Gynecologic Oncology 153 (2019) 41–48

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Association of chemotherapy and radiotherapy sequence with overall survival in locoregionally advanced endometrial cancer

Chelain R. Goodman [a,*], Saleh Hatoum [a], Brandon-Luke L. Seagle [b], Eric D. Donnelly [a], Emma L. Barber [b], Shohreh Shahabi [b], Daniela E. Matei [b], Jonathan B. Strauss [a]

[a] Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, United States of America
[b] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, United States of America

HIGHLIGHTS

- No randomized trial of advanced endometrial cancer has evaluated treatment with chemotherapy (CT) before radiotherapy (RT).
- Women who received RT after CT had longer survival than those who received RT before CT or either treatment alone.
- Treatment with multi-agent CT before RT should be considered for inclusion as a treatment arm in future prospective trials.

ARTICLE INFO

Article history:
Received 29 November 2018
Received in revised form 2 January 2019
Accepted 4 January 2019
Available online 16 January 2019

Keywords:
Radiotherapy
Chemotherapy
Endometrial cancer

ABSTRACT

Objective. The optimal adjuvant management of women with FIGO Stage III-IVA endometrial cancer (EC) is unclear. While recent prospective data suggest that treatment with pelvic radiotherapy (RT) prior to chemotherapy (CT) is not associated with a survival benefit compared to CT alone, no prospective randomized trial has included a treatment arm in which CT is given before RT.

Methods. An observational cohort study was performed on women with FIGO Stage III-IVA Type 1 (grade 1–2, endometrioid) EC who underwent hysterectomy and received multi-agent CT and/or RT from 2004 to 2014 at Commission on Cancer-accredited hospitals. Multivariable parametric accelerated failure time models were performed to estimate the association of sequence of adjuvant CT and RT with overall survival (OS) using propensity score-adjusted matched cohorts.

Results. Of 5795 women identified, 1260 (21.7%) received RT only, 2465 (42.5%) received CT only, 593 (9.7%) received RT before CT, and 1506 (26.0%) received RT after CT. Women who received RT after CT experienced significantly longer 5-year OS than women who received RT before CT (5-year OS: 80.1% vs 73.3%; time-ratio (TR) = 1.37, 95% CI = 1.18–1.58, $P < 0.001$), CT only (68.9%; TR = 1.33, 95% CI = 1.19–1.48, $P < 0.001$), or RT only (64.5%, TR = 1.50, 95% CI = 1.32–1.70, $P < 0.001$).

Conclusions. For women with advanced EC, treatment with multi-agent CT followed by RT is associated with longer OS compared with treatment with RT followed by CT or either treatment alone. These hypothesis-generating data support inclusion in future prospective trials of regimens in which multi-agent CT starts prior to RT.

1. Introduction

The optimal adjuvant management of stage III-IVA endometrial cancer (EC) remains a source of debate. Results from recent trials PORTEC-3 and the Gynecology Oncology Group (GOG) 258 suggest minimal improvement in overall survival (OS) with combined chemoradiotherapy (CRT) compared to chemotherapy (CT) or pelvic radiotherapy (RT) alone [1,2]. These data do, however, demonstrate the potential complementary roles of both adjuvant therapies: CT in the reduction of distant recurrence and RT in minimizing locoregional recurrence (LRR). A subset analysis of PORTEC-3 demonstrated that Stage III patients treated with CRT experienced longer 5-year (y) progression-free survival (PFS) [1]. No prospective trial has included a treatment arm in which CT is given before RT or sequenced in a "sandwich" fashion. This begs the question: should chemotherapy be the first adjuvant

* Corresponding author at: Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, 251 E Huron St, Room LC-178, Chicago, IL 60611, United States of America.
E-mail address: chelain.goodman@northwestern.edu (C.R. Goodman).

https://doi.org/10.1016/j.ygyno.2019.01.007
0090-8258/

therapy or the only adjuvant therapy? Furthermore, given that the addition of RT did not yield an OS benefit for the group as a whole, the patients for whom this treatment strategy may yield the greatest benefit would most likely have significant risk for LRR while a relatively low competing risk of distant failure. This may reflect a patient population with a combination of high-risk features for LRR, such as deep myometrial invasion, serosal involvement, cervical invasion, or large tumor size, in addition to the absence of high-risk features for distant failure, such as high grade or non-endometrioid histologies. To test this hypothesis, the National Cancer Database (NCDB) was queried for women with locally advanced Type 1 EC who underwent hysterectomy and received adjuvant CT and/or RT. Survival analyses were performed to estimate the association of sequence of CT and RT with OS in propensity score-matched cohorts.

2. Methods and materials

2.1. Cohort selection

The NCDB (2004–2015) was queried for women with FIGO Stage III-IVA (pT3–4 or pN1–2) Type 1 (grade 1–2, endometrioid histology) EC following hysterectomy (Fig. S1). The NCDB is a nationwide, facility-based comprehensive clinical surveillance resource oncology dataset established by the Commission on Cancer of the American College of Surgeons and the American Cancer Society in 1989 that captures 70% of all newly diagnosed malignancies [3]. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. Local institutional review board approval and informed consent were not required for analysis of de-identified data.

Women who received single-agent CT only, inadequate RT (<45 Gray (Gy), <25 fractions, or unknown) were excluded, as were women whose primary listed RT volume was other than pelvis or uterus. It was not possible to determine if pelvic and/or para-aortic lymph node volumes were included in the RT treatment plan. The sequence of RT and CT was determined by documented treatment start dates (RT before CT: RT start date ≥30 days (d) before CT start date; RT after CT: RT start date ≥ 62 d after CT start date). Women with unknown sequence of RT and CT were excluded. To clearly define sequence of RT and CT, women with a documented RT start date of 15–61 d following the start of CT were excluded, as were women for whom the start date for RT was >200 d either before or after the start date of CT (Fig. S2). To account for immortal-time bias, follow-up time was calculated from the start date of the patient's last initiated treatment. Covariates were included in the creation of the matched cohorts and to adjust for potential confounding during regression analyses (Supplemental Methods).

2.2. Statistical analyses

Baseline characteristics between patient groups were compared using the Fisher's exact test for categorical data, the Mann-Whitney *U* test for non-normally distributed numeric or ordinal data, or the *t*-test or ANOVA for normally distributed data. Five-year restricted mean survival times (RMST) for OS and 5 y OS proportions were estimated using the Kaplan-Meier method and compared with the log-rank test. Survival curves were plotted as unadjusted Kaplan-Meier estimates.

Multivariable parametric accelerated failure time (AFT) models using the generalized gamma distribution were used, as described previously, to evaluate the association of adjuvant therapy modality and sequence with OS [4]. This model was chosen in place of the Cox proportional hazards (PH) model due to the presence of significant non-PH among women who received CT only when the Cox model was used for the multivariable analyses [5]. When the PH assumption is found to be violated using the Cox model, the AFT model for multivariable analyses provides better goodness-of-fit to the observed data and therefore more robust statistical inference [6–9]. The AFT model estimates the time ratio (TR), which describes the multiplicative factor by which the time-to-event is related between two groups. A TR > 1 describes longer survival. Covariates utilized in analyses were selected a priori based on clinical knowledge and availability and are described in detail in Supplemental Methods.

To reduce potential confounding, nearest-neighbor propensity score-matching was performed without replacement using a caliper size of 0.05 for each paired subset to generate well-balanced matched cohorts, as described in detail in the Supplemental Methods. Propensity score-matched and inverse probability-weighted cohort analyses were performed to reduce treatment-assignment biases related to measured covariates [10]. Analyses were performed both for all patients as well as for the matched patient cohorts within each paired subset. All statistical tests were two-tailed with an alpha of 0.05 used as the cut-off for statistical significance. Sensitivity analyses were performed on an expanded cohort of women to also include Grade 3 endometrioid histology. To test the robustness of the observed results, sensitivity of TR estimates to a possible unmeasured confounder was explored [11,12]. Statistical analyses were performed in Rstudio v1.1.453 using MatchIt, survival, and flexsurv, packages [7,13–15].

3. Results

3.1. Cohort selection

Of the 5795 women identified with FIGO Stage III-IVA Type 1 (endometrioid histology, grades 1 or 2) uterine cancer with known type of adjuvant therapy who underwent hysterectomy and received either RT and/or CT, 1260 (21.7%) received RT only, 2465 (42.5%) received CT only, 564 (9.7%) received RT before CT, and 1506 (26.0%) received RT after CT. Clinicopathologic and demographic characteristics of women within each treatment subgroup are shown in Table S1. The most common fractionation scheme for RT was 45 Gy in 25 fractions, while the second most common was 50.4 Gy in 28 fractions. Clinicopathologic and treatment characteristics were well-balanced for all matched cohorts (Tables S2–S9).

3.2. Kaplan-Meier estimates and multivariable survival analyses

Unadjusted survival curves and estimates of 5 y survival probabilities, and RMST are shown for all women (Table 1; Fig. 1). In univariate analyses of the unadjusted cohorts, women who received RT after CT had significantly longer 5 y OS compared to women who received RT before CT (5 y OS: 80.1% vs. 73.3%) or women who received either RT alone (68.9%) or CT alone (64.5%; Log-Rank P < 0.001; Table 1). In multivariable analysis of all patients, treatment with RT after CT was associated with significantly longer OS than treatment with RT before CT (TR = 1.31, 95% CI = 1.08–1.58, P < 0.001), CT alone (TR = 1.37, 95% CI = 1.19–1.57, P < 0.001), or RT alone (TR = 1.41, 95% CI = 1.21–1.64, P < 0.001). Older age, more advanced tumor or nodal stage, higher grade, receipt of omentectomy, positive peritoneal cytology, positive margin status, black race, Medicare insurance or no insurance, higher comorbidity scores, a history of prior cancer, and treatment other than at an academic facility were also associated with significantly shorter OS in this model, while Hispanic ethnicity was associated with significantly longer OS (Table 1).

In multivariable analysis of propensity-score matched cohorts for the subset of women who received both RT and CT, treatment with RT after CT was associated with significantly longer OS than patients treated with RT before CT (TR = 1.37, 95% CI = 1.18–1.58, P < 0.001; Table 2, Fig. 2A), women who received CT only (TR = 1.42, 95% CI, 1.27–1.59, P < 0.001), or women who received RT only (TR = 1.50, 95% CI = 1.32–1.70, P < 0.001; Table 3, Fig. 2B–C). In contrast, women who received RT before CT did not experience significantly longer OS than women who received CT only (TR = 0.94, 95% CI, 0.82–1.09, P =

Table 1
Kaplan-Meier estimates of survival and multivariable parametric accelerated failure time models of all women who received adjuvant radiotherapy and/or chemotherapy.

Variable	Univariate analysis of all patients				Multivariable AFT model	
	N (events)	RMST (mo) (95% CI)	5 y OS (%) (95% CI)	P-value	TR (95% CI)	P-value
Adjuvant therapy				<0.001		
RT only	1260 (511)	93.4 (89.8–97.0)	64.5 (61.7–67.4)		1.00 (reference)	
CT only	2465 (705)	102.1 (99.1–105.2)	68.9 (66.8–71.1)		1.03 (0.91–1.16)	0.65
RT before CT	564 (148)	105.6 (99.5–111.6)	73.3 (69.2–77.8)		1.08 (0.90–1.29)	0.41
RT after CT	1506 (253)	112.9 (107.2–118.6)	80.1 (77.6–82.6)		1.41 (1.21–1.64)	<0.001
Age					0.97 (0.96–0.97)	<0.001
Tumor stage				<0.001		
pT1	1711 (323)	112.0 (108.3–115.7)	78.9 (76.5–81.3)		1.00 (reference)	
pT2	623 (165)	103.6 (97.8–109.3)	72.5 (68.6–76.8)		0.77 (0.65–0.92)	0.004
pT3	3294 (1031)	97.9 (95.5–100.4)	68.1 (66.3–70.0)		0.51 (0.44–0.59)	<0.001
pT4	167 (98)	67.7 (58.1–77.2)	41.5 (34.0–50.5)		0.28 (0.22–0.36)	<0.001
Nodal stage				<0.001		
pN0	2016 (528)	105.0 (102.0–107.9)	74.2 (72.0–76.4)		1.00 (reference)	
pN1	2770 (794)	100.2 (97.6–102.8)	70.1 (68.2–72.2)		0.58 (0.51–0.66)	<0.001
pN2	507 (88)	103.7 (87.0–120.4)	75.7 (70.6–81.1)		0.54 (0.43–0.69)	<0.001
pNx	502 (207)	75.6 (69.1–82.0)	56.3 (51.3–61.8)		0.57 (0.48–0.69)	<0.001
Nodal surgery				<0.001		
No LND	2961 (1177)	87.8 (86.0–89.6)	66.5 (64.7–68.3)		1.00 (reference)	
Pelvic LND	1063 (172)	101.9 (97.9–105.8)	74.8 (71.0–78.8)		0.91 (0.71–1.16)	0.41
Pelvic and PA-LND	1771 (268)	103.1 (99.6–106.6)	77.6 (74.8–80.5)		1.03 (0.82–1.30)	0.80
Grade				<0.001		
1	1903 (395)	112.5 (109.2–115.9)	77.9 (75.6–80.2)		1.00 (reference)	
2	3892 (1222)	97.9 (95.6–100.3)	67.5 (65.8–69.2)		0.74 (0.66–0.82)	<0.001
LVSI				<0.001		
LVSI−	1359 (191)	69.9 (68.3–71.5)	76.9 (73.5–80.4)		1.00 (reference)	
LVSI+	1592 (302)	66.4 (64.9–68.0)	72.2 (69.0–75.5)		0.85 (0.72–1.00)	0.05
Not reported	2844 (1124)	63.6 (62.6–64.6)	67.7 (65.9–69.5)		1.00 (0.75–1.32)	0.93
Omentectomy				<0.001		
No	2282 (350)	101.0 (96.5–105.5)	76.8 (74.3–79.4)		1.00 (reference)	
Yes	771 (161)	96.6 (92.1–101.2)	70.6 (66.3–75.3)		0.77 (0.65–0.92)	0.003
Not reported	2742 (1106)	88.2 (86.4–90.1)	66.8 (65.0–68.7)		0.74 (0.57–0.96)	0.03
Cytology				<0.001		
Negative	1738 (257)	88.9 (85.4–92.3)	77.9 (75.2–80.8)		1.00 (reference)	
Positive	509 (125)	80.5 (75.9–85.1)	65.9 (60.4–71.8)		0.74 (0.60–0.90)	0.003
Not reported	3548 (1235)	80.5 (79.2–81.9)	68.6 (66.9–70.3)		0.94 (0.79–1.11)	0.42
Margin status				<0.001		
Negative	4681 (1198)	102.9 (100.9–104.9)	73.3 (71.8–74.8)		1.00 (reference)	
Microscopic	236 (94)	83.8 (74.8–92.8)	56.1 (49.2–64.1)		0.72 (0.58–0.89)	<0.001
Macroscopic	231 (109)	74.8 (66.3–83.4)	52.4 (45.6–60.3)		0.64 (0.52–0.78)	<0.001
Positive (NOS)	80 (49)	54.4 (44.1–64.6)	40.3 (30.2–53.7)		0.43 (0.32–0.59)	0.002
Not reported	567 (167)	98.4 (92.7–104.0)	68.3 (64.0–73.0)		0.94 (0.80–1.10)	0.40
Race				<0.001		
White	5189 (1459)	98.8 (97.0–100.6)	71.0 (69.6–72.5)		1.00 (reference)	
Black	293 (99)	89.6 (81.7–97.5)	60.6 (54.0–68.0)		0.73 (0.59–0.90)	0.004
Other	313 (59)	110.3 (102.9–117.8)	76.9 (71.3–83.0)		1.15 (0.91–1.46)	0.24
Hispanic				0.008		
No	5175 (1447)	99.7 (97.8–101.7)	70.6 (69.2–72.1)		1.00 (reference)	
Yes	286 (48)	114.8 (106.7–122.9)	78.9 (73.1–85.3)		1.40 (1.07–1.82)	0.03
Not reported	334 (122)	98.2 (91.7–104.7)	68.3 (63.1–73.8)		0.96 (0.80–1.15)	0.99
Insurance status				<0.001		
Private	3104 (645)	111.8 (109.5–114.1)	78.9 (77.2–80.6)		1.00 (reference)	
Medicare	1968 (777)	82.6 (79.4–85.7)	58.7 (56.2–61.4)		0.81 (0.71–0.92)	0.001
Medicaid/Gov	423 (108)	97.7 (90.0–105.3)	71.3 (66.1–76.9)		0.84 (0.69–1.02)	0.06
Not insured	300 (87)	98.3 (90.2–106.5)	64.8 (58.4–71.9)		0.64 (0.52–0.80)	<0.001
Comorbidity score				<0.001		
0	4387 (1153)	103.8 (101.7–105.9)	72.8 (71.3–74.4)		1.00 (reference)	
1	1160 (362)	92.0 (87.7–96.4)	66.0 (62.8–69.5)		0.83 (0.74–0.93)	0.002
2 or 3	248 (102)	77.6 (68.3–86.9)	55.3 (48.4–63.2)		0.62 (0.51–0.76)	<0.001
Prior cancer				<0.001		
No	4955 (1311)	104.1 (102.0–106.3)	71.6 (70.1–73.1)		1.00 (reference)	
Yes	840 (306)	94.0 (89.3–98.7)	66.3 (62.8–70.0)		0.86 (0.76–0.98)	0.03
Income quartile				0.01		
Top	1855 (477)	106.0 (102.6–109.5)	72.9 (70.6–75.4)		1.00 (reference)	
2nd	1630 (458)	103.2 (99.7–106.8)	70.4 (67.9–73.1)		0.93 (0.82–1.06)	0.18
3rd	1464 (424)	99.6 (95.5–103.7)	69.9 (67.1–72.7)		0.92 (0.79–1.07)	0.29
Bottom	846 (258)	95.6 (90.3–100.8)	68.4 (64.8–72.2)		0.93 (0.78–1.13)	0.39
Education quartile				0.14		
Top	1423 (378)	105.5 (101.7–109.4)	72.5 (69.9–75.3)		1.00 (reference)	
2nd	2064 (564)	103.2 (100.0–106.5)	71.1 (68.9–73.5)		1.03 (0.90–1.17)	0.71
3rd	1473 (428)	99.8 (95.8–103.8)	69.7 (67.0–72.6)		1.00 (0.85–1.17)	0.95
Bottom	835 (247)	97.9 (92.7–103.1)	68.9 (65.2–72.7)		0.94 (0.78–1.15)	0.61
Treatment facility				0.01		

(continued on next page)

Table 1 (*continued*)

Variable	Univariate analysis of all patients				Multivariable AFT model	
	N (events)	RMST (mo) (95% CI)	5 y OS (%) (95% CI)	P-value	TR (95% CI)	P-value
Academic	2325 (593)	106.1 (103.0–109.2)	72.6 (70.4–74.8)		1.00 (reference)	
Cancer center	2760 (821)	100.3 (97.5–103.2)	69.7 (67.7–71.7)		0.81 (0.73–0.90)	<0.001
Integrated Network	710 (203)	99.2 (93.3–105.1)	69.4 (65.5–73.6)		0.85 (0.73–0.98)	0.04
Year diagnosed				<0.001		
2009 or before	2542 (1075)	82.4 (80.8–84.1)	66.8 (65.0–68.7)		1.00 (reference)	
2010 or after	3253 (542)	91.1 (87.6–94.7)	74.6 (72.4–76.8)		1.20 (0.89–1.63)	0.52

Significance determined by Log-Rank test (univariate analyses) or Wald test (multivariable analyses). OS: overall survival; mo: months; y: years; N: number; RMST: restricted mean survival time; TR (95% CI): time ratio (95% confidence interval); P: P-value; RT: radiotherapy; CT: chemotherapy; LND: lymph node dissection; PA: para-aortic; LVSI: lymphovascular space invasion; NOS: not otherwise specified; Gov: other government agency; ref.: reference level.

0.42) or RT only (TR = 1.00, 95% CI, 0.73–1.37, P = 0.99; Table 3, Fig. 2D–E). In addition, women who received CT only did not experience significantly longer or shorter OS than women who received RT only (TR = 1.03, 95% CI, 0.94–1.13, P = 0.49; Table 3, Fig. 2F). Multivariable models of unadjusted analyses are presented in Tables S10–S11.

When the number of days between RT and chemotherapy start dates for the patients who received RT after CT was plotted on a histogram there appeared to be a bimodal distribution (Fig. S2). One subset of patients started RT between 50 and 100 d following the start of CT (peak ~65 d), while a second subset started RT between 110 and 200 d following the start of CT (peak ~145 d). To explore whether the start date of RT following CT was associated with survival benefit, a multivariable analysis was performed of propensity-score matched cohorts of women whose RT start date was 126–200 d after her CT start date (and therefore thought to have received 5 or 6 cycles of CT) and women whose RT start date was 61–125 d after her CT start date (and therefore thought to have received 3 or 4 cycles of CT). There was no association of this variable with OS (TR = 0.87, 95% CI = 0.73–1.04, P = 0.13). When an expanded cohort including women with Grade 3 endometrioid histology was utilized, results were consistent those of the original cohort of Type 1 endometrioid histology alone. In this expanded cohort of women, treatment with RT after CT was associated with significantly longer OS compared to treatment with RT before CT (5 y OS: 72.6% vs 65.8%; time-ratio (TR) = 1.22, 95% CI = 1.05–1.42, P = 0.009), CT only (57.7%; TR = 1.45, 95% CI = 1.31–1.60, P < 0.001), or RT only (57.6%, TR = 1.40, 95% CI = 1.24–1.58, P < 0.001). Time ratio estimates for longer OS associated with treatment with RT after CT as compared to RT before CT were robust to introduction of a possible unmeasured confounder. For example, in order for the observed effect to be rendered nonsignificant, there would need to be a *moderately imbalanced* (prevalence of 60% vs. 40%) unmeasured confounder that demonstrated an association with OS with a TR ≥ 3 (Table S12). Further sensitivity analyses were performed on additional propensity-score matched cohorts of subsets of patients. When patients with <100 d between the start of chemotherapy and RT were excluded, patients who received RT after CT still experienced longer OS than those who received RT before CT (5 y OS: 80.7% vs 74.2%; TR = 1.21, 95% CI, 1.06–1.39, P = 0.006). Similarly, when only patients with positive nodes (FIGO Stage IIIC1 and IIIC2) were included, treatment with RT after CT was associated with longer OS compared to RT before CT (5 y OS: 80.7% vs. 71.9%; TR = 1.36, 95% CI, 1.10–1.67, P = 0.004).

4. Discussion

In this analysis of a large cohort of women from the NCDB with Stage III-IVA Type 1 EC following hysterectomy, treatment with RT after CT was associated with longer OS compared to treatment with RT before CT, or either treatment alone. Women who received RT before CT, however, did not experience significantly longer OS than women who received CT or RT alone, nor did women who received CT alone experience significantly different survival than women who received RT alone. Treatment with multi-agent CT followed by RT may therefore be the optimal adjuvant multimodality regimen for selected women with EC whose disease characteristics are prognostic for a high risk of LRR but a lower risk of distant recurrence.

Historical randomized trials addressing women with locally advanced EC have included heterogeneous cohorts and yielded results with limited applicability. An Italian trial of women with primarily Stage III non-serous or clear cell EC randomized after hysterectomy to RT to the pelvis ± para-aortic (PA) lymph node chain versus multi-agent CT found no difference in PFS or OS [16]. Similarly, a Japanese trial of women with a mix of stages and histological subtypes randomized following hysterectomy and lymph node dissection (LND) to RT or to cisplatin/doxorubicin CT demonstrated no differences in PFS or OS between arms, although subset analyses suggested superior survival for those patients deemed "high risk" treated with CT [17]. Subset analyses of matched cohorts of patients treated with either RT or CT reflect these data (Fig. 2F). The role of adjuvant CT in this setting was cemented following GOG-122, in which women with Stage III-IVA EC randomized after hysterectomy and LND to cisplatin/doxorubicin experienced significantly longer PFS and OS compared to women who received whole abdominal RT with a pelvic boost. Recurrences in the pelvis, however, were more common in the CT arm, comprising 21% of all first failures [18]. It seemed logical to next explore treatment with a combination of CT and RT, addressing the potential for both local and systemic relapse.

The GOG-258 and PORTEC-3 trials examined this question from complementary angles. PORTEC-3 enrolled 660 women with high-risk stage IB-III EC, weighted heavily towards stage III, randomized to receive either RT alone or RT with concurrent cisplatin followed by 4 cycles of carboplatin and paclitaxel (CRT) [1]. The addition of CT to RT was associated with a trend towards improved 5 y PFS and OS in the entire cohort. In a subset analysis limited to women with stage III disease, the 5 y PFS benefit reached statistical significance at 69% versus 58% (P = 0.03). Asking a mirror image question, GOG-258 randomized 813 women with stage III-IVA EC to 6 cycles of chemotherapy alone (carboplatin and paclitaxel) versus CRT per PORTEC (RT followed by carboplatin/paclitaxel) [2]. While the 5 y rates of vaginal and pelvic or PA recurrences were higher in the CT arm (7% vs. 3% and 19% vs. 10%, respectively), the rate of distant recurrences was lower in the CT arm (21% vs. 27%). There was a small, but non-significant numerical advantage in PFS favoring the CRT arm (HR 0.9), but no difference in OS. Exploratory subset analyses did not identify subgroups that derived benefit from CRT. Consistent with these data, subset analyses presented in this manuscript show no statistical difference in OS between women treated with RT before CT compared to either CT alone as was seen in GOG-258 (Fig. 2D), or RT alone, as was seen in PORTEC-3 (Fig. 2E).

An increase in distant failures and worse survival among women who receive RT before CT may potentially be due to delayed initiation of CT or delivery of a fewer number of total CT cycles due to either trial design (6 vs. 4 planned cycles) or tolerability (inability to complete CT after RT). Importantly, 25% and 29% of women enrolled in the CRT arms of GOG-258 and PORTEC-3, respectively, did not receive full CT, defined as 4 cycles of carboplatin and paclitaxel following RT [1,2].

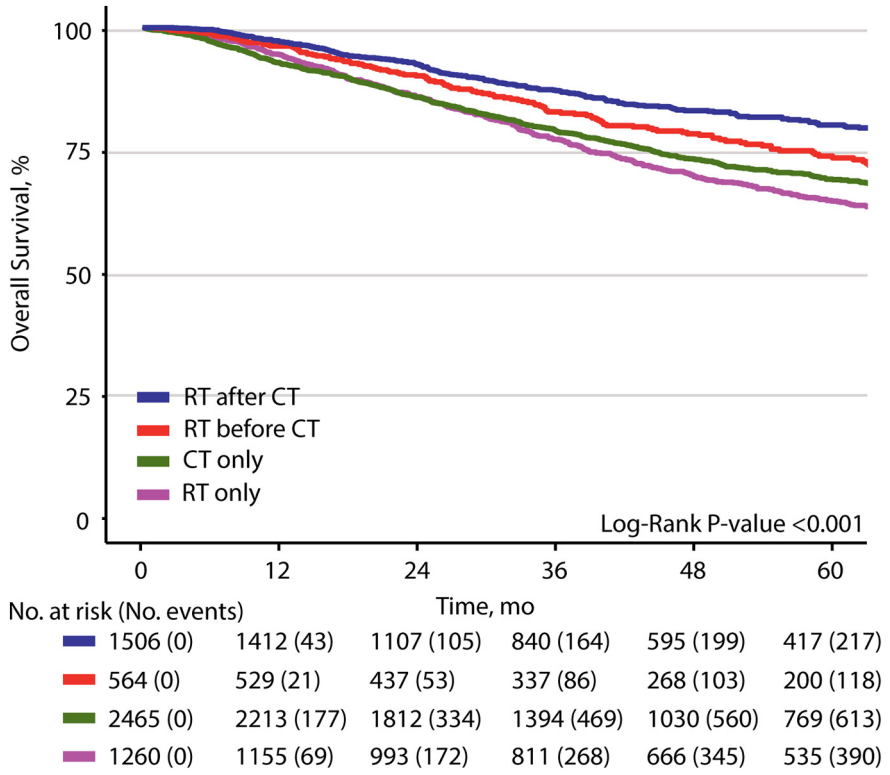

Fig. 1. Unadjusted survival curves for all women who received adjuvant chemotherapy or radiotherapy. Unadjusted overall survival curves based on Kaplan-Meier estimates for women who received radiotherapy alone (light gray, dotted), chemotherapy alone (medium gray, dashed), radiotherapy before chemotherapy (dark gray, large dashed), or radiotherapy after chemotherapy (black, solid). RT: radiotherapy; CT: chemotherapy; Mo: months; No: number.

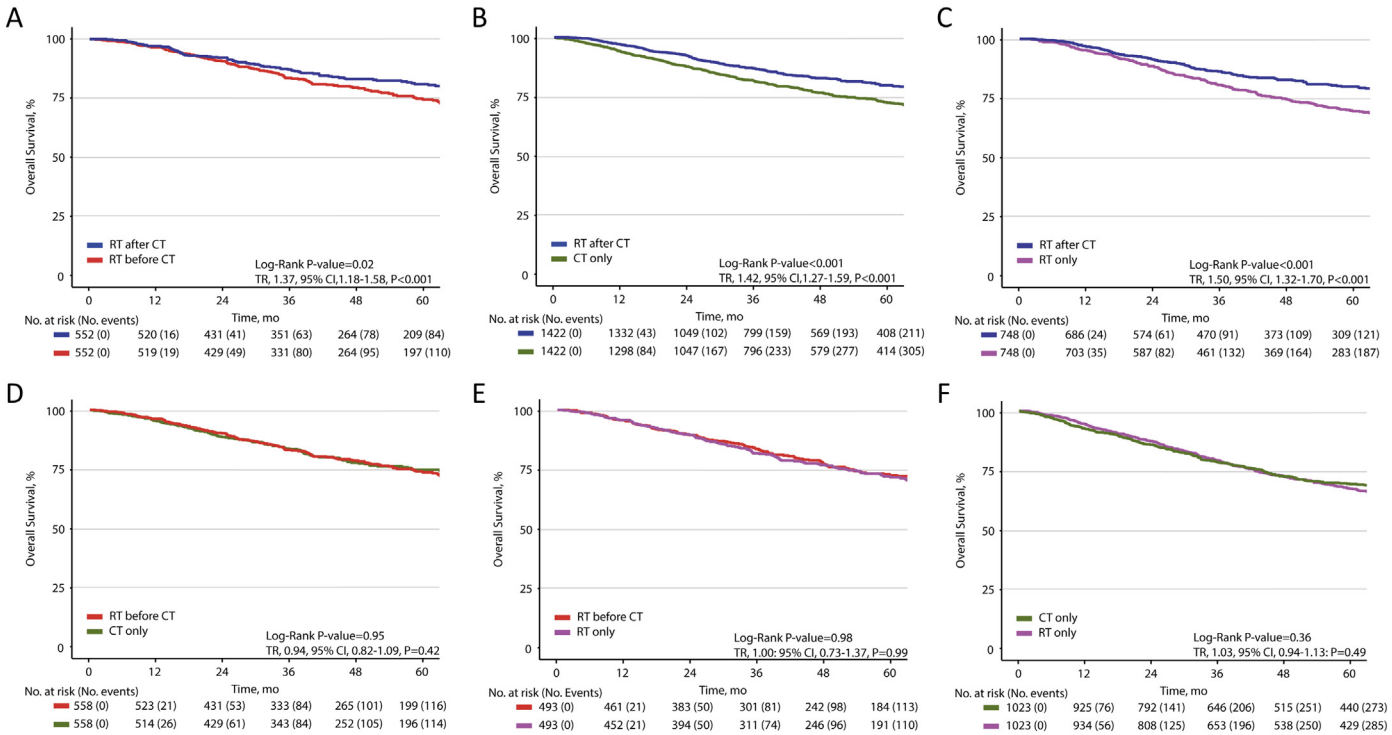

Fig. 2. Adjusted survival curves for pairs of matched cohorts of women who received adjuvant radiotherapy and/or chemotherapy. Overall survival curves based on Kaplan-Meier estimates for matched cohorts of women who received A) radiotherapy after chemotherapy (black) versus radiotherapy before chemotherapy (gray); B) radiotherapy after chemotherapy (black) versus chemotherapy alone (gray); C) radiotherapy after chemotherapy (black) versus radiotherapy alone (gray); D) radiotherapy before chemotherapy (black) versus chemotherapy alone (gray); E) radiotherapy before chemotherapy (black) versus radiotherapy alone (gray); or F) chemotherapy alone (black) versus radiotherapy alone (gray). RT: radiotherapy; CT: chemotherapy; TR: Time Ratio; 95% CI: 95% Confidence Interval; P: P-value; Mo: months; No: number.

Table 2
Kaplan-Meier estimates of overall survival and multivariable parametric accelerated failure time models of propensity score-matched cohorts of patients who received adjuvant radiotherapy and chemotherapy.

Variable	Univariate analysis of propensity score-matched cohorts				Multivariable AFT model	
	N (events)	RMST (mo) (95% CI)	5y OS (%) (95% CI)	P-value	TR (95% CI)	P-value
Adjuvant therapy				0.02		
RT before CT	553 (141)	104.6 (98.9–110.2)	74.4 (70.2–78.8)		1.00 (reference)	
RT after CT	553 (100)	113.6 (107.7–119.5)	80.9 (77.2–84.8)		1.37 (1.18–1.58)	<0.001
Age					0.98 (0.97–0.99)	<0.001
Tumor stage				0.004		
pT1	380 (60)	112.3 (105.9–118.8)	82.4 (77.8–87.2)		1.00 (reference)	
pT2	156 (34)	108.7 (99.3–118.1)	77.3 (70.2–85.1)		0.76 (0.62–0.93)	0.007
pT3	552 (139)	103.1 (97.9–108.2)	75.1 (71.0–79.4)		0.55 (0.46–0.66)	<0.001
pT4	16 (9)	75.2 (48.2–102.2)	61.9 (41.9–91.4)		0.24 (0.18–0.32)	<0.001
Nodal stage				0.10		
pN0	329 (66)	109.9 (103.9–115.9)	79.8 (74.8–85.1)		1.00 (reference)	
pN1	633 (144)	105.1 (100.4–109.7)	77.4 (73.7–81.2)		0.66 (0.56–0.77)	<0.001
pN2	76 (12)	111.5 (97.5–125.6)	75.1 (62.8–89.8)		0.72 (0.51–1.00)	0.05
pNx	66 (20)	89.3 (74.3–104.3)	70.5 (57.8–86.1)		0.68 (0.49–0.94)	0.02
Nodal surgery				0.08		
No LND	546 (171)	79.4 (76.7–82.0)	75.7 (72.0–79.5)		1.00 (reference)	
Pelvic LND	194 (29)	80.7 (74.6–86.7)	78.2 (70.0–87.3)		1.04 (0.70–1.53)	0.86
Pelvic & PA-LND	364 (42)	85.3 (81.7–88.8)	80.9 (74.9–87.4)		1.20 (0.81–1.78)	0.37
Grade				0.14		
1	346 (62)	113.8 (106.3–121.2)	79.7 (74.5–85.1)		1.00 (reference)	
2	758 (180)	107.5 (102.7–112.4)	76.7 (73.3–80.2)		0.80 (0.69–0.92)	0.003
LVSI				0.22		
LVSI−	263 (31)	69.1 (66.1–72.0)	80.1 (72.6–88.4)		1.00 (reference)	
LVSI+	276 (38)	67.6 (64.5–70.7)	77.3 (69.9–85.6)		0.98 (0.78–1.22)	0.83
Not reported	565 (173)	65.9 (64.0–67.8)	76.2 (72.6–80.0)		0.87 (0.63–1.20)	0.41
Omentectomy				0.66		
No	469 (66)	71.9 (69.1–74.7)	78.5 (73.0–84.4)		1.00 (reference)	
Yes	99 (14)	72.4 (66.9–77.9)	77.2 (65.7–90.7)		1.07 (0.82–1.40)	0.62
Not reported	536 (162)	70.6 (68.4–72.7)	76.7 (73.0–80.5)		0.85 (0.57–1.27)	0.44
Cytology				0.29		
Negative	375 (47)	83.2 (79.0–87.3)	79.6 (73.7–86.0)		1.00 (reference)	
Positive	76 (10)	84.4 (76.9–92.0)	82.1 (72.4–93.3)		1.27 (0.91–1.75)	0.16
Not reported	653 (185)	79.8 (77.4–82.3)	76.3 (72.9–79.9)		0.96 (0.77–1.19)	0.72
Margin status				0.008		
Negative	933 (193)	106.9 (103.2–110.7)	79.0 (76.0–82.1)		1.00 (reference)	
Positive	80 (26)	86.8 (73.1–100.6)	67.7 (56.6–81.0)		0.79 (0.65–0.97)	0.03
Not reported	91 (23)	103.1 (91.2–114.9)	72.8 (62.8–84.5)		0.92 (0.75–1.12)	0.40
Race				0.03		
White	995 (221)	107.5 (103.6–111.4)	77.8 (74.9–80.9)		1.00 (reference)	
Black	46 (14)	87.2 (66.8–107.5)	62.5 (45.2–86.2)		0.68 (0.52–0.89)	0.004
Other	63 (7)	124.9 (112.5–137.4)	83.6 (72.8–96.1)		1.52 (1.01–2.27)	0.04
Hispanic				0.26		
No	975 (218)	105.9 (101.9–109.9)	77.5 (74.4–80.6)		1.00 (reference)	
Yes	64 (7)	124.1 (111.1–137.0)	88.9 (80.7–97.9)		2.10 (1.24–3.56)	0.006
Not reported	65 (17)	108.8 (95.6–122.0)	72.9 (61.9–85.7)		1.56 (1.20–2.04)	<0.001
Insurance status				<0.001		
Private	678 (118)	110.6 (106.7–114.5)	82.9 (79.7–86.3)		1.00 (reference)	
Medicare	309 (98)	88.4 (81.5–95.4)	66.3 (60.3–73.0)		0.73 (0.61–0.87)	<0.001
Medicaid/Gov	58 (9)	104.2 (93.3–115.1)	87.0 (77.5–97.6)		0.82 (0.64–1.06)	0.12
Not insured	59 (17)	95.0 (79.2–110.9)	65.6 (52.3–82.4)		0.83 (0.65–1.07)	0.15
Comorbidity score				0.36		
0	866 (186)	104.3 (100.7–108.0)	78.4 (75.3–81.6)		1.00 (reference)	
1	206 (47)	97.1 (88.9–105.2)	76.5 (69.6–84.1)		0.82 (0.71–0.96)	0.01
2 or 3	32 (9)	96.9 (77.3–116.5)	62.3 (44.6–87.1)		0.93 (0.64–1.34)	0.68
Prior cancer				0.11		
No	971 (202)	109.6 (105.5–113.7)	78.1 (75.1–81.2)		1.00 (reference)	
Yes	133 (40)	99.5 (88.9–110.0)	75.2 (67.3–84.0)		1.19 (1.00–1.42)	0.05
Income quartile				0.08		
Top	390 (69)	112.7 (106.5–118.8)	82.8 (78.5–87.4)		1.00 (reference)	
2nd	284 (66)	106.7 (99.5–114.0)	79.5 (74.4–84.9)		0.90 (0.75–1.08)	0.26
3rd	296 (76)	102.9 (95.4–110.4)	70.7 (64.7–77.2)		0.71 (0.58–0.86)	<0.001
Bottom	134 (31)	106.4 (96.0–116.9)	75.0 (66.8–84.1)		0.88 (0.68–1.13)	0.31
Education quartile				0.16		
Top	288 (57)	110.1 (102.9–117.2)	80.6 (75.4–86.1)		1.00 (reference)	
2nd	384 (75)	110.0 (103.6–116.4)	80.3 (75.7–85.2)		1.18 (0.98–1.41)	0.07
3rd	277 (75)	101.8 (94.2–109.3)	72.8 (67.1–79.0)		1.02 (0.82–1.25)	0.88
Bottom	155 (35)	106.3 (96.2–116.3)	74.7 (66.9–83.4)		0.82 (0.64–1.07)	0.14
Treatment facility				0.41		
Academic	463 (87)	110.0 (103.9–116.0)	79.8 (75.4–84.4)		1.00 (reference)	
Cancer center	513 (129)	105.8 (100.5–111.1)	75.8 (71.7–80.1)		0.80 (0.69–0.93)	0.003
Network	128 (26)	106.7 (94.4–118.9)	77.9 (69.6–87.2)		0.69 (0.57–0.85)	<0.001
Year diagnosed				0.13		

Table 2 (*continued*)

Variable	Univariate analysis of propensity score-matched cohorts				Multivariable AFT model	
	N (events)	RMST (mo) (95% CI)	5y OS (%) (95% CI)	P-value	TR (95% CI)	P-value
2009 or before	489 (161)	90.7 (87.3–94.1)	76.1 (72.3–80.0)		1.00 (reference)	
2010 or after	615 (81)	97.1 (93.3–100.8)	78.8 (73.9–84.0)		0.61 (0.35–1.05)	0.08

Accelerated failure time (AFT) models for the matched cohorts were covariate-adjusted and inverse probability-weighted using propensity-weighted matched cohorts. Significance determined by Log-Rank test (univariate analyses) or Wald test (multivariable analyses). OS: overall survival; mo: months; y: years; N: number; RMST: restricted mean survival time; TR (95% CI): time ratio (95% confidence interval); P: P-value; RT: radiotherapy; CT: chemotherapy; LND: lymph node dissection; PA: para-aortic; LVSI: lymphovascular space invasion; Gov: other government agency; ref.: reference level.

Although the NCDB does not provide the number of CT cycles planned and/or received, the number of CT cycles received prior to RT was estimated by calculating the number of days between CT and RT start dates. Furthermore, as it was not possible to determine which women may have received adjuvant therapy using a "sandwich" approach, we considered all patients who started RT ≥ 62 d following the start of CT as one group. These analyses therefore do not clarify which regimen, if either, may be associated with longer survival. Employment of a "sandwich" regimen may enable a greater number of patients to complete at least 3 or 4 cycles of multi-agent CT as well as RT, thereby deriving the greatest benefit from both complementary therapy techniques. While a small number of retrospective and prospective cohort studies have utilized a sandwich approach with acceptable outcomes and toxicity profiles, the significant heterogeneity across studies and limited sample of patients renders further analysis difficult [19–24].

When considered in the context of PORTEC-3 and GOG-258, our results suggest that CT should be used as the first post-operative strategy for patients likely to both tolerate and benefit from RT. Such patients should likely be selected based on their expected ability to tolerate RT, a sufficiently high risk of LRR such that the absolute reduction in LRR is large, and a relatively low competing risk of distant failure, since a concurrent or subsequent distant failure would render pelvic control unimportant. To date, no randomized prospective trial has included a treatment arm in which CT is given before RT or sequenced in a "sandwich" fashion as a comparator to multi-agent CT or RT alone. To our knowledge, no other retrospective analysis has estimated the association of sequence of adjuvant multi-agent CT and RT with clinical outcomes, nor are we aware of a prospective or retrospective database with sufficient sample size with which these findings could be validated. The NCDB is therefore a valuable and appropriate resource for these analyses.

As the NCDB does not provide central pathologic or dosimetric review, we utilized strict exclusion criteria for the selection of our patient cohorts in order to achieve as homogeneous of a patient sample as possible. The GOG-258 and PORTEC-3 were obliged for the purposes of accrual to enroll not only patients with Stage IIIC-IVA endometrioid uterine cancer but also patients with earlier stage disease with high-risk histology [1,2]. For these analyses, however, we included only patients with "Type 1" uterine cancer, classically defined as Grade 1–2 endometrioid adenocarcinoma, to potentially improve patient homogeneity given the benefit of central pathologic review was not available. Sensitivity analyses using an expanded cohort of women that included those with Grades 1, 2, and 3 endometrioid histology yielded results that were similar to those seen when only patients with "Type 1" disease were included. Separate analyses should be considered for patients with "Type 2" disease in future analyses. An additional limitation of these analyses is the inability to consider clinical outcomes outside of OS, as the NCDB does not report locoregional or distant failures. Also unavailable to us for the purpose of cohort creation and inclusion in multivariable models includes detailed information regarding the number of CT cycles planned and received, type of CT regimen prescribed and delivered, therapy tolerability, and more granular data regarding RT technique and dosimetry. Lastly, compared with prospective trials, observational cohort analyses are limited due to potential selection bias and the inability to control for an unmeasured confounder. To help mitigate this, multiple bias-reducing statistical techniques were utilized to provide reliable and robust estimates, such as performing each multivariable analysis using matched cohorts of patients that were well-balanced along all clinicopathologic and relevant treatment criteria. In addition, a sensitivity analysis demonstrated the TR estimates were robust to the introduction of a possible unmeasured confounder.

Table 3
Kaplan-Meier estimates of overall survival and multivariable parametric accelerated failure time models of propensity score-matched pairs of women who received adjuvant radiotherapy and/or chemotherapy.

Variable	Univariate analysis of propensity score-matched cohorts				Multivariable AFT model	
	N (events)	RMST (mo) (95% CI)	5 y OS (%) (95% CI)	P-value	TR (95% CI)	P-value
RT after CT vs CT only				<0.001		
CT only	1422 (348)	104.0 (100.1–108.0)	72.3 (69.5–75.1)		1.00 (reference)	
RT after CT	1422 (245)	111.5 (107.0–116.1)	79.7 (77.1–82.3)		1.42 (1.27–1.59)	<0.001
RT before CT vs CT only				0.95		
CT only	558 (137)	105.1 (99.1–111.1)	74.6 (70.5–78.9)		1.00 (reference)	
RT before CT	558 (146)	103.7 (98.2–109.3)	73.5 (69.3–77.9)		0.94 (0.82–1.09)	0.42
RT after CT vs RT only				<0.001		
RT only	748 (239)	98.3 (93.7–103.0)	69.4 (65.7–73.3)		1.00 (reference)	
RT after CT	748 (152)	110.6 (105.5–115.7)	79.8 (76.5–83.2)		1.50 (1.32–1.70)	<0.001
RT before CT vs RT only				0.98		
RT only	493 (143)	104.1 (98.1–110.1)	72.3 (67.9–77.0)		1.00 (reference)	
RT before CT	493 (141)	103.8 (97.6–110.0)	71.5 (67.0–76.2)		1.00 (0.73–1.37)	0.99
CT only vs RT only				0.36		
RT only	1023 (370)	97.8 (93.7–101.8)	67.3 (64.1–70.5)		1.00 (reference)	
CT only	1023 (333)	102.0 (97.7–106.2)	69.2 (66.1–72.3)		1.03 (0.94–1.13)	0.49

Accelerated failure time (AFT) models for the matched cohorts were covariate-adjusted and inverse probability-weighted using propensity-weighted matched cohorts. Significance determined by Log-Rank test (univariate analyses) or Wald test (multivariable analyses). OS: overall survival; mo: months; y: years; N: number; RMST: restricted mean survival time; TR (95% CI): time ratio (95% confidence interval); P: P-value; RT: radiotherapy; CT: chemotherapy; ref.: reference level.

In conclusion, these hypothesis-generating findings support further consideration of adjuvant regimens that include the delivery of CT before RT. For women with locally advanced Type 1 EC, treatment with multi-agent CT before RT (or potentially employing a sandwich approach) may optimize control of both locoregional and distant disease, ultimately leading to longer PFS and OS. The findings presented here support the consideration of this regimen in the design of future prospective trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.01.007.

Acknowledgments

We acknowledge the NCDB for collecting the data used in these analyses. The NCDB and the participating hospitals are the source of the data. The NCDB has not verified and are not responsible for the statistical validity of the data analysis or conclusions.

Conflict of interest statement

Dr. Matei reports personal fees from Astra Zeneca, Genentech/Roche, Tesaro, Astex, Clovis, and the European commission that are outside the submitted work. All other authors report no conflicts of interest.

Author contributions

Conceptualization: Goodman, Seagle, Strauss. *Formal Analysis and Methodology*: Goodman, Strauss, Hatoum, Seagle. *Writing – Original Draft*: Goodman, Hatoum; *Writing – Review and Editing*: Goodman, Hatoum, Seagle, Barber, Matei, Strauss. *Project Administration*: Hatoum, Donnelly, Barber, Matei, Shahabi, Strauss. *Supervision*: Strauss, Shahabi.

References

[1] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (3) (2018) 295–309.
[2] D. Matei, V.L. Filiaci, M. Randall, et al., A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma, J. Clin. Oncol. 35 (15_suppl) (2017) 5505.
[3] K.Y. Bilimoria, A.K. Stewart, D.P. Winchester, C.Y. Ko, The National Cancer Data Base: a powerful initiative to improve cancer care in the United States, Ann. Surg. Oncol. 15 (3) (2008) 683–690.
[4] C.R. Goodman, B.L. Seagle, T.W.P. Friedl, et al., Association of circulating tumor cell status with benefit of radiotherapy and survival in early-stage breast cancer, JAMA Oncol. 4 (8) (2018), e180163. .
[5] P.M. Grambsch, T. Therneau, Proportional hazards tests and diagnostics based on weighted residuals, Biometrika 81 (1994) 515–526.
[6] G.E.P. Box, J.S. Hunter, W.G. Hunter, Statistics for Experimenters: Design, Innovation and Discovery, 2 ed. John Wiley & Sons, Hoboken, NJ, 2005.
[7] C.H. Jackson, Flexsurv: a platform for parametric survival modeling in R, J. Stat. Softw. 70 (2016) 1–33.
[8] G.P.S. Kwong, J.L. Hutton, Choice of parametric models in survival analysis: applications to monotherapy for epilepsy and cerebral palsy, Royal Statistical Society Appl. Stat. 52 (2003) 153–168.
[9] D. Collett, Modelling Survival Data in Medical Research, 3 ed. Chapman and Hall/CRC, Boca Raton, FL, 2014.
[10] P.C. Austin, An introduction to propensity score methods for reducing the effects of confounding in observational studies, Multivar. Behav. Res. 46 (3) (2011) 399–424.
[11] N. Mitra, D.F. Heitjan, Sensitivity of the hazard ratio to nonignorable treatment assignment in an observational study, Stat. Med. 26 (6) (2007) 1398–1414.
[12] P.C. Austin, The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments, Stat. Med. 33 (7) (2014) 1242–1258.
[13] MatchIt, Nonparametric Preprocessing for Parametric Causal Inference, computer program 2011.
[14] T.M. Therneau, A Package for Survival Analysis in S. Version 2.38, https://CRAN.R-project.org/package=survival 2015.
[15] Team RC (Ed.), R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2016.
[16] R. Maggi, A. Lissoni, F. Spina, et al., Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial, Br. J. Cancer 95 (3) (2006) 266–271.
[17] N. Susumu, S. Sagae, Y. Udagawa, et al., Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study, Gynecol. Oncol. 108 (1) (2008) 226–233.
[18] M.E. Randall, V.L. Filiaci, H. Muss, et al., Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study, J. Clin. Oncol. 24 (1) (2006) 36–44.
[19] H. Gao, Z. Zhang, Sequential chemotherapy and radiotherapy in the sandwich method for advanced endometrial cancer: a meta-analysis, Medicine (Baltimore) 94 (16) (2015) e672.
[20] M. Glasgow, R.I. Vogel, J. Burgart, P. Argenta, K. Dusenbery, M.A. Geller, Long term follow-up of a phase II trial of multimodal therapy given in a "sandwich" method for stage III, IV, and recurrent endometrial cancer, Gynecol. Oncol. Res. Pract. 3 (2016) 6.
[21] L.N. Abaid, M.A. Rettenmaier, J.V. Brown 3rd, et al., Sequential chemotherapy and radiotherapy as sandwich therapy for the treatment of high risk endometrial cancer, J. Gynecol. Oncol. 23 (1) (2012) 22–27.
[22] N.U. Dogan, G. Yavas, C. Yavas, O. Ata, S.A. Yilmaz, C. Celik, Comparison of "sandwich chemo-radiotherapy" and six cycles of chemotherapy followed by adjuvant radiotherapy in patients with stage IIIC endometrial cancer: a single center experience, Arch. Gynecol. Obstet. 288 (4) (2013) 845–850.
[23] M.H. Einstein, M. Frimer, D.Y. Kuo, et al., Phase II trial of adjuvant pelvic radiation "sandwiched" between combination paclitaxel and carboplatin in women with uterine papillary serous carcinoma, Gynecol. Oncol. 124 (1) (2012) 21–25.
[24] S.M. Lu, C. Chang-Halpenny, J. Hwang-Graziano, Sequential versus "sandwich" sequencing of adjuvant chemoradiation for the treatment of stage III uterine endometrioid adenocarcinoma, Gynecol. Oncol. 137 (1) (2015) 28–33.