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ORIGINAL RESEARCH

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Survival outcomes of neoadjuvant therapy for the treatment of stage IVB endometrial adenocarcinoma

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Abstract

Treatment for stage IVB endometrial adenocarcinoma is multimodal. Our objective is to evaluate the utility of neoadjuvant therapy (NAT) on survival outcomes for patients with stage IVB endometrial adenocarcinoma. A multi-institutional retrospective review was completed of patients from 1996 to 2018. Descriptive analyses compared baseline characteristics of the treatment groups. A two-sample test or Wilcoxon rank-sum test was used to compare the distribution of values. Hazard ratios were estimated by Cox proportional hazards regression models. Ninety-nine patients with stage IVB endometrial adenocarcinoma who received NAT (n = 35) or primary debulking surgery (PDS) (n = 64) were included for analysis. There was no difference in residual disease between those undergoing PDS or NAT. Interval debulking was performed in 68.6% of patients receiving NAT. Patients received a median of 6 cycles (range: 1–10) of platinum-based NAT. There was no significant difference in median progression-free survival (PFS) for those receiving NAT compared to PDS (adjusted hazard ratio (aHR) = 1.59; 0.98, 2.59) or overall survival (OS) (age adjusted HR = 1.70; 1.00, 2.88). Patients who received NAT but did not proceed to surgery (IDS) were at a higher risk of death compared to those that had surgery (aHR = 2.96; 1.43, 6.16). The role of surgery was largely negated if adjuvant therapy was not administered. Patients with stage IVB endometrial cancer can receive NAT without compromising median PFS or OS. The survival differences in patients that received only primary chemotherapy or chemoradiation points to the importance of surgery. Similarly, when electing for surgery the ability to receive adjuvant therapy is important.

Keywords

Advanced-stage endometrial; Neoadjuvant chemotherapy; Uterine; Interval debulking

1. Introduction

Endometrial cancer remains the most common gynecologic malignancy in the United States [1, 2]. Approximately 75% of these will present with disease confined to the uterus where five-year survival is 74–91% [3–5]. Cases with extrauterine metastasis have a worsened prognosis with a five-year survival of approximately 21% [4]. For women with stage IVB endometrial cancer, systemic therapy with surgery is recommended and preoperative chemotherapy should be considered standard approach per National Comprehensive Cancer Network (NCCN) ENDO-3 guidelines [6, 7].

The amount of residual disease after surgery has been found to have an impact on median progression free and overall survival [8–11]. However, some patients with advanced disease may present with clinically apparent unresectable disease. These patients are unlikely to be optimally cytoreduced at the time of presentation [12]. In the case of ovarian cancer, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is often used, particularly in patients with unresectable disease or those who are poor surgical candidates [13, 14]. In endometrial cancer, the experience with neoadjuvant therapy (NAT) is limited but growing [8, 11, 12, 15–19]. Studies suggest that the majority of advanced endometrial cancer responds to NAT (76–83%) and a majority of responders undergo a subsequent complete or optimal interval debulking surgery (60–75%) [15, 16, 20]. NAT was also associated with decreased operative times, decreased hospital stay, and lower rates of transfusion [12, 21].

Given the advantages of utilizing neoadjuvant therapy in select women with advanced stage ovarian cancer, we sought to evaluate the utility and outcomes of NAT in patients with stage IVB endometrial adenocarcinoma.

2. Materials and methods

We performed a multi-center retrospective review of all patients diagnosed with International Federation of gynecology and Obstetrics (FIGO) 2009 stage IVB endometrial cancer [22] from 1996 to 2018 who were treated at community and

tertiary cancer centers. Complete clinical data were collected by reviewing outpatient charts, operative records and pathology reports. The sites of metastases, surgical procedures and maximum diameter of residual disease after surgery were collected from radiology reports, intraoperative findings and pathology reports. The patients included in the study and labeled as FIGO 2009 stage IVB included patents with disease confined to the abdomen and extra-abdominal disease. Treatment data included type of initial treatment, adjuvant treatment after surgery and surgical procedure performed. Follow-up information included the date and disease status at the last follow-up visit. Patients were considered to have received NAT if the provider intended to perform an interval debulking surgery. Patients were excluded if non-surgical initial therapy was for palliative purposes only.

Patients were categorized by primary therapy: primary debulking surgery (PDS) *vs.* neoadjuvant therapy consisting of chemotherapy, chemoradiation or radiation. Outcomes by subgroups of NAT received were also assessed. The NAT group was also subdivided by receipt of IDS. Similarly, patients who underwent surgery were subdivided by those who received adjuvant therapy.

Descriptive analyses compared baseline characteristics between those receiving NAT and PDS treatment groups. Fisher's exact test of association was used to carry out comparisons for all categorical baseline characteristics. In the case of continuous baseline characteristics, a two-sample test (assuming unequal variance) or Wilcoxon rank-sum test was used to compare the distribution of values of the two treatment groups.

To assess the impact of chemotherapy on the risk of disease progression and eventual death, we carried out two separate analyses: (i) progression free survival (PFS) analysis, and (ii) overall survival (OS) analysis. In the case of PFS analysis, we measured the time at risk as the time between diagnosis and disease progression or death. Patients were censored at the date last known to be alive and without progressive disease. For OS, the time at risk is measured as the time between diagnosis and death. Patients were censored at the date last known to be alive for overall survival.

In both analyses hazard ratios (HR) were estimated by Cox proportional hazards regression models. Four separate comparisons were carried out to compare differences in survival in: (i) NAT *vs.* PDS, (ii) IDS *vs.* PDS *vs.* No Surgery, (iii) receipt of adjuvant therapy, and (iv) residual disease following surgery.

3. Results

Excluding those who received palliative care only (4), 99 patients received either NAT (n = 35) or PDS (n = 64) and are included in the following analysis. The most common histology was endometrioid (40.4%). Defining sites of IVB disease were omentum (54), lung (19), liver (9), inguinal canal (5), abdominal wall (2), spleen (2), umbilicus (2), hernia sac (1), brain (2), and indirect metastasis to the bladder (4) or GI tract (15). On average, patients receiving PDS were older, were more likely to have cardiac disease, had larger tumors (Table 1), and underwent lymph node dissection (Table 2).

European Cooperative Oncology Group (ECOG) performance status was not identified in the records of approximately 60% of patients who underwent NAT. Thirty-four out of 35 NACT regimens included platinum. Of 68 patients receiving adjuvant chemotherapy the most common regimen was carboplatin and paclitaxel (83.6%, n = 56). Others were carboplatin/paclitaxel/bevacizumab (n = 5), cisplatin (n = 2), and 4 patients received either carboplatin/docetaxel, cisplatin/paclitaxel, cisplatin/hydroxyurea or cisplatin/adriamycin. Of patients who received NAT, 68.6% subsequently underwent IDS. Progressive disease was seen in 5 cases and no surgery was performed. Objective responses to NAT were seen in 27 cases (11 complete responses (CR) and 16 partial responses (PR)) and 3 had stable disease. Of patients with an objective response, 6 did not proceed to IDS (3 CR and 3 PR).

Median PFS for all patients in the cohort was 12.7 months, 47% were without disease at 12 months and 28% at 18 months. Predictors of PFS are displayed in Table 2. PDS was not associated with improved PFS compared to NAT after adjusting for age (aHR 1.59; 0.98, 2.59) (Fig. 1) (Table 3). There were no differences in PFS in patients undergoing PDS, IDS or non-surgical management (Fig. 2). Improved age adjusted PFS was seen in those receiving adjuvant therapy following surgery (aHR 0.27; 0.15, 0.49) (Fig. 3) (Table 3).

Median OS for both groups was 17.8 months with 64% of patients alive at 12 months and 49% at 18 months. Predictors of OS are displayed in Table 2. PDS was associated with improved survival compared to NAT after adjusting for age (HR 1.7, 1.00–2.88) (Table 3) (Fig. 1). When comparing PDS to those that received NAT followed by IDS, no difference was seen in age adjusted OS (HR 1.29, 0.70–2.38) (Table 3).

Patients who underwent either PDS or IDS had improved survival compared to patients who had NAT alone (age aHR: 2.75; 1.35, 5.64) (Fig. 2) (Table 3). Adjuvant therapy was associated with improved OS when adjusted for age (aHR: 0.15; 0.07, 0.28) (Fig. 3). Residual disease burden following debulking surgery did not predict overall survival (Fig. 4) (Table 3).

4. Discussion

Our results suggest that PDS is associated with improved overall survival relative to those that received NAT and no IDS. However, when those that did not receive IDS are excluded, no significant difference was seen between NAT and PDS. Adjuvant therapy following PDS or IDS also conferred a possible survival benefit in this subset of patients. ECOG status prior to therapy could not be reliably compared due to lack of documentation, however, patients who underwent PDS were of older age, had a larger median tumor size, and a higher incidence of cardiac disease than patients undergoing NAT.

The feasibility of NAT for advanced and/or metastatic endometrial cancer has been examined both prospectively and retrospectively. Multiple studies noted that in advanced endometrial cancer, NACT is non-inferior to PDS with adjuvant therapy if followed by IDS citing a median PFS of 12–15 months and OS of 24–28 months with median OS of up to 51 months if optimally debulked [12, 15, 17, 19, 23]. Our study

TABLE 1. Patient and disease characteristics by type of therapy (n = 99).

	NACT	PDS	*p*-value*
	N = 35	N = 64	
Age			
mean (sd)**	66.2 (11.5)	75.9 (9.2)	<0.0001
median (min, max)^	67.8 (32.6, 85.7)	77.3 (55.7, 97.6)	<0.0001
Race			
Black	14 (40.0%)	14 (22.2%)	
White	21 (60.0%)	49 (77.8%)	0.122
Missing	0	1	
BMI (kg/m^2), mean (sd)	33.0 (8.2)	32.7 (8.3)	0.860
Obese (BMI ≥30)	23 (65.7%)	36 (56.3%)	0.517
Comorbidities			
COPD	3 (7.1%)	3 (3.5%)	0.782
HTN	26 (61.9%)	48 (55.2%)	0.99
Diabetes	11 (26.2%)	21 (24.1%)	0.99
Cardiac Disease	2 (4.8%)	15 (17.2%)	0.034
ECOG performance status			
0	4 (11.4%)	12 (18.8%)	
1	3 (8.6%)	19 (29.7%)	
2	5 (14.3%)	11 (17.2%)	0.026
3	2 (5.7%)	2 (3.1%)	
4	0 (0.0%)	1 (1.6%)	
Missing	21 (60.0%)	19 (29.7%)	
Histology			
Endometrioid	15 (42.9%)	25 (39.1%)	
Serous	10 (28.6%)	12 (18.8%)	
Carcinosarcoma	3 (8.6%)	16 (25.0%)	
Clear cell	2 (5.7%)	4 (6.3%)	
Mixed	2 (5.7%)	6 (9.4%)	
Other	3 (8.6%)	1 (1.6%)	
Tumor characteristics			
Size, median (min, max)	2.5 (0.3, 20.0), n = 12	6.5 (1.5, 17.5), n = 58	0.003^
Extrauterine disease[#]			
Omentum	16 (45.7%)	38 (59.4%)	
Lung	15 (42.9%)	4 (6.3%)	
GI Tract	4 (11.4%)	9 (14.1%)	
Vagina	7 (20.0%)	4 (6.3%)	
Liver	7 (20.0%)	2 (3.1%)	
Inguinal Canal	3 (8.6%)	2 (3.1%)	
Bladder	1 (2.9%)	3 (4.7%)	
Other	3 (8.6%)	6 (9.4%)	

**T-test or Fisher's Exact Test; ^Wilcoxon rank sum test. Data available on limited set of patients denoted by sample sizes listed. **missing for 1 patient; [#]includes patients with multiple disease sites. NACT: neoadjuvant chemotherapy; PDS: primary debulking surgery; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ECOG: European Cooperative Oncology Group.*

TABLE 2. Treatment characteristics (n = 99).

	NACT	PDS	*p*-value
	N = 35	N = 64	
Neoadjuvant therapy regimens			
Chemotherapy only	33		
Chemotherapy + pelvic RT	1		
Chemotherapy + brain RT	1		
Surgery			
None	11 (31.4%)	0 (0.0%)	
Laparotomy	20 (57.1%)	57 (89.1%)	<0.0001
Robotic/Laparoscopy	4 (11.4%)	7 (10.9%)	
Bowel resection	1 (2.9%)	9 (14.1%)	0.170
Pelvic LND	14 (40.0%)	41 (64.1%)	0.025
Paraaortic LND	11 (31.4%)	30 (46.9%)	0.190
Residual disease	N = 24 with surgery		0.105
>1 cm	3 (12.5%)	9 (14.1%)	
≤1 cm	8 (33.3%)	14 (21.9%)	
NGR	8 (33.3%)	37 (57.8%)	
Missing	5 (20.8%)	4 (6.3%)	
Adjuvant therapy			
Chemotherapy only	11 (31.4%)	34 (53.1%)	
Chemotherapy + RT	9 (25.7%)	14 (21.9%)	0.0004
None	12 (34.3%)	15 (23.4%)	
RT only	3 (8.67%)	1 (1.6%)	
Surgery type			
No surgery	11 (31.4%)		
Interval debulking surgery	24 (68.6%)		
PDS		64 (100.0)	

RT: radiation therapy; PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy; LND: lymph node dissection; NGR: no gross residual.

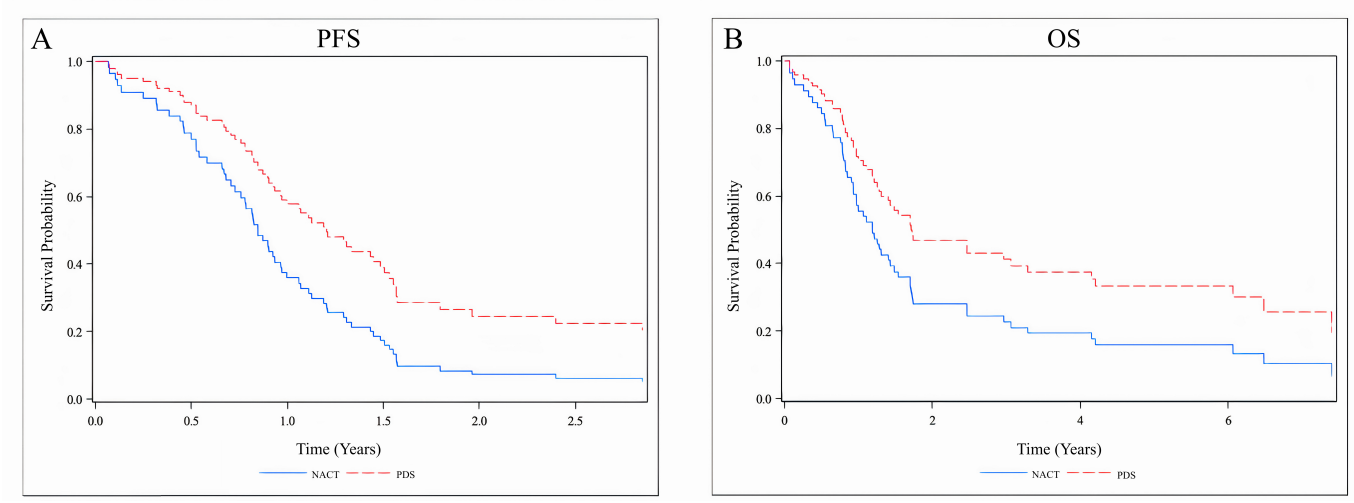

FIGURE 1. Survival outcomes for NACT *vs.* PDS. (A) PFS by NACT *vs.* PDS, (B) OS by NACT *vs.* PDS. PFS: progression free survival; OS: overall survival; NACT: neoadjuvant chemotherapy; PDS: primary debulking surgery.

TABLE 3. Survival outcomes-risk of disease progression or death (n = 99).

	Progression Free Survival		Overall Survival	
	# of Events	Age adjusted HR (95% CI)	# of Events	Age adjusted HR (95% CI)
NACT *vs.* PDS	84	1.59 (0.98, 2.59)	76	1.70 (1.00, 2.88)
IDS *vs.* PDS *vs.* No Surgery	84		76	
IDS *vs.* PDS		1.44 (0.82, 2.53)		1.29 (0.70, 2.38)
No Surgery *vs.* PDS		1.81 (0.90, 3.65)		2.96 (1.43, 6.16)
No Surgery *vs.* IDS		0.80 (0.36, 1.7)		0.45 (0.19, 1.05)
Any surgery *vs.* No Surgery		1.66 (0.84, 3.30)		2.75 (1.35, 5.64)
In those with surgery (n = 87)	# of Events	Age adjusted HR (95% CI)	# of Events	Age adjusted HR (95% CI)
Adjuvant therapy	74		66	
No therapy *vs.* CRT		4.06 (2.04, 8.09)		6.95 (3.28, 14.75)
Chemotherapy *vs.* CRT		1.08 (0.62, 1.89)		1.00 (0.54, 1.84)
RT *vs.* CRT		0.77 (0.17, 3.56)		1.40 (0.29, 6.84)
Chemotherapy vs. No therapy		0.27 (0.15, 0.49)		0.15 (0.07, 0.28)
No therapy *vs.* RT		5.20 (1.12, 24.24)		4.93 (1.02, 23.73)
Chemotherapy *vs.* RT		1.40 (0.31, 6.25)		0.71 (0.15, 3.31)
Residual Disease (n = 78)	65		57	
≤1 cm *vs.* NGR		1.15 (0.64, 2.07)		1.03 (0.54, 1.97)
>1 cm *vs.* NGR		1.81 (0.91, 3.61)		1.68 (0.81, 3.48)
≤1 cm *vs.* >1 cm		0.63 (0.30, 1.35)		0.61 (0.27, 1.38)

NACT: neoadjuvant chemotherapy; PDS: primary debulking surgery; IDS: interval debulking surgery; CTR: chemoradiation therapy; RT: radiation therapy; NGR: no gross residual; CI: confidence interval.

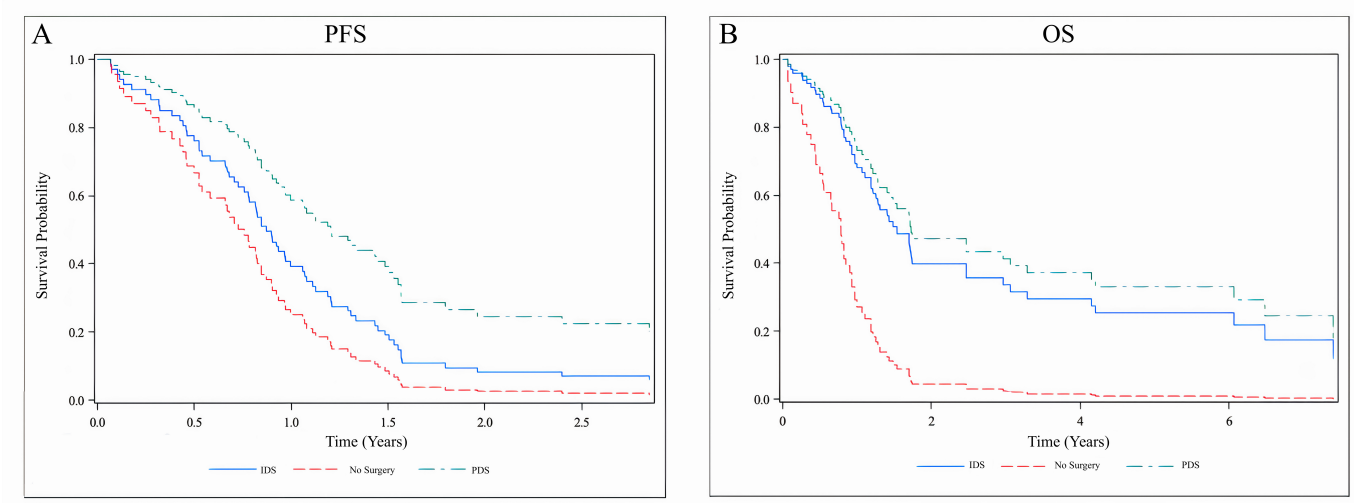

FIGURE 2. Survival outcomes by timing of surgery. (A) PFS by IDS *vs.* PDS *vs.* no surgery, (B) OS by IDS *vs.* PDS *vs.* no surgery. PFS: progression free survival; OS: overall survival; IDS: interval debulking surgery; PDS: primary debulking surgery.

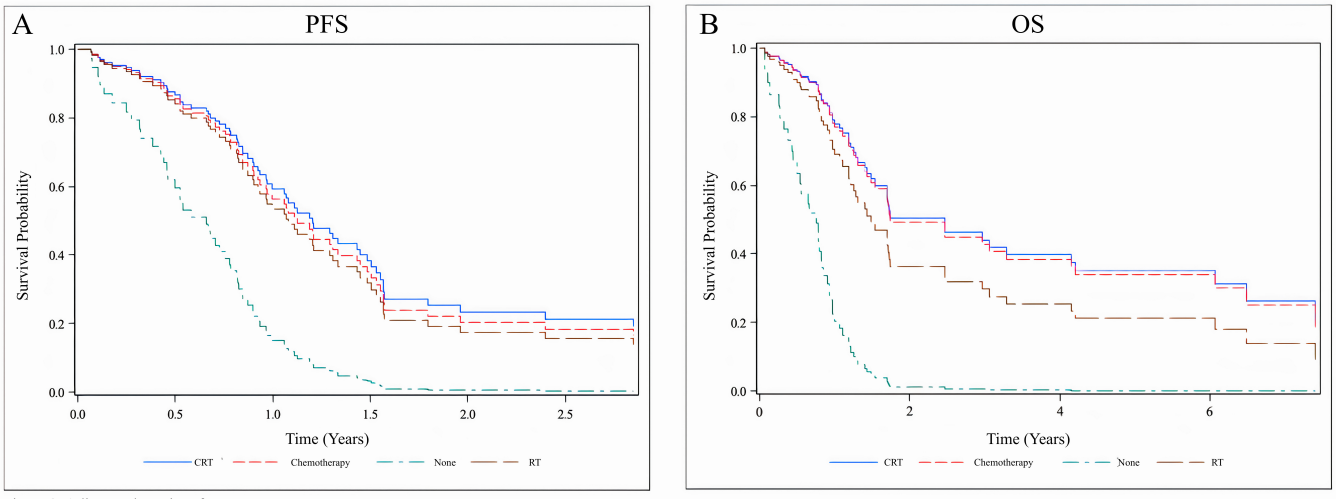

FIGURE 3. Survival by adjuvant therapy. (A) PFS Adjuvant therapies after surgery, (B) OS Adjuvant therapies after surgery. PFS: progression free survival; OS: overall survival; CRT: chemoradiation therapy; RT: radiation therapy.

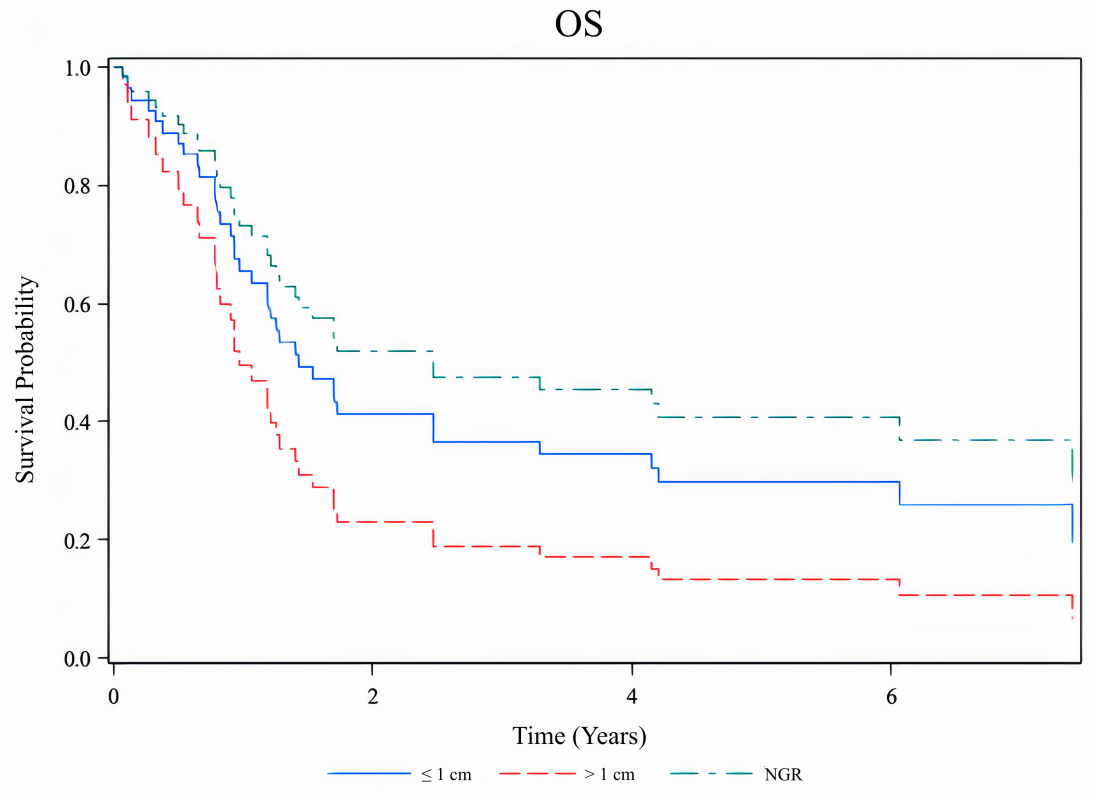

FIGURE 4. OS according to surgical outcome: optimal surgery ≤1 cm, suboptimal >1 cm, NGR. OS: overall survival; NGR: no gross residual.

of only stage IVB cases found an average PFS of 12.7 months and median OS of 17 months which mirrors other studies.

We found no statistically significant difference in OS and PFS between NAT and PDS if IDS surgery was performed. The importance of surgery was also seen in a recent National Cancer Database study of 48,179 women with advanced endometrial cancer [18]. In this study, overall survival was significantly improved with PDS followed by adjuvant therapy or NAT with IDS relative to NAT alone. While improved survival for those receiving PDS followed by adjuvant therapy relative to NAT with IDS was seen, their study did not include patients who received PDS alone. Other studies have found similar significantly shorter mean OS for patients who did not undergo surgery after NAT or before NAT in the case of IDS [16, 20, 24].

A strength of our study is the relatively large patient population. The retrospective design of the cohort analysis hindered full assessment of all variables pertinent to this patient population including indication for NAT, perioperative morbidity, response to NAT, number of chemotherapeutic cycles, chemotherapy complications and performance status.

The findings of the current analysis support the use of NAT

in patients who are not candidates for PDS. The patients who receive NAT benefit if they can subsequently undergo IDS. Our study also demonstrates the need for adjuvant chemotherapy with surgery (either PDS or IDS) to maximize survival outcomes. Based on current literature, the ability to perform an optimal cytoreduction is an important consideration prior to surgery. Other studies cite that OS for incomplete debulking or inoperable disease was comparable to no surgery [12, 15, 16]. In addition, our study suggests that clinicians should also consider the ability to administer adjuvant therapy before taking patients with advanced endometrial cancer to the operating room. Further studies are needed to confirm the efficacy and utility of neoadjuvant chemotherapy in patients with advanced endometrial cancer who are not candidates for surgery.

5. Conclusions

In conclusion, patients with stage IVB endometrial cancer are able to receive NAT without compromising median PFS or OS. The significant difference in PFS and OS in patients that received only primary chemotherapy or chemo-radiation points to the importance of surgery in this population, whether primary or interval cytoreduction. Similarly, when electing for surgery the ability to receive adjuvant therapy is equally important.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ACE—idea conception, data acquisition, data analysis, interpretation, manuscript editing; RN—idea conception, study design, data acquisition; MP—data analysis and interpretation; SP—data acquisition, data management, manuscript writing; MU—data interpretation, manuscript editing; JG—data acquisition, data analysis, data interpretation, manuscript writing, editing; NZ—data acquisition, data analysis, data interpretation, manuscript writing, editing; TDT—data interpretation, manuscript editing; DC—project oversight, idea conception, data acquisition, data analysis, interpretation, manuscript editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The IRB determined exempt review under 45CFR46.101(b)(4). All STROBE guidelines were followed. Consent was waived as this was a retrospective review and no patient identifiers are present.

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CONFLICT OF INTEREST

ElNaggar reports owning stock in Natera Inc. and is an employee of Natera. Tillmanns reports being a member of the advisory board for Intuitive. All fees are outside of submitted work.

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