Gynecologic Oncology 154 (2019) 13–21

Contents lists available at ScienceDirect

Gynecologic Oncology

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

The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Group (GOG) study

Nick M. Spirtos [a,*], Danielle Enserro [b], Howard D. Homesley [c,1], Susan K. Gibbons [d], David Cella [e], Robert T. Morris [f], Koen DeGeest [g,2], Roger B. Lee [h], David S. Miller [i]

[a] Women's Cancer Center, Las Vegas, NV 89169, United States of America
[b] NRG Oncology, Clinical Trial Development Division, Biostatistics & Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, United States of America
[c] Gynecologic Oncology Network/Brody School of Medicine, Division of Gynecologic Oncology, Leo Jenkins Cancer Center, Greenville, NC 28734, United States of America
[d] Albany Medical Center, Dept. of Radiation Oncology, Albany, NY 12208, United States of America
[e] Northwestern University, Dept. of Medical Social Sciences, Feinberg School of Medicine, Chicago, IL 60201, United States of America
[f] Wayne State University, Dept. of Gynecologic Oncology, Detroit, MI 48201, United States of America
[g] University of Iowa Hospitals and Clinics, Iowa City, IA, United States of America
[h] Obstetrics & Gynecology, Tacoma General Hospital, Tacoma, WA, United States of America
[i] Division of Gynecologic Oncology, UT Southwestern Medical Center at Dallas, Dallas, TX 75390-9032, United States of America

HIGHLIGHTS

- No significant difference in OS in women with advanced-stage endometrial cancer on cisplatin and doxorubicin +/− paclitaxel
- Despite a slight protective effect on OS and long-term RFS, the addition of paclitaxel comes with increased neurotoxicity.
- Second malignancies were reported in 36 patients, including 13 breast cancers occurring mostly in the arm with paclitaxel.

ARTICLE INFO

Article history:
Received 16 October 2018
Received in revised form 11 March 2019
Accepted 15 March 2019
Available online 30 April 2019

Keywords:
Advanced endometrial cancer
Optimal surgery
Chemotherapy and radiation
Long-term follow-up

ABSTRACT

Objectives. To determine if the addition of paclitaxel (P) to cisplatin and doxorubicin (CD) following surgical debulking and volume-directed radiation therapy improved long-term, recurrence-free survival (RFS) and overall survival (OS) in patients with advanced-stage endometrial cancer (EC).

Methods. Prospective, randomized GOG trial comparing (CD) (50 mg/m^2)/(45 mg/m^2) +/− (P) (160 mg/m^2) following volume-directed radiation and surgery in advanced EC. A Kaplan-Meier (KM) analysis characterized the relationship between treatment arms and the OS outcome, a log-rank test assessed the independence of treatment with the OS outcome, and the treatment effect on estimated OS was determined using a Cox proportional hazards (PH) model stratified by stage. The PH assumption was assessed using a test of interaction between treatment variable and the natural logarithm of survival time. Adverse events, regardless of attribution, were graded.

Results. Since initial publication, 60 deaths occurred, leaving 311 patients alive with 290 (93.8%) recurrence-free. There was no significant decrease in the risk of recurrence or death associated with the CDP treatment regimen stratified for stage ($p = 0.14$, one-tail). The exploratory analysis for OS and the corresponding homogeneity tests for different effects across subgroups revealed only EFRT and EFRT & GRD status to have significantly different treatment effects ($p = 0.027$ and $p = 0.017$, respectively). Second primary malignancies were identified in 17/253 (6.4%) and 19/263 (7.0%) of patients treated with CD and CDP respectively. Breast (2.4%) followed by colon (1%) were the two cancers most frequently diagnosed in this setting.

* Corresponding author at: Women's Cancer Center of Nevada, Las Vegas, NV, United States of America.
E-mail addresses: nspirtos@wccenter.com (N.M. Spirtos), denserro@gogstats.org (D. Enserro), gibbons@mail.amc.edu (S.K. Gibbons), d-cella@northwestern.edu (D. Cella), rmorris@med.wayne.edu (R.T. Morris), degeest@ohsu.edu (K. DeGeest), David.Miller@utsouthwestern.edu (D.S. Miller).
[1] Currently at Wake Forest University School of Medicine, Mooresville, NC 28117, United States of America.
[2] Currently at Oregon Health & Science University (OHSU), Portland, OR 97239, United States of America.

https://doi.org/10.1016/j.ygyno.2019.03.240
0090-8258/© 2019 Published by Elsevier Inc.

Conclusion. No significant difference between treatment arms was identified. Subgroup analysis both in the initial and current reports demonstrated a trend towards improved RFS and OS in patients treated with CDP and EFRT. This long-term analysis of outcomes also identified the necessity of providing on-going cancer screening to patients enrolled in trials.

© 2019 Published by Elsevier Inc.

1. Introduction

Excluding node positive patients, <10% of all endometrial cancer (EC) are considered advanced stage. Historically, Stage IV disease was associated with such poor survival, the term curative intent was rarely used in the context of treating this condition. Macroscopic intraperitoneal disease was considered inoperable and cytoreductive efforts rarely undertaken. Successful use of whole-abdominal radiation (WAR) therapy at single institutions led to its adoption in treating advanced-stage EC with small-volume residual disease [1–5]. Evolution in thought and protocol development resulted in GOG #94, wherein Stage III/IV EC patients with small-volume residual disease were treated with WAR, as were all clear cell or papillary serous cancers [6,7]. Contemporaneous studies provided the basis to add chemotherapy to treatment regimens [8–10]. Consequently, GOG#122 opened for accrual for stage III/IV EC patients with residual disease <2 cm, treating with WAR or eight cycles of cisplatin plus doxorubicin (CD) [11]. This trial closed in 2000 with data too immature for analysis. Nevertheless, evidence suggested a possible benefit in combining radiation and chemotherapy in treating advanced stage EC [11]. Resultantly, GOG#184 opened to patients with stage III/IV disease and small volume residual disease. Treatment included volume-directed radiation therapy followed either by CD and filgrastim (G-CSF) or 3-h paclitaxel (P) + CD + G-CSF. The primary endpoint RFS, as well as acute and late adverse events, were reported in 2009 [12]. In comparing the two treatment arms, no difference in the primary endpoint, RFS, was identified, however those treated with CDP suffered from increased neurotoxicity when compared to those treated with CD alone [12]. Primary and secondary study endpoints, overall survival (OS) and long-term RFS are herein reported.

2. Materials and methods

In July, 2000, protocol accrual was open to patients diagnosed with Stage III or IV endometrial carcinoma of any histology if the disease was limited to the pelvis and abdomen. Required surgery included hysterectomy and bilateral salpingo-oophorectomy with residual disease measuring <2 cm. in diameter. Retroperitoneal node sampling was not required, but if positive para-aortic lymph nodes were identified, a negative scalene node biopsy and/or chest CT scan, were requirements. Radiotherapy (RT) was to be initiated within 8 weeks after surgery, and chemotherapy within 8 weeks after radiation. Once GOG-122 identified superior outcomes associated with chemotherapy vs. WAR, only patients with disease in the adnexae, pelvic and/or para-aortic nodes, vagina within the radiation port, involvement of the uterine serosa, or with positive pelvic washings, remained protocol eligible.

Pre-entry requirements, eligibility, and the specifics related to radiation therapy and chemotherapy can be reviewed in the publication by Homesley et al. [12].

Ineligible patients included those with co-morbid conditions precluding completion of protocol treatment; recurrent disease; prior pelvic or abdominal RT; a history of malignancy evident within the last 5 years or treatment with radiation or chemotherapy for that malignancy.

Following RT, the GOG Statistical and Data Center (SDC), randomly assigned the chemotherapy regimen, administered every 21 days for a maximum of six cycles, if patients were recurrence-free and agreeable. The sequence of treatment assignments, allocated with equal probability within strata using balanced blocks, was concealed from institutions and patients until randomization. Stratum levels were defined by the use of extended field radiation.

The GOG review process of eligibility, including central pathology review; protocol treatment; and adverse events was previously described in detail [12].

Of the 659 patients initially registered, 586 were randomized; 270 of 288 patients allocated to CD (control arm) were eligible, while 282 of 298 patients allocated to CDP (experimental arm) were eligible, resulting in 552 eligible patients for an intent-to-treat analysis. Patient and tumor characteristics for the eligible patients are presented in Table 1. The age range in the CD treatment arm was 26 to 84 years

Table 1
Patient and tumor characteristics for all eligible patients in GOG-0184.

Characteristic	Regimen				Total	
	CD		CDP			
	N	%	N	%	N	%
Age group						
20–29	1	0.4	0	0	1	0.2
30–39	15	5.6	4	1.4	19	3.4
40–49	42	15.6	46	16.3	88	15.9
50–59	91	33.7	114	40.4	205	37.1
60–69	78	28.9	83	29.4	161	29.2
70–79	37	13.7	32	11.3	69	12.5
≥80	6	2.2	3	1.1	9	1.6
Ethnicity						
Hispanic or Latino	8	3.0	6	2.1	14	2.5
Non-Hispanic	244	90.4	257	91.1	501	90.8
Unknown/not specified	18	6.7	19	6.7	37	6.7
Race						
White	236	87.4	258	91.5	494	89.5
Black/African American	16	5.9	13	4.6	29	5.3
Asian	10	3.7	3	1.1	13	2.4
Am Indian/Alaskan Native	0	0	1	0.4	1	0.2
Native Hawaiian/PI	3	1.1	1	0.4	4	0.7
Unknown	5	1.9	6	2.1	11	2.0
Performance status						
0	186	68.9	194	68.8	380	68.8
1	79	29.3	85	30.1	164	29.7
2	5	1.9	3	1.1	8	1.4
Cell type						
Adenocarcinoma, NOS	2	0.7	1	0.4	3	0.5
Clear cell	12	4.4	13	4.6	25	4.5
Endometrioid	185	68.5	197	69.9	382	69.2
Mucinous	1	0.4	0	0	1	0.2
Mixed epithelial	24	8.9	30	10.6	54	9.8
Adenosquamous	3	1.1	2	0.7	5	0.9
Undifferentiated	7	2.6	2	0.7	9	1.6
Serous	36	13.3	37	13.1	73	13.2
Histologic grade						
1	46	17.0	45	16.0	91	16.5
2	98	36.3	100	35.5	198	35.9
3	108	40.0	120	42.6	228	41.3
Not specified	18	6.7	17	6.0	35	6.3
Stage						
III	238	88.1	248	87.9	486	88.0
IV	32	11.9	34	12.1	66	12.0
Residual disease size						
Microscopic residual	245	90.7	250	88.7	495	89.7
Gross residual	25	9.3	32	11.3	57	10.3
Total	270	48.9	282	51.1	552	100.0

and in the CDP treatment arm was 36 to 86 years (median age of both being 58 years). The patient characteristics in Table 1 of the 2009 RFS paper were found to be correct when re-examined with the exception of two points: (1) the RFS paper listed 16 women aged 30–39, which appears to be incorrect, and (2) the RFS paper incorrectly listed18 patients and 11 patients in the CD arm and CDP arm respectively as being "Other" race, while the numbers for the "Race not specified", "Asian", "American Indian/Alaskan native", and "Native Hawaiian/PI" were still listed out. As the totaled numbers and percentages were slightly askew, they were adjusted accordingly and the correct information can be seen in Table 1.

The cumulative incidence of local-regional recurrences (LRR) counted recurrences when the initial site of recurrence was limited to the following areas: pelvis, vagina, and pelvic or para-aortic nodes. The cumulative incidence of distant recurrence (DR) counted any distant recurrence outside these areas of LRR. Deaths prior to recurrence, were considered competing events for estimating cumulative incidence. Distant recurrences were also considered as competing events for calculating the cumulative incidence of local-regional recurrence. All acute adverse events, regardless of attribution, were graded using the Common Toxicity Criteria Version 2.0 for patients who received study chemotherapy [13]. Adverse events occurring after completion of treatment were graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme [14]. The cumulative incidence of treatment-related grade 3 or higher gastrointestinal (GI) effects during follow-up was estimated. Deaths prior to documentation of late GI toxicity were considered competing events.

The previously reported primary endpoint used to compare the treatment regimens was RFS, defined as the number of months a patient survives without reappearance or progression of disease starting from chemotherapy randomization. Patients alive without disease recurrence were censored at the date of last contact. Primary and secondary endpoints for this study were OS and long-term RFS, where OS was defined as observed length of life from entry onto the study until death or for living patients the last date of contact. Although not explicitly stated, the difference in survival between patients with stage III and IV disease; statistical design balancing the two treatment arms relative to stage; and ultimately the exclusion of patients with stage IV disease prior to patient accrual to the study being completed, led to the stratification of both results by stage when reporting the primary and secondary study endpoints.

2.1. Statistical methods

Treatment-specific and pooled patient information and tumor characteristics were summarized, as well as second malignancy information. A Kaplan-Meier (KM) analysis was used to characterize the relationship between treatment arm and the OS outcome [15]. A log-rank test was calculated to test the independence of treatment with the OS outcome [16]. The treatment effect on OS was estimated using a Cox proportional hazards (PH) model [17,18]. The model assumption was assessed using an interaction test between the treatment variable and the natural logarithm of survival time. All survival analyses were stratified by stage. In exploratory analyses, the treatment effect on the OS outcome within subgroups of baseline clinical, pathologic, and host characteristics were estimated and displayed in a forest plot. Homogeneity tests using Q-statistics were performed to assess if treatment effect varied across subgroups. A multiple-variable PH model was used to assess the relationship between OS and age at study entry, tumor histology and grade, pelvic cytology, para-aortic nodes, and pelvic metastasis. All variables were modeled in one Cox PH model adjusted for treatment, stage, gross residual disease (GRD), extended field radiation therapy (EFRT), interaction between treatment and GRD and interaction between treatment and EFRT. The same methods applied to the OS outcome were also applied to long-term RFS outcome.

Exploratory analyses evaluating the effect of lymph node metastases and lymphadenectomy were performed in stage IV patients only. Finally, the effect of number of treatment cycles with respect to OS and RFS was also explored.

All analyses assumed an intent-to-treat framework among eligible patients. Analyses assumed a significance level of 0.05 on a one-tailed test, with the exception of exploratory analyses, which assumed a significance level of 0.05 on a two-tailed test. All analyses were completed using SAS 9.4.

The study had the original accrual goal of 218 RFS events among a projected 434 patients. After the amendment restricting enrollment to patients with stage III disease, the sample size was increased to 614 in order to offset the decrease in overall risk of recurrence. A sample of 218 RFS events would detect a proportional decrease of 29% in the hazard rate with 80% statistical power, assuming a one-tailed test at a significance level of 0.05. A planned interim efficacy and futility analysis of RFS with 137 disease recurrences or deaths was presented to the Data Monitoring Committee in January 2005. No action was taken as a result.

3. Results

The updated CONSORT diagram is presented in Fig. 1. As of September 13, 2017, 290 patients were still alive without recurrence, 21 patients alive with recurrence, and 241 of the 552 patients eligible for analysis were dead. Online Tables 1 and 2 display information related to survival status, mortality and second primary malignancies by treatment arm. Of the 123 deaths in the CD arm, 96 were due to disease, 1 treatment-related, 26 to other and unknown causes, Of the 118 deaths in the CDP arm, 93 were due to disease, 3 were treatment-related, 22 were due to other and unknown causes. Thirty-six patients (6.5%) reported new malignancies including 13 (36.1%) breast cancers, with the majority in the CDP arm. Colon cancer was the second most common with 5 (13.9%) occurrences. New malignancies suspected of representing recurrent (EC) were queried.

Fig. 2 displays OS survival curves for chemotherapy regimens and on-line Table 3 summarizes OS survival proportions for 2-year intervals. In the stage III patients, the difference in survival proportions comparing CDP to CD ranged from ~3 percentage points to ~7 percentage points in the interval of 24 months to 120 months. In the stage IV patients, neither treatment demonstrated superiority in year one. Subsequently, between 24 and almost 90 months, CD was associated with improved OS, but after 96 months CDP had a higher survival probability. There was no significant decrease in the risk of death associated with CDP treatment when stratified for stage ($p = 0.14$, one-tail). The (HR) of death relative to CD treatment stratified by stage is 0.87 (95% CI: 0.68–1.12).

The exploratory analyses for OS are presented in Fig. 3 and Table 2. The corresponding homogeneity tests testing for different effects across subgroups revealed only EFRT and EFRT & GRD status to have significantly different treatment effects ($p = 0.027$ and $p = 0.017$, respectively). EFRT showed evidence of a qualitative interaction; the treatment (HR) for death in patients with EFRT is 1.15 (95% CI: 0.81–1.63) while the treatment (HR) for death in patients without EFRT is 0.65 (95% CI: 0.45–0.93). For the EFRT and GRD combination, the treatment hazard risks (HR) for death in patients with yes/yes, no/yes, no/no, and yes/no combinations are 0.46 (95% CI: 0.22–0.97), 0.87 (95% CI: 0.26–2.83), 0.61 (95% CI: 0.42–0.91), and 1.35 (95% CI: 0.90–2.01), respectively. Among patients with GRD who received EFRT (yes/yes) the effect of treatment favors the CDP regimen as was the case for those patients without EFRT or GRD (no/no). However, treatment of patients who received EFRT without GRD (yes/no) slightly favored CD and not CDP, while no advantage associated with either treatment arm could be identified in those not receiving EFRT with GRD (no/yes). Stage, age group, GRD alone, EFRT prescribed/received, and tumor cell type and grade were all non-significant ($p > 0.05$).

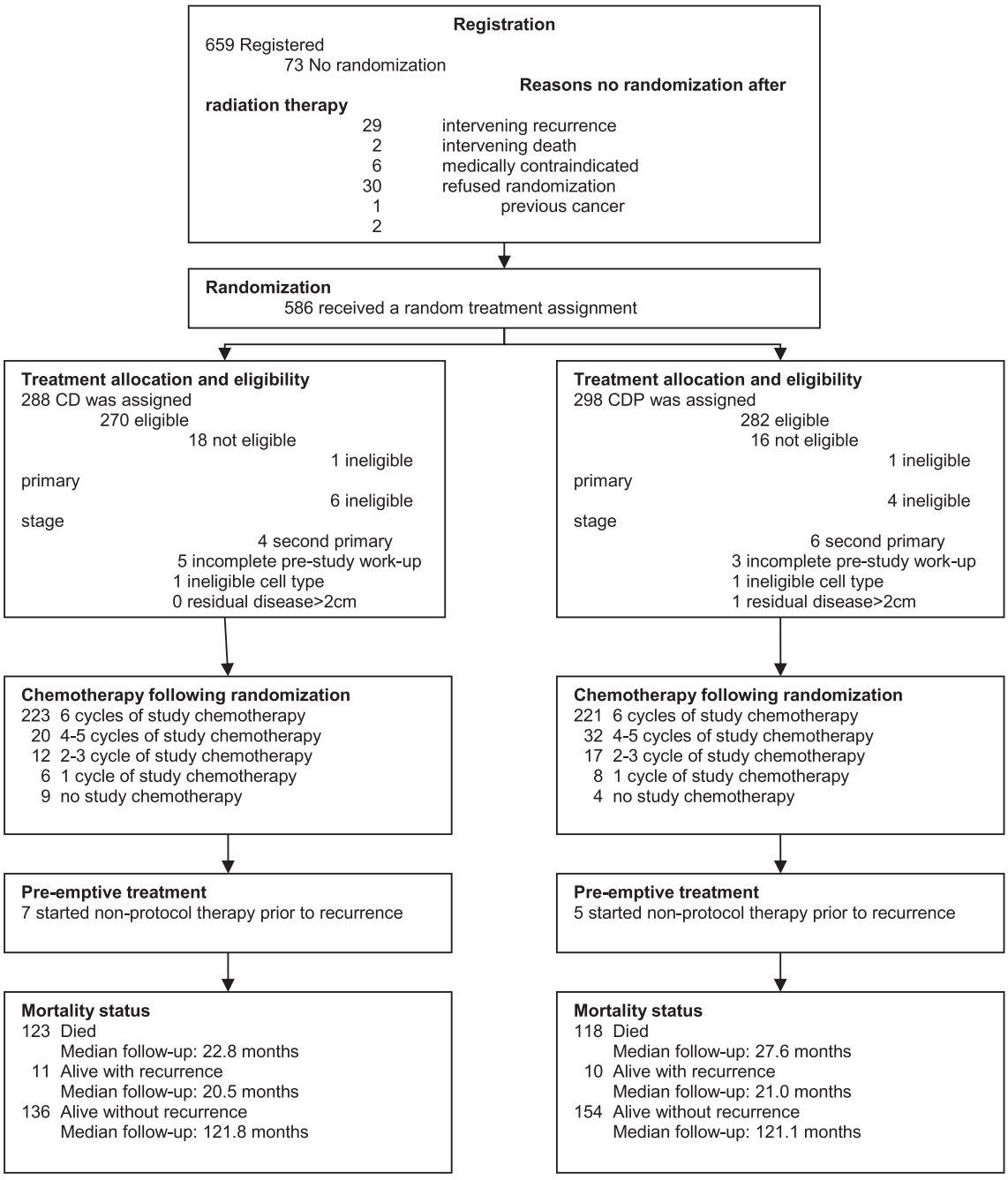

Fig. 1. Updated CONSORT diagram.

Table 2 summarizes the association between OS with age at study entry, tumor histology/grade, pelvic cytology, para-aortic nodes, and pelvic metastasis, providing evidence of prognostic factors for OS.

On-line Fig. 1 displays long-term RFS for chemotherapy regimens and on-line Table 4 summarizes RFS survival proportions for 2-year intervals. In stage III patients, differences in RFS survival proportions comparing CDP to CD ranged from 3.4 percentage points to 7.4 percentage points in the interval of 24 to 120 months. During year one, improved RFS was associated with CDP treatment for those with stage IV disease, but thereafter, the CD arm prevailed. When stratified by stage ($p = 0.14$, one-tail), no decrease in the risk of recurrence or death was associated with CDP treatment. The HR of recurrence or death relative to the CD treatment arm, stratified by stage, was 0.88 (95% CI: 0.69–1.12). This approximated the RFS in the 2009 paper ((HR): 0.90, 95% CI: 0.69–1.17).

Online Fig. 2 summarizes exploratory analyses for long-term RFS. Corresponding homogeneity tests for different effects across subgroups revealed only EFRT and EFRT & GRD status subgroups to have significantly different treatment effects on long-term RFS ($p = 0.031$ and $p = 0.013$, respectively). EFRT showed evidence of a qualitative interaction; the treatment (HR) for recurrence or death in patients with and without EFRT is 1.13 (95% CI: 0.80–1.59) and 0.66 (95% CI: 0.47–0.93), respectively. For the EFRT and GRD combination, the treatment hazard ratios (HR) for long-term RFS in patients with yes/yes, no/yes, no/no, and yes/no combinations are 0.44 (95% CI: 0.21–0.92), 0.49 (95% CI: 0.16–1.48), 0.65 (95% CI: 0.45–0.94), and 1.32 (95% CI: 0.90–1.95), respectively and were similar to those calculated for the risk of death. Patients with GRD who received EFRT (yes/yes) the effect of treatment favors the CDP regimen as was the case for those patients without GRD or EFRT (no/no). However, treatment of patients who

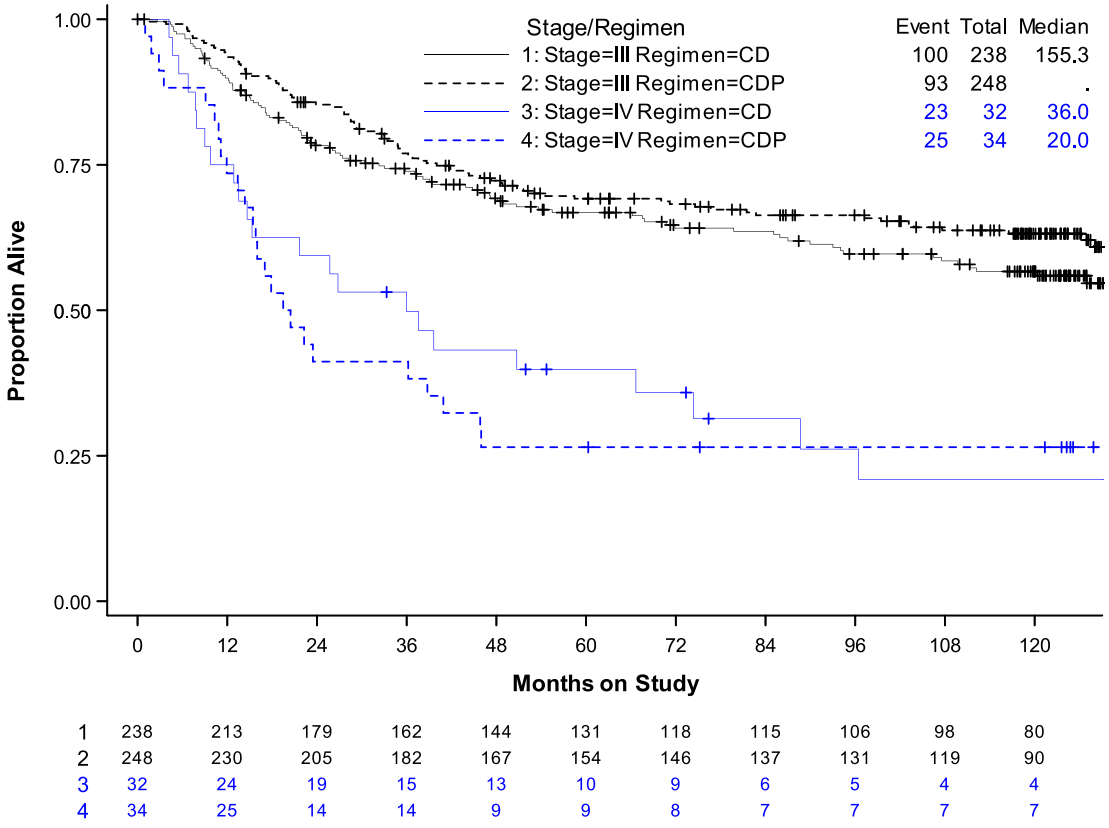

Fig. 2. Overall survival for chemotherapy regimens stratified by stage. CD = cisplatin and doxorubicin; CDP = cisplatin, doxorubicin, and paclitaxel. Median measured in months.

received EFRT without GRD (yes/no) slightly favored CD and not CDP, while no advantage associated with either treatment arm could be identified in those not receiving EFRT with GRD (no/yes). The relationship between long-term RFS and GRD showed borderline evidence of a quantitative interaction ($p = 0.052$), as those with microscopic residual disease had a HR of 0.91 (95% CI: 0.70–1.18) and those with GRD had a

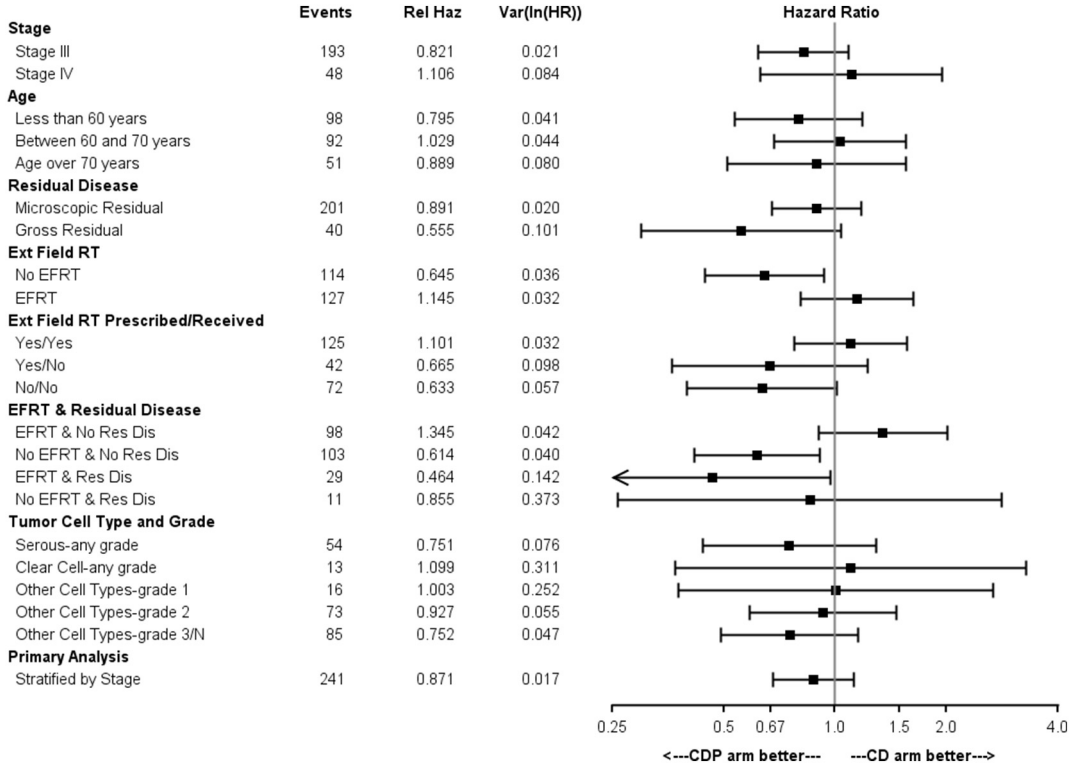

Fig. 3. Overall survival treatment ((HR)) s by subgroup. CD = cisplatin and doxorubicin; CDP = cisplatin, doxorubicin, and paclitaxel.

Table 2
Multiple variable-adjusted proportional hazards model ratio estimates for OS.

Covariate name	Covariate value	OS ((HR))	95% confidence interval
Age at study entry	Relative to a 1 year increase	1.05	(1.04–1.07)
Tumor histology/grade	Non-serous/non-clear cell grade 1	1.00	Reference group
	Non-serous/non-clear cell grade 2	2.44	(1.41–4.21)
	Non-serous/non-clear cell grade 3	3.65	(2.12–6.27)
	Uterine clear cell carcinoma	3.64	(1.72–7.67)
	Uterine papillary serous carcinoma	4.65	(2.61–8.28)
Pelvic cytology	Negative	1.00	Reference group
	Positive	1.48	(1.11–1.97)
	Missing, suspicious, unknown	1.19	(0.77–1.83)
Para-aortic nodes	Negative	1.00	Reference group
	Positive	2.62	(1.75–3.94)
	Not evaluated	1.72	(1.16–2.56)
Pelvic metastasis	Tubes, ovaries, or serosa vs. all others without metastasis to the tubes, ovaries, and serosa	1.61	(1.13–1.99)

Adjusted for treatment, stage, gross residual disease (GRD), extended field radiation therapy (EFRT), interaction between treatment and GRD and interaction between treatment and EFRT.

HR of 0.47 (0.26–0.86). Stage, age group, EFRT prescribed/received, and tumor cell type and grade were non-significant ($p > 0.05$). Table 3 summarizes the RFS HRs and 95% confidence intervals for age at study entry, tumor histology/grade, pelvic cytology, para-aortic nodes, and pelvic metastasis.

In evaluating the effect of lymph node metastases and lymphadenectomy in stage IV patients ($n = 66$), 20 patients had positive pelvic nodes; 26 negative pelvic nodes, and 20 with nodes not evaluated. In comparing positive pelvic to negative pelvic nodes, the (HR) for death in stage IV disease was 2.12 (95% CI: 1.04–4.31) and when women in whom the lymph nodes were not evaluated were compared to those with negative pelvic nodes the (HR) was 1.63 (95% CI: 0.80–3.29). The treatment effect on OS related to this parameter was not significant ($p = 0.31$).

The same analysis for long-term RFS provided similar results. The HR for recurrence or death when comparing positive pelvic nodes to negative pelvic nodes was 1.72 (95% CI: 0.87–3.39), while the HR for recurrence or death comparing women not evaluated to those with negative pelvic nodes was 1.77 (95% CI: 0.91–3.47). The effect of treatment effect on RFS ($p = 0.49$) was insignificant.

No significant interaction existed between treatment regimen and the number of cycles on OS ($p = 0.67$) or RFS ($p = 0.39$). For OS, the treatment (HR) of CDP vs CD in 1–3 cycles was 1.21 (95% CI: 0.60–2.44), in 4–5 cycles 0.66 (95% CI: 0.30–1.45), and 6 cycles 0.84 (95% CI: 0.63–1.13). For long-term RFS, the treatment (HR) of CDP vs CD in 1–3 cycles was 1.36 (95% CI: 0.68–2.72), in 4–5 cycles 0.55 (95% CI: 0.25–1.19), and 6 cycles 0.86 (95% CI: 0.65–1.14). While statistically insignificant, it appeared 4 to 6 cycles of chemotherapy may be protective and it was less likely 1–3 cycles offered equivalent treatment advantage. Second primary malignancies were identified in 17/253 (6.4%) and 19/263 (7.0%) of patients treated with CD and CDP respectively. Breast (2.4%) followed by colon (1%) were the two cancers most frequently diagnosed in this setting. Second primary malignancies were identified in 17/253 (6.4%) and 19/263 (7.0%) of patients treated with CD and CDP respectively. Breast (2.4%) followed by colon (1%) were the two cancers most frequently diagnosed in this setting.

Table 3
Multiple variable-adjusted proportional hazards model ratio estimates for long-term RFS.

Covariate name	Covariate value	RFS ((HR))	95% confidence interval
Age at study entry	Relative to a 1 year increase	1.04	(1.02–1.05)
Tumor histology/grade	Non-serous/non-clear cell grade 1	1.00	Reference group
	Non-serous/non-clear cell grade 2	2.08	(1.28–3.38)
	Non-serous/non-clear cell grade 3	2.85	(1.76–4.61)
	Uterine clear cell carcinoma	3.09	(1.57–6.07)
	Uterine papillary serous carcinoma	4.10	(2.43–6.91)
Pelvic cytology	Negative	1.00	Reference group
	Positive	1.53	(1.16–2.02)
	Missing, suspicious, unknown	1.24	(0.82–1.87)
Para-aortic nodes	Negative	1.00	Reference group
	Positive	2.26	(1.54–3.32)
	Not evaluated	1.60	(1.10–2.32)
Pelvic metastasis	Tubes, ovaries, or serosa vs. all others without metastasis to the tubes, ovaries, and serosa	1.47	(1.14–1.90)

Adjusted for treatment, stage, gross residual disease (GRD), extended field radiation therapy (EFRT), interaction between treatment and GRD and interaction between treatment and EFRT.

4. Discussion

Defining optimal treatment for advanced stage EC has proven to be problematic. In GOG-94 cytoreductive surgery (<2 cm of residual disease) was incorporated with WAR to treat stage III/IV disease. Reported RFS and OS were 29% and 31% with tolerable toxicity [6,7]. Significantly improved RFS and response associated with (CD) when compared to (D) alone had been reported in patients with stage III/IV or recurrent (EC), providing foundation for GOG-122 (WAR vs CD x8) [8–10]. Randall et al. projected 50% of the patients treated with CD and 38% of those treated with WAI would be alive and recurrence-free with 5 years of follow-up. [Patterns of recurrence combining both adjuvant treatment modalities and studies defining the role of taxanes led to the development of GOG-184 [11]. In 2009, the primary study objectives RFS, and short and long-term toxicity were reported [12] and OS data was not sufficiently mature to report. No significant difference in RFS had been identified between the two study arms. Acute and long-term adverse events, including the increased risk of febrile neutropenia, infection, pain, myalgia, and sensory neuropathy, occurred more frequently in the CDP arm [19]. In this report of the secondary study endpoints, long-term RFS and OS, treatment with CDP when compared to CD was not associated with any significant decrease at $p < 0.05$ in either RFS or OS (On-line Table 2). The unadjusted Kaplan-Meier estimates of both RFS and OS (Fig. 2 and On-line Fig. 1) are illustrative of the impact stage, not treatment regimen, had on RFS and OS. This is similar to the findings reported previously by Homesley et al. [12]. Median survival with over 100 months of follow-up in each arm (CD and CDP) approximated 50% and but for likely different study populations (more stage III patients in GOG#184 vs #122) it would appear that the OS associated with GOG#184 (combined modalities) was superior to either treatment arm chemotherapy or radiation alone in GOG#122.

Also of note, such an analysis of long-term outcomes are not often undertaken, but when performed allows for revisiting the initial data set and correction of any discrepancies identified.

In comparing the consort diagram in Fig. 1 to the same initially provided, there are currently 136/270 (50%) and 154/282 (55%) (RFS) in the CD and CDP arms respectively, down from 159/270 (62%) and 175/282 (64%) patients that were alive (RFS) treated similarly [13]. In the first 48 months of follow-up 111 and 107 patients either died or were alive with disease and, over the last 60 months, an additional 23 and 21 patients either died or recurred. This finding provided an understanding of the natural history of this disease following treatment and reinforced the importance of continuing long-term follow-up. This is best illustrated in Table 3.

By comparing (1) the forest plots summarizing the RFS treatment HRs by subgroup in the original report to that representing long-term RFS (On-line Fig. 2) and (2) the corresponding homogeneity tests for different effects across the subgroups, a small number of significant changes were identified [13]. The initial p-values associated with the testing for homogeneity defined by EFRT or the EFRT & GRD were not significant. Similar statistical analysis pertaining to long-term RFS, revealed subgroups of EFRT and EFRT&GRD status, to have significantly different treatment effects on long-term RFS ($p = 0.031$) and ($p = 0.013$), respectively. The no EFRT group was better served by treatment with CDP in comparison to the EFRT group that was on a relative basis better treated with CD. Similar to initial findings ($p = 0.076$), the remaining p-values for stage, age group, EFRT prescribed/received, and tumor cell type and grade were non-significant ($p > 0.05$) [11].

The difference in treatment effects for EFRT and GRD and the multiple variable-adjusted proportional HRs for long-term RFS and OS (95% confidence intervals) for age at study entry, tumor histology/grade, pelvic cytology, para-aortic nodes, and pelvic metastasis (Tables 2 and 3) remain unchanged from the original report. The treatment effects for EFRT and GRD and HRs are not surprising with serous and clear cell histology followed by positive aortic lymph nodes being associated with the largest HRs. Identifying the increased HR associated with positive cytology is not a new finding, being first identified in GOG-33 and suggests ignoring this independent prognostic factor comes with risk [20].

Treatment with CDP when compared to CD was not associated with any significant decrease at $p < 0.05$ in either RFS or OS (On-line Table 2). The unadjusted Kaplan-Meier estimates of both RFS and OS (Fig. 2 and On-line Fig. 1) are illustrative of the impact stage, but not treatment regimen, had on RFS and OS. Again, this is similar to the findings reported previously by Homesley et al. [12].

Subgroup analysis both in the initial and current reports demonstrated a trend towards improved RFS and OS in patients treated with CDP and EFRT. Of interest, it would appear in patients with GRD, regardless of EFRT status, the CDP regimen offers some slight advantage in treatment. However, with no GRD it could be argued on one hand, if EFRT was provided then the increased toxicity, particularly the neurotoxicity, associated with the CDP regimen could be avoided. On the other hand, in patients with no GRD, if no EFRT was not to be integrated into the management, then apparently the added toxicity of CDP may be acceptable as it seems to offer some protective effect over CD. This current analysis and the results of GOG-94, wherein no patient with GRD survived, speak to the importance of combining adjuvant modalities in the treatment of advanced stage EC [6,7].

When GOG-184 was developed, little was known about combining radiation therapy and chemotherapy in the adjuvant treatment for advanced stage EC and much less about the best order of administration. Subsequently there have been reports favoring using chemotherapy sandwiched around radiation therapy [21–23]. Theoretically, this approach offers a means to minimize distant and upper abdominal recurrences associated with radiation therapy given alone, while minimizing toxicity with fewer up-front cycles of chemotherapy and still allowing directed radiation therapy to be administered, thereby decreasing local recurrences [11]. The recently reported PORTEC-3 trial, determined adding chemotherapy to radiation compared to radiation alone did not improve overall survival but did improve RFS [24]. Consensus regarding this issue is lacking, but nevertheless it seems reasonable to compare sandwiched chemotherapy/radiotherapy to the current standard of care [25,26].

Additional subgroup analysis was done to identify if the removal of retroperitoneal pelvic lymph nodes in Stage IV patients affected either RFS or OS and if treatment with either arm had an effect in this situation. Not surprisingly, the hazard risk associated with positive versus negative or unsampled lymph nodes and RFS and OS was increased, even though there was no difference in effect associated with either CDP or CD. The question regarding the therapeutic benefit has long remained unanswered by direct study despite indirect evidence from a SEER analysis by Chan et al. demonstrating that the extent of the lymph node dissection by count was directly related to improved OS [27]. The findings of Yoon et al. include a significant effect of lymphadenectomy when patients are treated with radiation therapy alone and although there was a trend towards a similar result in those patients receiving chemotherapy and radiation, it did not reach statistical significance [28]. As a practical matter, the inability to identify macroscopic involvement of the retroperitoneal nodes without subjecting patients to additional surgical morbidity, is problematic. Future protocol development will require careful consideration of this issue and perhaps incorporating sentinel lymph node sampling and possible mandatory aortic lymph node evaluation into the treatment plans as it pertains to advanced stage (EC).

Treatment with as few as 3 cycles of intraperitoneal (IP) chemotherapy in treating stage III epithelial ovarian cancer has been found to be beneficial, but this analysis of GOG-184, indicates >3 cycles of chemotherapy and probably closer to the 6 planned cycles of chemotherapy are needed to achieve similar results [29]. Other authors have reported excellent results using 3 cycles of chemotherapy (CD) followed by radiation in EC and EOC, but there has been little support in pursuing this avenue of investigation [30,31]. IP chemotherapy followed by WAR in the treatment of advanced stage (EC) has been reported and gives rise to the need for further study [32,33].

The importance of long-term follow-up of any study population cannot be overstated given new cancers were identified in 17/253 (6.7%) and 19/263 (7.2%) of the patients receiving CD and CDP respectively. Breast cancer, the most frequently diagnosed secondary malignancy, was found in 3/253 (1.2%) of patients treated with CD and 10/263 (3.8%) of those treated with CDP. The small sample size of new cancers precluded any meaningful statistical analysis, but not the identification of the need to maintain routine screening for other malignancies. It is not unreasonable to retrospectively test tissue from this study population for molecular markers associated with genetically linked cancers such as BRCA 1/2 and Lynch syndrome. This analysis of primary and secondary study endpoints of GOG #184, has substantiated that long-term RFS and OS are not impacted by the addition of (P) to (C,D) following volume-directed radiation and optimal surgical debulking. It is also clear from the discussion that despite many efforts by US and international co-operative groups to design a protocol that would have allowed for the determination of the "best treatment" for patients with advanced endometrial cancer, this issue remains unresolved. The historical method of developing sequential large-scale protocols was costly and time consuming and it is unlikely that cooperative groups will be able to attempt to address this issue due to these constraints. Even if this was financially feasible, consensus is lacking as it pertains almost every aspect of protocol development, be it the standardization of surgical requirements, chemotherapy agents and schedules, or how and when to deliver radiation therapy. Unfortunately, this lack of knowledge will be covered up by the disguise of individualized care. One important finding that can be acted upon is the need to continue to ensure patients participating in protocol or non-protocol cancer therapy receive routine cancer screening to identify new cancers as early as possible.

5. Conclusion

There is no significant difference in OS and long-term RFS associated with CD + P compared to CD alone. This result differs little from that first reported and the addition of P comes with increased toxicity, particularly neurotoxicity. The HR's associated with higher grade endometrioid cancers; serous and clear cell cancers; positive aortic lymph nodes; positive cytology and pelvic metastases were all increased and again consistent with the previous report.

Additionally, analysis of long-term study outcomes allows for the comparison with the evolving literature and to stimulate thought regarding future study design as well as the necessity of providing ongoing screening to patients enrolled in trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.240.

Conflicts of interest

Dr. Nick Spirtos receives money from a grant to the Women's Cancer Center of Nevada, Inc. and also support for travel to meetings for the study or other purposes. He also receives royalties paid to him regarding Wiley – textbook authorship.

Dr. Danielle Enserro receives money to her institution from NCI for Cooperative Group/NCTN Grant Funding for all aspects of this trial, including travel to Group meetings; statistical analysis, study monitoring, etc. She also receives monies from a NCTN Group Funding Grant through NCI, as well as monies from the GOG Foundation, Inc.

Dr. David Cella received money from GOG/NRG for support for travel to meetings for the study or other purposes.

Dr. Robert Morris served as a consultant for Clovis Oncology and Janssen.

Dr. David Miller served as a consultant for Tesaro, Janssen, Clovis and Genentech. His institution also received grant funding through Advenchen, Takeda, Tesaro and Xenetic. He also received monies from Genentech and Clovis for payment for lectures, including service on speakers' bureaus.

Author contributions

Study concept and design: Dr. Nick Spirtos, Dr. Susan Gibbons, Dr. David Cella

Provision of materials or patients: Dr. Nick Spirtos, Dr. Howard Homesley, Dr. Robert Morris, Dr. Koen DeGeest, Dr. Roger B. Lee, Dr. David S. Miller

Acquisition of data: Dr. Nick Spirtos, Dr. Koen DeGeest, Dr. Roger B. Lee, Dr. David S. Miller

Analysis and interpretation of data: Dr. Nick Spirtos, Dr. Danielle Enserro, Dr. Susan Gibbons, Dr. David Cella, Dr. David S. Miller

Manuscript writing: Dr. Nick Spirtos, Dr. Danielle Enserro, Dr. Susan Gibbons, Dr. Howard Homesley

Critical review of the manuscript: Dr. Nick Spirtos, Dr. Danielle Enserro, Dr. Howard Homesley, Dr. David Cella, Dr. Robert Morris, Dr. Koen DeGeest, Dr. Roger B. Lee, Dr. David S. Miller

Final approval of manuscript: Dr. Nick Spirtos, Dr. Danielle Enserro, Dr. Howard Homesley, Dr. Susan Gibbons, Dr. David Cella, Dr. Robert Morris, Dr. Koen DeGeest, Dr. Roger B. Lee, Dr. David S. Miller

All authors provided data, were involved in writing, revision, and approved the final manuscript. Dr. Enserro performed the statistical analyses of this study.

Acknowledgment

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical Office (CA 37517), NRG Oncology (1 U10 CA180822), NRG Operations (U10CA180868) and UG1CA189867 (NCORP).

The following Gynecologic Oncology institutions participated in this study: Women's Cancer Center of Nevada, Ohio State University Comprehensive Cancer Center, MD Anderson Cancer Center, University of Iowa Hospitals and Clinics, Tacoma General Hospital, University of Oklahoma Health Sciences Center, University of Minnesota Medical Center-Fairview, University of California Medical Center at Irvine-Orange Campus, Washington University School of Medicine, Case Western Reserve University, Indiana University Hospital/Melvin and Bren Simon Cancer Center, Stony Brook University Medical Center, Walter Reed National Military Medical Center, Gynecologic Oncology Network/Brody School of Medicine, University of Massachusetts Memorial Health Care, University of Kentucky, Ellis Fischel Cancer Center, Cleveland Clinic Foundation, University of Colorado Cancer Center – Anschutz Cancer Pavilion, Mayo Clinic, University of Mississippi Medical Center, Fred Hutchinson Cancer Research Center, Abramson Cancer Center of the University of Pennsylvania, Albany Medical College, Memorial Sloan Kettering Cancer Center, Abington Memorial Hospital, Duke University Medical Center, Cooper Hospital University Medical Center, ECOG Statistical Center, Wake Forest University Health Sciences, Moffitt Cancer Center and Research Institute, Wayne State University/Karmanos Cancer Institute, University of North Carolina at Chapel Hill, University of Texas Southwestern Medical Center, State University of New York Downstate Medical Center, Roswell Park Comprehensive Cancer Center, University of Cincinnati, Cancer Research for the Ozarks NCORP, Penn State Milton S. Hershey Medical Center, Tufts-New England Medical Center, Community Clinical Oncology Program, Thomas Jefferson University Hospital, Northern Indiana Cancer Research Consortium, University of Virginia, University of Chicago, Fletcher Allen Health Care, Cancer Research Consortium of West Michigan NCORP, University of Alabama at Birmingham, University of Pittsburgh Cancer Institute, University of New Mexico, Fox Chase Cancer Center, Yale University, University of Texas – Galveston, University of Hawaii, Missouri Valley Cancer Consortium CCOP, Metro-Minnesota CCOP, Geisinger Medical Center and Central Illinois CCOP.

References

[1] B.E. Greer, A. Hamberger, Treatment of intraperitoneal metastatic adenocarcinoma of the endometrium by whole-abdominal moving strip technique and pelvic boost irradiation, Gynecol. Oncol. 16 (3) (1983) 365–373.
[2] A.J. Dembo, Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience, Cancer 55 (1985) 2285–2290.
[3] R.A. Potish, L.B. Twiggs, L.L. Adcock, K.A. Prem, Role of whole abdominal radiation therapy in the management of (EC): prognostic importance of factors indicating peritoneal metastases, Gynecol. Oncol. 21 (1985) 80–86.
[4] A. Martinez, M. Schray, K. Podratz, R. Stanhope, G. Malkasian, Postoperative whole abdomino-pelvic irradiation for patients with high risk (EC), Int. J. Radiat. Biol. Phys. 17 (1989) 371–377.
[5] S. Gibbons, A. Martinez, M. Schray, Adjuvant whole abdominal pelvic irradiation for high risk endometrial carcinoma, Int. J. Radiat. Oncol. Biol. Phys. 21 (1991) 1019–1025.
[6] Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley H, Lee RB, et al. Adjuvant whole abdominal irradiation in clinical stage I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. Gynecol. Oncol. 2006; 100:349–354.
[7] Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley H, Malfetano JH, e al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV (EC): a Gynecologic Oncologic Group study. Gynecol. Oncol. 2005; 97:755–763.
[8] Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, et al. Phase III trial of doxorubicin with or without cisplatin in advanced (EC): a Gynecologic Oncology Group study. J. Clin. Oncol. 2004; 22:3902–3908.
[9] Fleming GF, Brunetto, VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgastrim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J. Clin. Oncol. 2004; 22: 2159–2166.
[10] S. Lincoln, J.A. Blessing, R.B. Lee, T.F. Rocereto, Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study, Gynecol. Oncol. 88 (2003) 271–281.
[11] Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, 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. 2006; 24:36–44.
[12] Homesley HD, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos, NM, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol. Oncol.. 2009: 112:543–552.
[13] S.G. Arbuck, J. McClure, S.P. Ivy, A. Setser, The Common Toxicity Criteria Manual. National Cancer Institute, Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events; CTC v2.0, NCI, NIH, DHHS, April 30, 1999http://ctep.nci.nih.gov.
[14] J.D. Cox, J. Stetz, T.F. Pajak, Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC), Int. J. Radiat. Oncol. Biol. Phys. 1 (1995) 1341–1346.
[15] E.L. Kaplan, P. Meier, Nonparametric estimation from incomplete observations, J. Am. Stat. Assoc. 53 (1958) 457–481.
[16] N. Mantel, Evaluation of survival data and two new rank order statistics arising from its consideration, Cancer Chemother. Rep. 50 (1996) 163–170.
[17] D.R. Cox, Regression model and life tables (with discussion), J. R. Stat. Assoc. 53 (1958) 457–481.
[18] D.A. Schoenfeld, Sample size formula for the proportional hazards regression model, Biometrics 39 (1983) 499–503.

[19] Cella D, Huang H, Homesley HD, Montag A, Salani R, DeGeest K, et al. Patient-reported peripheral neuropathy of doxorubicin and cisplatin with and with paclitaxel in the treatment of advanced (EC): results from GOG 184. Gynecol. Oncol. 2010; 119:539–542.
[20] W.T. Creasman, C.P. Morrow, B.N. Bundy, H.D. Homesley, J.E. Graham, P.B. Heller, Surgical pathologic spread patterns of (EC). A Gynecologic Oncology Group Study, Cancer 60 (8 Suppl) (1987) 2035–2041.
[21] M.A. Geller, J. Ivy, K.E. Dusenbery, R. Ghebre, R. Isaksson Vogel, P.A. Argenta, A single institution experience using sequential multimodality adjuvant chemotherapy and radiation in the "sandwich" method for high risk endometrial carcinoma, Gynecol. Oncol. 118 (2010) 19–23.
[22] A.L. Fields, M.H. Einstein, A.P. Novetsky, J. Gebb, G.L. Goldberg, Pilot phase II trial of radiation "sandwiched" between combination paclitaxel/platinum chemotherapy in patients with uterine papillary serous carcinoma (UPSC), Gynecol. Oncol. 108 (2008) 201–206.
[23] Lupe K, D'Souza DP, Kwon JS, Radwan JS, Harle IA, Hammond JA, et al. Adjuvant carboplatin and paclitaxel chemotherapy interposed with involved field radiation for advanced (EC). Gynecol. Oncol.. 2009; 114: 94–98.
[24] de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C 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. 2018; 19(3):295–309.
[25] Secord AA, Geller MA, Broadwater G, Holloway R, Shuler K, Dao ND, et al. A multicenter evaluation of adjuvant therapy in women with optimally resected stage III (EC). Gynecol. Oncol. 2013; 128:65–70.
[26] Hogberg T, Signorelli M, Freire de Oliveira C, Fossati R, Lissoni AA, Sorbe B et al. Sequential adjuvant chemotherapy and radiotherapy in (EC) - results from two randomized trials. Eur. J. Cancer 2010; 46:2422–2431.
[27] Chan JK, Cheung MK, Huh WK, Osann K, Hussain A, Teng NN, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer 2006. 107:1823–1830.
[28] Yoon MS, Park W, Huh SJ, Kim HJ, Kim YS, Kim YB, et al. Impact of paraaortic lymphadenectomy for endometrial cancer with positive pelvic lymph nodes: a Korean Radiation Oncology Group study (KROG 13-17). Eur. J. Surg. Oncol. 2016; 42: 1497–1505.
[29] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N. Engl. J. Med. 2006; 354:34–43.
[30] J.M. Fowler, W.E. Brady, P.W. Grigsby, D.E. Cohn, R.S. Mannel, J.S. Rader, Sequential chemotherapy and irradiation in advanced stage (EC): a Gynecologic Oncology Group phase I trial of doxorubicin-cisplatin followed by whole abdomen irradiation, Gynecol. Oncol. 112 (2009) 553–557.
[31] Randall ME, Barrett RJ, Spirtos NM, Chalas E, Homesley HD, Lentz SL, et al. Chemotherapy, early surgical reassessment, and hyperfractionated abdominal radiotherapy in stage III ovarian cancer: results of a gynecologic oncology group study. Int. J. Radiat. Oncol. Biol. Phys.. 1996; 34:139–147.
[32] L. Lee, P. Bu, C. Feltmate, A.N. Viswanathan, Adjuvant chemotherapy with external beam radiation therapy for high-grade, node positive (EC), Int. J. Gynecol. Cancer 24 (2014) 1441–1448.
[33] McMeekin DS, Sill MW, Walker JL, Moore KN, Waggoner SE, Thaker PH, et al. A phase I study of IV doxorubicin plus intraperitoneal (IP) paclitaxel and IV or IP cisplatin in (EC) patients at high risk for peritoneal failure (GOG 9920): and NRG Oncology/Gynecologic Oncology Group study. Gynecol. Oncol. 2015:138; 36–40.