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Adjuvant radiotherapy and survival outcomes in early-stage endometrial cancer: A multi-institutional analysis of 608 women

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Abstract

Objective. The role of post-operative radiotherapy (RT) in women with early-stage, low to intermediate risk cancer of the uterine corpus remains controversial. The primary objective of this analysis was to evaluate the survival outcomes of women with early-stage endometrial cancer treated with surgery alone or surgery followed by RT.

Methods. Data from two institutions were collected from 1990 to 2003. The 608 eligible women had FIGO stage IA to IIA endometrial cancer and underwent primary surgery ± RT. Univariate and multivariate analyses of pertinent variables were performed for the end points of disease-free survival (DFS) and overall survival (OS).

Results. The median age for all women was 64 years. RT was delivered to 133 women (22%). Unfavorable histologic grade ($P < 0.0001$) and stage ($P < 0.0001$) were significantly more prevalent in the adjuvant RT group. At a median follow-up of 5.2 years, 26 pelvic (11 vaginal) and 16 distant failures occurred along with 110 deaths (with no significant differences between women undergoing surgery alone or followed by RT). Adjuvant RT, younger age, and lower stage predicted for improved DFS and OS on multivariate analysis. Stratified analysis revealed that adjuvant RT conferred a survival benefit in women with stage IC or IIA disease.

Conclusions. Adjuvant RT was associated with improved disease-free and overall survival in women with higher risk disease. Despite significantly worse disease characteristics among women in the adjuvant RT group, the analyzed end points were equivalent among the two groups. These findings suggest that adjuvant radiotherapy has a significant benefit in reducing mortality and disease progression in early-stage carcinoma of the uterine corpus.

Keywords: Endometrial cancer; Adjuvant radiation therapy; Early stage disease

Introduction

The American Cancer Society estimates that 40,880 new cases of endometrial cancer will be diagnosed in the United States in 2005 [1]. Although it is the most common gynecologic malignancy, recent analysis has indicated a decline in the number of new cases and mortality due to endometrial cancer. Currently, the estimate is that 72% of women diagnosed with endometrial cancer will have locally confined disease [1].

In 1988, the staging of endometrial carcinoma was changed from a clinical to a surgical staging method [2], recognizing the prognostic implications of adequate tissue sampling. Subsequently, the role of adjuvant therapy has been more intensely scrutinized, considering the added morbidity of radiotherapy (RT) compared to surgery alone [3,4]. Recent attempts to clarify the role of adjuvant RT in early-stage disease through prospective randomized trials have as yet failed to reveal an overall survival benefit associated with RT [4,5].

Although a survival benefit is yet unproven, the contemporary literature confirms a significant reduction in the risk of pelvic and vaginal recurrence when radiotherapy follows surgery [4–11].

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Table 1
Adjuvant RT treatment policy

	Myometrial invasion		
	None	<50%	>50%
Women with lymph node dissection			
Grade 1	0	0	BT
Grade 2	0	± BT	EBRT
Grade 3	BT	BT	EBRT
Women without lymph node dissection			
Grade 1	0	0	BT
Grade 2	0	BT	EBRT
Grade 3	BT	EBRT	EBRT

RT = radiotherapy; 0 = no RT; BT = vaginal brachytherapy; EBRT = external beam RT.

Randomized studies by the Gynecological Oncology Group (GOG) and the Post-operative Radiation Therapy in Endometrial Cancer (PORTEC) study group have reported significantly less pelvic and vaginal recurrences with post-operative RT compared to surgery alone. [4,5] Aalders et al. have documented a similar benefit in reducing pelvic and vaginal recurrences with adjuvant RT [6]. These and other reports highlight the benefit of adjuvant RT in early-stage disease despite the desire of some to abandon adjuvant RT altogether. Based on these data, our institutions developed and maintained a standardized policy for adjuvant RT based on certain pretreatment disease characteristics.

The intent of this retrospective analysis was to evaluate disease outcomes in women with early-stage (FIGO stage IA to IIA) endometrial cancer, comparing results for those who underwent primary surgery alone to those who received RT after surgery. Clinical and pathologic factors were evaluated for potential prognostic significance. Lastly, the effect of a standardized adjuvant RT treatment policy, implemented in 1997, was evaluated.

Methods

For the years 1990 through 2003, we identified 608 women with early-stage (FIGO IA to IIA) endometrial adenocarcinoma treated with primary surgery registered in the tumor registries of two tertiary-care centers. Women with serous papillary or clear cell histology were excluded along with those with follow-up of less than 1 year. Women who received adjuvant chemotherapy are not included in this analysis. Information regarding patient, disease, and treatment characteristics was retrospectively collected from patient records and the tumor registry with the approval of the Institutional Review Boards at the two participating institutions. For purposes of comparative analysis, the women were divided into two groups: surgery alone versus surgery and adjuvant RT. The women were also analyzed based on the era of therapy, the time preceding or following the implementation of the standardized treatment policy.

Primary surgery consisted of total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAH/BSO). Owing to the long time span encompassed in this analysis, early lymph node evaluation most often consisted of random sampling [an incidental or determined removal of lymph node(s) without clearing the lymphatics in a systematic, complete and orderly manner] even among gynecologic oncologists (GYO). However, since 1997, the lymph node evaluation performed by the GYO was formalized and includes a thorough and complete dissection of the lymphatics of the common iliac, internal iliac, external iliac, obturator, and paraaortic (up to the level of the inferior mesenteric artery) nodal groups. However, formal lymph node dissection is not routinely performed on women with grade 1 disease found on initial endometrial biopsy unless intraoperative findings indicate a more aggressive or widespread disease process. Complete surgical staging also includes pelvic washings for cytologic review.

Historically, referral for adjuvant radiotherapy (RT) was not based on a defined institutional standard. However, since 1997, women were referred for RT based on the treatment policy established and shared between the two institutions (Table 1). This policy indicates adjuvant RT, external beam (EBRT) or brachytherapy (BT), for the subset of women with disease that is considered high-intermediate risk (HIR) for local failure, including FIGO stage IB grade III, IC grade II or III, or IIA disease in women who are node negative with surgical staging. Three hundred fifty five women were treated before implementation of this policy (55 by a GYO) and 253 women after 1997 (167 by a GYO).

RT was administered with EBRT alone (n = 75), BT alone (n = 29) or a combination of the two (EBRT + BT, n = 29). Seventy-four women received adjuvant RT prior to the development of the adjuvant RT policy and the remaining 59 women received it thereafter. EBRT was delivered using megavoltage equipment using a 4-field technique and custom blocks to encompass the pelvic nodal regions at risk. The median prescription dose for EBRT was 4860 cGy (range: 1440 to 5040 cGy) prescribed to the isocenter. Post-operative vaginal cuff BT was delivered using a vaginal cylinder in one or three treatments with a low-dose rate (LDR, n = 7) or a high-dose rate applicator (HDR, n = 22), respectively. The median dose prescribed to 0.5 cm for LDR and HDR treatment was 5600 (range 3000 to 6580 cGy) and 1950 (range 1800 to 2100 cGy), respectively. Women receiving both modalities underwent a single fraction of BT (LDR, n = 27, HDR, n = 3) prescribed to the vaginal surface following a course of EBRT to a total median prescription dose of 7055 cGy (range 5500 to 9180 cGy).

Women were routinely followed by physical examination every 3 to 6 months for 2 years and then annually thereafter. Radiographic surveillance was not routinely performed except for suspicion of disease recurrence or metastasis. Failures found on clinical or radiographic examination were classified as vaginal, local–regional (recurrence within the pelvis including vaginal cuff), or distant (abdomen, bone, lung, or otherwise). Deaths were recorded for analysis.

The evaluated end points were overall survival (OS), disease-free survival (DFS, any local or distant failure or death), vaginal recurrence (VR), local–regional recurrence (LR, any pelvic-confined recurrence, including disease at the vaginal apex), and distant metastasis (DM). Chi-square analysis or analysis of variance (ANOVA)

Table 2
Demographic, pathologic, and treatment characteristics by group

	S	S + RT	P value
	n = 472	n = 136	
	n (%)	n (%)	
Median age, years	63	66	0.309
range	27 to 87	33 to 87	
FIGO stage			<0.0001
IA	190 (40)	3 (2)	
IB	240 (51)	46 (34)	
IC	33 (7)	66 (49)	
IIA	9 (2)	21 (15)	
Pathologic grade			<0.0001
I	278 (59)	37 (27)	
II	137 (29)	64 (47)	
III	46 (10)	32 (24)	
Unknown	11 (2)	3 (2)	
Treating surgeon			0.05
General GYN	312 (66)	74 (54)	
Oncologic GYN	160 (34)	62 (46)	
Formal LN evaluation	118 (25)	47 (35)	0.03
Median follow-up, years	5.3	5.1	0.11
Range	1 to 13	1 to 13	
Crude failures			
Vaginal	8 (2)	3 (2)	0.7
Pelvic	11 (2)	4 (3)	0.57
Distant	7 (1.5)	9 (7)	0.003
Total deaths	87 (18)	23 (17)	0.68
Deaths due to disease	6 (1)	4 (3)	0.21

S = surgery alone; S + RT = surgery + RT; GYN = gynecologist; LN = lymph node.
P value is for the comparison of groups, S vs. S + RT.

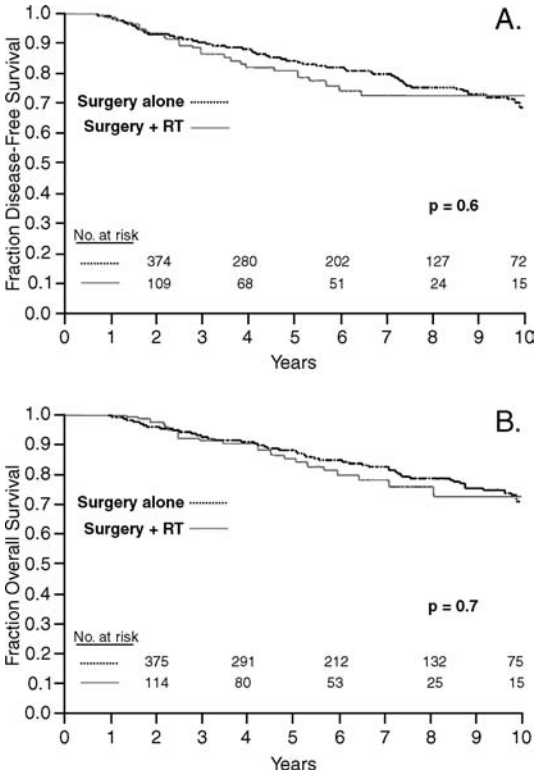

Fig. 1. Estimated survival end points adjusted for surgery alone or surgery followed by RT. (A) Disease-free survival; (B) overall survival.

was performed to test for differences between the two treatment groups. Rates of survival and freedom from failure were calculated using the Kaplan–Meier method, and significance was determined by the log-rank test [12,13]. Univariate and multivariate analyses were performed using the Cox proportional hazards model [14]. JMP™ release 5.1 software (SAS Institute Inc., North Carolina, USA) was used for the statistical analyses. Statistical significance was declared for a $P < 0.05$.

Results

Patient and disease characteristics are depicted in Table 2. Of the 608 women, 165 (27%) underwent formal lymph node dissection with a median 12 lymph nodes examined pathologically (range 5–66). The median number of lymph nodes dissected and examined prior to 1997 was 10 (range 5 to 50), compared to a median 15 (range 5 to 66) since that time (total women with lymph node staging, $n = 165$; $P = 0.23$). The remaining women had random lymph node sampling ($n = 63$) or did not have a recorded surgical evaluation of their lymph nodes ($n = 380$). The median age at diagnosis was 64 (range 27 to 87) years for the entire series. The tumor characteristics within the RT arm were significantly more unfavorable by grade ($P < 0.0001$) and stage ($P < 0.0001$). Women in the RT arm were also more likely to be treated by a GYO ($P = 0.05$) and to undergo pathologic lymph node evaluation ($P = 0.03$). Significantly more women were managed primarily by a GYO in the years following 1997 (66% vs. 16%, $P < 0.0001$).

At a median follow-up of 5.2 years (range: 1.1 to 13.4 years), 26 LR (11 VR), 16 DM, and 110 deaths occurred. Ten deaths were due to progressive endometrial malignancy. Among the women who received RT, 7 experienced failure within the pelvis, 6 within

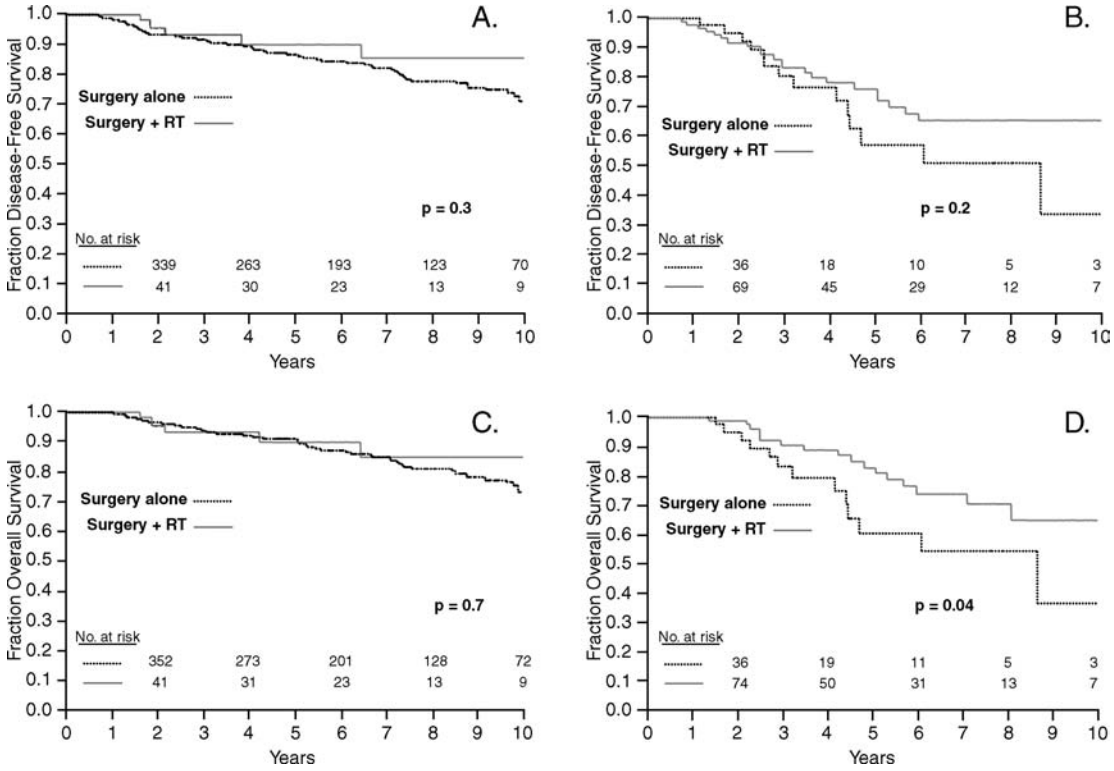

Fig. 2. Estimates survival end points stratified by FIGO stage grouping and adjusted for primary therapeutic approach. (A) Stages IA–IB, disease-free survival; (B) stages IC–IIA, disease-free survival; (C) stages IA–IB, overall survival; (D) stages IC–IIA, overall survival.

the EBRT pelvic fields and 1 within the pelvis after vaginal cuff BT. There were no significant differences observed in the 5-year rates of VR (98% vs. 97%, $P = 0.68$), LR (96% vs. 93%, $P = 0.54$), DFS (84% vs. 81%, $P = 0.59$), and OS (88% vs. 86%, $P = 0.92$) between the surgery and surgery + RT groups (Fig. 1). However, those in the surgery alone group experienced significantly less DM at 5 years, 2% vs. 7% ($P = 0.0009$), compared to those who received RT. The median survival was 13 years in the surgery only arm and has not yet been reached in the adjuvant RT group. Kaplan–Meier analysis of DFS and OS stratified by stage (stage IA–IB vs. stage IC–IIA) revealed that women with stage IC–IIA disease (79% were surgically staged) experienced a significant improvement in OS at 5 years with the addition of RT (83% vs. 60%, $P = 0.04$, Fig. 2) without a significant benefit in DFS ($P = 0.22$).

The end points of VR, LR, DFS, DM and OS when stratified by treatment era (prior to or after 1997) revealed no significant differences in outcomes. As expected, the women treated prior to 1997 have a significantly longer median follow-up (7.5 years) compared to the more recently treated women (2.7 years, $P < 0.0001$).

Those women meeting criteria for HIR disease ($n = 135$), regardless of treatment modality, experienced inferior 5-year rates of DM-free survival (92% vs. 98%, $P = 0.0004$), DFS (67% vs. 88%, $P < 0.0001$), and OS (75% vs. 91%, $P = 0.0005$) compared to those without HIR disease. The 5-year rates of freedom from VR and LR were not significantly different between those with and without HIR disease. Women with HIR disease composed 22% of the entire study population, but accounted for 50% ($n = 21$) of all treatment failures. Of 110 total deaths, 35 occurred within the women of the HIR subgroup.

Table 3
Five-year rates of freedom from failure by Kaplan–Meier analysis and log-rank test

	DFS	*P* value	OS	*P* value
Age				
≤64	95%	0.006	96%	<0.0001
>64	90%		79%	
Pathologic grade				
I	94%	0.07	93%	0.02
II	93%		83%	
III	85%		78%	
FIGO stage				
IA	98%	0.0005	89%	0.02
IB	92%		91%	
IC	85%		76%	
IIA	82%		77%	
High-intermediate risk				
Yes	84%	0.0004	75%	0.0005
No	95%		91%	
Surgical staging performed				
Yes	92%	0.47	85%	0.26
No	94%		88%	
Adjuvant radiation				
Yes	86%	0.59	85%	0.26
No	94%		88%	
Treatment by GYO				
Yes	89%	0.10	78%	0.03
No	86%		89%	

GYO = gynecologic oncologist; DFS = disease-free survival; OS = overall survival.

Table 4
Multivariate analysis for disease-free and overall survival

	Disease-free survival		Overall survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
<64	ref	<0.0001	ref	<0.0001
≤64	0.23 (0.15 – 0.36)		0.18 (0.11 – 0.30)	
Grade				
3	ref	0.06	ref	0.09
1	0.74 (0.57 – 0.96)		0.73 (0.55 – 0.97)	
2	0.98 (0.76 – 1.27)		1.03 (0.78 – 1.36)	
FIGO stage				
IA	ref	0.006	ref	0.02
IB	0.67 (0.50 – 0.90)		0.63 (0.45 – 0.88)	
IC	1.29 (0.87 – 1.87)		1.44 (0.94 – 2.17)	
IIA	1.99 (1.20 – 3.10)		1.77 (0.98 – 2.92)	
Adjuvant therapy				
−RT	ref	0.001	ref	0.004
+RT	0.43 (0.25 – 0.74)		0.41 (0.22 – 0.75)	
GYO care				
No	ref	0.04	ref	0.16
Yes	0.77 (0.61 – 0.98)		0.83 (0.65 – 1.1)	

ref = reference; GYO = gynecologic oncologist.
Hazard ratio (RR) represents the relative hazard for age ≤64 versus >64 years, tumor grade as listed, FIGO stage as listed, adjuvant radiotherapy (RT) versus no RT, and primary management by a GYO versus GYN.

Patient, tumor, and treatment characteristics were evaluated for potential prognostic value in predicting DFS and OS using univariate (Table 3) and multivariate methods (Table 4). On univariate analysis, the factors that associated significantly with improved DFS included younger age (≤64 years, the median age) and lower FIGO stage. The presence of HIR disease was associated with a significant decrement in DFS. Younger age, lower grade, and favorable FIGO stage were associated with improved OS. HIR disease and GYO are associated with a significantly worse OS.

The multivariable analysis (Table 4) for DFS revealed age ≤64 years ($P < 0.0001$), lower FIGO stage ($P = 0.006$), adjuvant RT ($P = 0.001$), and treatment by a GYO ($P = 0.04$) to independently predict for a significant benefit. Younger age ($P < 0.0001$), lower FIGO stage ($P = 0.02$), and adjuvant RT ($P = 0.004$) predicted for significantly improved OS. On separate multivariate analyses analyzing for LR and VR, adjuvant RT (RR = 0.30, 0.08 – 0.98 95% CI, $P = 0.04$), GYO care (RR = 0.41, 0.24 – 0.69 95% CI, $P = 0.0009$) and lower FIGO stage (RR = 0.88, 0.46 – 1.76 95% CI, $P = 0.017$) independently predicted LR disease control. GYO care (RR = 0.29, 0.12 – 0.65 95% CI, $P = 0.003$) alone was found to predict for vaginal recurrent-disease control.

Discussion

This retrospective analysis of 608 women with early-stage endometrial cancer reveals statistically significant differences in pathologic disease characteristics among those with early-stage adenocarcinoma of the endometrium receiving surgery alone or

surgery followed by adjuvant RT at our two institutions. Despite significantly worse pretreatment pathologic disease characteristics among women receiving adjuvant RT, their observed rates of DFS and OS at 5 years were equivalent to women who had more favorable disease characteristics undergoing surgery alone. This analysis further reveals a significant benefit with the addition of adjuvant RT on multivariate analysis to disease-free and overall survival with hazard ratios of 0.43 and 0.41, respectively. This analysis confirms that advanced age, higher stage, and worse grade predict for diminished overall and disease-free survival, substantiating similar reports in the literature [4,15–17].

Despite endometrial carcinoma being the most common gynecologic malignancy in the United States, controversy exists regarding the role of adjuvant radiotherapy. Several reports have failed to document a survival benefit from adjuvant RT in women with [4,18,19] or without [5,6] pathologic node assessment. Yet, some of these reports used the primary end point of disease recurrence or disease-free survival, not overall survival, precluding adequate evaluation of the overall survival end point due to a lack of power. Furthermore, several series were reported with relatively short follow-up and have not yet been updated in spite of the known relative long natural history of early-stage disease. One report, however, provides evidence that RT confers a survival benefit in the subset of women with grade 3, deeply invasive (>50% of myometrium) disease [6]. A recent retrospective analysis of the National Cancer Data Base found women with clinical Stages IC and IIA to benefit from the addition of adjuvant RT, a finding that did not persist among women with surgically staged IC to IIA disease [20]. Univariate analysis stratified by FIGO stage revealed a significantly improved 5-year rate of OS for women with stages IC–IIA disease receiving adjuvant RT. The multivariate analysis revealed that adjuvant RT significantly predicted for improved OS ($P = 0.004$), conferring a relative 59% decrease in the risk of mortality.

A similar benefit from adjuvant RT for women with stage IC–IIA disease was not found to be statistically significant on stratified univariate analysis. The disparate results of the stratified analyses could be due to a lack of control of other variables that significantly associate with these end points that were not accounted for in the univariate model. However, adjuvant RT independently predicted for DFS with a relative 57% reduction (RR = 0.43, $P = 0.001$) in disease-free events on multivariate analysis. This benefit was present in the analysis of any pelvic recurrence (LR) but was not present when analyzing for vaginal cuff recurrence (VR) alone, although both of these analyses are limited by relatively few events. The significance of this benefit cannot be underestimated in light of the growing body of evidence of the more aggressive behavior of higher grade, deeply invasive disease. The GOG staging study revealed microscopic pelvic nodal metastases to be present in 18% of clinical stage I patients with deep myometrial invasion (outer third of the myometrium) vs. <10% for superficial invasion [16]. The risk of disease recurrence in tumors with these more aggressive disease characteristics has been documented by others [21] and has influenced inclusion criteria for major randomized studies [5]. Our findings confirm those of large randomized studies that have reported a benefit in control of local–regional disease from adjuvant RT in early-stage disease [4–6] and validate the standardized treatment policy of our institutions that was established in 1997.

The development and implementation of a treatment policy for the addition of adjuvant RT following surgery in early-stage endometrial cancer coincided with the increased presence and participation of gynecologic oncologists at our two institutions. Though significantly more women have been evaluated and managed by a GYO since 1997, no significant differences were found in the analyzed end points for one treatment era compared to the other. The lack of significance, however, could relate to the significant deficiency in follow-up of the more contemporarily treated women in a disease with a relatively long natural history. Although the addition of RT following surgery did not significantly differ from one era to the next, women were more likely to undergo complete primary surgical staging in the recent era. Furthermore, the heterogeneity in treatment patterns has dramatically decreased since 1997 with fewer general gynecologists involved in primary patient care and a written policy regarding the implementation of post-operative RT at our two institutions.

Despite the statistically significant benefit of adjuvant RT on DFS and OS observed in the adjusted analysis, we recognize that this is a retrospective study that is prone to inherent bias. Furthermore, our patient population is a heterogeneous series in that only one third of women were treated by a gynecologic oncologist. The remaining women were primarily treated with varying approaches to primary resection that were not generally defined by a single standard. Pathologic review was not standardized and the pathologic information was collected from a variety of institutions where the primary surgeries were performed. Important pathologic and clinical factors, including lymphovascular space invasion and adequate lymph node evaluations, were not sufficiently represented to allow for evaluation and adjustment in this series' analysis. Additionally, the addition of radiotherapy as a single adjuvant entity was evaluated and was not analyzed based on its method of delivery. Lastly, the relative number of failures (vaginal, pelvic or distant) is limited despite the large sample size and the results of the analyses for separate failures should be considered cautiously. We recognize the potential biases that these and other factors can introduce into an analysis of this kind and do not espouse these data as definitive proof of the benefit of RT in the adjuvant setting.

The role of oncologic specialization in the treatment of early-stage disease is further addressed by our results. In a report that does not describe patient outcomes, Roland et al. found that comprehensive staging and less referrals for adjuvant RT were more common among women treated primarily by a GYO versus a GYN [22]. A recent analysis from our institution revealed a relative 31% reduction in local and distant failures in women treated by a GYO despite significantly more unfavorable disease characteristics compared to those treated by a GYN [23]. The current analysis shows that treatment by a GYO significantly predicts for improved DFS on multivariate analysis (RR = 0.77, $P = 0.04$) despite significantly worse disease characteristics. On separate proportional hazards models evaluating LR and VR, GYO treatment was similarly found to significantly reduce the risk of failure, but these results should be viewed cautiously in light of the relatively few events in the separately analyzed groups. Interestingly,

GYO treatment was associated with a significantly poorer OS on univariate analysis but trended ($P = 0.15$) towards a predicted benefit in the proportional hazards model. This contradiction could relate to the propensity in our community for general gynecologists to refer women who not only have more unfavorable disease but also who are poorer surgical candidates with greater co-morbidities to the gynecologic oncologists.

The disparity in distant failures, favoring those who underwent surgery only, does not correspond with the benefit of adjuvant RT in local disease control and survival. Close inspection of the distant failure data reveals that of the 9 distant failures in the adjuvant RT arm 6 occurred within 2 years following definitive treatment while 1 of the 7 failures in the surgery alone group occurred within the same time frame. Furthermore, 3 of those distant failures in the adjuvant RT arm occurred within a year of initial diagnosis, suggesting that metastatic disease was present at the time of diagnosis, albeit not clinically apparent. This disparity in outcomes–that of improved local control with no impact on or worse distant disease control–confirms the observations of Aalders et al. [6] in that those women who are most likely to fail in the pelvis are also those who are most likely to fail distantly. These women were those most likely to receive adjuvant RT and are those who experience a local control benefit in both series.

In summary, women with significantly worse disease characteristics who received adjuvant RT experienced equivalent outcomes at the evaluated end points with women who had more favorable disease characteristics. This analysis reveals that adjuvant radiotherapy confers a relative reduction in overall and disease-free survival of greater than 50% on Cox proportional hazards modeling. Stratified analysis suggests that the major benefit of adjuvant radiotherapy was in women with higher risk disease. We conclude that adjuvant radiotherapy should be considered an integral component of definitive treatment for women with unfavorable disease as a means to decrease mortality and improve patient outcomes. Future work is needed to delineate clinical and biologic factors that can guide treatment and account for disparities in outcomes between subsets of women with endometrial adenocarcinoma, including patterns of care analyses and prospective studies of adjuvant radiotherapy modalities and tumor-specific treatment strategies.

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References

[1] Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55(1):10–30.
[2] Announcement. FIGO stages—1988 revision. Gynecol Oncol 1989;35 (1):125–7.
[3] Creutzberg CL, van Putten WL, Koper PC, et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 2001;51(5):1246–55.
[4] Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92(3):744–51.
[5] Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355 (9213):1404–11.
[6] Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56(4):419–27.
[7] Greven KM, Corn BW, Case D, et al. Which prognostic factors influence the outcome of patients with surgically staged endometrial cancer treated with adjuvant radiation? Int J Radiat Oncol Biol Phys 1997;39 (2):413–8.
[8] Irwin C, Levin W, Fyles A, et al. The role of adjuvant radiotherapy in carcinoma of the endometrium—results in 550 patients with pathologic stage I disease. Gynecol Oncol 1998;70(2):247–54.
[9] Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. Gynecol Oncol 1990;38(1):99–104.
[10] Piver MS, Hempling RE. A prospective trial of postoperative vaginal radium/cesium for grade 1–2 less than 50% myometrial invasion and pelvic radiation therapy for grade 3 or deep myometrial invasion in surgical stage I endometrial adenocarcinoma. Cancer 1990;66(6):1133–8.
[11] Alektiar KM, Venkatraman E, Chi DS, et al. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005;62(1):111–7.
[12] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Am Stat Assoc J 1958;53:457–81.
[13] Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35(1):1–39.
[14] Cox DR. Regression models and life tables. J R Stat Soc B 1972; 34:187–220.
[15] Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical–pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40(1):55–65.
[16] Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. Cancer 1987;60(8 Suppl):2035–41.
[17] Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 2004;22(7):1234–41.
[18] Straughn Jr JM, Huh WK, Kelly FJ, et al. Conservative management of stage I endometrial carcinoma after surgical staging. Gynecol Oncol 2002;84(2):194–200.
[19] Straughn JM, Huh WK, Orr Jr JW, et al. Stage IC adenocarcinoma of the endometrium: survival comparisons of surgically staged patients with and without adjuvant radiation therapy. Gynecol Oncol 2003;89 (2):295–300.
[20] Straughn Jr JM, Numnum TM, Kilgore LC, et al. The use of adjuvant radiation therapy in patients with intermediate-risk Stages IC and II uterine corpus cancer: a patient care evaluation study from the American College of Surgeons National Cancer Data Base. Gynecol Oncol 2005;99(3):530–5 [Electronic publication 2005 Sep 29].
[21] Meerwaldt JH, Hoekstra CJ, van Putten WL, et al. Endometrial adenocarcinoma, adjuvant radiotherapy tailored to prognostic factors. Int J Radiat Oncol Biol Phys 1990;18(2):299–304.
[22] Roland PY, Kelly FJ, Kulwicki CY, et al. The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment. Gynecol Oncol 2004;93(1):125–30.
[23] Macdonald OK, Sause WT, Lee RJ, et al. Does oncologic specialization influence outcomes following surgery in early stage adenocarcinoma of the endometrium? Gynecol Oncol 2005;99(3):730–5 [Electronic publication 2005 Sep 1].