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ORIGINAL REPORT

Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study

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ABSTRACT

Purpose
To compare whole-abdominal irradiation (WAI) and doxorubicin-cisplatin (AP) chemotherapy in women with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease.

Patients and Methods
Four hundred twenty-two patients were entered onto this trial. Of 396 assessable patients, 202 were randomly allocated to receive WAI, and 194 were allocated to receive AP. Irradiation dosage was 30 Gy in 20 fractions, with a 15-Gy boost. Chemotherapy consisted of doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for seven cycles, followed by one cycle of cisplatin.

Results
Most patient and tumor characteristics were well balanced. The median patient age was 63 years; 50% had endometrioid tumors. Median follow-up time was 74 months. The hazard ratio for progression adjusted for stage was 0.71 favoring AP (95% CI, 0.55 to 0.91; $P < .01$). At 60 months, 50% of patients receiving AP were predicted to be alive and disease free when adjusting for stage compared with 38% of patients receiving WAI. The stage-adjusted death hazard ratio was 0.68 (95% CI, 0.52 to 0.89; $P < .01$) favoring AP. Moreover, at 60 months and adjusting for stage, 55% of AP patients were predicted to be alive compared with 42% of WAI patients. Greater acute toxicity was seen with AP. Treatment probably contributed to the deaths of eight patients (4%) on the AP arm and five patients (2%) on the WAI arm.

Conclusion
Chemotherapy with AP significantly improved progression-free and overall survival compared with WAI. Nevertheless, further advances in efficacy and reduction in toxicity are clearly needed.

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INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy in the United States, with approximately 7,100 deaths in 2004, usually from metastatic disease.[1] Surgical staging (including lymph node assessment and/or dissection) has better defined this disease.[2] Nevertheless, stage III and IV endometrial carcinoma is a heterogeneous group of tumors with variable prognoses.[3,4] A significant rate of relapse within the abdomen has given impetus to the use of whole-abdominal irradiation (WAI),[5-9] whereas, for extra-abdominal sites, cytotoxic chemotherapy[10-17] or combinations of chemotherapy and radiation have been used.[18-21]

Using WAI, Smith et al[7] reported 3-year estimated progression-free survival (PFS) and overall survival (OS) rates of 79% and 89%, respectively, in stage III and IV patients with adenocarcinoma (not papillary serous or clear cell) and PFS and OS rates of 32% and 61%, respectively, in patients with stage III and IV clear-cell or serous papillary carcinoma. In that study, WAI was well tolerated, with a 7% actuarial risk of major complications at 3 years. Gibbons et al[5] reviewed 56 patients at high risk for abdominal recurrences who were treated with WAI. Seven-year PFS rates were 58% and 25% for stage III and IV patients, respectively. Potish[8] reported a 5-year PFS rate of 63% in stage III and IV patients after WAI.

Cytotoxic chemotherapy has been used primarily as palliative therapy for patients with advanced endometrial carcinoma. In previous trials by the Gynecologic Oncology Group (GOG) and others, doxorubicin, cisplatin, and other single agents have shown complete and partial response rates of 20% to 45%.[22-25] In two randomized trials, the response rate for the combination of doxorubicin and cisplatin (AP) was superior to doxorubicin alone.[11,12] Response rates up to 71% with multiagent regimens have been reported in phase II trials.[15] These results indicated the need for a direct comparison of WAI and chemotherapy, which is the subject of this report.

PATIENTS AND METHODS

Patient Eligibility

Patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV endometrial carcinoma of any histology were eligible for this trial. Eligibility required total abdominal hysterectomy and bilateral salpingo-oophorectomy, surgical staging, tumor resection, and no single site of residual tumor more than 2 cm. Nodal sampling was optional for patients with stage III or IV disease by clinical or surgical criteria. Patients with positive para-aortic lymph nodes (PALNs) were required to have negative scalene node biopsies and chest computed tomography scans. Adequate hematologic (WBC $\geq$ 3,000/μL, platelets $\geq$ 100,000/μL, and granulocytes $\geq$ 1,500/μL), renal (creatinine $\leq$ 2 mg %), and hepatic (bilirubin $\leq$ 1.5$\times$ the institutional normal value and AST $\leq$ 3$\times$ the institutional normal value) function was required, as was a normal cardiac ejection fraction and Zubrod (GOG) performance status of 0 to 3. Ineligible patients included patients with recurrent disease; parenchymal liver, lung, or other hematogenous metastasis; inguinal lymph node involvement; or a history of pelvic or abdominal radiation therapy or chemotherapy.

Protocol treatment was to be started within 8 weeks of surgery. The institutional review board at each participating institution approved the protocol, and all patients provided written informed consent consistent with all institutional, state, and federal regulations before study randomization.

Radiation Therapy

WAI was delivered with an open-field anterior-posterior/posterior-anterior technique. The prescribed dose was 30 Gy in 20 daily fractions. Kidney blocks were used posteriorly during WAI; no liver shielding was used. After WAI, patients received a boost to the true pelvis or to an extended field encompassing pelvic lymph nodes (PLNs) and PALNs. A boost to both areas was administered to patients with positive PLN and no PALN sampling or patients with neither PLN nor PALN sampling.

Pelvic ($\pm$ para-aortic) boosts were accomplished using a four-field box technique with custom blocking to minimize the treated small-bowel volume. The boost dose was 15 Gy in 8 fractions. All fields were treated once daily, 5 days per week. If more than a 2-week treatment interruption was required, resumption of treatment was at the physician's discretion, and follow-up continued regardless of treatment.

Chemotherapy

Chemotherapy consisted of doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks for eight cycles. The maximum allowable cumulative dose of doxorubicin was 420 mg/m^2; therefore, only cisplatin was to be infused during the eighth cycle. Hydration was maintained by administering normal saline at 500 mL/h for 2 hours before and after the cisplatin dose. Treatment with chemotherapy required a minimum pretreatment granulocyte count of 1,500/μL and a minimum platelet count of 100,000/μL. Doxorubicin doses were reduced based on pretreatment blood counts, with dose levels reduced from 60 to 15 mg/m^2 in 15-mg/m^2 increments. Doses were reinstituted with recovery of myelosuppression. Treatment interruption caused by myelosuppression exceeding 6 weeks required discontinuation of protocol therapy. The use of growth factors was not controlled, and data regarding their use were not routinely gathered.

A normal cardiac ejection fraction based on institutional values was required. A decline in the ejection fraction of 20% of the baseline value or development of congestive heart failure or other life-threatening cardiac problems required discontinuation of doxorubicin; however, cisplatin treatment continued. Only cisplatin was withheld for serum creatinine more than 2.0 mg. Treatment interruptions as a result of neurotoxicity, including hearing loss, were left to the discretion of the patient and physician.

Patient Follow-Up

Patients were to be evaluated weekly during WAI with monitoring of blood counts, creatinine, and liver function. Before each chemotherapy cycle, patients had a physical examination, and CBC counts and serum creatinine were measured. Ejection fraction was evaluated immediately before cycle 6 (or earlier, if clinically indicated) for patients on the AP arm. All adverse effects thought to be related to protocol treatment were assessed according to the GOG Common Toxicity Criteria.

After protocol treatment, patients were evaluated every 3 months for 2 years and then every 6 months. A chest radiograph was required every 6 months for the first 2 years and then annually. Patients were observed for progression and survival. PFS was defined as the length of time a patient survived from study entry without reappearance or progression of tumor. Patients alive without tumor recurrence or progression were censored at the date of last contact. OS was defined as the observed length of life from study entry to death from any cause or, for living patients, the date of last contact.

Quality Assurance

The study chair (M.E.R.) and members of the GOG Radiation Oncology Committee reviewed the simulation and port films, isodose computations, and radiation summary forms. Dosimetry quality control was the responsibility of the Radiological Physics Center in Houston, Texas. Chemotherapy records were reviewed by the study chair and medical oncology cochair (H.M.). Pathology materials, including slides documenting primary and metastatic disease, were reviewed by members of the GOG Pathology Committee. The GOG Gynecologic Oncology Committee conducted a central review of all patient eligibility data without knowledge of outcome. The Study Chair reviewed all patient records and data forms.

Statistical Considerations

The GOG Statistical and Data Center randomly assigned therapy to each patient with equal probability of assignment to each treatment regimen. A balanced block randomization was used to balance assigned treatment regimens within each institution. The sequence of treatment assignments was concealed from institutions and patients until telephone registration with verification of eligibility.

The primary end point for comparison of the treatment regimens was PFS; OS was a secondary end point. The original accrual goal was 240 patients, with follow-up to continue until 192 treatment failures (tumor recurrence, progression, or death) were reported. This sample size was increased when a review of the original statistical assumptions revealed that the hazard decreased over time, as in a Gompertz survival distribution, in contrast to the assumed constant hazard of an exponential distribution. The original assumption overestimated the number of treatment failures at the planned time of analysis. Simply extending follow-up was not considered a sufficient remedy. The plan to increase accrual was approved by the GOG Data Monitoring Committee without knowledge of treatment results.

One hundred ninety-two treatment failures would provide statistical power of 80% to detect a proportional decrease of 33% in the hazard rate when testing at the level of 0.05 with a two-tailed test.[25] This report includes 246 treatment failures and 222 deaths, with a median follow-up of 74 months among living patients. An interim analysis of PFS was completed, with 109 reported disease recurrences using an O'Brien and Fleming type spending function,[26] and was reported to the Data Monitoring Committee in July of 1998.

The intent-to-treat principle was applied in treatment group comparisons of PFS and OS after excluding ineligible patients. A log-rank test[27] stratified by FIGO stage (III *v* IV) was used to test the independence of treatment with PFS and OS. The product-limit method[28] was used to obtain PFS and OS estimates. The treatment effect on PFS and survival, adjusted for FIGO stage,

was estimated using a Cox proportional hazards model.[29] Analyses using proportional hazards regression models of clinical, pathologic, and host characteristics were carried out to identify putative prognostic factors. Exploratory analyses of OS and PFS were performed within subgroups to crudely assess the heterogeneity of treatment effects. Treatment hazard ratios with 95% CIs are reported. Additionally, toxicity analyses included only patients who received assigned treatment.

RESULTS

Patient Characteristics

Four hundred twenty-two women were entered between May 1992 and February 2000, of whom 388 were initially eligible (198 were randomly assigned to receive WAI and 190 were assigned to receive AP). Reasons for the exclusion of 34 patients (15 on the WAI arm and 19 on the AP arm) included wrong stage (n = 3), double primary (n = 8), wrong cell type (n = 4), prior malignancy (n = 1), residual disease more than 2 cm (n = 1), incomplete lymph node sampling or laparoscopic surgery (n = 8), registration error (n = 1), and inadequate documentation of pathology (n = 8). The eight patients (four on each arm) deemed ineligible because of unilateral lymph node sampling or use of laparoscopic surgery are included in the analyses. Since this study was initiated, acceptance and use of laparoscopic surgery has widened, and these patients are otherwise eligible. Their inclusion does not change the study results.

The treatment arms were balanced in terms of patient characteristics. There are slight imbalances with respect to mixed cell type and FIGO stage (Table 1). More notable imbalances between treatment arms are apparent in nodal involvement and individual sites of disease (Table 2). Most imbalances are skewed toward poor prognosis in the AP arm.

Table 1. Patient Characteristics

Characteristic	WAI Regimen (n = 202) No.	%	AP Regimen (n = 194) No.	%
Age at study entry, years				
21-50	29	14.4	32	16.4
51-60	55	27.2	46	23.7
61-70	76	37.6	76	39.2
71-90	42	20.8	40	20.6
Race/ethnicity				
Black	30	14.9	33	17.0
Hispanic	11	5.4	3	1.5
White	157	77.7	151	77.8
Other*	4	2.0	7	3.6
Performance status				
0	103	51.0	101	52.1
1	87	43.1	84	43.3
2	12	5.9	7	3.6
3	0	0	2	1.0
Cell type				
Adenocarcinoma, unspecified	8	4.0	5	2.6
Clear cell	7	3.5	10	5.2
Endometrioid	106	52.5	92	47.4
Mucinous	3	1.5	1	0.5
Mixed epithelial	19	9.4	31	16.0
Adenosquamous	12	5.9	12	6.2
Squamous cell carcinoma	1	0.5	0	0
Undifferentiated	1	0.5	2	1.0
Villoglandular	2	1.0	1	0.5
Serous	43	21.3	40	20.6
Histologic grade				
1	30	14.9	25	12.9
2	59	29.2	59	30.4
3	105	52.0	102	52.6
Not specified	8	4.0	8	4.1
FIGO stage†				
IIIA	57	28.2	35	18.0
IIIB	4	2.0	4	2.1
IIIC	90	44.6	100	51.5
IVA/IVB	51	25.2	55	28.4
Residual tumor				
Microscopic	176	87.1	164	84.5
Gross ≤ 1 cm	22	10.9	23	11.9
Gross > 1 cm	4	2.0	7	3.6

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin; FIGO, International Federation of Gynecology and Obstetrics.
*Includes Asian, Hawaiian, and Native American.
†Nodal evaluation was optional.

Treatment

Approximately 84% of patients completed radiation therapy, and 63% of patients completed eight cycles of chemotherapy (Table 2). Patients discontinued therapy early most often as a result of toxicity (17% in the AP arm *v* 3% in the WAI arm; Table 2). Five patients died before completing therapy; four were on the AP arm.

The median radiation dose (WAI + boost) was 45 Gy; the median number of fractions (WAI + boost) was 28. The median radiation boost (to the true pelvis or extended field) was 15 Gy; the median number of fractions was 8 (range, 1 to 28 fractions). The median dose delivered to the PALN area was 15 Gy (range, 0 to 45 Gy); the median number of fractions was 8 (range, 1 to 25 fractions). The median duration of radiation treatment was 1.3 months (range, 2 days to 2 months).

In 94% of patients, the timing of chemotherapy administration was consistent with protocol requirements, and 84% of patients received their calculated drug dose. Chemotherapy dose reductions without justification constituted protocol violations in 11% of patients based on dose and time parameters up to the time point that chemotherapy was completed (eight cycles) or discontinued. The median cumulative dose of doxorubicin for all patients was 405 mg/m^2 (range, 0 to 487 mg/m^2), and the median dose of cisplatin was 392 mg/m^2 (range, 0 to 461 mg/m^2). The median duration of chemotherapy was 5.1 months (range, 1 day to 8.3 months). Any exposure to protocol chemotherapy up to the maximum of eight cycles constitutes assessability for toxicity.

Twelve patients on the WAI arm did not receive abdominal irradiation; four of these patients received radiotherapy (RT) to the pelvis with or without extended-field RT to the para-aortic chain. None of these patients received chemotherapy before progression. Three patients on the AP arm received no protocol chemotherapy. One of these patients received WAI, one received alternate chemotherapy (carboplatin and paclitaxel), and one died of sepsis within 1 month of surgery and received no adjuvant therapy. These 15 patients are not included in the toxicity analysis but are included in PFS and OS calculations.

Adverse Effects of Treatment

Adverse events are listed in Table 3. The most common acute grade 3 to 4 toxicities were hematologic. Comparisons of grade 3 to 4

Table 2. Nodal Involvement and Sites of Disease

Nodal Involvement and Site of Disease	WAI Regimen (n = 202) No.	WAI Regimen (n = 202) %	AP Regimen (n = 194) No.	AP Regimen (n = 194) %
Nodal involvement				
Pelvic nodes				
Negative	81	40.1	55	28.4
Positive	91	45.1	113	58.2
Not Assessed	30	14.9	26	13.4
Aortic Nodes				
Negative	114	56.4	96	49.5
Positive	40	19.8	49	25.3
Not Assessed	48	23.8	49	25.3
Site of disease				
Adnexa/serosa				
Positive	112	55.4	107	55.2
Vagina				
Positive	5	2.5	4	2.1
Other pelvic				
Positive	120	59.4	139	71.6
Abdomen				
Positive	84	41.6	98	50.5
Bladder				
Positive	5	2.5	11	5.7
Colon				
Positive	18	8.9	27	13.9
Positive cytology	73	40.3	65	36.9

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin.

Table 3. Patients* Experiencing Adverse Events

Adverse Event	% of Patients: WAI Regimen (n = 190) Grade 1	Grade 2	Grade 3	Grade 4	AP Regimen (n = 191) Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	4	17	4	< 1	11	23	44	18
Neutropenia	4	4	< 1	0	4	4	18	67
Thrombocytopenia	11	3	2	< 1	34	15	11	10
Other hematologic	18	15	7	< 1	28	31	17	3
Maximum hematologic	17	29	13	2	4	5	20	69
GI	32	36	11	2	20	38	13	7
Hepatic	3	3	2	1	< 1	2	1	0
Genitourinary	13	4	< 1	0	9	9	2	1
Cardiac	0	0	0	0	5	12	11	4
Vascular	1	0	0	0	2	2	< 1	1
Pulmonary	2	2	0	0	4	4	1	< 1
Neurologic	4	1	< 1	0	25	10	6	1
Pain	1	0	< 1	0	8	5	< 1	0
Weakness	2	2	2	0	6	3	3	0
Fatigue	12	5	1	0	14	11	5	< 1
Metabolic	9	6	0	0	6	8	4	< 1
Infection	0	< 1	< 1	0	1	2	4	3
Fever	< 1	2	0	0	6	12	4	2
Allergy	< 1	0	0	0	0	0	0	0
Dermatologic	12	5	< 1	0	10	4	1	< 1
Alopecia†	< 1	0	NA†	NA†	6	69	NA†	NA†

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin; NA, not available.
*Excluded from the analysis are 15 patients (12 on WAI and three on AP) who did not receive protocol therapy.
†Alopecia, grades 3 and 4 not defined.

hematologic toxicities between WAI and AP are as follows: WBC (4% *v* 62%, respectively), absolute neutrophil count (< 1% *v* 85%, respectively), platelets (3% *v* 21%, respectively), and maximum hematologic toxicity (defined as percentage of patients who developed at least one grade 3 or 4 hematologic toxicity of any type; 14% *v* 88%, respectively). The second most commonly reported acute toxicity was grade 3 to 4 GI toxicity, which was reported in 13% *v* 20% of patients in the WAI and AP arms, respectively, and hepatic toxicity was reported in 3% *v* 1% of patients in WAI and AP arms, respectively. Grade 3 to 4 cardiac and neurologic toxicities were seen in 15% and 7% of patients, respectively, receiving AP compared with 0% and less than 1% of patients, respectively, receiving WAI. Other infrequent grade 3 to 4 toxicities not appearing in Table 4 included hip osteonecrosis, vaginal vault necrosis, and dehydration (one patient each) in the WAI arm and ventral hernia (one patient) in the AP arm. Additionally, in the AP arm, one patient developed leukemia and myelofibrosis 10 years after completing eight cycles of chemotherapy. The toxicity rates given represent combined acute and late effects as reported by the investigators. Some of the late RT effects, such as liver toxicity, are reflected in the treatment-related death data.

Treatment probably contributed to eight deaths on the AP arm (two patients had sepsis, two patients had congestive heart failure, and one patient each had sepsis plus left ventricular/aortic thrombus, hypoglycemic shock with myelosuppression, stroke secondary to congestive heart failure, and renal failure with severe thrombocytopenia) and five deaths on the WAI arm (one patient each had veno-occlusive liver disease, disease progression with hepatomegaly, aspiration and liver necrosis, renal and liver failure secondary to sepsis with severe ascites, and sepsis and liver failure; Table 5). The age range of patients suffering treatment-related deaths was 48 to 68 years (median, 62 years) and 50 to 76 years (median, 68.5 years) in the WAI and AP arms, respectively. Initial performance status was 0 to 1 in all patients experiencing treatment-related deaths, except for one patient on the AP arm who had a performance status of 2.

Patterns of Initial Treatment Failure

Of the 202 patients whose random treatment assignment was WAI, 109 (54%) had documented tumor recurrence. The initial site of recurrence was limited to the pelvis in 27 patients (13%), within the abdomen in 33 patients (16%), and extra-abdominal or liver

Table 4. Reason for Treatment Discontinuation

Reason	WAI Regimen (n = 202) No.	WAI Regimen (n = 202) %	AP Regimen (n = 194) No.	AP Regimen (n = 194) %
Completed treatment	170	84.2	123	63.4
Progression	9	4.5	18	9.3
Patient refusal	8	4.0	14	7.2
Toxicity	6	3.0	33	17.0
Death	1	0.5	4	2.1
Other	8	4.0	2	1.0

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin.

Table 5. Factors Contributing to Death

Cause of Death	No. of Patients: WAI Regimen (n = 126)	No. of Patients: AP Regimen (n = 96)
Treatment	4	8
Disease	100	78
Treatment and disease	1	0
Other*	15	6
Unknown	6	4

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin.
*Not related to protocol treatment or endometrial cancer.

metastases in 45 patients (22%). In four patients on the WAI arm and in two patients on the AP arm, sites of initial recurrence were unknown.

Of the 194 patients whose random treatment assignment was to AP, 97 (50%) had documented tumor recurrence. The initial site of recurrence was limited to the pelvis in 34 patients (18%); 27 patients (14%) experienced disease recurrence within the abdomen, and, in 34 patients (18%), the first recurrence included extra-abdominal or liver metastases.

Treatment Outcomes

At the time of final analysis, 76 patients (38%) on the WAI arm were alive compared with 98 patients (51%) on the AP arm. Patients, alive or deceased, without evidence of tumor progression included 93 (46%) and 97 patients (50%) in the WAI and AP arms, respectively, including 22 and 18 patients, respectively, who died before documentation of tumor progression. The majority of deaths were attributed to cancer progression (Table 5).

There is a statistically significant difference in PFS between the two regimens (Fig 1). The progression hazard ratio relative to the WAI arm, adjusted for stage, was 0.71 (95% CI, 0.55 to 0.91; $P = .007$). This adjusted relative hazard ratio was associated with a predicted increase in PFS at 60 months of 12% (50% for AP *v* 38% for WAI). There was also a statistically significant difference in OS between the two arms (Fig 2).

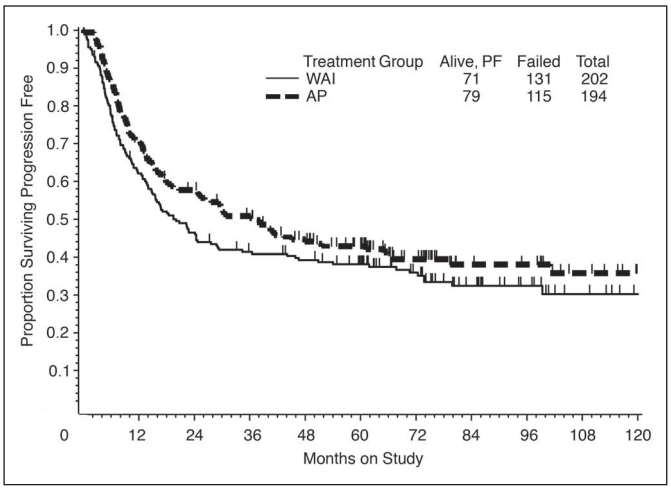

Fig 1. Progression-free survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

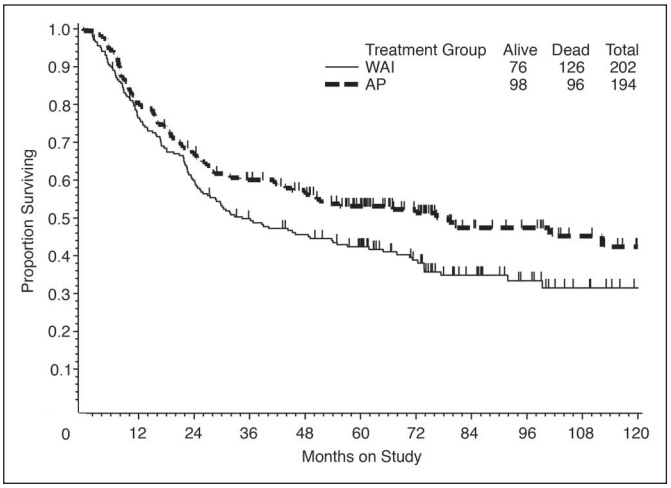

Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

The hazard ratio of death relative to the WAI arm, adjusted for stage, was 0.68 (95% CI, 0.52 to 0.89; $P = .004$). This adjusted relative hazard estimate was associated with a predicted increase in survival at 60 months of 13% for patients on the AP arm versus WAI patients (55% *v* 42%, respectively). Unadjusted Kaplan-Meier estimates of 5-year PFS and OS were 42% and 53%, respectively, in the AP arm compared with 38% and 42%, respectively, in the WAI arm.

Subsequent Treatment

Among patients in the WAI arm, 132 (65%) received no subsequent treatment. Patients treated with initial salvage therapy subsequent to protocol treatment included 42 patients (21%) who received various chemotherapy regimens, 13 patients (6%) who received further RT, 14 patients (7%) who received hormonal therapy (HT) only, and one patient (0.5%) who received surgery only. Among patients on the AP arm, 107 (55%) received no further treatment, 41 (21%) received chemotherapy, 24 (12%) received RT, 17 (9%) received HT only, and five (3%) were treated with surgery only after initial relapse. One patient who received HT and surgery is included in the HT only group.

Prognostic Factors

Stage IV disease was a very strong indicator of shorter PFS and OS when compared with stage III disease (Table 6; Figs 3 and 4). Additionally, in exploratory multivariate analysis, grade 3 tumor, older age, serous histology, and African American race were associated with shorter PFS and OS. Gross residual disease was associated with significantly shorter PFS but not OS. Fourteen percent and 24% of patients did not undergo optional pelvic or para-aortic nodal evaluation, respectively (Table 2). The effects of positive versus negative PLN or PALN on PFS and OS were not analyzed.

Subgroup Analyses

The treatment effects given by the AP death hazard ratio relative to that of WAI within subgroups of stage were as follows: IIIA, 0.47; IIIB, 0.54; IIIC, 0.75; and IV, 0.68. For combined subcategories of stage III, the relative hazard ratio was 0.68 (Fig 5). All 95% CIs for these estimates included the overall adjusted hazard ratio. Similar results for age, cell type, and residual disease status subgroups are also illustrated in Figure 5.

Table 6. Multiple Regression Analysis

Prognostic Factor	Progression-Free Survival		Overall Survival	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Treatment, AP *v* WAI	0.67*	0.52 to 0.87	0.69*	0.53 to 0.89
Stage, IV *v* III	2.29*	1.68 to 3.11	1.90*	1.36 to 2.66
Residual disease, gross *v* microscopic	1.82*	1.26 to 2.63	1.26	0.85 to 1.86
Age, 70 *v* 60 years†	1.25*	1.08 to 1.45	1.29*	1.10 to 1.51
Race, black *v* all others	1.94*	1.41 to 2.66	1.63*	1.16 to 2.28
Cell type				
Serous *v* all others	1.39*	1.01 to 1.91	1.56	1.13 to 2.16
Clear cell *v* all others	0.65	0.33 to 1.26	0.80	0.41 to 1.55
Grade				
2 *v* 1	1.39	0.83 to 2.32	1.79	0.99 to 3.23
3 *v* 1	2.24*	1.37 to 3.68	2.45*	1.37 to 4.36
Cytology, positive *v* all others‡	1.18	0.89 to 1.55	1.32	0.99 to 1.75

Abbreviations: AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.
*$P < .05$.
†Model included both linear and quadratic terms; age terms were tested jointly. The coefficients for the age and age^2 terms in the model for progression-free survival are −0.00759 and 0.0002288, respectively. The coefficients for the age and age^2 terms in the model for overall survival are −0.00161 and 0.0002086, respectively.
‡Included one patient with missing cytology report.

DISCUSSION

For the first time, this trial has demonstrated that chemotherapy of advanced endometrial carcinoma significantly improves both PFS and OS when compared with WAI. Adverse effects of treatment tended to be more frequent and more severe on the AP arm, but the majority of acute toxicities were expected and manageable.

Standardized surgical staging and analysis of treatment failure in endometrial carcinoma have provided clinicians with a better understanding of prognostic groups, risk factors, and limitations of previously used therapies.[2,31,32] Randall and Reisinger[3] suggested that patients with surgical stage III and IV disease can be separated into favorable or unfavorable categories. Characteristics of favorable patients include FIGO stage IIIA with positive peritoneal cytology in the absence of other extrauterine disease or isolated adnexal or serosal involvement, a concept supported by data from Mariani et al[33] and others.[34,35] Subsequently, studies suggested that isolated PLN involvement with surgically confirmed negative PALN potentially constitutes an additional favorable subset of patients who may be candidates for less intensive therapies,[4,36] although other investigators disagree.[37-39] Unfavorable patients include those with positive PALN (and possibly PLN), gross residual tumor after surgery, multiple sites of extrauterine cancer spread, high histologic grade, lymphovascular space invasion, peritoneal dissemination, and papillary serous or clear-cell histologies.[2,3,40-43] Patients with advanced endometrial carcinoma often have a combination of these high-risk features, with a significant risk of locoregional recurrence (including the peritoneal cavity), as well as a substantial risk of developing extra-abdominal spread.

The data reported herein suggest that AP chemotherapy decreased the distant failure rate, reducing the crude percentage of initial extra-abdominal failure from 19% to 10%. However, this analysis

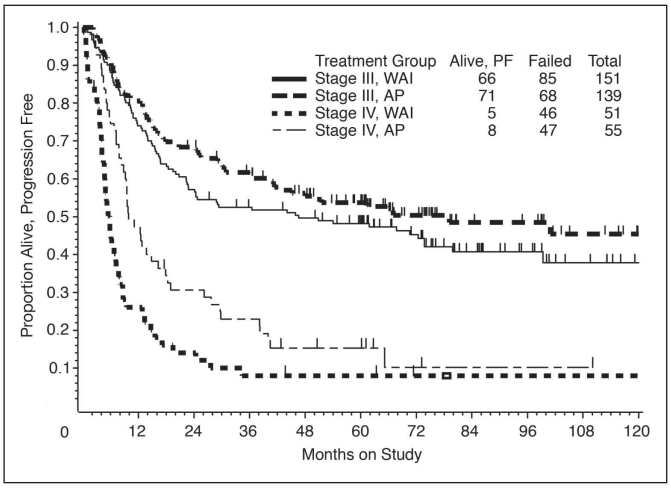

Fig 3. Progression-free survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

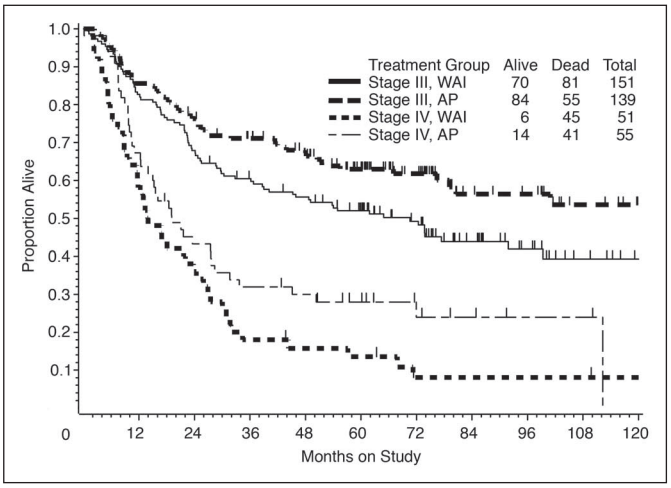

Fig 4. Survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

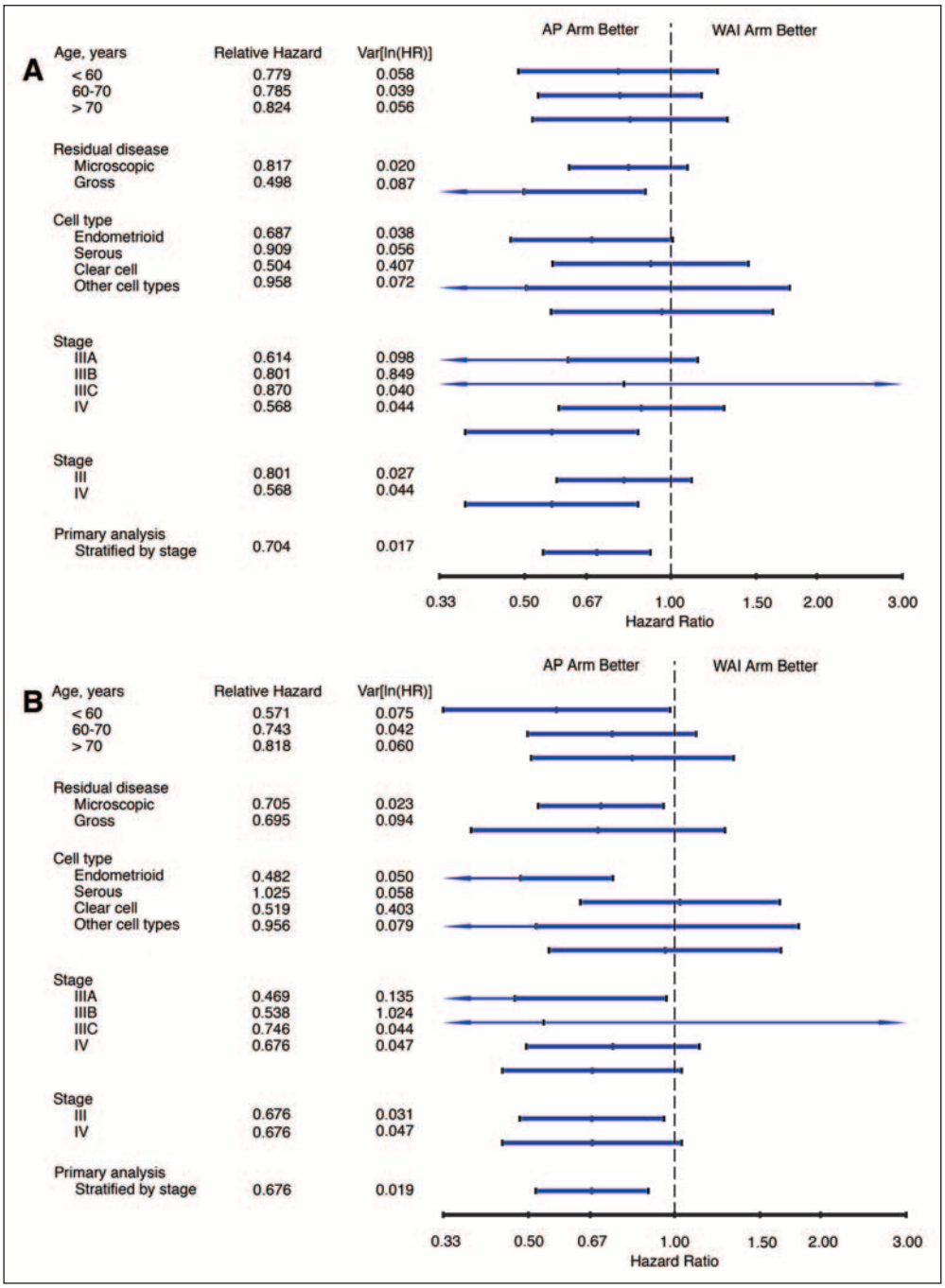

Fig 5. Treatment hazard ratio with 95% CI by prognostic group and end point. (A) Progression-free survival; (B) overall survival. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; HR, hazard ratio; Relative Hazard, treatment hazard ratio estimate; Var[ln(HR)], variance of the log treatment hazard ratio estimate.

only provides the initial reported sites of failure. Furthermore, the protocol did not require a complete evaluation of all potential sites of recurrence. Thus, this report does not account for competing risks of ever developing a distant metastasis and may not completely identify all sites of failure for each patient.

Grade 3 and 4 adverse effects (particularly hematologic, GI, cardiac, and neurologic) were significantly more common in the AP arm, and treatment may have contributed to the death of five patients on the WAI arm and eight patients on the AP arm. The use of hematopoietic growth factors to minimize complications associated with neutropenia should be considered in selected high-risk patients. In addition, patients receiving more than 300 mg/m^2 of doxorubicin should be closely monitored for left ventricular function. Of note, less than two thirds of patients in this study completed all eight cycles of chemotherapy as prescribed.

Unfortunately, the data do not permit definitive subset analyses assessing heterogeneity of the treatment effect within smaller groups of patients. However, there is no evidence to suggest that the study conclusions apply only to a subset of patients. For example, the treatment effects within stage subcategories are all in the direction favoring the AP arm. Furthermore, each 95% CI of the treatment effect within subgroups contained the estimated overall treatment effect value.

WAI may not be the most effective RT approach. For example, there is literature suggesting that WAI has, at best, a limited therapeutic role in patients with stage III disease[4,40,44,45] either because good outcomes have been demonstrated using less aggressive therapies with lower complication risks or because of the high rates of distant failure in these patients.[37,39,44,46] As noted previously, patients with endometrial adenocarcinoma and extrauterine spread limited to the peritoneal fluid and/or adnexae (stage IIIA) have favorable outcomes compared with patients with aortic nodal or intra-abdominal metastasis.[2,31] Many clinicians recommend no adjuvant therapy for stage IIIA (grade 1 or 2) patients who have positive cytology as the only component of extrauterine disease. Patients with isolated adnexal involvement and even positive lymph nodes confined to the pelvis may have a favorable prognosis.[3,4,47] Even in patients with involved PALNs, published series have consistently reported a long-term no evidence of disease survival of approximately 50% with extended-field RT.[46,48-51] More tailored (pelvic or pelvic and para-aortic) radiation fields when treated with higher doses of conventional fractionation may produce a higher therapeutic ratio. Adjuvant chemoradiotherapy might further improve results, which is a concept supported by Onda.[52] In addition, the use of RT after chemotherapy has yielded median survival times in excess of 2 years in 42 patients with unresectable stage III or IV endometrial carcinoma.[53] Regarding chemotherapy, paclitaxel has displayed antitumor activity in patients with metastatic endometrial cancer; regimens including this agent are being evaluated in the adjuvant setting.

In summary, patients with surgical stage III or IV endometrial carcinoma treated with AP experienced a statistically significant improvement in survival when compared with patients who received WAI, but they also experienced more frequent and more severe acute toxicity. Clearly, greater efficacy and less toxicity are needed. Avenues for further progress remain to be explored.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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