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NRG ONCOLOGY/RTOG 0921: A PHASE II STUDY OF POSTOPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT) WITH CONCURRENT CISPLATIN AND BEVACIZUMAB FOLLOWED BY CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ENDOMETRIAL CANCER

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Abstract

Purpose—To assess acute and late adverse events (AEs), overall survival (OS), pelvic failure (PF), regional failure, distant failure, and disease-free survival (DFS) in a prospective phase II clinical trial of bevacizumab (Bev) and pelvic intensity modulated radiation therapy (IMRT) with chemotherapy in high-risk endometrial-cancer patients.

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Materials/Methods—Patients had a hysterectomy, lymph node removal, and ≥1 of the following high-risk factors: grade 3 carcinoma with >50% myometrial invasion; grade 2 or 3 disease with any cervical stromal invasion; or known extrauterine extension confined to the pelvis. Treatment included pelvic IMRT and concurrent cisplatin on days 1 and 29 of radiation and Bev (5 mg/kg on days 1, 15 and 29 of radiation) followed by adjuvant carboplatin and paclitaxel for 4 cycles. The primary endpoint was grade ≥3 AEs in the first 90 days.

Results—Thirty-four patients were accrued from November 2009 through December 2011, 30 of whom were eligible and received study treatment. Seven out of 30 patients (23.3%, 90% CI: 10.6%-36.0%) had grade ≥3 treatment-related non-hematologic toxicities within 90 days; an additional 6 patients had grade ≥3 toxicities between 90 and 365 days after treatment. Two-year OS was 96.7% and DFS was 79.1%. No patient developed a within-field PF and no patients with stage I-IIIA disease relapsed after a median follow-up of 26 months.

Conclusion—Postoperative Bev added to chemotherapy and pelvic IMRT is well tolerated and results in high overall survival rates at 2 years for patients with high-risk endometrial carcinoma.

INTRODUCTION

Endometrial cancer is the most common cancer of the female reproductive organs in the United States. Over 50,000 women are diagnosed annually, with the majority presenting with early-stage disease curable by surgery alone.[1] Nevertheless, more than 8,000 women die of the disease each year due to a combination of local and distant failures.[1] Prior studies have indicated that pelvic external beam radiation may reduce the risk of local recurrence in high-risk patients, while chemotherapy may decrease the risk of distant metastasis. In the Gynecologic Oncology Group (GOG) randomized trial, chemotherapy was associated with reduced distant metastases (22 vs. 18%) in stage III/IV patients,[2] but not in stage I/II patients.[3] The Radiation Therapy Oncology Group (RTOG) 9708 phase II clinical trial treated women with high-risk endometrial cancer with pelvic radiation and concurrent cisplatin, followed by additional cisplatin and paclitaxel chemotherapy. Results showed a low rate of local recurrence (2%), but a high rate of distant metastases (19%).[4] Given these and other findings, it was postulated that the addition of bevacizumab (Bev), an anti-angiogenic agent, may further reduce the risk of distant metastases. With prior trials demonstrating the feasibility of using pelvic intensity modulated radiation therapy (IMRT) in postoperative patients,[5] IMRT was chosen in the hope of reducing the incidence or severity of bowel toxicity, which might be exacerbated by Bev.

The primary objective of this trial was to assess the rates of grade ≥3, non-hematologic, treatment-related adverse events (AEs) within 90 days from the start of treatment when administering concurrent Bev, cisplatin, and IMRT followed by carboplatin and paclitaxel chemotherapy in patients with high-risk endometrial cancer. The secondary objectives were to evaluate treatment-related AEs occurring within one year from start of treatment; all treatment-related AEs; disease-free and overall survival (DFS, OS); and local, regional and distant failure. Two-year efficacy rates are reported.

MATERIALS AND METHODS

Eligibility requirements for RTOG 0921

A hysterectomy and bilateral salpingo-oophorectomy must have been completed within 56 days prior to study entry with pathologic confirmation of uterine cancer meeting one or more of the following criteria: grade 3 carcinoma with >50% myometrial invasion (all papillary serous and clear cell carcinomas were considered grade 3); grade 2 or 3 carcinoma with any cervical stromal invasion; or known extra-uterine disease confined to the pelvis, any grade. The following histologies were allowed: endometrioid endometrial adenocarcinoma, clear cell carcinoma, papillary serous adenocarcinoma, adenosquamous carcinoma or other adenocarcinoma variant. All patients had Zubrod performance status 0-1, were ≥18 years of age, and were able to sign a study-specific informed consent. Patients must have had adequate bone marrow, renal and hepatic function as indicated by the following laboratory assessments within 21 days prior to study entry: ANC ≥1500 cells/mm^3 without use of growth factors; platelets ≥100,000/mm^3; serum creatinine ≤1.5 mg/dl; total bilirubin ≤1.5 times institutional upper normal limit; hemoglobin ≥10 g/dl (transfusion may have been used to meet this criterion); AST and ALT ≤2 times institutional upper normal limit; INR <1.5 for patients treated with warfarin within 14 days prior to study entry; urine protein creatinine (UPC) ratio (if UPC ratio >0.5, 24-hour urine protein should be obtained and should be <1000 mg for patient enrollment) ; in patients with FIGO stage III or IVA disease, CT or PET-CT of the abdomen and pelvis was required within 56 days of study entry. To assess the chest for all patients regardless of stage, a chest x-ray or chest CT or PET-CT was required within 56 days of study entry.

Treatment

No sooner than 29 days and no later than 56 days after surgery, patients began a course of IMRT with concurrent cisplatin (50 mg/m^2 on days 1 and 29 of radiation) and Bev (5 mg/kg on days 1, 15 and 29 of radiation) followed by an optional boost with either high-dose-rate (HDR, 6 Gy for 3 fractions) or low-dose-rate (LDR, 25 Gy at 0.8-1.2 Gy per hour) vaginal brachytherapy. This was followed by 4 cycles of carboplatin (AUC 5) and paclitaxel (135 mg/m^2).

Full- and empty-bladder CT scans were required and were fused together prior to outlining target volumes. Contours were recommended to follow the RTOG IMRT for postoperative endometrial and cervical cancer guideline atlas[6] and underwent central review with corrections recommended prior to initiating treatment.

The vaginal planning target volume (PTV) (integrated target volume with a 7-mm margin) and nodal PTV (nodal CTV with a 7-mm margin) were prescribed 45 Gy in 25 fractions. The dose was prescribed to cover 97% of the vaginal PTV and nodal PTV. Bone-marrow sparing with IMRT was not required and no bone dose-volume constraints were implemented as part of this protocol. Patients with pelvic lymph node(s) ≥2 cm in any dimension on the diagnostic or planning CT or biopsy-proven to be positive were candidates to receive, at the discretion of the treating radiation oncologist, 8 additional fractions to the enlarged node(s) in 1.8-Gy daily fractions for a total dose of 59.4 Gy to the nodal boost

PTV. Patients were followed for disease status with history and physical examination every 3 months for 1 year, every 6 months for another 2 years, and annually thereafter.

Statistical analysis

Primary endpoint—Given that the rate of acute grade ≥3 non-hematologic treatment-related AEs from RTOG 9708 (RT + cisplatin) was 44%, the hypothesis for the current trial was that the addition of Bev to IMRT + cisplatin would not increase this rate beyond 60%. This study was designed with a 1-sided, upper-bound confidence interval to estimate this AE rate. Twenty-seven evaluable patients were required to have 95% confidence that the true grade ≥3, non-hematologic, treatment-related AE rate is not greater than 60%. To allow for ineligible/non-protocol treatment patients, a total sample size of 34 patients was required for this study. AEs were scored according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0 (MedDRA version 12.0).

Secondary endpoints—For overall survival (OS), failure was defined as death due to any cause and survival time was measured from date of study entry to death or last follow-up for non-failures. Data for living patients were censored at the date of last contact. Pelvic failure (PF) was defined as recurrence in the pelvis, including the pelvic or sacral nodes, and required confirmation by histologic or cytologic biopsy of the recurrent lesion. Regional failure (RF) was defined as recurrence in the para-aortic nodal region. Distant failure (DF) was defined as the appearance of distant metastasis. Death was considered a competing risk for PF, RF, and DF and each were measured from date of study entry to date of first failure or last follow-up for non-failures. For disease-free survival (DFS), failure was defined as PF, DF, or death due to any cause and was measured from date of study entry to date of first failure or last follow-up for non-failures. OS and DFS were estimated univariately with the Kaplan-Meier method[7] and PF, RF, and DF rates were estimated using the cumulative incidence method.[8]

RESULTS

A total of 34 patients were accrued from November 6, 2009 until December 12, 2011. Four patients were excluded from analysis: 1 did not receive protocol treatment and 3 were ineligible (1 had a PET/CT scan >56 days prior to study registration, 1 had positive peritoneal cytology, and 1 had urinary protein creatinine >1). Detailed baseline patient characteristics of the 30 patients included in the analysis are listed in Table 1. A total of 29 of 30 patients underwent bilateral pelvic lymph node dissection and 19 had para-aortic lymph node removal.

Protocol Treatment Compliance

A total of 93% of patients were treated per protocol with concurrent chemotherapy and 90% received their adjuvant chemotherapy per protocol. All patients received Bev in full and on time.

Radiation treatment compliance was assessed in terms of whether physician contours of the tumor volume and organs at risk, which underwent rapid review within 24 hours, followed

the protocol-recommended contouring guidelines. For tumor-volume contouring, 23 were per protocol and 7 (23%) had an acceptable variation.

For organs-at-risk contouring, 27 patients were considered per protocol while 3 (10%) had acceptable variations. Bladder, sigmoid, femur and tumor volume were all contoured per protocol on final submission (after rapid review for institutional first case). Barium contrast given by mouth to opacify the small bowel was allowed at the physician's discretion. Two patients (6.7%) had unacceptable deviations on small-bowel contouring, where the bowel loops were contoured instead of the bowel space; in the other 28 cases, the small bowel was contoured per protocol. One patient had an acceptable variation on rectum contouring, with the inferior portion of the rectal contour overlapping the vaginal integrated target volume (ITV); the other 29 rectal contours were per protocol.

Compliance was also assessed with regard to treatment planning, with assessments of whether the nodal and vaginal PTV, bladder, rectum, femoral heads and bowel planned doses met the protocol set dose limits. With regard to treatment planning, 5 cases had ‘deviation unacceptable’ (>0.03 cc of PTV receiving <91% of prescription) and 12 had ‘variation acceptable’ (>0.03 cc of PTV receiving 91-93% of prescription) scores for the tumor dose-volume analysis, due to the minimum dose requirements. For normal tissues, only one ‘deviation unacceptable’ was recorded for small bowel and no ‘deviation unacceptable’ cases were noted for bladder, rectum or femoral heads, though 12 patients had acceptable variations for the dose-volume analysis recorded (Table 2).

Primary Endpoint

Acute Adverse Events—Of the 30 patients, 7 (23.3%, 95% CI: 10.6%-36.0%) developed grade ≥3, treatment-related, non-hematologic AEs ≤90 days from the start of concurrent treatment (i.e., acute AEs). Table 3a lists the grade 3 and 4 side effects, including hematologic toxicity, in detail. As the one-sided, upper-bound confidence interval for the rate of grade ≥3, treatment-related, nonhematologic AEs occurring ≤90 days from the start of concurrent treatment is 36%, there is 95% confidence that the true grade ≥3, non-hematologic, treatment-related AE rate is not greater than 60%. One acute toxicity, a thromboembolic event, was considered possibly attributable to Bev.

Secondary Endpoints

Late Adverse Events—Treatment-related grade ≥3 AEs occurring >90 days but ≤365 days from the start of concurrent treatment are listed in Table 3b. Nine patients reported late AEs, three of whom also had acute toxicities.

AEs occurring during concurrent treatment, adjuvant chemotherapy treatment, and after the end of all treatment are shown in Table 4. One late toxicity, epistaxis, was considered possibly attributable to Bev.

Survival outcomes—The median follow-up time for all patients was 25.9 months (min-max: 13.6-43.4). The 2-year estimate of OS was 96.7% (95% CI: 78.6%-99.5%) with a total of 4 deaths, all from endometrial cancer. None of the 30 patients enrolled had a within-field pelvic-only failure. The cumulative incidences for RF and DF at 2 years were 7.2% (95%

CI: 0.0%-17.1%) and 17% (95% CI: 3.2%-30.9%), respectively. The 2-year estimate of DFS was 79.1% (95% CI: 59.2%-90.1%). A total of 6 patients had recurrent disease. Two of the 6 had para-aortic nodal failures; one of these also had distant-nodal metastases, and both subsequently died. One of the two patients with para-aortic nodal failure had undergone a para-aortic lymph node dissection at diagnosis; both had undergone pelvic node lymphadenectomy at diagnosis. Two of the other four patients died of distant disease. The remaining two patients were alive with distant failure at the time of this analysis; one remains on chemotherapy and the other had a 1-cm recurrence in the peritoneum above the pelvic field at a laparoscopic port site, which was resected laparoscopically with negative margins. She remains on megestrol acetate and has been disease free for 2 years. Detailed characteristics of the patients with recurrence are shown in Table 5.

DISCUSSION

This phase II prospective trial demonstrates the feasibility of administering bevacizumab (Bev) with pelvic intensity modulated radiation therapy (IMRT) followed by carboplatin/paclitaxel chemotherapy in high-risk endometrial cancer. The rate of acute grade >3, non-hematologic, treatment-related toxicity was 23.3% and the hypothesis that the true rate of such AEs is not greater than 60% was confirmed. This treatment regimen is feasible with few Bev-related toxicities. A total of 93% of patients were treated per protocol with concurrent chemotherapy and 90% received their adjuvant chemotherapy per protocol. All patients received Bev in full and on time. Compared to RTOG 9708, changes in this trial include adding Bev to concurrent cisplatin-based chemoradiation, switching from cisplatin/paclitaxel to carboplatin/paclitaxel after concurrent chemoradiation, and using IMRT instead of 3D conformal radiation.

In this RTOG 0921 trial of concurrent Bev, cisplatin and radiation, one acute toxicity, a thromboembolic event, and one late toxicity, epistaxis, were considered possibly attributable to Bev. Therefore, this study uniquely finds that Bev may be administered during pelvic radiation to the post-operative pelvis without increasing pelvic complications. There were no side effects attributable to the use of carboplatin instead of cisplatin in conjunction with paclitaxel. The use of adjuvant chemotherapy in comparison to radiation in high-intermediate or advanced-stage endometrial-cancer patients has been reported in three randomized trials; none used carboplatin/paclitaxel.

Other studies have shown an effect of Bev in endometrial cancer. One study treated patients with recurrent disease definitively to a local field with concurrent radiation and Bev 10 mg/m2 every 2 weeks for 3 doses; no other chemotherapy was administered.[9] Results showed 2 out of 19 patients had thromboembolic events, 2 patients had grade 1 and 3 patients had grade 2 proteinuria, 2 patients had grade 1 and 2 patients had grade 2 hypertension, and 1 patient had a grade 1 nosebleed. Dramatic shrinkage of the tumor was noted for patients with recurrent endometrial cancer, with a 3-year overall survival rate of 80%. Another study analyzed data from patients with persistent or recurrent endometrial cancer treated with Bev 15 mg/kg every 3 weeks until disease progression or prohibitive toxicity without other chemotherapy.[10] The authors reported an overall response rate of 13.5%, a median progression-free survival of 4 months and a median overall survival time

of 10 months. In comparison, in the current study, patients were treated immediately postoperatively rather than at the time of recurrence, and they received a dose of 5mg/kg in order to minimize side effects related to Bev.

Chemotherapy has been variously compared to radiation and combined with it. In trials comparing the two modalities, the chemotherapy-alone arms demonstrate local relapse rates of 18% for women with stage III-IV disease[2] and 11%[11] or 7%[12] for those with stage IC-IIIC disease. Chemotherapy is thought to confer a survival advantage when combined with radiation.[13] For patients with high-intermediate and advanced disease, a combination of chemotherapy and radiation offers potential reductions in both local and distant relapses. The GOG 0184 trial randomized patients treated with surgery and pelvic and/or para-aortic radiation to cisplatin and doxorubicin with or without paclitaxel; 10% had a local-regional recurrence and 30% had distant recurrence.[14] RTOG 9708, a phase II trial of concurrent cisplatin with radiation and 4 cycles of cisplatin (50 mg/m^2) and paclitaxel (175 mg/m^2 every 4 weeks) after radiation, showed a 4-year pelvic recurrence rate of 2%, a regional recurrence rate of 2% and a distant recurrence rate of 19%.[4] No recurrences occurred in the 13 stage IC, IIA, or IIB patients.[15] In terms of clinical outcomes, at 2 years, RTOG 9708 had a 2-year overall survival rate of 91% compared to this study at 97%, however continued follow-up is required for more complete conclusions. These studies indicate the efficacy of combined chemo-radiation at improving local control, but demonstrate the need for novel agents to reduce the rate of distant relapse. This trial was administered to patients with performance status 0-1; it is not clear whether patients with worse performance status would tolerate the addition of bevacizumab and chemotherapy.

IMRT treats regions at risk for disease spread while sparing adjacent normal tissues. IMRT may reduce the dose to normal tissues, thereby potentially decreasing acute and chronic toxicity.[16,17] Retrospective studies of pelvic IMRT indicate that the volume of small bowel treated to more than 45 Gy is smaller with IMRT than with whole-pelvic radiation. Portelance et al. showed a >60% reduction in the volume of small bowel irradiated to more than 45 Gy with IMRT.[18] A study by Roeske and colleagues showed a 50% reduction in the volume of small bowel irradiated to more than 45 Gy.[19]

Overall, the grade 3 or higher toxicity rate reported during concurrent treatment in RTOG 9708 (3D conformal pelvic radiation and concurrent cisplatin chemotherapy followed by adjuvant cisplatin and paclitaxel) was 30%. To determine whether IMRT may be of benefit in reducing this rate, toxicities during radiation in the current study (RTOG 0921) were compared to those of the precursor trial RTOG 9708. In RTOG 9708, during the concurrent portion of the treatment, 43% of participants had grade 2, 27% had grade 3, and 2% had grade 4 acute toxicity; in this RTOG 0921 trial, these rates were 30%, 23% and 7%, respectively. Of note, though the systems are similar, toxicity in RTOG 9708 was assessed according to the Cooperative Group Common Toxicity Criteria 1989, the Acute Radiation Morbidity Scoring Criteria, and the Late Radiation Morbidity Scoring Scheme of the RTOG and the European Organization for Research and Treatment of Cancer, whereas the current trial used the subsequent CTCAE version 4.0 which developed from the preceding scales. Prospective results from the ongoing RTOG 1203 TIME-C randomized trial may help to clarify whether IMRT reduces toxicity compared to 3D conformal radiation.

Relative to RTOG 0418, a prospective series of patients treated with postoperative pelvic IMRT, the less strict dose-volume histogram criteria used in the current trial resulted in higher compliance for constraints. In RTOG 0418, dose criteria were not met in 67% of cases for bladder, in 76% for rectum, and in 17% for small bowel. In comparison, in the current trial, dose criteria were not met in 14% (4/29) of cases for bladder, in 24% (7/29) for rectum, and in 14% (4/28) for bowel. To illustrate the effect of stringency, the femoral head constraint in RTOG 0921 was met in all cases (all had DVH value of 15% receiving < 35 Gy); in contrast, the RTOG 0418 constraint was not met in 33% of cases (<15% of the femoral heads receiving ≥30 Gy). No increase in toxicity was noted with the less stringent constraints. The high number of variations in PTV calculations indicates the need for relaxation of these constraints in future trials.

In conclusion, treating endometrial-cancer patients with concurrent bevacizumab, cisplatin and pelvic radiation followed by carboplatin/paclitaxel chemotherapy is feasible, has low rates of bevacizumab-specific toxicities and a high survival rate at 2 years. Future randomized trials should further address the use of bevacizumab in endometrial cancer.

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Table 1

Baseline characteristics (n=30)

Age (years)	
Median (min-max)	59 (34 – 80)
Hysterectomy procedure	
Robotic-assisted vaginal hysterectomy	30% (9)
Total abdominal hysterectomy	23.3% (7)
Radical hysterectomy	23.3% (7)
Laparoscopic-assisted vaginal hysterectomy	23.3% (7)
Pelvic lymph node removal	
Yes	96.7% (29)
No	3.3% (1)
Para-aortic lymph node removal	
Yes	63.3% (19)
No	36.7% (11)
Histologic type	
Endometrioid endometrial adenocarcinoma	60% (18)
Papillary serous adenocarcinoma	30% (9)
Clear cell carcinoma	10% (3)
Stages	
Papillary serous or clear cell adenocarcinoma:	
I	16.7% (5)
II	13.3% (4)
IIIC1	10% (3)
Endometrioid endometrial adenocarcinoma:	
II	6.7% (2)
IIIA	16.7% (5)
IIIB	3.3% (1)
IIIC1	33.3% (10)

Table 2

Tumor and Normal-Tissue Dose-Volume Analysis Criteria and Score Statistics

Structure	Per Protocol		Variation Acceptable		Deviation Unacceptable	
PTV	≥0.03 cc of PTV with ≥93% of prescribed dose	43% (13)	≥0.03 cc of PTV with 91-<93% of prescribed dose	40% (12)	≥0.03 cc of PTV with <91% of prescribed dose	17% (5)
Small bowel (missing, n=2)	30% receives <40 Gy	86% (24)	30% receives >40-<45 Gy	11% (3)	>30% receives >45 Gy and ≥0.03 cc .receives >65 Gy	4% (1)
Rectum (missing, n=1)	60% receives ≤40 Gy	76% (22)	60% receives 40-< 45 Gy	24% (7)	>60% receives >45 Gy and ≥0.03 cc receives >65 Gy	0% (0)
Bladder (missing, n=1)	35% receives ≤45 Gy	86% (25)	35% receives 45-<50 Gy	14% (4)	>35% receives >50 Gy and ≥0.03 cc receives >65 Gy	0% (0)
Femoral heads	15% receives <35 Gy	100% (30)	>15% - ≤50% receives >35 Gy	0% (0)	>50% receives >35 Gy and ≥0.03 cc receives >65 Gy	0% (0)

Key: Rx=prescription; Gy = Gray, PTV = planning target volume

Table 3a

a. Adverse events ≥ grade 3 in the first 90 days from the start of concurrent treatment (acute)

System Organ Class	Term	Grade	Relationship to Treatment	Days from Concurrent RX start
Nervous system disorders	Headache	3	Probable	78
General disorders and administration site conditions	Fatigue	3	Probable	85
Nervous system disorders	Syncope	3	Possible	89
Vascular disorders	Thromboembolic event*	4	Probable	42
Metabolism and nutrition disorders	Hyponatremia	3	Probable	55
	Hyperglycemia	3	Possible	90
Infections and infestations	Vaginal infection	3	Probable	28
Reproductive system and breast disorders	Vaginal inflammation	3	Possible	27
Investigations	Alanine aminotransferase increased	3	Possible	12
Blood and lymphatic system disorders	Febrile neutropenia	4	Probable	88
General disorders and administration site conditions	Fatigue	3	Possible	4

Table 3b

b. Adverse events ≥ grade 3 occurring >90 days but ≤365 from the start of concurrent treatment (late)

System Organ Class	Term	Grade	Relationship to Treatment	Days from Concurrent RX start
General disorders and administration site conditions	Fatigue	3	Probable	105
Metabolism and nutrition disorders	Hypomagnesemia	4	Possible	183
	Hypokalemia	3	Possible	168
Respiratory, thoracic and mediastinal disorders	Epistaxis*	3	Probable	176
Nervous system disorders	Headache	3	Probable	98
Metabolism and nutrition disorders	Hyponatremia	3	Possible	98
Vascular disorders	Hot flashes	3	Definite	300
General disorders and administration site conditions	Pain	3	Possible	180
Ear and labyrinth disorders	Hearing impaired	3	Probable	333
Metabolism and nutrition disorders	Hypokalemia	4	Probable	136
Nervous system disorders	Neuralgia	3	Possible	126
Infections and infestations	Skin infection	3	Possible	126

Key: RX=treatment

* probably attributable to bevacizumab

Table 4

Summary of Worst Adverse Event per Patient (definitely, probably, or possibly related to treatment) comparing RTOG 9708 with RTOG 0921

	AEs ≤90 days from the start of all RX[1]	AEs >90 days from the start of all RX[2]		AEs occurring during concurrent RX[3]		AEs occurring during adjuvant chemo[4]	
Grade	*RTOG 0921*	*RTOG 0921*	*RTOG 9708*	*RTOG 0921*	*RTOG 9708*	*RTOG 0921*	*RTOG 9708*
1	0 (0%)	3 (10%)	9 (20%)	1 (3%)	12 (27%)	0 (0%)	3 (7%)
2	10 (33%)	10 (33%)	17 (39%)	9 (30%)	19 (43%)	6 (20%)	3 (7%)
3	11 (37%)	9 (30%)	7 (16%)	7 (23%)	12 (27%)	12 (40%)	9 (21%)
4	5 (17%)	6 (20%)	1 (2%)	2 (7%)	1 (2%)	6 (20%)	26 (62%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Key: RX=treatment

[1] AE date ≤ (start of all treatment +90 days)

[2] AE date > (start of all treatment +90 days)

[3] Concurrent treatment start date ≤ AE date ≤ concurrent treatment end date

[4] Adjuvant treatment start date ≤ AE date ≤ adjuvant treatment end date

Table 5

Characteristics of patients with relapsed disease

Patient	Stage	Histology	First recurrence	Areas of spread	Time from first recurrence to death (months)
1	IIIC1	UPSC	Regional	Para-aortic node	10
2	IIIC1	UPSC	Regional	Para-aortic node	4
3	IIIC1G2	EAC	Distant	Lung, bone, brain	8
4	IIIC1G3	EAC	Distant	Lung	6
5	IIIBG3	EAC	Distant	Lung	Alive
6	IIIAG1	EAC	Distant	Abdominal	Alive

Key: EAC= Endometrioid endometrial adenocarcinoma; CC=Clear cell carcinoma; UPSC=Papillary serous adenocarcinoma