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Sequencing of therapy in women with stage III endometrial carcinoma receiving adjuvant combination chemotherapy and radiation

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HIGHLIGHTS

- Use of chemotherapy before radiation is increasing for with stage IIIC endometrial carcinoma.
- Among women with stage IIIC endometrial carcinoma treated with combination chemotherapy and external beam radiation.
- A strategy employing chemotherapy first is associated with improved survival compared to concurrent therapy.
- Prospective studies investigating optimal individualized sequences after initiation of chemotherapy are still needed.

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ABSTRACT

Objective. While women with stage III endometrial cancer are often treated with chemotherapy and external beam radiation, the optimal sequence of these modalities is unknown. We examined the association between the sequence of chemotherapy (CT) and external beam radiation therapy (RT) on survival for women with stage IIIC endometrial carcinoma.

Methods. The National Cancer Database was used to identify women with stage IIIC endometrial carcinoma treated with adjuvant CT and RT from 2004 to 2015. Patients were stratified based on the sequence of therapy: RT before CT, CT before RT, or concurrent therapy. The association between treatment sequence and mortality was examined through a weighted propensity score analysis.

Results. A total of 6981 patients were identified, including 5116 (73.3%) who received CT before RT, 696 (10.0%) who received RT before CT, and 1169 (16.7%) who received concurrent therapy. The use of CT-RT increased from 39.9% in 2004 to 75.5% in 2015, while use of RT-CT decreased from 34.0% to 4.4% and concurrent therapy decreased from 26.1% to 20.2% over the same period ($P < 0.001$). Compared to CT-RT, there was no difference in risk of mortality with RT before CT (HR = 1.01; 95% CI, 0.86–1.19) while concurrent therapy was associated with a 47% increased risk of mortality (HR = 1.47; 95% CI, 1.31–1.66). In a sensitivity analysis combining the groups that received RT first (RT before CT or concurrent RT-CT), mortality was 25% higher (HR = 1.25; 95% CI, 1.13–1.39) compared to a strategy of CT followed by RT.

Conclusion. Among women with stage IIIC endometrial carcinoma treated with combination chemotherapy and external beam radiation, a strategy employing chemotherapy first is associated with improved survival compared to concurrent therapy.

1. Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States [1]. While early-stage disease predominates

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and is associated with a favorable prognosis, advanced-stage disease is associated with higher rates of recurrence and decreased survival [2]. The 5-year survival rate is approximately 45–60% for stage III disease and 15–25% for stage IV disease, leading to the majority of endometrial carcinoma-associated deaths [3].

The optimal adjuvant therapy for women with advanced stage endometrial cancer remains uncertain. In 2006, GOG protocol 122 found that chemotherapy was superior to whole abdominal radiation [4]. Multiple studies have demonstrated that a combination of chemotherapy and radiation therapy is well tolerated and have suggested that combination therapy may improve survival [5–7]. As such, a combination of chemotherapy and external beam radiation is often used adjuvantly in women with stage III endometrial cancer.

While combination adjuvant therapy is often utilized, less is known about the optimal sequencing of chemotherapy and radiation therapy. One recently proposed approach is the "sandwich" method that involves chemotherapy followed by interval radiation followed by the completion of chemotherapy. This approach has been shown to be tolerable and effective [8–11]. A phase II trial examined the long-term effects of multimodal therapy in which the "sandwich" method was used for stage III, IV, and recurrent endometrial cancer in 41 women; it reported an overall survival of 70% [11]. However, there is little data comparing the "sandwich" method to sequential therapy in which chemotherapy is completed before radiation therapy.

In order to further elucidate the optimal sequence of adjuvant therapy, we analyzed the use and outcomes of various sequences of chemotherapy and radiation for women with endometrial cancer. Specifically, we explored the association between the sequence of chemotherapy (CT) and external beam radiation therapy (RT) on survival in women with stage IIIC endometrial cancer.

2. Methods

2.1. Data source and patient selection

The National Cancer Database (NCDB) was used as the data source for analysis. The NCDB is a clinical oncology database created and sponsored by both the American College of Surgeons and the American Cancer Society [12,13]. As a hospital-based registry, it gathers information on newly diagnosed cancer patients from over 1500 Commission on Cancer (CoC) affiliated hospitals across the country. Over one million cancer cases are reported to the NCDB from these CoC affiliated hospitals, allowing the database to capture approximately 70% of the new cancer diagnoses in the country [12]. Data collected includes tumor characteristics and staging, treatment and survival, and demographic and hospital characteristics [12,13]. Data collection occurs by trained registrars, and all data is regularly audited to maintain accuracy. All data used was de-identified and the Columbia University Institutional Review Board deemed the study exempt.

We identified women with stage IIIC endometrial carcinoma who underwent hysterectomy and were treated with both adjuvant chemotherapy (CT) and external beam radiation (RT) from 2004 to 2015 (Fig. 1). Staging was based on the TNM pathology stage group with stage IIIC defined as cancer growing in the body of the uterus without bladder or rectum involvement with spread to pelvic or para-aortic lymph nodes but not distant sites. Tumor histology was limited to carcinomas (endometrioid, serous, clear cell, endometrial not otherwise specified (NOS), and other) with exclusion of carcinosarcomas and sarcomas. The cohort was further limited by timing and type of chemotherapy and radiation therapy. Timing was determined by comparing the number of days from diagnosis to initiation of CT or RT versus the number of days from diagnosis to most definitive surgical procedure performed on the primary site. Women who had received any neoadjuvant therapy (CT or RT) prior to hysterectomy were excluded. In addition, radiation therapy was limited to external beam radiation or a combination of external beam radiation and brachytherapy with exclusion of brachytherapy alone. Any patients with missing CT or RT day variables or unknown adjuvant therapy status were also excluded.

Sequencing of adjuvant therapy was defined by comparing the days from diagnosis to initiation of either CT or RT. Three sequence groups were identified: CT before RT, RT before CT, and concurrent therapy. A window of 21 days between first day of CT and first day of RT was used to define concurrent therapy regardless of whether CT or RT was initiated first. The primary objective of this analysis was to examine

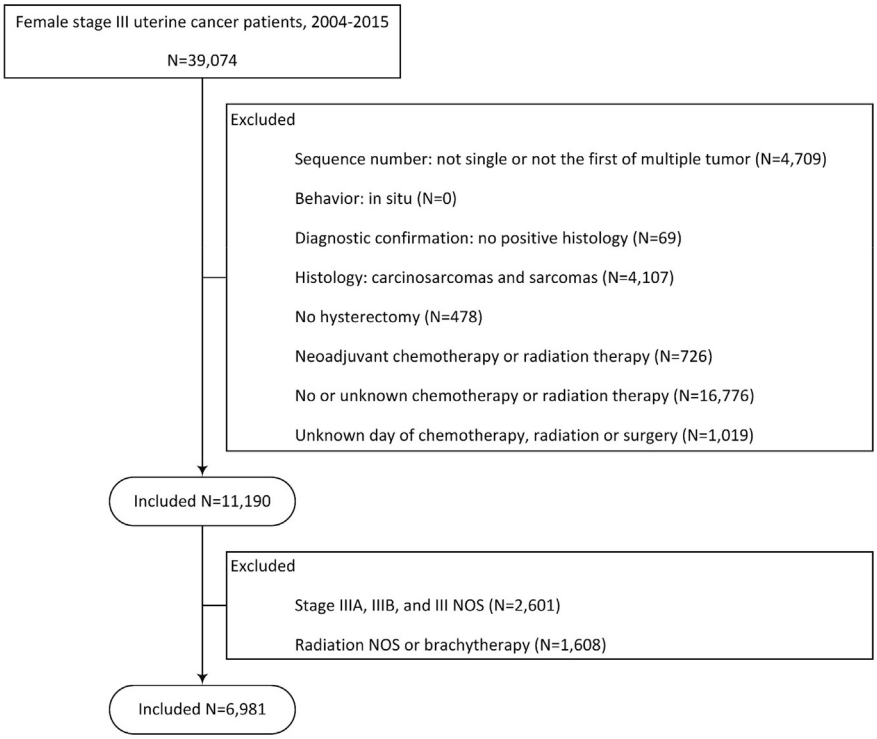

Fig. 1. Flowchart of cohort selection.

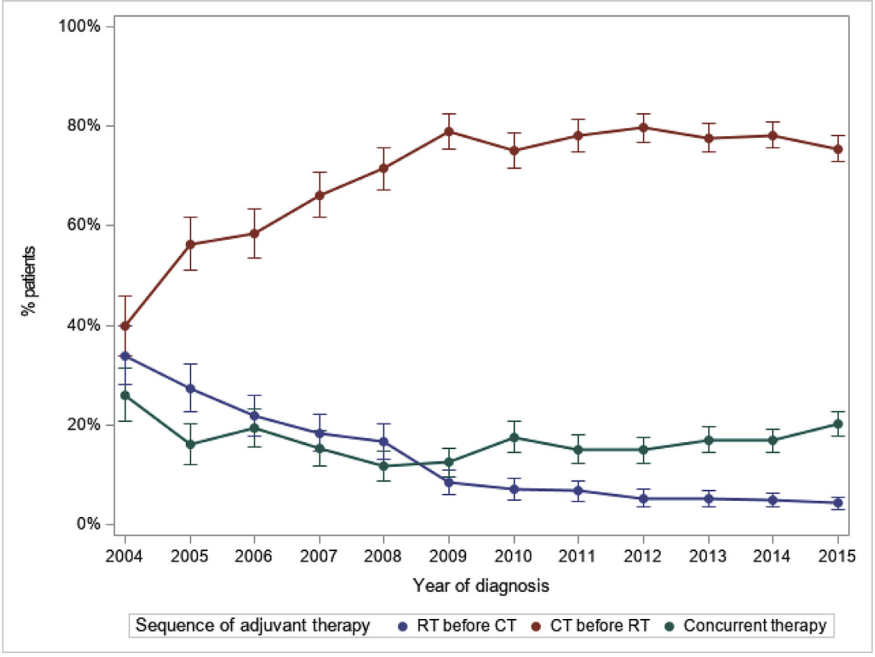

Fig. 2. Trend in adjuvant therapy sequence. Error bar represented 95% confidence interval ($P < 0.001$).

the association between the type of adjuvant therapy sequence and overall survival.

2.2. Clinical and demographic characteristics

Demographic characteristics of the cohort included age (<50, 50–59, 60–69, 70–79, ≥80 years), race (white, black, Hispanic, Other, Unknown), year of diagnosis, insurance status (private, Medicaid, Medicare, uninsured, other government/unknown), annual income (<$38,000, $38,000–$47,999, $48,000–$62,999, ≥$63,000, unknown), and area of residence (metropolitan, urban, rural, unknown). Comorbidity was estimated by the Deyo classification of the Charlson comorbidity score (0, 1, ≥2) [14,15].

Tumor characteristics included histology (endometrioid, serous, clear cell, EM NOS, other) and grade (well, moderate, poorly differentiated). Hospitals were classified as academic/research centers, community cancer centers, comprehensive community cancer centers, or integrated network cancer centers using the ACS CoC criteria, and also by region (northeast, midwest, south, west). Radiation type was classified as external beam alone or combination of external beam and brachytherapy. Data on specific chemotherapy agents used as well as number of courses was not available.

2.3. Statistical analysis

Trends in choice of adjuvant therapy sequence are reported by year with 95% confidence intervals from a multinomial regression model [16]. A univariate analysis of the sequence selection across the clinical and demographic variables was performed using χ^2 tests. A multivariable polytomous logistic regression model was developed to estimate predictors of RT before CT and for concurrent therapy compared to CT before RT. The model included all of the demographic and clinical variables as well as hospital factors. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

A propensity score (PS) analysis was conducted using the inverse probability treatment weighted (IPTW) to balance the clinical and demographic characteristics. We estimated each patient's PS to have RT before CT or concurrent therapy from the same polytomous logistic regression model. The weight was calculated as 1/PS and stabilized to reduce variability induced by large weights. An IPTW univariate analysis of the sequence selection across the clinical and demographic variables was performed to examine if all the covariates included in the PS model were well balanced.

An IPTW Cox proportional hazards model was developed to examine the effect of sequence selection on overall survival. Overall survival was estimated as the number of months from diagnosis until death from any cause. Results from survival analysis were reported as hazard ratios (HR) with 95% confidence intervals (CI). A sensitivity analysis was also conducted in which RT before CT and concurrent were combined using a Cox proportional hazards model adjusting for all the covariates. The proportional hazards assumption was tested by examining the correlation between Schoenfeld residuals and the function of time (as a linear term, log of time, and square of time). A sensitivity analysis was performed in which the chemotherapy cohorts were limited to only women coded as having received multiagent chemotherapy. All hypothesis tests were two-sided. A P-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3. Results

A total of 6981 patients was identified, including 5116 (73.3%) women who received CT before RT, 696 (10.0%) who received RT before CT, and 1169 (16.7%) who received concurrent therapy (Fig. 1). The use of CT before RT increased from 39.9% (95% CI, 33.9–46.0%) in 2004 to 75.5% (95% CI, 72.8–78.1%) in 2015, while use of RT before CT decreased from 34.0% (95% CI, 28.2–39.8%) to 4.4% (95% CI, 3.2–5.6%) and concurrent therapy decreased from 26.1% (95% CI, 20.7–31.5%) to 20.2% (95% CI, 17.7–22.6) over the same time period ($P < 0.001$) (Fig. 2).

Patient demographics stratified by sequence of adjuvant therapy were displayed in Table 1. Compared to women who received radiation first, women who received chemotherapy first were older, diagnosed more recently, more commonly Medicare recipients, more likely to be treated at comprehensive community cancer centers, residents of the western U.S., and in patients with serous histology ($P < 0.05$). After propensity score weighting, the cohorts were well-balanced (Table 2).

In a multivariable model, uninsured women (OR = 2.02; 95% CI, 1.38–2.97) and those treated at facilities in the midwest (OR = 2.09;

Table 1
Demographic and clinical characteristics of the cohort.

	RT before CT		CT before RT		Concurrent therapy		
	N	%	N	%	N	%	P-value
All	696	(10.0)	5116	(73.3)	1169	(16.7)	
Age							0.01
<50	101	(14.5)	535	(10.5)	140	(12.0)	
50–59	226	(32.5)	1573	(30.7)	384	(32.8)	
60–69	247	(35.5)	2054	(40.1)	432	(37.0)	
70–79	112	(16.1)	836	(16.3)	184	(15.7)	
≥80	10	(1.4)	118	(2.3)	29	(2.5)	
Race							0.15
White	564	(81.0)	4010	(78.4)	911	(77.9)	
Black	65	(9.3)	590	(11.5)	129	(11.0)	
Hispanic	32	(4.6)	255	(5.0)	72	(6.2)	
Other	30	(4.3)	229	(4.5)	43	(3.7)	
Unknown	*	*	32	(0.6)	14	(1.2)	
Year							<0.001
2004	85	(12.2)	100	(2.0)	65	(5.6)	
2005	89	(12.8)	184	(3.6)	52	(4.4)	
2006	85	(12.2)	228	(4.5)	75	(6.4)	
2007	75	(10.8)	272	(5.3)	62	(5.3)	
2008	72	(10.3)	310	(6.1)	50	(4.3)	
2009	41	(5.9)	391	(7.6)	61	(5.2)	
2010	39	(5.6)	417	(8.2)	97	(8.3)	
2011	41	(5.9)	482	(9.4)	93	(8.0)	
2012	37	(5.3)	563	(11.0)	105	(9.0)	
2013	40	(5.7)	608	(11.9)	133	(11.4)	
2014	47	(6.8)	772	(15.1)	166	(14.2)	
2015	45	(6.5)	789	(15.4)	210	(18.0)	
Insurance status							0.01
Private	383	(55.0)	2749	(53.7)	646	(55.3)	
Medicaid	44	(6.3)	333	(6.5)	64	(5.5)	
Medicare	211	(30.3)	1754	(34.3)	374	(32.0)	
Uninsured	42	(6.0)	171	(3.3)	50	(4.3)	
Other government/unknown	16	(2.3)	109	(2.1)	35	(3.0)	
Income							0.06
<$38,000	99	(14.2)	780	(15.2)	172	(14.7)	
$38,000–$47,999	174	(25.0)	1223	(23.9)	255	(21.8)	
$48,000–$62,999	192	(27.6)	1436	(28.1)	315	(26.9)	
≥$63,000	219	(31.5)	1641	(32.1)	415	(35.5)	
Unknown	12	(1.7)	36	(0.7)	12	(1.0)	
Area of residence							0.37
Metropolitan	556	(79.9)	4145	(81.0)	974	(83.3)	
Urban	105	(15.1)	740	(14.5)	139	(11.9)	
Rural	11	(1.6)	80	(1.6)	20	(1.7)	
Unknown	24	(3.4)	151	(3.0)	36	(3.1)	
Comorbidity							0.25
0	551	(79.2)	3966	(77.5)	912	(78.0)	
1	121	(17.4)	955	(18.7)	227	(19.4)	
≥2	24	(3.4)	195	(3.8)	30	(2.6)	
Hospital type							<0.001
Academic/research	307	(44.1)	2068	(40.4)	581	(49.7)	
Community cancer	39	(5.6)	308	(6.0)	64	(5.5)	
Comprehensive community cancer	273	(39.2)	2088	(40.8)	374	(32.0)	
Integrated network cancer	77	(11.1)	652	(12.7)	150	(12.8)	
Hospital region							<0.001
Northeast	129	(18.5)	1115	(21.8)	319	(27.3)	
Midwest	309	(44.4)	1477	(28.9)	344	(29.4)	
South	176	(25.3)	1637	(32.0)	385	(32.9)	
West	82	(11.8)	887	(17.3)	121	(10.4)	
Histology							<0.001
Endometrioid	446	(64.1)	3029	(59.2)	741	(63.4)	
Serous	61	(8.8)	811	(15.9)	131	(11.2)	
Clear cell	19	(2.7)	158	(3.1)	42	(3.6)	
EM NOS	165	(23.7)	1049	(20.5)	227	(19.4)	
Other	*	*	69	(1.3)	28	(2.4)	
Grade							<0.001
Well	77	(11.1)	690	(13.5)	163	(13.9)	
Moderate	240	(34.5)	1369	(26.8)	360	(30.8)	
Poorly	299	(43.0)	2215	(43.3)	444	(38.0)	
Unknown	80	(11.5)	842	(16.5)	202	(17.3)	
Radiation type							0.20
Combination	261	(37.5)	1934	(37.8)	409	(35.0)	
External beam	435	(62.5)	3182	(62.2)	760	(65.0)	

* Cells <10.

Table 2
Inverse probability of treatment weighted demographic and clinical characteristics.

	RT before CT		CT before RT		Concurrent therapy		
	N	%	N	%	N	%	P-value
All	700	(10.0)	5113	(73.2)	1173	(16.8)	
Age							0.85
<50	70	(9.9)	567	(11.1)	128	(10.9)	
50–59	236	(33.7)	1602	(31.3)	373	(31.8)	
60–69	281	(40.1)	1997	(39.1)	456	(38.8)	
70–79	101	(14.5)	831	(16.3)	189	(16.1)	
≥80	12	(1.8)	116	(2.3)	28	(2.3)	
Race							0.94
White	538	(76.9)	4023	(78.7)	923	(78.6)	
Black	91	(12.9)	570	(11.2)	131	(11.2)	
Hispanic	39	(5.6)	263	(5.1)	58	(4.9)	
Other	28	(4.0)	219	(4.3)	53	(4.6)	
Unknown	*	*	38	(0.7)	*	*	
Year							0.99
2004	25	(3.6)	183	(3.6)	46	(3.9)	
2005	34	(4.8)	240	(4.7)	57	(4.9)	
2006	38	(5.4)	285	(5.6)	69	(5.9)	
2007	41	(5.8)	300	(5.9)	70	(6.0)	
2008	42	(6.0)	315	(6.2)	72	(6.2)	
2009	51	(7.3)	363	(7.1)	85	(7.3)	
2010	55	(7.9)	405	(7.9)	89	(7.6)	
2011	59	(8.5)	453	(8.9)	115	(9.8)	
2012	65	(9.2)	516	(10.1)	116	(9.9)	
2013	71	(10.1)	570	(11.1)	124	(10.5)	
2014	91	(12.9)	720	(14.1)	160	(13.6)	
2015	129	(18.4)	764	(14.9)	170	(14.5)	
Insurance status							0.70
Private	384	(54.9)	2760	(54.0)	624	(53.1)	
Medicaid	45	(6.5)	324	(6.3)	81	(6.9)	
Medicare	218	(31.2)	1714	(33.5)	397	(33.9)	
Uninsured	29	(4.1)	193	(3.8)	48	(4.1)	
Other government/unknown	24	(3.4)	121	(2.4)	24	(2.0)	
Income							0.98
<$38,000	105	(15.0)	768	(15.0)	175	(14.9)	
$38,000–$47,999	179	(25.6)	1209	(23.6)	283	(24.1)	
$48,000–$62,999	188	(26.8)	1425	(27.9)	334	(28.4)	
≥$63,000	223	(31.9)	1669	(32.6)	371	(31.6)	
Unknown	*	*	42	(0.8)	11	(0.9)	
Area of residence							1.00
Metropolitan	572	(81.7)	4153	(81.2)	950	(81.0)	
Urban	94	(13.4)	722	(14.1)	168	(14.3)	
Rural	13	(1.9)	82	(1.6)	19	(1.6)	
Unknown	21	(3.0)	156	(3.1)	37	(3.1)	
Comorbidity							0.94
0	539	(77.0)	3977	(77.8)	906	(77.2)	
1	134	(19.2)	953	(18.6)	228	(19.5)	
≥2	27	(3.8)	183	(3.6)	39	(3.3)	
Hospital type							0.46
Academic/research	297	(42.4)	2175	(42.5)	503	(42.9)	
Community cancer	55	(7.8)	304	(5.9)	75	(6.4)	
Comprehensive community cancer	274	(39.2)	2001	(39.1)	447	(38.1)	
Integrated network cancer	74	(10.6)	633	(12.4)	148	(12.6)	
Hospital region							0.71
Northeast	151	(21.5)	1150	(22.5)	259	(22.1)	
Midwest	199	(28.5)	1556	(30.4)	359	(30.6)	
South	245	(35.0)	1610	(31.5)	371	(31.6)	
West	105	(15.0)	797	(15.6)	184	(15.7)	
Histology							0.86
Endometrioid	414	(59.1)	3077	(60.2)	700	(59.7)	
Serous	95	(13.5)	736	(14.4)	173	(14.8)	
Clear cell	18	(2.6)	162	(3.2)	35	(3.0)	
EM NOS	165	(23.5)	1063	(20.8)	247	(21.1)	
Other	*	*	75	(1.5)	18	(1.6)	
Grade							0.86
Well	100	(14.3)	683	(13.4)	160	(13.6)	
Moderate	202	(28.8)	1437	(28.1)	320	(27.2)	
Poorly	300	(42.8)	2171	(42.5)	505	(43.0)	
Unknown	99	(14.1)	822	(16.1)	189	(16.1)	
Radiation type							0.82
Combination	252	(36.0)	1904	(37.2)	435	(37.1)	
External beam	448	(64.0)	3209	(62.8)	739	(62.9)	

* Cells <10.

Table 3
Multivariable polytomous logistic regression model for predictors of RT before CT and concurrent therapy, comparing to CT before RT.

	OR, RT before CT vs. CT before RT	OR, concurrent therapy vs. CT before RT
Age		
<50	Referent	Referent
50–59	0.91 (0.69–1.20)	0.97 (0.77–1.21)
60–69	0.94 (0.71–1.25)	0.91 (0.72–1.14)
70–79	1.11 (0.77–1.59)	0.99 (0.74–1.32)
≥80	0.75 (0.36–1.57)	1.15 (0.71–1.87)
Race		
White	Referent	Referent
Black	1.09 (0.80–1.49)	1.02 (0.82–1.28)
Hispanic	1.15 (0.77–1.73)	1.28 (0.96–1.70)
Other	1.31 (0.85–2.01)	0.92 (0.65–1.30)
Unknown	1.15 (0.42–3.13)	1.95 (1.02–3.72)*
Year		
2004	Referent	Referent
2005	0.49 (0.33–0.73)*	0.41 (0.26–0.64)*
2006	0.40 (0.27–0.60)*	0.48 (0.32–0.72)*
2007	0.29 (0.19–0.43)*	0.33 (0.22–0.51)*
2008	0.24 (0.16–0.36)*	0.23 (0.15–0.36)*
2009	0.11 (0.07–0.17)*	0.23 (0.15–0.35)*
2010	0.10 (0.06–0.15)*	0.34 (0.23–0.50)*
2011	0.09 (0.06–0.14)*	0.28 (0.19–0.42)*
2012	0.07 (0.04–0.11)*	0.28 (0.19–0.41)*
2013	0.07 (0.04–0.11)*	0.32 (0.22–0.47)*
2014	0.06 (0.04–0.10)*	0.31 (0.22–0.45)*
2015	0.06 (0.04–0.09)*	0.39 (0.27–0.56)*
Insurance status		
Private	Referent	Referent
Medicaid	1.13 (0.79–1.61)	0.84 (0.63–1.12)
Medicare	0.96 (0.76–1.21)	0.95 (0.79–1.14)
Uninsured	2.02 (1.38–2.97)*	1.21 (0.86–1.70)
Other government/unknown	1.10 (0.62–1.93)	1.34 (0.90–2.00)
Income		
<$38,000	Referent	Referent
$38,000–$47,999	0.95 (0.71–1.26)	0.96 (0.77–1.20)
$48,000–$62,999	0.97 (0.73–1.29)	1.00 (0.80–1.24)
≥$63,000	1.03 (0.77–1.37)	1.08 (0.87–1.35)
Unknown	1.48 (0.60–3.67)	1.29 (0.59–2.82)
Area of residence		
Metropolitan	Referent	Referent
Urban	0.93 (0.47–1.84)	1.21 (0.72–2.02)
Rural	0.87 (0.48–1.57)	0.87 (0.57–1.34)
Unknown	1.08 (0.84–1.39)	0.86 (0.70–1.06)
Comorbidity		
0	Referent	Referent
1	0.99 (0.79–1.23)	1.07 (0.90–1.26)
≥2	1.07 (0.67–1.70)	0.70 (0.47–1.04)
Hospital type		
Academic/research	Referent	Referent
Community cancer	0.70 (0.48–1.03)	0.76 (0.56–1.01)
Comprehensive community cancer	0.86 (0.71–1.04)	0.68 (0.59–0.79)*
Integrated network cancer	0.91 (0.68–1.21)	0.90 (0.73–1.11)
Hospital region		
Northeast	Referent	Referent
Midwest	2.09 (1.64–2.65)*	0.86 (0.72–1.03)
South	1.03 (0.79–1.34)	0.89 (0.74–1.06)
West	0.86 (0.63–1.18)	0.51 (0.41–0.65)*
Histology		
Endometrioid	Referent	Referent
Serous	0.47 (0.34–0.64)*	0.69 (0.55–0.87)*
Clear cell	0.85 (0.50–1.43)	1.17 (0.81–1.69)
EM NOS	1.04 (0.85–1.29)	0.95 (0.80–1.12)
Other	0.35 (0.13–0.88)*	1.55 (0.98–2.46)
Grade		
Well	Referent	Referent
Moderate	1.40 (1.05–1.87)*	1.09 (0.88–1.34)
Poorly	1.27 (0.95–1.69)	0.88 (0.71–1.09)
Unknown	1.24 (0.87–1.76)	1.07 (0.84–1.36)
Radiation type		
External beam	Referent	Referent
Combination	1.00 (0.84–1.19)	0.88 (0.77–1.01)

Polytomous logistic regression model included age, race, year, insurance status, income, area of residence, comorbidity, hospital type and region, histology, grade, and radiation type.
* p-Value <0.05.

95% CI, 1.64–2.65) were more likely to receive RT before CT as compared to CT before RT (Table 3). In contrast, women with serous tumors (OR = 0.47; 95% CI, 0.34–0.64) and other histologies (OR = 0.35; 95% CI, 0.13–0.88) were less likely to receive RT before CT as compared to CT before RT. Use of concurrent chemotherapy and radiation was lower in women treated in the west (vs. northeast), those with serous histologic subtypes (vs. endometrioid tumors), and in women treated at comprehensive community cancer centers (vs. academic/research facilities) ($P < 0.05$ for all). Use of radiation first and concurrent chemotherapy and radiation both decreased over time compared to chemotherapy followed by radiation ($P < 0.05$).

The median follow-up of the cohort was 43 months (IQR 25–71), while 5-year survival was 69.2% (67.8–70.6%). Compared to those who received CT before RT, there was no difference in risk of mortality with RT then CT (HR = 1.01; 95% CI, 0.86–1.19) while concurrent therapy was associated with a 47% increased risk of mortality (HR = 1.47; 95% CI, 1.31–1.66). Fig. 3 displays the IPTW survival curves by sequence of treatment ($P < 0.001$). Five-year survival was 70.8% (95% CI, 69.1–72.4%) among women who received CT before RT, 69.9% (95% CI, 64.7–74.5%) for those treated with RT before CT, and 61.2% (95% CI, 57.4–64.8%) for those who received concurrent therapy. In a sensitivity analysis comparing all women who received RT first (RT first then CT or concurrent RT-CT), mortality was 25% higher (HR = 1.25; 95% CI, 1.13–1.39) compared to a strategy of CT followed by RT. A second sensitivity analysis was performed in which the cohort was limited to patients who were recorded as having received multiagent chemotherapy. Overall, 89.9% of the cohort received multiagent chemotherapy. Survival findings from this analysis were similar to the primary cohort.

4. Discussion

This analysis suggests that the use of chemotherapy before radiation is increasing while use of RT before CT has decreased for women with stage IIIC endometrial carcinoma. An adjuvant therapy sequence selection using chemotherapy first was associated with improved survival compared to concurrent therapy.

In the past decades, external beam radiotherapy had been the standard adjuvant treatment for women with high-risk endometrial cancer. However, while radiotherapy was shown to delay pelvic recurrences, there was no survival benefit associated with adjuvant pelvic radiotherapy [17,18]. In order to decrease the risk of systemic disease, chemotherapy has been added to treatment approaches for women with advanced stage endometrial cancer [19,20].

The optimal adjuvant therapy for women with stage III endometrial cancer remains an area of controversy. While multiple studies have suggested that combination chemoradiotherapy is associated with improved overall survival and progression-free survival in women with stage III endometrial carcinoma, recent randomized trials have questioned the value of combination therapy [5–7,21]. The PORTEC-3 trial compared external beam radiotherapy to chemotherapy with external beam radiation in women with stage I-III endometrial cancer.

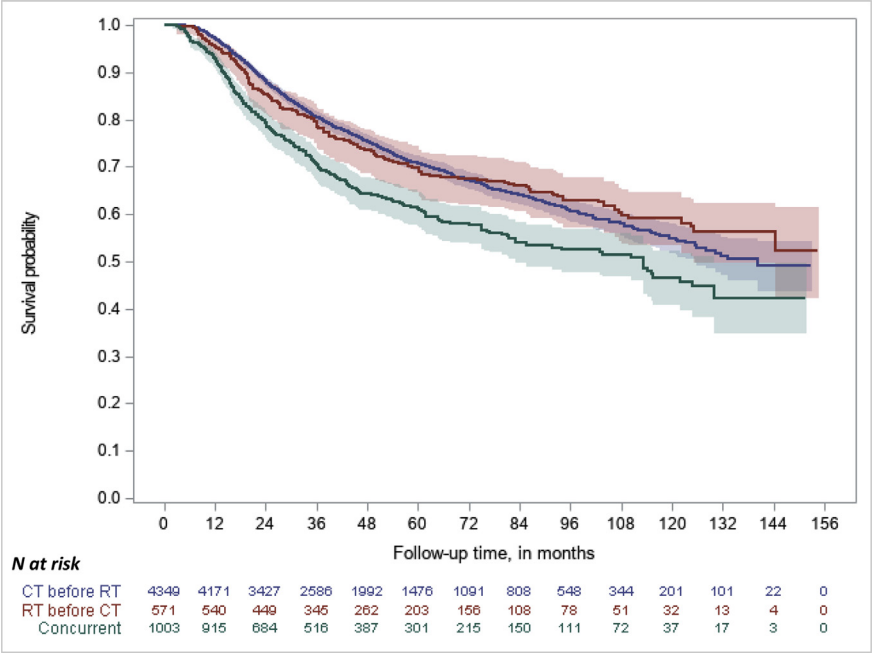

Fig. 3. IPTW survival curves by adjuvant therapy sequence. Shade represented 59% confidence interval ($P < 0.001$).

The study found that combination therapy was associated with improved progression free survival, but no difference in overall survival [22]. Of note, the PORTEC-3 trial's adjuvant therapy sequence approach used external beam pelvic radiotherapy first with adjuvant chemotherapy started within 3 weeks after completion of radiotherapy [22].

Similarly, GOG 258 compared six cycles of chemotherapy alone to external beam radiation in combination with chemotherapy in patients with stage III-IVA endometrial cancer [23]. Though the data is not yet mature, combination therapy was more toxic and there was no difference in recurrence free or overall survival [23]. Preliminary results suggested no difference in overall or recurrence-free survival between the two groups, but reported significantly more toxicity in women who received combination therapy [23]. Like PORTEC-3, GOG 258 utilized a similar adjuvant therapy sequence with radiation before chemotherapy.

For women receiving combination chemotherapy and radiation, determining the optimal sequence of therapy remains an area of uncertainty. Clinical issues as well as proposed treatment advantages have all contributed to the debate around the optimal sequence. In one phase II trial, Glasgow and colleagues found that if radiation therapy were given prior to chemotherapy, it took a median of 42.5 days (range 34–62) to complete the radiation therapy, resulting in a treatment break before beginning chemotherapy [11]. Conversely, they also found that patients had difficulty finishing radiation therapy if all six courses of chemotherapy were given initially [11]. However, one retrospective analysis determined that systemic failures were lower for patients who received all six cycles of chemotherapy upfront compared to those who received fewer cycles after radiation therapy [24]. One hypothesis for this decrease in systemic failures is the earlier treatment of occult disseminated micrometastatic disease and decreased likelihood of chemotherapy delay due to radiation-induced toxicity [10]. While few studies examined concurrent therapy, Modh and colleagues concluded that patients treated with concurrent combined modality treatment had higher toxicity events and worse quality of life metrics [24].

In order to balance the benefits of each treatment modality while limiting therapy toxicities, "sandwich" therapy, in which chemotherapy is followed by interval radiation then completion of chemotherapy, has been shown to be feasible and effective [8–11]. A study by Secord et al. concluded that the sandwich method was superior to sequential therapy, reporting an improved 3-year overall survival of 88% and progression-free survival of 69% in patients with stage III-IV endometrial cancer [8]. However, more recent studies found no statistically significant differences in overall survival, local progression-free survival, or distant metastasis-free survival [10]. As pointed out by Lu and colleagues, there is little data on the long-term impact of disrupting chemotherapy mid-course as well as on the optimal number of chemotherapy cycles to administer before and after radiotherapy [10]. Despite continued uncertainties around sandwich versus sequential adjuvant therapy, both approaches initiate treatment with chemotherapy and thus, as per our results, confer better survival than sequences without chemotherapy first. Our findings suggest that sequential therapy, whether beginning with radiation or chemotherapy, is superior to concurrent treatment.

While this study benefits from the inclusion of a large number of patients, we recognize several important limitations. First, although NCDB captures data on use of chemotherapy, specifics, such as the agents utilized, number of cycles, and timing, are not recorded. As such, it is difficult to distinguish patients who received radiosensitizing chemotherapy from those who received traditional systemic therapy. However, in a sensitivity analysis excluding patients who received single agent chemotherapy, a surrogate for radiosensitizing chemotherapy, our results were largely unchanged. Similarly, specifics on radiation treatment are lacking, including fields and information on dosing. Second, while overall mortality is captured, cancer-specific survival is unavailable. Third, unmeasured confounders may have influenced not only the allocation of treatment, but also outcomes. Finally, data on toxicity, both short and long term, are lacking. Clearly how adjuvant treatment influences quality of life is of great importance, particularly among elderly women.

In summary, our data suggest that the use of CT before RT is increasing among women with stage IIIC endometrial cancer. While there was no clear difference in survival whether chemotherapy or radiation was initiated first, concurrent therapy is associated with decreased survival. Further data to develop individualized adjuvant treatment strategies for women with stage IIIC endometrial cancer is clearly needed.

Author contributions

Conception and design: all authors.
Data acquisition: Wright.

Data analysis: Wright, Chen, Latham.
Manuscript drafting, revision: all authors.
Final approval: all authors.

Declaration of Competing Interest

Dr. Wright has served as a consultant for Tesaro and Clovis Oncology. Dr. Neugut has served as a consultant to Otsuka, Hospira, and United Biosource Corporation. He is on the scientific advisory board of EHE, Intl. No other authors have any conflicts of interest or disclosures.

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