Frequency and Effect of Adjuvant Radiation Therapy Among Women With Stage I Endometrial Adenocarcinoma

Christopher M. Lee, MD
Aniko Szabo, PhD
Dennis C. Shrieve, MD, PhD
O. Kenneth Macdonald, MD
David K. Gaffney, MD, PhD

Context The benefit of adjuvant radiation therapy (RT) in stage I endometrial adenocarcinoma remains controversial despite several phase 3 trials.

Objective To evaluate the frequency and effect of adjuvant RT on overall and relative survival within a large US population database.

Design, Setting, and Population A retrospective analysis that used data from the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute from January 1, 1988, to December 31, 2001. A total of 21 249 patients with American Joint Committee on Cancer stage IA-C node-negative endometrial adenocarcinoma comprised the study population.

Main Outcome Measures Overall survival curves were constructed using Kaplan-Meier method and compared via stratified log-rank test within T stage/grade combinations, adjusted for age. Relative survival was performed to assess the effects of age, race, stage, grade, whether nodes were examined, and whether adjuvant RT was administered.

Results Of 21 249 women, 4080 received adjuvant RT (19.2%) and 17 169 did not receive adjuvant RT (80.8%). The mean age at diagnosis was 63.2 years (range, 14-99 years). Adjuvant RT significantly improved overall survival for patients with stage IC/grade 1 ($P<.001$) and stage IC/grades 3 and 4 ($P<.001$). Cox proportional hazards regression analysis revealed a statistically detectable association of adjuvant RT with improved relative survival in patients with stage IC/grade 1 and stage IC/grades 3 and 4 (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.31-0.63; $P<.001$; and HR, 0.72; 95% CI, 0.57-0.92; $P=.009$; respectively). A separate analysis of those patients with a surgical lymph node examination at the time of total abdominal hysterectomy and bilateral salpingo-oophorectomy revealed similar estimates (HR, 0.59; 95% CI, 0.39-0.90; $P=.01$; and HR, 0.73; 95% CI, 0.55-0.96; $P=.02$; respectively).

Conclusions As the largest reported population analysis to date of adjuvant RT in early stage endometrial adenocarcinoma, our study reveals a statistically significant association between improved overall and relative survival and adjuvant RT in stage IC disease (grades 1 and 3-4). Future work is needed to continue to delineate clinical and biological factors, which can guide treatment decisions and account for disparities in outcome between varied subsets of patients.

JAMA. 2006;295:389-397 www.jama.com

Endometrial cancer remains the most common gynecological malignancy in the United States; however, the optimal adjuvant treatment for stage I endometrial adenocarcinoma remains elusive despite published results from randomized trials. Recent publications have revealed 5-year overall survival rates of 80% to 90% for women with stage I disease who have received total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and adjuvant radiation therapy (RT) based on clinical and pathological characteristics.[1-7] Despite these encouraging results, the specific subgroup of patients with American Joint Committee on Cancer stage IC (>50% myometrial invasion) and high-grade disease (grade 3 or 4) are known to have relatively poorer outcomes with higher rates of both local and distant relapses.[8]

Variability in survival outcome across select patient groups has also been identified through clinical research. Postoperative RT with either external beam radiation, vaginal brachytherapy, or both have led to improved locoregional control of disease in multiple trials, although a consistent survival benefit for select subsets of patients has been difficult to determine. The study by Aalders et al[1] reported the results of a phase 3 trial of women with stage I endometrial adenocarcinoma randomized to adjuvant pelvic external beam radiation or observation following TAH-BSO and vaginal brachytherapy. This

Author Affiliations: Department of Radiation Oncology, Huntsman Cancer Hospital and University of Utah Medical Center (Drs Lee, Shrieve, Macdonald, and Gaffney), and Department of Oncological Sciences, University of Utah and Biostatistics Shared Resource, Huntsman Cancer Institute (Dr Szabo), Salt Lake City.
Corresponding Author: David K. Gaffney, MD, PhD, Department of Radiation Oncology, Huntsman Cancer Hospital and University of Utah Medical Center, 1950 Circle of Hope, Salt Lake City, UT 84112-5560 (david.gaffney@hci.utah.edu).

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

study revealed that pelvic RT led to reduced vaginal and pelvic recurrence rates, although 5-year survival was not improved (89% vs 91%, respectively). However, a survival benefit was suggested for only those patients with grade 3 tumors and stage IC disease (18% vs 27% cancer deaths, respectively).[1] The Gynecologic Oncology Group[9] recently reported results of a randomized trial that assessed specifically whether adjuvant RT would decrease relapses following hysterectomy and surgical staging of intermediate-risk endometrial cancer. The cumulative incidence of recurrence was 12% in the observation group vs 3% in the adjuvant RT group (hazard ratio [HR], 0.42; 90% confidence interval [CI], 0.25-0.73; $P=.007$); however, this improvement in recurrence-free survival did not translate into a statistically significant difference in overall survival at a median follow-up of 69 months. The study by Keys et al[9] used known clinicopathological risk factors to define a high-intermediate risk subgroup of patients. Those patients within the high-intermediate risk subgroup were more prone to relapse and experienced a significant benefit in disease-free survival from pelvic irradiation.[9] Creutzberg et al[8] have also recently reported that patients with stage IC/grade 3 or 4 disease are at higher risk of early distant spread and endometrial carcinoma–related death compared with other patients with stage I endometrial carcinoma. In this large randomized trial from the Netherlands, there was no significant survival benefit reported for adjuvant RT in patients with intermediate-risk stage I cancer. Hence, significant controversy continues to exist in regards to the role of adjuvant RT in stage I endometrial cancer.

Population-based studies are needed to further delineate the impact of adjuvant RT on survival outcomes for women with stage I endometrial carcinoma and to analyze the practice patterns of physicians in the United States. Using population-based cancer data, our goal was to quantitatively evaluate the frequency and effect of adjuvant RT on overall and relative survival.

METHODS

Data and Study Population

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute (NCI) using the SEER 11-Registries plus Alaska 1988-2001 data set (November 2003 edition).[10] The SEER database is composed of a set of geographically defined, population-based, central cancer registries in the United States (data from Connecticut, Iowa, Hawaii, New Mexico, Utah, metropolitan areas of Atlanta, Detroit, Los Angeles, Oakland, San Francisco, San Jose–Monterey, Seattle–Puget Sound, and Alaska Native populations) and is operated by local nonprofit organizations under contract with the NCI. Serial registry data are submitted electronically without personal identifiers (deidentified) to the NCI on a biannual basis and the NCI thereafter makes the data available to the public for research purposes.[10] Because all SEER database information remains deidentified, approval by an ethics committee and informed consent by the study participants were not necessary to perform the analyses. The case ascertainment rate from the SEER registries has been reported to be 97.5%. The SEER database is the authoritative source of population-based information on cancer incidence and survival in the United States. In general, the populations covered by SEER are known to be representative of the whole United States.[11]

The analyzed study population included women diagnosed with American Joint Committee on Cancer stage IA-C (T1a-T1c disease without nodal involvement or distant disease spread) endometrial adenocarcinoma who underwent TAH-BSO. Histological classification was based on the *International Classification of Diseases for Oncology* codes (*ICD* 8380).[12] Patients were included who were diagnosed between January 1, 1988, and December 31, 2001, and for whom complete data sets were available. The following prognostic factors were included in the analysis: age, race, stage, grade, extent of surgery (whether pelvic or paraaortic lymph nodes were sampled in addition to TAH-BSO), and whether postoperative adjuvant RT was administered. Sampling of pelvic or paraaortic lymph nodes at time of TAH-BSO was designated as surgical lymph node examination. Information on race was used as entered in the SEER database (self-determined). This information was analyzed to evaluate known differences in prognosis according to race. The following were causes for patient exclusion from the analysis: clinical or pathological lymph node involvement (N1 disease), distant spread (M1 disease), surgery did not include TAH-BSO, lack of pathological staging, and cases with missing variables. Of 39 205 women diagnosed with stage IA-C endometrial cancer between January 1, 1988, and December 31, 2001, 21 249 women met the above criteria and serve as the patient population for our study. A total of 17 956 patients did not meet the above criteria due to multiple reasons (some patients had >1 exclusion criteria), such as lack of tumor grade information (n = 2816), lack of documented hysterectomy (n=1341), lack of known T status or lymph node status (n=15 133), presence of N1 disease (n=793), or unknown administration of RT (n=487). All participants in the SEER program routinely link patient files with vital records (ie, death certificates) in their respective areas of coverage to identify patients with cancer who have died (regardless of cause of death); therefore, death certificates are the source for information regarding underlying cause of death as recorded in the SEER program database. Furthermore, the National Center for Health Statistics conducts routine reviews of death certificates to ensure quality of data.[11]

Statistical Analysis

Survival curves for overall survival were estimated using the Kaplan-Meier method and compared via stratified log-rank test within each stage/grade com-

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

bination, adjusting for age group (<56 years, 56-75 years, >75 years). The standard estimator of the survival function is the Kaplan-Meier (product-limit estimator). With the Kaplan-Meier survival curve, a consistent estimate of the survival curve can be computed from randomly censored data. At each patient death, the conditional probability of survival during the interval since the last death is calculated as the number of patients observed to survive beyond that point (those patients who have not yet died and have not left the trial for other reasons) divided by the number at risk. The value of the survival curve at that point is calculated as the product of the conditional probabilities of survival for all of the intervals up to that point. Using the stratified log-rank test instead of doing an individual log-rank test provides a more precise summary of the treatment effect within each stage/grade combination adjusting for age group. An overall stratified log-rank test for comparing RT groups was also performed.

Proportional hazards modeling was used to study the association between the prognostic factors and survival end points. Proportional hazards means that the hazard of death at any given time for an individual in the group without RT is proportional to the hazard at that same time for a similar individual in the group with RT. Survival variability was examined with respect to overall survival, with rates measured from the date of diagnosis to either the date of death from any cause or the date of last contact. SEER unfortunately does not contain data on induction failures or relapses, which are necessary to determine event-free survival. As expected, we found overall survival to be highly affected by age. To ensure that any differences attributed to age are disease specific, we modeled survival relative to the US population. Cox proportional hazards regression modeling is based on the proportional hazards assumption, which states that each covariate affects the hazard of the event of interest (for overall survival, death) occurring multiplicatively. To adapt the classic Cox proportional hazards regression model for relative survival, for each patient the expected probability P of survival through the follow-up time was calculated based on US life-tables for women based on the patient's age, race, and year of diagnosis.[11,13] Then, $log(1/P)$ gives the total hazard experienced up to the patient's observed death or censoring time. Because technically Cox proportional hazards regression software works with additive effects on the log-hazard (which are equivalent to multiplicative effects on the hazard), a $log[-log(P)]$ term with its coefficient fixed at 1 was included in the model; therefore, the regression described the effect of the covariates on survival beyond this known hazard.

We used proportional hazards modeling of the relative survival to assess the effects of clinicopathological factors.[14] First, we fitted a preliminary model containing all the explanatory variables: stage, grade, race, age at diagnosis, lymph node examination, and RT (allowing the effect of radiation to vary depending on the other covariates). We next examined the residuals and conducted a formal test of the underlying assumption of proportional hazards, which revealed that the effects of stage, grade, and age at diagnosis were not well described by that assumption. We extended our model to allow different baseline hazards for each stage/grade combination via stratification and thus eliminating the proportional hazards assumption for them. For age at diagnosis, the associated hazard appeared to decrease linearly by time from diagnosis; therefore, we added an appropriate time-dependent covariate: the interaction of time since diagnosis and age at diagnosis. The resulting model showed no evidence of nonproportional hazards. Further investigation of interactions prompted the inclusion of additional terms accounting for variability of the covariates by stage and grade. No other first-order interactions or second-order interactions involving radiation were found (global likelihood-ratio test, $P=.72$). Some of the terms in the model are not statistically significant; however, we have made no attempts to eliminate them as our goal is the estimation of the radiation-related effects and extensive model pruning can bias those estimates.

SEER*Stat software version 6.1.4 (Surveillance Research Program, NCI, Bethesda, Md) was used to extract case level data from the SEER Cancer Public-Use Database 1973-1999, November 2003 Submission. R version 2.1.0 was used for statistical analyses.[15] We defined $P<.05$ to be statistically significant.

RESULTS

A total of 21 249 women were included in our analysis. The mean age at diagnosis was 63.2 years (range, 14-99 years). A total of 4080 women (19.2%) received postoperative RT as part of their initial treatment. Within the RT cohort, 2551 patients (62.5%) had external beam radiation, 732 (17.9%) had vaginal brachytherapy, and 1078 (26.4%) received a combination of external beam radiation with vaginal brachytherapy. The prevalence of RT use by grade and stage, as well as the corresponding sample sizes, are shown in TABLE 1. Higher stage and higher grade were found to be associated with both older age and increased use of postoperative RT. Table 1 also shows the frequency of surgical nodal sampling performed at the time of TAH-BSO for each patient cohort. White women comprised 88.5% of the total analyzed study population. A total of 18 255 women were alive at the time of last follow-up (709 died due to endometrial cancer, 2165 died from other causes, and 120 had no recorded cause-of-death information). The median follow-up time for women included in the analysis was 46 months (range, 0.1-167.0 months).

Survival Probabilities

FIGURE 1 shows Kaplan-Meier survival curves for overall survival with or without RT compared via stratified log-

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

rank test within each stage/grade combination adjusting for age. As expected, overall survival was highly affected by age for each of the specific stage/grade combinations. Stage IC/grade 1 and stage IC/grades 3 and 4 cohorts were found to have statistically significant improvements in overall survival with the addition of adjuvant RT (both $P<.001$). The 5-year overall survival rates for patients with stage IC/grade 1 disease for the age groups younger than 56 years, 56 to 75 years, and older than 75 years with and without adjuvant RT were 98% vs 88%, 94% vs 85%, and 84% vs 67%, respectively. The 10-year overall survival rates for the same group stratifications were 92% vs 69%, 76% vs 72%, and 59% vs 42%, respectively. The 5-year overall survival rates for patients with stage IC/grades 3 and 4 disease for the age groups younger than 56 years, 56 to 75 years, and older than 75 years with and without adjuvant RT were 86% vs 77%, 66% vs 56%, and 53% vs 39%, respectively. The 10-year overall survival rates for the same group stratifications (stage IC/grades 3 and 4 disease) were 86% vs 77%, 51% vs 42%, and 27% vs 11%, respectively. No additional stage/grade groups were found to have statistically significant differences in overall survival associated with RT.

Table 1. Patient Characteristics and Prevalence of Adjuvant Radiation Therapy Use by Grade and AJCC Stage

	Grade			
	1	2	3-4	1-4
Stage IA				
No. of women	4155	1896	739	6790
Age, mean (SD), y	58.4 (12.3)	60.4 (12.5)	64.7 (11.7)	59.6 (12.5)
White race, No. (%)	3557 (85.6)	1638 (86.4)	587 (79.4)	5785 (85.2)
Surgical nodal sampling, No. (%)	1039 (25.0)	779 (41.1)	499 (67.5)	2315 (34.1)
Adjuvant RT, No. (%)	91 (2.2)	104 (5.5)	145 (19.6)	340 (5.0)
Adjuvant RT by age group, No. (%), y				
<40	9 (2.5)	3 (2.4)	5 (23.8)	17 (3.4)
40-55	29 (2.0)	25 (4.5)	26 (19.7)	80 (3.8)
56-75	41 (2.0)	64 (6.5)	93 (21.1)	198 (5.8)
>75	11 (3.1)	13 (5.6)	21 (14.4)	45 (6.1)
Stage IB				
No. of women	5054	4316	1948	11 318
Age, mean (SD), y	62.4 (11.7)	63.9 (11.5)	65.7 (11.8)	63.6 (11.7)
White race, No. (%)	4619 (91.4)	3859 (89.4)	1667 (85.6)	10 152 (89.7)
Surgical nodal sampling, No. (%)	1587 (31.4)	2041 (47.3)	1367 (70.2)	5003 (44.2)
Adjuvant RT, No. (%)	359 (7.1)	751 (17.4)	838 (43.0)	1947 (17.2)
Adjuvant RT by age group, No. (%), y				
<40	11 (5.2)	27 (19.9)	19 (41.3)	57 (14.4)
40-55	87 (7.1)	149 (17.0)	170 (49.4)	406 (16.6)
56-75	218 (7.5)	472 (18.3)	525 (47.0)	1215 (18.4)
>75	41 (5.8)	101 (13.9)	124 (28.1)	266 (14.2)
Stage IC				
No. of women	901	1354	886	3141
Age, mean (SD), y	69.1 (11.0)	69.3 (10.9)	69.0 (11.7)	69.2 (11.2)
White race, No. (%)	842 (93.5)	1243 (91.8)	787 (88.8)	2871 (91.4)
Surgical nodal sampling, No. (%)	429 (47.6)	760 (56.1)	605 (68.3)	1794 (57.1)
Adjuvant RT, No. (%)	438 (48.6)	792 (58.5)	556 (62.8)	1787 (56.9)
Adjuvant RT by age group, No. (%), y				
<40	10 (55.6)	11 (47.8)	7 (58.3)	28 (52.8)
40-55	40 (50.0)	71 (56.8)	73 (65.2)	184 (58.0)
56-75	289 (54.8)	504 (64.3)	321 (69.3)	1114 (62.8)
>75	99 (35.9)	206 (48.8)	155 (51.8)	460 (46.1)
Combined stage IA-C				
No. of women	10 110	7566	3573	21 249
Age, mean (SD), y	61.4 (12.3)	64.0 (12.0)	66.3 (11.9)	63.1 (12.3)
White race, No. (%)	9018 (89.2)	6741 (89.1)	3041 (85.1)	18 805 (88.5)
Surgical nodal sampling, No. (%)	3053 (30.2)	3579 (47.3)	2469 (69.1)	9116 (42.9)
Adjuvant RT, No. (%)	890 (8.8)	1649 (21.8)	1540 (43.1)	4080 (19.2)
Adjuvant RT by age group, No. (%), y				
<40	30 (5.1)	41 (14.4)	31 (39.2)	102 (10.7)
40-55	156 (5.7)	245 (15.8)	269 (45.7)	670 (13.7)
56-75	548 (10.1)	1040 (23.9)	939 (46.5)	2527 (21.4)
>75	151 (11.3)	320 (23.2)	300 (33.9)	771 (21.4)

Abbreviations: AJCC, American Joint Committee on Cancer; RT, radiation therapy.

FIGURE 2 illustrates the estimated relative survival within each stage/grade combination with and without the addition of RT. The estimates of relative survival were obtained by SEER*Stat software. Relative survival can go above or below 1 as the selected population could have better or worse survival than the overall population, respectively. These plots are not broken down by age groups as no statistically significant age effect on relative survival was observed ($P=.60$). These analyses reveal that for the specific stage IC/grade 1 and stage IC/grades 3 and 4 patient cohorts statistically significant improvements in relative survival were evident with the addition of adjuvant RT ($P<.001$ and $P=.009$, respectively). No additional stage/grade patient groups were found to have statistically significant differences in relative survival associated with RT.

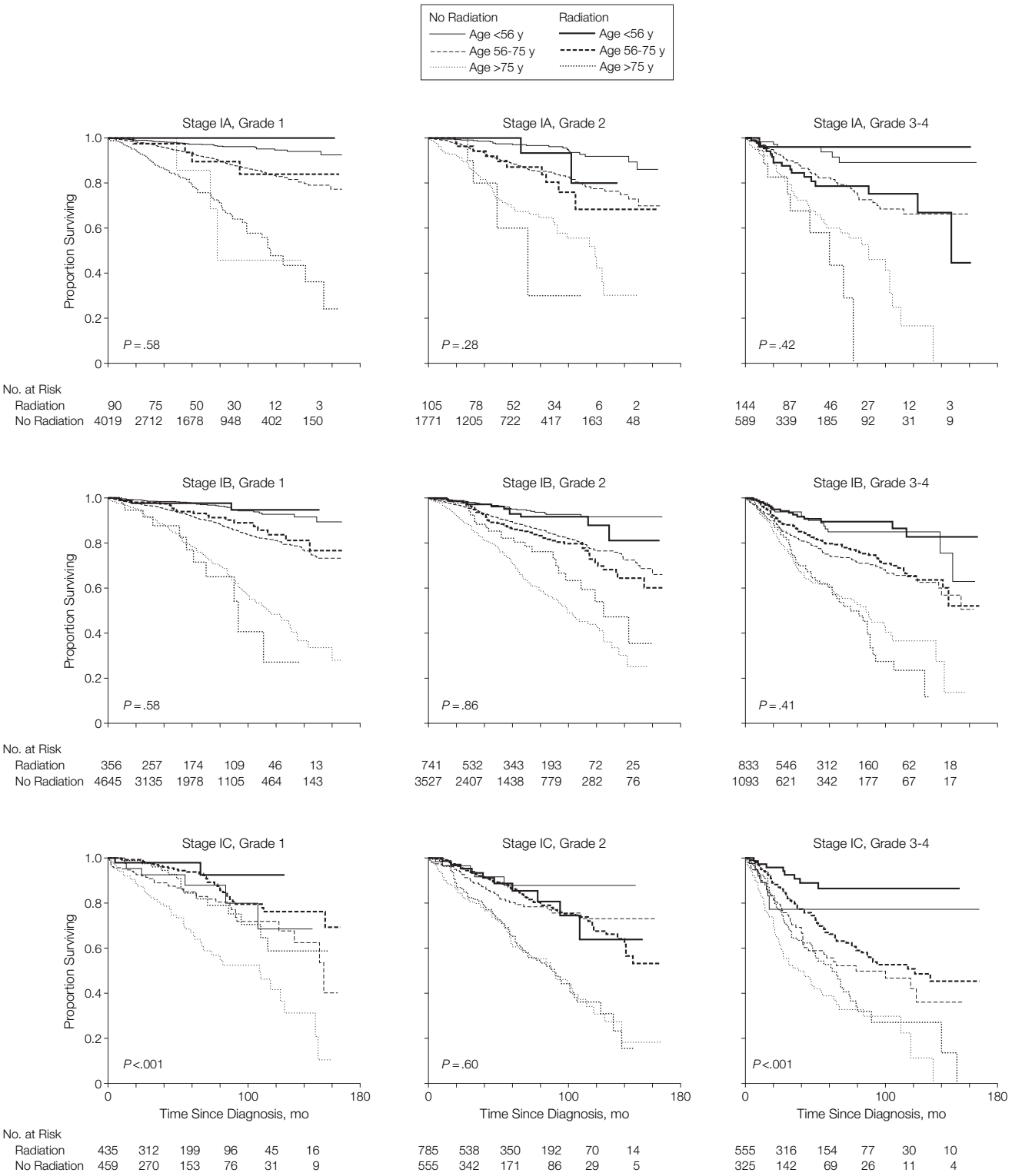
Hazard Ratios

Because the effect of stage and grade on relative survival was not well described by a proportional hazards model and thus separate hazard functions were used for each stage/grade combination, the difference between any 2 groups cannot be summarized with 1 HR value. Nonetheless, investigation of the 9 baseline hazard estimates showed that both higher stage and higher grade disease were

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

Figure 1. Kaplan-Meier Curves for Overall Survival by Stage, Grade, Age at Diagnosis, and Radiation Therapy



Log-rank *P* values are stratified by age. The number of patients at risk in all groups are at time points for every 30 months.

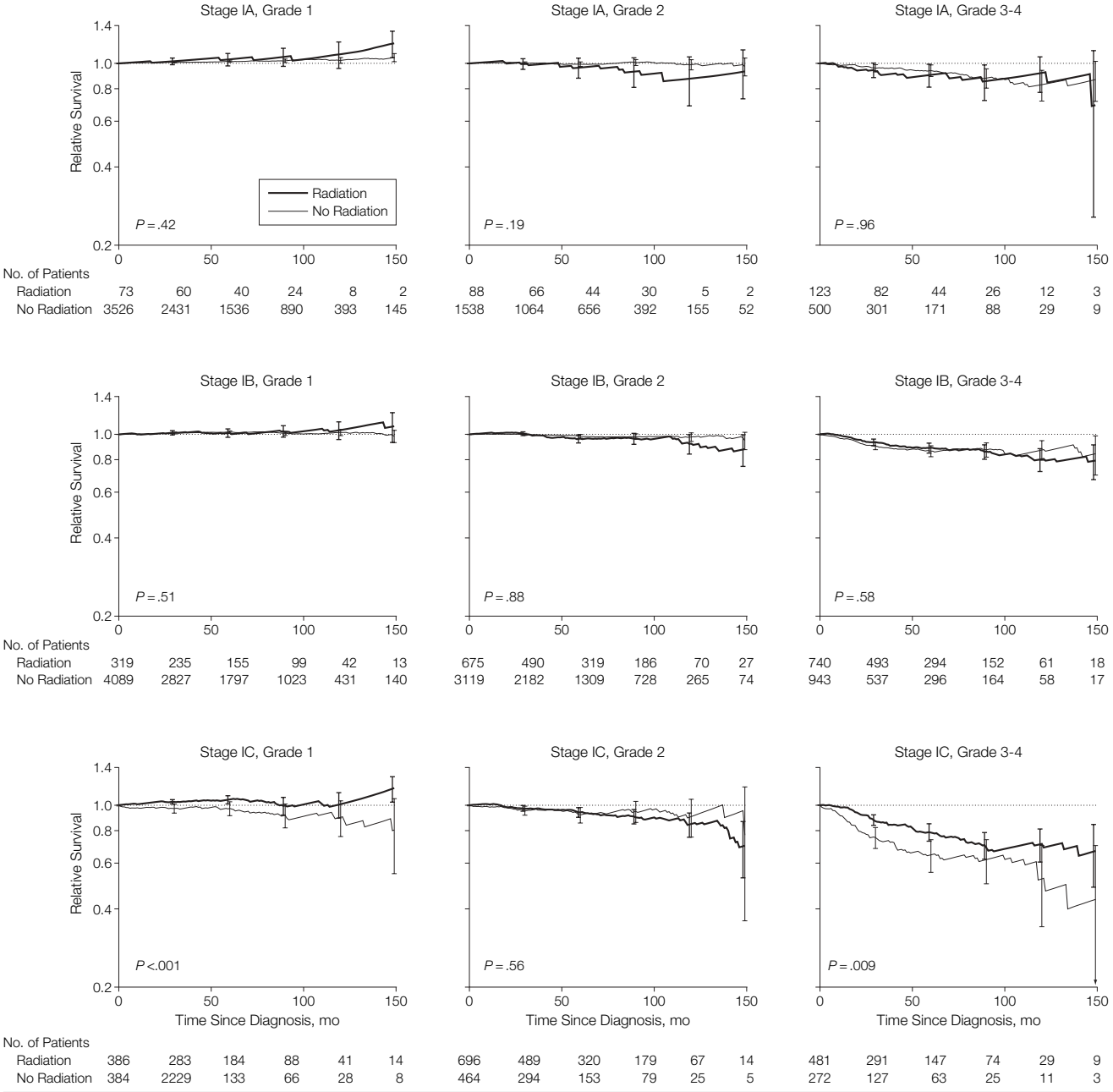
©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

associated with worsened survival. For the remaining covariates, HRs with the relative survival end point were calculated based on the fitted model. In short term, higher age at diagnosis was associated with improved relative survival per decade (HR, 0.85; 95% CI, 0.76-0.94; $P<.001$) but the effect diminished with passage of time after diagnosis, disappearing in approximately 5 years. White race and having had a surgical lymph node examination at the time of TAH-BSO led to statistically nonsignificant improvements in relative survival that did not appear to depend on whether RT was administered (HR, 0.80; 95% CI, 0.62-1.02; and HR, 0.89; 95% CI, 0.80-1.00; respectively, averaged over all interactions).

Our regression analysis further revealed an interesting pattern of depen-

Figure 2. Effect of Radiation on Relative Survival by Stage and Grade



P values are for radiation effect averaged over the observed race, lymph node examination status, and age at diagnosis specific for each stage/grade combination and adjusted for interactions and nonproportional hazard effects. Survival in plots for radiation therapy and non–radiation therapy groups is relative to survival of overall US population of women, according to age, race, and year of diagnosis. The number of patients at risk in both groups are at time points for every 30 months. Error bars represent SE.

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

dence of the effectiveness of RT depending on stage and grade: higher grade was associated with diminished effect of radiation, and higher stage was associated with increase in the relative survival. Detailed HR estimates for each stage/grade combination for a typical patient from each of the 9 groups (averaged over age, race, and presence of lymph node examination) are shown in TABLE 2. The interplay of the various influences resulted in statistically detectable beneficial effect of adjuvant RT in stage IC/grade 1 and stage IC/grades 3 and 4 patient cohorts (HR, 0.44; 95% CI, 0.31-0.63; $P<.001$; and HR, 0.72; 95% CI, 0.57-0.92; $P=.009$; respectively).

The estimated effect size is equally impressive for the stage IA-B/grade 1 cohorts; however, the CIs are wide due to the relatively small number of patients receiving RT. Our model has not revealed noticeable variability of the effect of RT depending on whether surgical lymph node examination was performed. To confirm this, we performed a separate analysis of those patients who received a surgical lymph node examination at the time of TAH-BSO. These results are also shown in Table 2 and reveal that the determined estimates are similar to the entire cohort.

Table 2. Estimated Hazard Ratios of Radiation vs No Radiation for All Patients and Patients With Surgical Lymph Node Examinations*

	All Patients		Patients With Surgical Lymph Node Examination	
Stage/ Grade	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
IA/1	0.73 (0.34-1.57)	.42	0.80 (0.44-1.45)	.46
IB/1	0.89 (0.62-1.27)	.51	0.75 (0.49-1.16)	.20
IC/1	0.44 (0.31-0.63)	<.001	0.59 (0.39-0.90)	.01
IA/2	1.42 (0.84-2.37)	.19	1.15 (0.68-1.94)	.59
IB/2	1.02 (0.81-1.28)	.88	1.08 (0.80-1.45)	.62
IC/2	0.93 (0.73-1.19)	.56	0.84 (0.62-1.14)	.26
IA/3-4	1.01 (0.65-1.56)	.96	1.03 (0.64-1.66)	.90
IB/3-4	0.94 (0.77-1.16)	.58	0.95 (0.74-1.21)	.66
IC/3-4	0.72 (0.57-0.92)	.009	0.73 (0.55-0.96)	.02

*Estimates are averaged over the observed race, lymph node examination status, and age at diagnosis specific for each stage/grade combination.

COMMENT

Our study was performed to evaluate the frequency of utilization and effect of adjuvant RT on overall survival and relative survival for stage I endometrial adenocarcinoma by analyzing a large US population database. Radiation therapy was significantly associated with improved overall survival and relative survival for the stage IC/grade 1 and stage IC/grades 3 and 4 cohorts. To our knowledge, as the largest reported population analysis of the use of adjuvant RT in early stage endometrial adenocarcinoma to date, it is significant that our study reveals an association in both overall survival and relative survival for adjuvant RT in stage IC disease (grades 1 and 3-4 cohorts).

A central strategy used to improve patient outcomes in the treatment of all cancers is to customize therapy based on risk stratification. Multiple studies have shown that patients with stage I endometrial carcinoma who are treated with therapy tailored to known prognostic factors have 5-year overall survival rates of 80% to 90%, and 5-year cancer-specific survival rates of 90% to 95%.[1-7] Studies have also revealed that the particular patient cohort with high-grade tumors and deep (>50%) myometrial invasion have a significantly higher risk of both locoregional and distant relapse.[8] The Gynecologic Oncology Group staging study[16] revealed that microscopic pelvic nodal metastases were present in 18% of patients with clinical stage I and deep myometrial invasion (defined as outer third of the myometrial wall) in comparison with less than 10% for the rest of the population. The randomized trial results reported by Aalders et al[1] revealed that the addition of external beam radiation after TAH-BSO and vaginal brachytherapy led to reduced vaginal and pelvic recurrence rates, although a statistically significant survival benefit was not observed (5-year survival rate, 89% vs 91%). This study also suggested a survival benefit for the specific subgroup of patients with grade 3 tumors and deep (stage IC) myometrial invasion. The study by Meerwaldt et al[17] also reported an increase in local-regional relapse rate for the specific subgroup of patients with stage IC/grade 3 disease. Due to these previous studies, it was decided to exclude this higher-risk subgroup from random assignment within the multicenter Postoperative Radiation Therapy in Endometrial Carcinoma trial of stage I disease.[2] As shown in the study by Creutzberg et al,[8] the high-risk patients (stage IC/grade 3) who were excluded from randomization but who were registered experienced a 5-year local-regional relapse rate of 14%, distant metastatic rate of 31%, and overall survival of 58% ($P<.001$) compared with 5-year local-regional relapse rate of 1%, distant metastatic rate of 3%, and overall survival of 83% to 85% for stage IA-C/grades 1 and 2 tumors within the randomized portion of the Postoperative Radiation Therapy in Endometrial Carcinoma trial.[2] Creutzberg et al[8] reported that grade 3 disease was the most important adverse prognostic factor on multivariate analysis associated with relapse and death as a result of endometrial cancer.

Although adjuvant RT has not led to clear statistically significant differences in survival end points from past randomized trials, it is significant that our population analysis reveals a benefit in both overall and relative survival for adjuvant RT in stage IC disease (grades 1 and 3-4 cohorts). It has been postulated that the lack of clear

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

survival benefit in these prior randomized trials has been due to poor accrual and insufficient patient numbers at the time of analysis. As described above, RT has been shown in numerous phase 3 trials of early stage endometrial cancer to improve both the local and regional control of tumor.[1-3,5,9,17] In addition, the study by Creutzberg et al[8] reported that the disease-free and overall survival rates of patients with stage IC/grade 3 endometrial cancer are heavily influenced by the increased risk of distant relapse rates. Due to this risk and in an attempt to control distant disease, several groups are currently performing randomized phase 3 trials to compare outcomes for patients with high-risk disease with adjuvant chemotherapy and RT vs adjuvant RT alone (stage IC/grade 3, stages II and III, and/or papillary serous or clear-cell histology). In addition, 2 randomized trials have been completed evaluating the efficacy of chemotherapy in the adjuvant setting. The study by Morrow et al[18] reported no benefit to adding single-agent doxorubicin in the postoperative setting. Multiagent chemotherapy has also been shown to be of benefit in those women with metastatic endometrial carcinoma.[19] Given that our analysis as well as other analyses have revealed that advanced age is a strong adverse prognostic factor,[1,2,4,20] it would seem that this would lead to relatively favorable patients being studied on chemotherapy trials; one should be aware of potential selection bias.

Several limitations of this US population-based study must be considered. Although there is a reported 97.5% ascertainment at the participating SEER sites, these sites only comprise approximately 10% of the US population.[11] In addition, specific clinical and pathological data known to be of prognostic significance are not readily available, including information regarding lymphovascular invasion, precise depth of myometrial invasion, lower uterine segment involvement, or specifics of RT, such as radiation dose, field sizes, and compliance with therapy.[10] Therefore, we were unable to adjust for these factors in our analyses. Our results reveal a statistical association between adjuvant RT and survival; however, these data do not prove a causal relationship. We observed an improvement in survival for stage IC/grade 1 and stage IC/grades 3 and 4 but not for stage IC/grade 2, which may be due to the relatively small sample size in each subgroup or due to inherent difficulties assigning grade. In addition, the SEER database does not record history of treatment failure (whether local-regional or distant spread) or time of relapse. The lack of these data prevent SEER population analyses from containing an event-free survival component. Individual data on socioeconomic status were not analyzed in our study and may play a role in patient outcomes. However, due to recent collaborations by the NCI with the Census Bureau, the National Heart, Lung, and Blood Institute, the National Institute on Aging, and the National Center for Health Statistics, an analysis of socioeconomic status using SEER data are possible. The SEER project has been formulated to allow future researchers to more comprehensively analyze race/ethnicity, socioeconomic, and treatment differences in cancer outcomes for major cancer sites.[21]

Our study is an observational study in which patients were not randomized to whether or not to receive radiation. The choice was made based on the patient's clinical status and the treating physician's beliefs and judgment. It would be tempting to include all possible influences affecting survival and the decision to administer RT in a model; however, having too many covariates reduces the power for the main comparison of interest. Thus, we try to strike a balance between including too many factors in the analyses and biasing our conclusions. The factors affecting the postdiagnosis survival can be of several types: those that affect survival but do not contribute to the decision whether to administer RT, known factors that affect both survival and the decision to administer RT, or unknown or unmeasured factors that affect both survival and the decision to administer RT. For those factors that affect survival but do not contribute to the decision whether to administer RT and the effect of which does not change if RT is administered or vice versa (factors that affect the decision to give RT but do not affect survival independently of other covariates included in the analysis), the omission of such factors reduces the precision of the estimates of the effect of radiation; however, it does not bias the results. We believe geographical differences are included in the latter category. When the known factors that affect both survival and the decision to administer RT are included in the model, the estimated effect of radiation is adjusted for such factors, as long as the model adequately captures the effect of the variable. T stage, grade, race, age at diagnosis, and history of surgical lymph node examination belong in this category. The most difficult type to deal with is unknown or unmeasured factors that affect both survival and the decision to administer RT. We believe that the general tendency would be to treat more advanced cases using RT, thus confounding poorer prognosis with the effect of radiation and biasing our results against RT. Therefore, any findings of beneficial effect of RT are likely to be real (if underestimated), although findings of no effect are less conclusive.

As the largest reported population analysis to our knowledge of adjuvant RT in early stage endometrial adenocarcinoma to date, it is significant that our study reveals a benefit in overall and relative survival for adjuvant RT in stage IC/grade 1 and stage IC/grades 3 and 4 disease. This information should be added to previous articles in the literature that confirm beneficial effects of adjuvant RT on both local and distant tumor control for certain patient cohorts.

Endometrial cancer remains the most common gynecological malignancy in the United States. Statistical analysis cannot replace clinical judgment when considering the individual patient, tumor characteristics, and the potential risks and benefits of adjuvant RT. Hope-

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

fully, appropriate adjuvant RT will be used to decrease the death rate from this most common of gynecological malignancies. Future work is needed to continue to delineate clinical and biological factors that can guide treatment and account for disparities in outcome between varied subsets of patients.

Author Contributions: Dr Gaffney had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lee, Gaffney.
Acquisition of data: Lee, Szabo.
Analysis and interpretation of data: Lee, Szabo, Shrieve, Macdonald, Gaffney.
Drafting of the manuscript: Lee, Szabo, Macdonald.
Critical revision of the manuscript for important intellectual content: Lee, Shrieve, Macdonald, Gaffney.
Statistical analysis: Szabo.
Obtained funding: Szabo.
Administrative, technical, or material support: Lee.
Study supervision: Lee, Shrieve, Gaffney.
Financial Disclosures: None reported.
Funding/Support: This study was supported in part by grant 2P30CA042014-17 from the Cancer Center Support.
Role of the Sponsor: The Cancer Center Support did participate in the collection, analysis, and interpretation of the data of this manuscript.

REFERENCES

1. 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;56:419-427.
2. 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;355:1404-1411.
3. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. *Gynecol Oncol*. 2003;89:201-209.
4. 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;39:413-418.
5. 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;70:247-254.
6. 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;38:99-104.
7. 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;66:1133-1138.
8. 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;22:1234-1241.
9. 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;92:744-751.
10. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1999), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Available at: http://seer.cancer.gov/publicdata/. Accessed May 6, 2005.
11. Surveillance, Epidemiology, and End Results (SEER) Program Web site. Data quality. Available at: http://seer.cancer.gov/about/quality.html. Accessed May 6, 2005.
12. Piercy C, Van Holten V, Muir C. *International Classification of Diseases for Oncology*. 2nd ed. Geneva, Switzerland: World Health Organization; 1990.
13. SEER*Stat Version 4.2. Bethesda, Md: National Cancer Institute; 2002. Available at: http://seer.cancer.gov/seerstat. Accessed May 6, 2005.
14. Andersen PK, Borch-Johnsen K, Deckert T, et al. A Cox regression model for the relative mortality and its application to diabetes mellitus survival data. *Biometrics*. 1985;41:921-932.
15. The R Project for Statistical Computing. R version 2.1.0. Vienna, Austria: R Foundation for Statistical Computing; 2005. Available at: http://www.r-project.org. Accessibility verified December 20, 2005.
16. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group Study. *Cancer*. 1987;60(8 suppl):2035-2041.
17. Meerwaldt JH, Hoekstra CJ, van Putten WL, et al. Endometrial adenocarcinoma, adjuvant radiotherapy tailored to prognostic factors. *Int J Radiat Oncol Biol Phys*. 1990;18:299-304.
18. Morrow CP, Bundy BN, Homesley HD, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1990;36:166-171.
19. Aapro MS, van Wijk FH, Bolis G, et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. *Ann Oncol*. 2003;14:441-448.
20. 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;40:55-65.
21. National Cancer Institute Cancer Control and Population Sciences. Ecological surveillance.**d** Available at: http://surveillance.cancer.gov/disparities/socioecon/ecologic.html. Accessed June 20, 2005.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017

Table. Annual Number of Laparoscopic Cases

	Years Since Introduction														
Procedure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cholecystectomy	16 247	93 464	270 991	363 161	354 565	348 323	331 076	333 600	327 092	316 733	319 793	346 157	351 736	360 844	358 069
Fundoplication	19	184	1613	5299	11 245	13 111	15 802	18 399	23 993	24 761	24 188	18 981	19 042		
Hysterectomy	4838	6181	13 102	38 929	44 852	41 401	42 335	48 578	68 455	60 805	60 733	64 639	69 659	71 977	76 033
Nephrectomy indication															
Cancer	35	236	215	199	283	308	563	532	701	1226	1968	4221	5093		
Benign disease	452	454	573	614	767	898	1261	1055	1947	1662	1896	2823	3388		
Donor	11	4	19	21	40	154	473	449	510	1589	1305	1648	1789		

Critical revision of the manuscript for important intellectual content: Miller, Dunn, Wei, Hollenbeck.
Statistical analysis: Dunn.
Obtained funding: Hollenbeck.
Administrative, technical, or material support: Hollenbeck.
Study supervision:, Wei, , Hollenbeck.
Financial Disclosures: None reported.
Funding/Support: Dr Miller is supported by grant NIH-1-T-32 DKO7782 (DCM), a clinical research training grant, from the National Institute of Diabetes and Digestive and Kidney Diseases.
Role of the Sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

1. Best S, Ercole B, Lee C, Fallon E, Skenazy J, Monga M. Minimally invasive therapy for renal cell carcinoma: is there a new community standard? *Urology*. 2004;64:22-25.
2. Dunn MD, Portis AJ, Shalhav AL, et al. Laparoscopic versus open radical nephrectomy: a 9-year experience. *J Urol*. 2000;164:1153-1159.
3. Huynh PN, Hollander JB. Trends toward laparoscopic nephrectomy at a community hospital. *J Urol*. 2005;173:547-551.
4. Agency for Healthcare Research and Quality. *Healthcare Cost and Utilization Project: Nationwide Inpatient Sample*. Rockville, Md: Agency for Healthcare Research and Quality; 2005.
5. Rudich SM, Marcovich R, Magee JC, et al. Hand-assisted laparoscopic donor nephrectomy: comparable donor/recipient outcomes, costs, and decreased convalescence as compared to open donor nephrectomy. *Transplant Proc*. 2001;33:1106-1107.
6. Johnson N, Barlow D, Lethaby A, Tavender E, Curr L, Garry R. Methods of hysterectomy: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2005;330:1478-1485.
7. Miller DC, Taub DA, Dunn RL, Wei JT, Hollenbeck BK. Laparoscopy for renal cell carcinoma: diffusion versus regionalization? *J Urol*. In press.
8. Escarce JJ. Externalities in hospitals and physician adoption of a new surgical technology: an exploratory analysis. *J Health Econ*. 1996;15:715-734.

CORRECTIONS

Incorrect Unit of Measure: In the Original Contribution entitled "Effect of 6-Month Calorie Restriction on Biomarkers of Longevity, Metabolic Adaptation, and Oxidative Stress in Overweight Individuals: A Randomized Controlled Trial" published in the April 5, 2006, issue of *JAMA* (2006;295:1539-1548), an incorrect unit of measure was given for dehydroepiandrosterone sulfate (DHEAS). On page 1543 (Table 1) and page 1544 (Figure 3), the unit of measure for DHEAS should be μg/dL (not ng/mL).

Error in Byline: In the Original Contribution entitled "Incidence and Prognostic Implications of Stable Angina Pectoris Among Women and Men" published in the March 22/29, 2006, issue of *JAMA* (2006;295:1404-1411), the byline contained an incorrect academic degree. Alison McCallum should have been listed as having an MBChB, FFPH.

Incorrect Data: In the Original Contribution entitled "Frequency and Effect of Adjuvant Radiation Therapy Among Women With Stage I Endometrial Adenocarcinoma" published in the January 25, 2006, issue of *JAMA* (2006;295:389-397), incorrect data were reported in the "Results" section of the article. On page 391, the sentence "Within the RT cohort, 2551 patients (62.5%) had external beam radiation, 732 (17.9%) had vaginal brachytherapy, and 1078 (26.4%) received a combination of external beam radiation with vaginal brachytherapy" should have read "Within the RT cohort, 2378 patients (58.3%) received external beam radiation, 962 (23.6%) received external beam and brachytherapy radiation, 654 (16.0%) received brachytherapy radiation alone, and for 86 (2.1%) the radiation modality was not specified." The authors verified that this error did not have an impact on the data set or subsequent statistical analyses.

Incorrect Statements on Funding/Support and Role of the Sponsors and Incorrect and Incomplete Financial Disclosures: In the Review entitled "Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials" published in the May 17, 2006, issue of *JAMA* (2006;295:2275-2285), the following errors appeared:

After this issue was printed and mailed, *JAMA* was informed by the authors that information reported on page 2284 of the article was incorrect.

The Funding/Support statement should have read "This study was supported by the Mayo Foundation. Additional data were provided by Abbott and Centocor. Data provided by Abbott were subject to a confidentiality agreement."

The Role of the Sponsors statement should have read "Abbott and Centocor did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation or approval of the manuscript. The manuscript was sent to Abbott for review prior to submission for publication."

The Financial Disclosures statement should have read: "Dr Bongartz reported that he has given lectures for Abbott as part of seminars for study nurses and received honorarium in the form of a medical textbook for the Internal Medicine library; he received an educational grant from Amgen in February 2006 to perform the same type of analysis of harmful events under anti-TNF treatment for etanercept; and he received the 2005 Fellow's Award of the American College of Rheumatology, which was supported by Amgen."

Dr Matteson reported that he has been a paid consultant for Centocor for work unrelated to this study and has been working with Wyeth and Amgen to perform a similar analysis for etanercept; he has been an Investigator for the American College of Rheumatology, Amgen, Asta, Biogen-IDEC, Burroughs-Wellcome, Centocor, Cypress, Endocyte Inc, Genentech, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Nastech, Pharmacia & Upjohn, Schering, Wyeth, and Xoma Corp; he has received grant support from Amgen, Aventis, Centocor/Johnson & Johnson, Genentech, Immunex, Mayo Foundation, Novartis, and the National Institutes of Health; and he has been a consultant for Amgen, BoneandJoint.org, Burroughs-Wellcome, Centocor, Regeneron, Takeda, Upjohn, Watermark Research, and the Vasculitis Foundation."

This correction was published online on May 16, 2006. Because of the nature and extensiveness of this incorrect and incomplete reporting, *JAMA* has requested that the Mayo Clinic College of Medicine conduct an investigation. *JAMA* will publish another correction or clarification once the results of that investigation become available.

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/30/2017