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Clinical outcomes and the role of adjuvant therapy sequencing in Type II uterine cancer following definitive surgical treatment

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Summary

Purpose of Investigation: Because of rarity, consensus on adjuvant therapies for Type II endometrial cancers (EC) remains undefined. Reporting their institutional outcomes, the present authors assessed the impact of adjuvant therapies on recurrence and overall survival in women with 2009 FIGO Stage I-III Type II EC. *Material and Methods:* The authors identified 108 women, treated with definitive surgery between 2000-2013, with pathologically-confirmed Type II EC (non-endometrioid [NEM, n=80] and high grade endometrioid [G3EEC, n=28]) Cox proportional hazard models were used to assess the effect of prognostic variables on disease-free (DFS) and overall survival (OS). Kaplan-Meier method was used to assess survival. *Results:* Of the 108 women, 83 (77%) were African American (AA). Fifty-nine (55%), 12 (11%), and 37 (34%) were Stage I, II, and III, respectively. Ninety-seven patients received adjuvant therapy: 52 (radiation only), four (chemotherapy only), and 40 (combined). During follow-up (median 41 months), 44 patients (41%) recurred. Five-year DFS was 53% overall (48% [NEM], 80% [G3EEC]). Five-year OS was 75% overall (68% [NEM], 95% [G3EEC]). On multivariate analysis, lower stage and adjuvant radiation improved DFS. Higher stage, NEM, and increasing age were poor prognostic indicators of OS. *Conclusion:* Representing a large single institutional cohort for Type II EC, the present study's observed survival rates are consistent with previous studies, despite the relatively high frequency of carcinosarcoma and Stage III/nodal disease. The protective effect on recurrence was not lost when radiation was delayed for chemotherapy. The present results support a multimodal adjuvant approach for treating all stages of invasive NEM EC.

Key words: Endometrial neoplasms; Surgical pathology; Chemotherapy; Adjuvant; Radiotherapy; Adjuvant.

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the US, with an estimated 54,870 new cases expected to be diagnosed in 2015. African American (AA) women suffer from a higher mortality rate compared to Caucasians (7.0 versus 3.8 per 100,000 women, respectively) [1]. Most cases of endometrial cancers are categorized as Type I, with characteristic endometrioid morphology (EM), that respond well to treatment with close to a 90% five-year survival rate [2]. Though accounting for less than 15% of newly-diagnosed cases, Type II ECs are responsible for close to half of all uterine cancer-associated deaths [3-5]. These high-risk variants, with a propensity for extrauterine spread and recurrence, include non-endometrioid morphologies (NEM): uterine papillary serous carcinoma (UPSC), clear cell carcinoma (CCC), and carcinosarcoma (CS). Poorly differentiated, Grade 3 endometrioid carcincoma (G3EEC) is often grouped with Type II EC in high-risk cohort studies, given a similar molecular profile [6], distinct from low-grade EM, and comparable clinical outcomes [6-8].

Due to high rates of recurrence, multimodal adjuvant treatment, including radiation therapy (RT) and chemotherapy (CT), has shown benefits in recurrence and survival in early-stage Type II EC cohorts [3, 4, 9, 10]. However, the true survival benefit of combined adjuvant therapies [11], and, even general effectiveness of any adjuvant therapy [12], remains in dispute. The poor prognosis carried by Type II EC and the general lack of consensus regarding standard management underscore the need to further explore and optimize adjuvant therapies for these rare variants [4, 13]. Reporting the authors' single institutional clinical outcomes in a, largely, AA treatment population with a uniquely high prevalence of these aggressive cancer entities, the present study aims to clarify the impact of adjuvant therapies and their sequence on recurrence and sur-

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vival in FIGO Stage I-III Type II EC following definitive surgical treatment.

Materials and Methods

Using an institutional review board-approved protocol, the authors retrospectively identified women with non-metastatic Type II EC who underwent definitive surgical treatment from 2000 to 2013. Patient electronic medical charts were used to ascertain information regarding demographics, diagnosis, pathology, staging, adjuvant treatment regimens, follow up, recurrence, and overall survival. Eligibility criteria for study included women with histologically-confirmed UPSC, CCC, CS, or G3EEC disease who underwent definitive surgical treatment. Patients with low-intermediate grade Type I EC and Stage IV disease were excluded. Two hundred fifty patients were treated for EC at multiple institutional-affiliated hospitals between 2000-2013; 90 (36%) of these patients were diagnosed NEM. Ten patients did not receive definitive surgical treatment due to presence of Stage IV disease. The remaining 80 women with NEM were combined with 28 patients with similarly staged and surgically treated G3EEC for a total cohort of 108 eligible patients. Follow up period extended through 2015.

All patients underwent definitive surgical treatment that included total abdominal hysterectomy, salpingo-oophorectomy, and pelvic and para-aortic lymph node (LN) dissection. No study patients had residual tumors after hysterectomy. Pathologic evaluation included depth of myometrial invasion (MMI), lymphovascular space involvement (LVSI), cervical stromal invasion (CSI), tumor histology, grade, and LN assessment. All were reviewed and confirmed by an institutional board-certified pathologist.

Adjuvant treatment regimens were chosen at the discretion of the providing radiation and medical oncologists after being discussed by a multidisciplinary tumor board. Radiation boost regimens were typically chosen for women with node positive and/or margin positive disease. External beam therapy (EBRT) to the whole pelvis/abdomen (median dose = 45 Gy) was done using the four-field technique. Intravaginal brachytherapy (IVB), which has become more common over the past few years with emerging results of clinical trials, was either given as primary adjuvant RT (median dose 21 Gy in 3 fractions prescribed at at depth 0.5 cm from the applicator surface) or to boost EBRT (median dose 18 Gy in 3 fractions prescribed at applicator surface). In either case, high-dose RT was administered to at least the proximal two-thirds of the vagina.

Adjuvant chemotherapy, prescribed for locally-advanced, node positive, and/or margin positive disease, consisted of three to six cycles of platinum-based chemotherapy every three weeks. Combined CT and RT adjuvant treatments were classified as the following: concurrent chemoradiation (CCRT), sequential CT followed by RT, sequential RT followed by CT, and 'sandwich therapy' (RT preceded by three cycles of CT and followed by an additional three cycles of CT).

Covariates of interest included: age at surgery, race, histology, FIGO 2009 Stage, tumor size, MMI, CSI, LVSI, LN disease, adjuvant therapy and type, 'time from surgery to start of RT', 'time from surgery to start of CT', 'RT timing' (see below), and recurrence. In addition, patients who received adjuvant RT were further categorized into 'upfront' (RT alone, concurrent, and sequential RT followed by CT regimens) and 'delayed' (sequential CT followed by RT and 'sandwich'). These covariates were evaluated within the overall cohort and compared across morphology groups (NEM v. G3EEC).

Key outcome measure included disease-free survival (DFS), local disease-free survival (L-DFS), distant disease-free survival (D-DFS), and overall survival (OS) defined as follows: DFS - time from surgery (initiation of first-course treatment) to time of disease recurrence (detected by imaging or biopsy) or last follow up/date of death; L-DFS/D-DFS - time from surgery to detection of loco-regional recurrence (pelvic structures, local LN [pelvic and para-aortic]), and distant recurrence, respectively; OS - time from surgery to date of last follow up or death. If patient was living/did not recur by last follow up, they were censored in their respective survival analyses.

Univariate associations and comparisons across morphology groups were conducted by Chi-square test/Fisher's exact test for categorical covariates, where appropriate, and ANOVA for numerical covariates. DFS, L-DFS, D-DFS, and OS were compared across race, tumor characteristics, adjuvant treatments, etc., using log-rank tests and Cox proportional hazards models. Multivariate Cox models were fit, adjusting for 2009 FIGO Stage and Type II EC morphology group. Kaplan-Meier (KM) method was used to produce survival curves. Significance was set at an alpha of 0.05. Analyses was done using SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute [14].

Results

As shown in Table 1, a total of 108 women with high-risk uterine cancer underwent definitive surgical treatment – 28 (26%) G3EEC, 56 (52%) UPSC/CC, and 24 (22%) CS. Eighty-three patients (77%) were AA. Fifty-nine (55%), 12 (11%), and 37 (34%) were FIGO 2009 Stage I, II, and III, respectively. Twenty patients (all NEM) presented with a non-invasive disease confined to an endometrial polyp. Ninety-seven patients (89%) received some type of adjuvant therapy: 52 (48%) RT only, four (4%) CT only, and 40 (37%) combined CT + RT therapy. Combined adjuvant regimens were as follows: five (5%) concurrent CCRT, five (5%) sequential RT followed by CT, 16 (15%) sequential CT followed by RT, and 15 (14%) 'sandwich' (½ CT then RT then ½ CT) therapy. Of the total 108, 61 (57%) received upfront RT (either in combination or single modality) and 31 (29%) received delayed RT (RT preceded by 3+ cycles of CT). Median time to start of adjuvant RT was 3.5 months and median time to start of adjuvant CT was 1.5 months from date of surgery. During the follow up with a median of 41 months, 44 patients (41%) recurred with 27 (25%) loco-regional recurrences and 30 (28%) distant recurrences. Comparing morphology groups, NEMs were more likely to have positive LVSI, cervical stromal invasion. G3EEC cases were more likely to have had adjuvant therapy (100% vs. 85% in NEM, p=.034), specifically, adjuvant RT ($p = 0.010$). NEM patients were more likely to have combined CT+RT regimens as compared to G3EEC patients.

Results of DFS analysis are shown in Figure 1 and Table 2. The following five-year DFS rates were observed: 53% for combined cohort, 49% NEM (53% [UPSC/CCC], 41% [CS]), and 63% for G3EEC. Five-year L-DFS/D-DFS rates

Table 1. — *Characteristics and descriptive statistics for overall cohort and by Type II endometrial cancer morphology group.*

Covariate	Statistics	Level/units	Entire cohort (N=108)	NEM (n=80)	G3EEC (n=28)	*p*-value
Age at surgery	Median	Years	61	61	61.5	0.295
	Mean (Std Dev.)		62.6 (8.9)	63.4 (8.5)	60 (9.9)	
Race	N (%)	African American	83 (76.9)	65 (81.3)	18 (64.3)	0.185
		White	25 (23.1)	15 (18.7)	10 (35.7)	
Tumor details						
FIGO 2009 Stage [General]	N (%)	I	59 (54.6)	43 (53.8)	16 (57.1)	0.952
		II	12 (11.1)	9 (11.3)	3 (10.7)	
		III	37 (34.3)	28 (35.0)	9 (32.1)	
FIGO 2009 Stage [Specific]		IA	49 (45.4)	37 (46.3)	12 (42.9)	—
		IB	10 (9.3)	6 (7.5)	4 (14.3)	
		IIIA	14 (13)	11 (13.8)	3 (10.8)	
		IIIB	3 (2.8)	3 (3.8)	0 (0)	
		IIIC1	9 (8.3)	6 (7.5)	3 (10.8)	
		IIIC2	11 (10.2)	8 (10)	3 (10.8)	
Confined to polyp (Stage IA)	N (%)		20 (5.4)	20 (25)	0 (0)	—
Histology	N (%)	G3EEC	28 (25.9)	—	28 (100)	—
		UPSC	48 (44.4)	39 (56)	—	
		CS	24 (22.2)	24 (34)	—	
		CCC	8 (7.4)	7 (10)	—	
Tumor size	Median	Millimeters	50	53	40	0.263
	Mean (Std Dev.)		57.5 (35.8)	60 (39)	50.9 (24.6)	
Depth of myometrial invasion						
	N (%)	≥ 50% MMI	36 (35.0)	25 (32.5)	11 (42.3)	0.363
		< 50% MMI	67 (65.0)	52 (67.5)	15 (57.69)	
Cervical stromal invasion	N (%)	Positive	27 (26.7)	24 (32)	3 (11.5)	0.042
		Negative	74 (73.3)	51 (68)	23 (88.5)	
Nodal disease	N (%)	Positive	18 (20)	12 (18.2)	6 (25)	0.554
		Negative	72 (80)	54 (81.8)	18 (75)	
LVSI	N (%)	Positive	43 (44.8)	38 (52.1)	5 (21.7)	0.011
		Negative	53 (55.2)	35 (48)	18 (78.3)	
First course therapy						
Surgery (definitive)	N (%)	Yes	108 (100)	80 (100)	28 (100)	—
		No	0 (0)	0 (0)	0 (0)	
Adjuvant therapy	N (%)	Yes	97 (88.8)	68 (85.0)	28 (100)	0.034
		No	11 (10.2)	12 (15.0)	0 (0)	
Radiation [RT] (adjuvant)	N (%)	Yes	92 (85.2)	64 (80)	28 (100)	0.010
		No	16 (14.8)	16 (20)	0 (0)	
Chemotherapy [CT] (adjuvant)	N (%)	Yes	44 (40.7)	36 (45)	8 (28.6)	0.128
		No	64 (59.3)	44 (55)	20 (71.4)	
Adjuvant therapy details						
Adjuvant therapy type	N (%)	RT only	52 (48.1)	32 (40)	20 (71.4)	0.071
		CT only	4 (3.7)	4 (5)	0 (0)	
		RT + CT	40 (37)	32 (40)	8 (28.6)	
Adjuvant radiation type	N (%)	EBRT primary	69 (63.9)	50 (62.5)	19 (67.9)	0.295
		IVB primary	23 (21.3)	14 (17.5)	9 (32.1)	
		RT boost	61 (56.5)	44 (55.0)	17 (60.7)	0.600
Combined RT + CT regimens						
	N (%)	Sandwich (CT-RT-CT)	15 (13.9)	13 (16.3)	2 (7.1)	0.653
		CT then RT	16 (14.8)	12 (15)	4 (14.3)	
		RT then CT	5 (4.6)	3 (3.8)	2 (7.1)	
		CCRT	5 (4.6)	4 (5)	1 (3.6)	
Radiation treatment timing *(includes RT alone & RT + CT)*	N (%)	Upfront	61 (56.5)	39 (48.8)	22 (78.6)	0.100
		Delayed	31 (28.7)	25 (31.3)	6 (21.4)	
Time from surgery to start of RT *(for those who got RT)*	Median	Months	3.5	2.9	2.2	0.212
	Mean (Std. Dev)		2.4 (3.1)	3.8 (3.4)	2.9 (2.1)	
Time from surgery to start of CT *(for those who got CT)*	Median	Months	1.6	1.4	1.7	0.129
	Mean (Std. Dev)		1.9 (1.2)	1.8 (1.1)	2.5 (1.4)	
Follow up/outcomes						
Follow up time	Median	Months	41.4	44.1	39.3	0.297
	Mean (Std. Dev.)		51.7 (3.7)	53.8 (6.3)	50.5 (4.6)	
Recurrence	N (%)	Yes	44 (39.7)	35 (43.7)	9 (32.1)	0.282
		No	64 (59.3)	45 (56.2)	19 (67.9)	
Recurrence site*	N (%)	Local site	27 (25)	23 (28.7)	4 (14.3)	0.128
		Distant site	30 (27.8)	24 (30)	6 (21.4)	0.383

NEM = non-endometriod morphology endometrial carcinoma; G3EEC = high-grade endometrioid endometrial carcinoma; UPSC = uterine papillary serous carcinoma; CS = carcinosarcoma; CCC = clear cell carcinoma; MMI = myometrial invasion; LVSI = lymphovascular space invasion; RT = radiation therapy; CT= chemotherapy (3+ complete cycles); RT + CT = combined/multimodal adjuvant regiments; EBRT = external beam radiation therapy (whole pelvis/abdomen); IVB = intravaginal brachytherapy; RT boost = RT (EBRT or IVB) given in addition to primary RT prescription dose; CCRT = concurrent chemoradiation; upfront = RT given soon after definitive surgery (includes: 'RT alone', 'RT then CT', 'CCRT' adjuvant regiments); Delayed= RT given after three or more cycles of adjuvant CT (includes: 'CT then RT,' 'Sandwich' adjuvant regiments); Local site = pelvis, pelvic LN, para-aortic LN; distant site = distant LN, extrapelvic organ, peritoneum; * includes patients who had both local and distant recurrence; *p*-values calculated using Chi-square/Fisher's Exact or ANOVA.

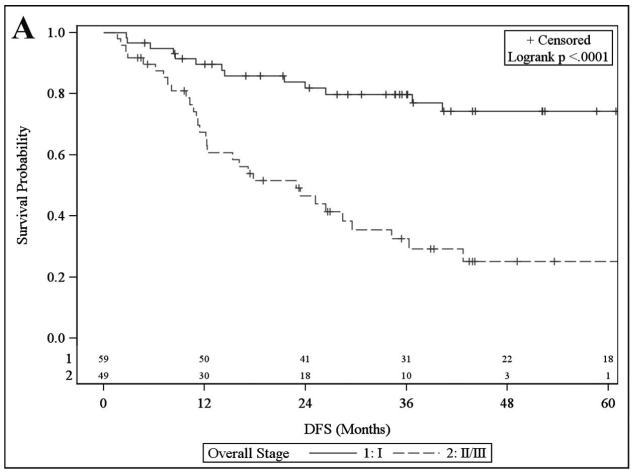
Table 2. — *Summary median disease-free survival (DFS), two- and five-year DFS rates, stratified by FIGO Stage and Type II morphology group.*

FIGO Stage	Median DFS (months) NEM	G3EEC	*p*	2-year DFS (%) NEM	G3EEC	5-year DFS (%) NEM	G3EEC
ALL	42.7	N/A*	0.204	61.3	80.3	48.9	62.8
I	N/A*	N/A*	0.968	82.3	81.3	73.4	75.0
II/III	17.2	36.3	0.154	38.5	78.8	21.9	N/A+

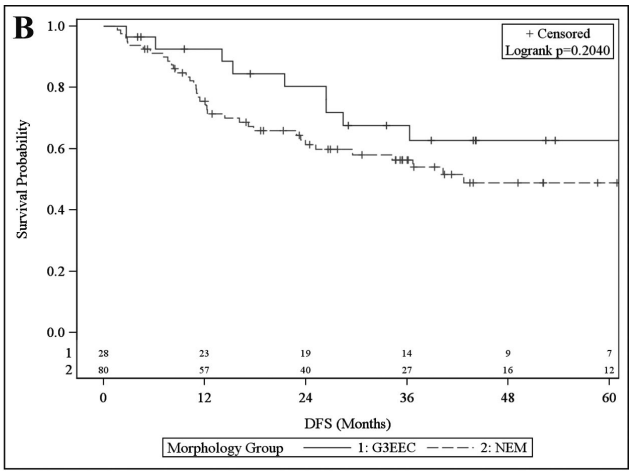
Abbreviations as seen in Table 1; DFS = time from surgery to disease recurrence; Median DFS, two-year DFS%, five-year DFS% calculated using Kaplan-Meier method; *p*-values calculated using Log-rank tests; *N/A – less than 50% had an event (recurrence); +N/A – maximum follow up was less than five years.

were 62/63% for NEM and 83/75% for G3EEC. Median DFS for NEM patients was estimated at 43 months. In the combined cohort and NEM group, Stage I had a significantly longer DFS when compared to Stage II/III ($p \leq 0.0001$). No significant differences were observed in overall DFS or by stage when comparing across NEM and G3EEC groups.

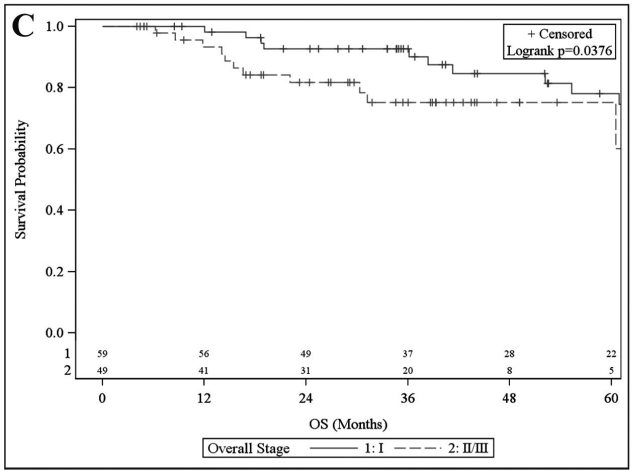
Table 3 shows the results of the present multivariate analysis for DFS (overall DFS, L-DFS, D-DFS), controlling for 2009 FIGO Stage and morphology groups. In this model, patients who did not receive adjuvant RT were more likely to recur overall (HR 2.46, 95% CI [1.20−5.04], p =



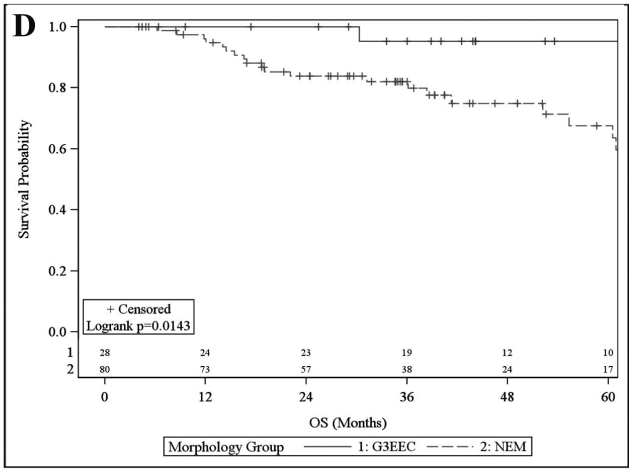
Overall Stage	No. of Subject	Event	Censored	Median Survival (95% CI)	24 Mo Survival	60 Mo Survival
All Stages	108	44 (41%)	64 (59%)	NA (29.5, NA)	66.1% (55.9%, 74.5%)	52.5% (41.4%, 62.5%)
I	59	13 (22%)	46 (78%)	NA (NA, NA)	81.9% (68.9%, 89.8%)	74.2% (59.2%, 84.4%)
II/III	49	31 (63%)	18 (37%)	22.9 (12.1, 29.5)	46.6% (31.4%, 60.4%)	25.1% (12.2%, 40.3%)



Morphology Group	No. of Subject	Event	Censored	Median Survival (95% CI)	24 Mo Survival	60 Mo Survival
G3EEC	28	9 (32%)	19 (68%)	NA (26.4, NA)	80.3% (58.8%, 91.3%)	62.8% (40.4%, 78.8%)
NEM	80	35 (44%)	45 (56%)	42.7 (23.9, NA)	61.3% (49.2%, 71.4%)	48.9% (35.7%, 60.8%)



Overall Stage	No. of Subject	Event	Censored	Median Survival (95% CI)	24 Mo Survival	60 Mo Survival
All Stages	108	24 (22%)	84 (78%)	111.8 (77.7, NA)	87.8% (79.5%, 92.9%)	75.2% (62.6%, 84.1%)
I	59	12 (20%)	47 (80%)	111.8 (87.2, NA)	92.7% (81.7%, 97.2%)	78.1% (61.3%, 88.3%)
II/III	49	12 (24%)	37 (76%)	77.7 (60.5, 77.7)	81.7% (66.6%, 90.4%)	75.1% (58.2%, 86.0%)



Morphology Group	No. of Subject	Event	Censored	Median Survival (95% CI)	24 Mo Survival	60 Mo Survival
G3EEC	28	2 (7%)	26 (93%)	NA (87.2, NA)	100.0% (NA, NA)	95.2% (70.7%, 99.3%)
NEM	80	22 (28%)	58 (73%)	111.8 (60.5, NA)	83.9% (73.3%, 90.5%)	67.6% (51.5%, 79.4%)

Figure 1. — Disease-free and overall survival curves stratified by 2009 FIGO Stage and morphology group. A: DFS KM curve, entire cohort, by 2009 FIGO Stage; B: DFS KM curve, entire cohort, by Type II EC morphology group; C: OS KM curve, entire cohort, by 2009 FIGO Stage; D: OS KM curve, entire cohort, by Type II EC morphology group.

Table 3. — *Multivariable analysis of disease-free survival (overall, local, and distant), controlling for 2009 FIGO Stage and Type II endometrial cancer morphology group.*

		DFS		Local DFS		Distant DFS	
Covariate	Level	Hazard ratio (95% CI)	HR *p*-value	Hazard ratio (95% CI)	HR *p*-value	Hazard ratio (95% CI)	HR *p*-value
Age at surgery (years)	≥ 60	0.81 (0.44-1.47)	0.483	0.59 (0.27-1.27)	0.175	1.04 (0.50-2.17)	0.923
	< 60	-	-	-	-	-	-
Race	White	1.18 (0.58-2.42)	0.643	0.84 (0.32-2.27)	0.738	1.66 (0.73-3.76)	0.226
	Black	-	-	-	-	-	-
Morphology (group)*	NEM	1.54 (0.74-3.21)	0.249	2.20 (0.76-6.39)	0.147	1.44 (0.59-3.53)	0.424
	G3EEC	-	-	-	-	-	-
Morphology (individual)*	UPSC	1.58 (0.72-3.48)	0.257	2.64 (0.87-8.00)	0.085	1.50 (0.58-3.91)	0.406
	CS	1.53 (0.65-3.62)	0.329	1.81 (0.52-6.29)	0.348	1.27 (0.44-3.70)	0.659
	CCC	1.26 (0.27-5.85)	0.769	1.02 (0.11-9.21)	0.983	1.92 (0.38-9.56)	0.427
	G3EEC	-	-	-	-	-	-
Depth of myometrial invasion (MMI)	< 50% MMI	1.37 (0.68-2.76)	0.373	1.92 (0.73-5.06)	0.187	1.34 (0.59-3.07)	0.487
	≥ 50% MMI	-	-	-	-	-	-
LVSI	Absent	0.57 (0.25-1.34)	0.197	0.42 (0.13-1.30)	0.131	0.70 (0.26-1.86)	0.469
	Present	-	-	-	-	-	-
Cervical stromal invasion	No	0.80 (0.32-2.00)	0.637	0.48 (0.13-1.85)	0.288	0.73 (0.23-2.27)	0.585
	Yes	-	-	-	-	-	-
Presence of nodal disease	No	0.63 (0.29-1.37)	0.243	0.34 (0.12-0.97)	0.044	0.91 (0.36-2.31)	0.847
	Yes	-	-	-	-	-	-
Adjuvant radiation (any)	No	2.46 (1.20-5.04)	0.014	4.42 (1.92-10.17)	<.001	0.89 (0.33-2.38)	0.812
	Yes	-	-	-	-	-	-
Adjuvant chemotherapy (any)	No	1.30 (0.67-2.54)	0.438	1.40 (0.59-3.32)	0.444	1.19 (0.54-2.62)	0.674
	Yes	-	-	-	-	-	-
Type of adjuvant therapy	RT only	0.60 (0.23-1.58)	0.303	0.37 (0.12-1.17)	0.092	1.86 (0.49-7.10)	0.362
	CT only	2.48 (0.70-8.82)	0.161	3.33 (0.89-12.48)	0.074	2.00 (0.33-12.14)	0.450
	RT + CT	0.47 (0.19-1.16)	0.101	0.27 (0.09-0.80)	0.018	1.21 (0.34-4.34)	0.766
	None	-	-	-	-	-	-
Sandwich therapy	No	1.91 (0.79-4.65)	0.151	2.40 (0.70-8.22)	0.164	1.00 (0.39-2.53)	0.997
	Yes	-	-	-	-	-	-
Adjuvant radiation timing	Upfront	0.93 (0.42-2.02)	0.846	0.87 (0.29-2.60)	0.804	1.18 (0.49-2.83)	0.718
	Delayed	-	-	-	-	-	-
Primary radiation technique	EBRT	0.94 (0.30-2.92)	0.919	1.70 (0.33-8.81)	0.529	0.51 (0.15-1.76)	0.284
	IVB	-	-	-	-	-	-
Radiation boost	No	1.49 (0.66-3.35)	0.332	1.62 (0.55-4.77)	0.377	2.13 (0.88-5.16)	0.095
	Yes	-	-	-	-	-	-
Age (years)	Continuous	1.01 (0.98-1.04)	0.652	0.99 (0.95-1.04)	0.671	1.02 (0.98-1.06)	0.356
Time to chemo (months)	Continuous	0.78 (0.51-1.18)	0.235	0.89 (0.52-1.51)	0.656	0.68 (0.38-1.23)	0.204
Time to radiation (months)	Continuous	1.02 (0.90-1.16)	0.757	1.09 (0.96-1.24)	0.203	1.01 (0.87-1.17)	0.922
Time to surgery (months)	Continuous	0.97 (0.76-1.26)	0.840	1.00 (0.74-1.35)	0.991	0.93 (0.65-1.32)	0.669
Tumor size (mm)	Continuous	1.00 (1.00-1.01)	0.421	1.00 (0.99-1.01)	0.523	1.00 (0.99-1.01)	0.388

Abbreviations as seen in Tables 1 and 2; Local DFS = time from surgery to local site recurrence; Distant DFS = time from surgery to distant site recurrence; HR (hazard ratio) and *p*-value calculated using Cox proportional hazard models; HR > 1 = associated with less time to recurrence (poorer prognosis); *Controlling for FIGO Stage only.

0.014), and, specifically, locally (HR 4.42, 95% CI [1.92−10.17], $p \leq 0.001$). In a similar trend (not shown in Table 3), compared to combined adjuvant regimens, women receiving only adjuvant CT were significantly more likely to recur overall (HR 5.76 [1.85−17.95], $p = 0.003$), and, especially, locally (HR 12.98, 95% CI [3.56–47.30], $p \leq 0.0001$). While not significantly associated with overall DFS, patients who received combined adjuvant regimens were less likely to recur locally compared to patients who received no adjuvant therapy (HR 0.27, 95% CI [0.09−0.80], $p = 0.018$). Also, absence of LN disease at time of surgery was associated with better L-DFS (HR 0.34 [0.12−0.97], $p = 0.044$). Radiation timing (upfront *vs*. delayed) and 'time from surgery to RT' were not significantly associated with DFS or L-DFS. After adjusting for stage and morphology groups, no other measured covariate was significantly associated with distant disease progression (D-DFS).

Results of OS analysis are shown in Figure 1 and Table 4. Five-year OS rates were as follows: 75% for combined, 68% for NEM (67% [UPSC/CCC], 68% [CS]), and 95% for G3EEC. NEM patients had a median OS of 112 months for all stages, 112 months for Stage I and 78 months for stage II/III. Median OS for G3EEC patients could not be esti-

Table 4. — *Summary of median overall survival (OS), two- and five-year OS rates, stratified by FIGO Stage and Type II endometrial cancer morphology group.*

FIGO Stage	Median OS (months) NEM	G3EEC	*p*	2-year OS (%) NEM	G3EEC	5-year OS (%) NEM	G3EEC
ALL	111.8	N/A*	0.014	83.9	100.0	67.6	95.2
I	111.8	N/A*	0.048	89.7	100.0	68.0	100.0
II/III	77.7	N/A*	0.315	77.5	100.0	73.2	85.7

Abbreviations as seen in Table 1; OS= time from surgery to death/last follow up; Median OS, two-year OS%, five-year OS% calculated using Kaplan-Meier method; *p*-values calculated using Log-rank tests; *N/A – less than 50% had an event (death).

mated using KM method because more than 50% of patients with this histology survived to the end of follow-up. For total cohort and, specifically, among NEM patients, Stage I disease had a significantly longer OS when compared to Stage II/III ($p = 0.041$). When comparing across Type 2 EC groups, NEM patients had significantly poorer OS when compared to G3EEC overall ($p = 0.014$) and, specifically, within Stage I ($p = 0.048$).

Results of the multivariate regression model for OS, controlling for FIGO Stage and morphology groups, are shown in Table 5. NEM patients displayed a strongly association with worse OS when compared to G3EEC patients (HR 4.82, 95% CI [1.10−21.04, $p = 0.036$) when controlling for FIGO stage only. This association was particularly strong with CS patients (HR 5.98, 95% CI [1.20−29.79], $p = 0.029$). Compared to women who did not receive adjuvant therapy, a combined CT+RT approach significantly improved OS (HR 0.21, 95% CI [0.06−0.79], $p = 0.011$). Women who did not receive adjuvant CT had significantly worse OS when compared to those women who did receive an adjuvant CT regimen (HR 4.21, 95% CI [1.40−12.64], $p = 0.011$). Similarly, patients who received adjuvant RT without CT had significantly worse OS compared to patients treated with a combined (CT+RT) regimens (HR 6.53, 95% CI [1.79−23.77], $p = 0.004$). For age, as a continuous variable, risk of dying increased by 8% with each increasing year (HR 1.08, 95% CI [1.03−1.13], $p = 0.002$); however, there was no observed effect when this covariate was dichotomized above and below the cohort median cohort age of 60 years.

Table 5. — *Multivariable analysis of overall survival, controlling for FIGO Stage and Type II endometrial cancer morphology group*

Covariate	OS (Months) Level	Hazard Ratio (95% CI)	HR *p*-value
Age at surgery (years)	≥ 60	1.75 (0.72-4.25)	0.217
	< 60	-	-
Race	Caucasian	1.30 (0.49-3.44)	0.601
	Other	-	-
Morphology (group)*	NEM	4.82 (1.10-21.03)	0.036
	G3EEC	-	-
Morphology (individual)	UPSC	4.43 (0.97-20.22)	0.055
	CS	5.98 (1.20-29.79)	0.029
	CCC	4.36 (0.57-33.42)	0.156
	G3EEC	-	-
Depth of myometrial invasion (MMI)	< 50% MMI	0.94 (0.34-2.61)	0.907
	≥ 50% MMI	-	-
LVSI	Absent	1.08 (0.36-3.24)	0.888
	Present	-	-
Cervical stromal invasion	No	0.64 (0.13-3.20)	0.585
	Yes	-	-
Presence of nodal disease	No	1.21 (0.31-4.73)	0.779
	Yes	-	-
Adjuvant therapy (any)	No	2.08 (0.75-5.78)	0.159
	Yes	-	-
Adjuvant radiation (any)	No	1.99 (0.75-5.24)	0.166
	Yes	-	-
Adjuvant chemotherapy (any)	No	4.21 (1.40-12.64)	0.011
	Yes	-	-
Type of adjuvant therapy	RT only	1.03 (0.32-3.35)	0.956
	CT only	0.63 (0.07-5.48)	0.679
	RT + CT	0.21 (0.06-0.79)	0.021
	None	-	-
Sandwich therapy	No	2.62 (0.58-11.82)	0.210
	Yes	-	-
Radiation timing	Upfront	3.09 (0.86-11.08)	0.083
	Delayed	-	-
Primary radiation technique	EBRT	0.88 (0.24-3.26)	0.849
	IVB	-	-
Radiation boost	No	1.06 (0.37-3.00)	0.919
	Yes	-	-
Age (years)	Continuous	1.08 (1.03-1.13)	0.002
Time to chemo (months)	Continuous	0.65 (0.16-2.76)	0.562
Time to radiation (months)	Continuous	0.74 (0.53-1.02)	0.067
Time to surgery (months)	Continuous	1.10 (0.86-1.42)	0.452
Tumor size (mm)	Continuous	1.00 (0.98-1.01)	0.539

Abbreviations as seen in Tables 1 and 4; HR (hazard ratio) and *p*-value calculated using Cox proportional hazard models; HR > 1 = poorer prognosis; *Controlling for FIGO Stage only.

Discussion

This retrospective cohort study examined the clinical outcomes and impact of adjuvant therapies in women with FIGO 2009 Stage I-III Type II EC following definitive surgical treatment. The authors observed that adjuvant radiotherapy prolonged DFS through improved local control. While systemic chemotherapy was not shown to protect against local or distant recurrence, it significantly improved OS. Taken together, these results support a multimodal adjuvant approach for treatment of non-endometrioid (UPSC, CCC, CS) and high-grade endometrioid (G3EEC) morphologies.

The present two- and five-year OS rates of 88% and 75%, respectively, are consistent with previous reports [3, 4, 11, 15-18] even with over one-third of this study cohort presenting with Stage III disease (nearly 20% with nodal disease). Adjuvant CT significantly improved OS. The observed survival benefit of adjuvant CT was largely driven

by combined regimens since single modality adjuvant CT was rare in this cohort (n=4). That said, though adjuvant RT did not improve OS alone, the possibility of a synergistic benefit to OS for combined modalities should not be discounted.

The present two- and five-year observed DFS rate of 66 and 53%, respectively, were lower than previous reports [3, 18, 19]. This is likely due to the distribution of stages, the relatively high frequency of nodal disease in this cohort, and inclusion of potentially treatment resistant CS cases. Unlike in previous studies [9, 20], adjuvant CT failed to improve DFS. However, in agreement with previous reports [3, 4, 15, 19], adjuvant RT improved DFS in patients, regardless of stage or histology, with no significant difference between EBRT and IVB approaches. Desai *et al.* evaluated patterns of relapse in Stage I-II UPSC patients receiving adjuvant IVB ± CT and concluded that the risk of isolated pelvic recurrence was too low to warrant routine use of external pelvic RT [21]. Robbins *et al.* found no clinical benefit by adding pelvic radiation to an adjuvant regimen containing CT and IVB for Stage I-II UPSC. Despite these studies, some still favor pelvic RT in early stage UPSC for the potential benefit of preventing pelvic nodal recurrences [16, 22]. The ongoing GOG 249 (pelvic RT *vs.* IVB + CT) and PORTEC-3 (Pelvic RT *vs*. Pelvic RT + CT) trials will provide more insight into optimal RT and CT combinations for high-risk EC [19].

Studies across multiple solid tumor types have theorized that delaying RT/local therapy with induction regimens may select for resistant clones and thereby worsen outcomes [23]. The present results did not show this: local disease control was not reduced by having RT follow adjuvant full-course CT or sandwiched in between two three-cycle courses of CT. Similarly, 'time from surgery to start of RT' was also not significantly associated with DFS.

Sequencing of combined adjuvant regimens has significant institutional variability. 'Sandwich therapy' is one promising approach proposed for high-risk EC, where RT is given halfway through CT and followed by the remaining rounds of CT. This hypothetically allows for control of systemic disease with chemotherapy while treating micrometastasis in the pelvis with RT so that treatment sequence limits the overall toxicity and allows for maximum therapeutic dosing for both adjuvant modalities. Though phase II trials with both UPSC and CS have shown this treatment approach to be well-tolerated and efficacious [13, 16], 'sandwich therapy' was not associated with improved survival in the present study when compared to those with conventionally-sequenced CT+RT regimens. The main role of optimizing sequencing may be minimizing toxicity to ensure the completion of the prescribed treatment course.

When comparing high-risk morphology groupings, after adjusting for stage, NEM patients had worse overall prognoses compared to women with G3EEC. Although a high-grade endometrioid tumor, G3EEC has been reported to have a molecular profile somewhere between UPSC and lower grade EECs with similar immunohistologic characteristics compared to UPSC [7]. Due to conflicting data regarding similar [6, 7, 24] or better [8,25] outcomes compared to NEMs (including CS), G3EEC patients were treated as a distinct entity while all NEM patients were grouped together. Choosing to include CS with UPSC/CCC had a significant impact on results: compared to G3EEC patients, UPSC and CCC patients trended towards worse OS, while CS patients demonstrated a significantly worse prognosis consistent with previous CS studies [7, 12, 26]. Additionally, CS had been found to be particularly poorly-responsive to adjuvant treatment [12] with RT only shown to improve L-DFS and CT failing to show consistent survival benefit. A few small nonrandomized studies have shown a small but significant survival benefit with combined CT+RT, however randomized control trials will be needed to validate this approach [27].

OS outcome for NEMs compared to G3EECs were influenced by unbalanced rates of treatment failure for disease confined to the uterus (Stage I). Since these patients were primarily treated with adjuvant RT alone, this observed trend would seem to support an earlier role for multimodal adjuvant regimen for NEM. Previous studies have suggested a larger role for CT in early invasive Type 2 EC. In their cohort of Stage I UPSC, Fader *et al.* found that women with Stage IB UPSC had improved DFS when treated with CT ± RT compared to adjuvant RT alone [9]. Other studies comparing adjuvant RT alone *vs*. sequential CT+RT [11, 15] for early-stage, high-risk EC do not present nor discuss Stage I findings separate from Stage II outcomes.

A rare and perplexing subset of Stage IA EC is non-invasive high-risk EC confined to an endometrial polyp for which the role of adjuvant therapy remains controversial [17, 28-31]. A sub-analysis on the 20 patients (19 UPSC and one CS) with this type of presentation revealed five-year OS of 78%, which is consistent with a previous series by Chang-Halpenny *et al.* (N=32) [30]. Compared to only 20% of their cohort receiving adjuvant therapy, 80% of the present non-invasive high-risk polyps were treated with adjuvant therapy. However, in both cases, no adjuvant therapy of any type significantly affected DFS or OS outcomes. While observation alone following surgical staging may be appropriate for a subpopulation of these non-invasive Stage IA disease variants, further studies with larger cohorts are needed to reliably identify clinical markers for justifying the omission of adjuvant treatment [17]. For example, a recent multi-institutional study on UPSC polyp-confined disease, that included a portion of the present institution's patients, showed that UPSC polyps with positive peritoneal washings were associated with significantly poorer DFS compared to polyp disease with negative washings [31].

Given the rare incidence NEMs, the present cohort, though small, is among the largest reported by a single in-

stitution. Additionally, this study was conducted in a major AA patient population setting, with NEMs accounting for nearly 40% of all EC patients treated during the study period. This observed over-representation is well above the national average of 15% and supports the hypothesis that worse outcomes seen in the AA patients may be due to a higher relative incidence of Type II EC [1]. The present authors also chose to include CS in this study, and decided to group these patients with conventional Type II ECs (UPSC and CCC) in order to compare a collective NEM entity to G3EEC. The present two- and five-year survival rates were consistent with previous studies despite a relatively high frequency of Stage III patients. The present cohort's stage distribution provides a more realistic sample for assessing Type II EC patient outcomes treated with definitive surgery and impact of adjuvant treatments. Finally, with the increasing role of combined CT+RT regimens and sequencing, the present study is one of the first to assess and confirm that delaying RT in favor of initiating CT did not weaken local disease control.

In addition to the relatively small size of the cohort, the present study is inherently limited by its retrospective, non-randomized design. Longer follow up is needed to fully estimate median DFS and OS values. Small numbers of Stage II and CCC patients made it necessary to combine these with Stage III and UPSC, respectively, for relevant analyses. Variability of adjuvant regimens combined with less information regarding specific chemotherapeutic agents tempered conclusions the present authors could draw from their data, especially in regards to the role of single modality adjuvant CT.

Type II ECs are disproportionately responsible for nearly half of all EC-related deaths, with no clear consensus on the optimal role, combination, or sequence of adjuvant therapies for these highly-aggressive subtypes. The present results support a multimodal adjuvant approach for treating invasive NEM EC and locally-advanced stages of G3EEC. Since there was no observed difference in outcomes comparing different multimodal sequences, it is likely that optimal sequencing may best be used to maximize treatment tolerability, however, larger treatment groups are needed to further compare sequences and further assess its potential survival impact.

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