analysis, increasing grade of disease and carcinosarcoma were found to negatively affect OS as was, not surprisingly receiving chemotherapy alone. These findings suggest that while surgery is an important component in the management of advanced endometrial cancer, undergoing a suboptimal debulking may not confer a survival advantage as compared to receiving chemotherapy alone.

There are very limited data describing outcomes in advanced endometrial cancer patients treated with chemotherapy alone. Among stage IV endometrioid endometrial cancer patients included Shih et al, median OS was 2.2 months among the six patients who did not undergo a cytoreductive surgery (Shih et al., 2011). This is seven months less than a median OS of 9.8 months in our study however those authors did not provide any detail on other comorbidities or circumstances of treatment courses. Most of the available literature focuses only on the question of upfront debulking versus neoadjuvant chemotherapy, and, not surprisingly, reported overall survival is significantly improved when compared to our patients who did not have any surgical intervention. However, when other studies restricted survival analysis to patients who only had suboptimal debulkings, survival was similar (range 10.3–12 months) when compared to a median overall survival of 9.8 months in our chemotherapy only cohort and 9.4 months in our suboptimal cytoreduction group (THOMAS et al., 2007; Shih et al., 2011; Patsavas et al., 2011). This may indicate that in patients for whom aggressive cytoreduction may be too morbid or optimal debulking not feasible, chemotherapy alone may result in similar outcomes, prevent unnecessary surgical risk, and potentially improve quality of life.

Table 2
Multivariable analysis for overall survival.

	Adjusted hazard ratio (95% CI)	P-value
Age at diagnosis	1.02 (0.98–1.05)	0.38
ECOG		
0	Reference	–
1	0.50 (−1.04–1.76)	0.37
2	1.94 (0.29–3.59)	0.43
3	0.15 (−0.02–1.91)	0.03
Unknown	0.42 (−0.81–1.64)	0.16
Stage		
3A	Reference	–
3B	1.77 (−1.08–4.61)	0.70
3C	0.30 (−1.81–2.47)	0.27
4A	0.59 (−2.54–3.72)	0.74
4B	1.26 (−0.84–3.36)	0.83
Grade		
1	Reference	–
2	9.22 (7.57–10.86)	0.008
3	10.33 (8.87–11.80)	0.002
Histology		
Endometrioid	Reference	–
Serous	0.27 (−1.06–1.60)	0.05
Clear cell	0.53 (−1.01–2.03)	0.42
Carcinosarcoma	5.23 (3.91–6.56)	0.02
Other	0.84 (−0.32–2.00)	0.77
Treatment		
Surgery and chemotherapy	Reference	–
Chemotherapy alone	4.37 (3.35–5.38)	0.005

As mentioned, little data exist describing survival in advanced endometrial cancer patients who never undergo surgery, much less on the decision to omit a cytoreductive procedure. Nearly 30% of patients were deemed too unwell to undergo surgery, slightly higher when compared to similar studies in ovarian cancer, quoting a 10–18% rate of non-surgical management (Shalowitz et al., 2016; Marchetti et al., 2017). Almost half of all patients mananged non-surgically (11% of all patients) were deemed not surgically resectable due to burden of disease. While we did not consider survival of patients who did not receive any treatment in this study, omission of surgery and administration of chemotherapy alone in patients with significant medical co-morbidities or disease burden likely improves survival and minimize *peri*-operative morbidity and mortality.

While a small, single institution retrospective study, there are several strengths. By including all advanced endometrial cancer patients and not just those initially deemed fit for surgical intervention, we can more accurately reflect the realities of treating this cohort of patients, many of whom may not ultimately be surgical candidates. Similarly, we

included all histologic subtypes to capture a more usual distribution of these patients. Our total cohort was small, with only 96 patients appropriate for inclusion in the study period; however, in cited studies, the included patients only ranged from 30 to 125. In addition, this is to our knowledge one of the only studies specifically aimed at understanding survival among patients with non-surgical management, adding to the body of literature on this topic. As it was not prospective, there was no defined algorithm for clinicians to follow to determine patients appropriate for surgical intervention or how aggressively to cytoreduce patients. In addition, ECOG performance status was not available for approximately half of patients included, which may be minimizing a source of bias with regards to overall survival. Finally, we did not consider patients who did not receive any treatment and could not assess survival as compared to the chemotherapy alone group.

Our results suggest that suboptimal debulking does not confer a survival advantage as compared to chemotherapy alone among advanced endometrial cancer patients. This could inform how we counsel specifically medical unwell women with advanced disease and spare them an otherwise ineffective and morbid procedure. Despite these results, we are aware that the size of the study limits any practice-changing conclusions. Indeed, most studies attempting to elucidate a best treatment approach for this cohort of patients share this limitation. Organizing a prospective randomized trial to answer this question would be difficult given the small number of patients with this diagnosis. However, a retrospective analysis of data pooled from multiple institutions including patients managed with neoadjuvant chemotherapy, chemotherapy alone, and upfront surgical debulking may help us better ascertain how to best advise and treat these patients and reduce the number of futile debulking surgeries.

Author contribution

Dr. Lisa Rauh performed the data abstraction and analysis and was the primary author of the manuscript. Dr. Jeanine Staples assisted with the final data analysis and assisted in the drafting and revision of the manuscript. Dr. Linda Duska proposed the original research question and provided guidance in the drafting of the manuscript.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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