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A proposal for a new classification of "unfavorable risk criteria" in patients with stage I endometrial cancer

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HIGHLIGHTS

- We compared PORTEC-1 and GOG-99 risk classification systems for high-intermediate risk stage I endometrial cancer.
- Adjuvant radiation is associated with improved survival in patients meeting GOG alone but not PORTEC alone criteria.
- We propose a unified definition of "unfavorable risk": ≥2 factors of LVSI, age ≥70, grade 2-3 disease, and FIGO stage IB.

ABSTRACT

Background Randomized trials describe differing sets of high–intermediate risk criteria.

Objective To use the National Cancer Database to compare the impact of radiation therapy in patients with stage I endometrial cancer meeting different criteria, and define a classification of "unfavorable risk."

Methods Patients with stage I endometrial cancer between January 2010 and December 2014 were identified in the National Cancer Database and stratified into two cohorts: (1) patients meeting Gynecologic Oncology Group (GOG)-99 criteria only for high–intermediate risk, but not Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 criteria and (2) those meeting PORTEC-1 criteria only. High-risk stage I patients with both FIGO stage IB (under FIGO 2009 staging) and grade 3 disease were excluded. In each cohort, propensity score-matched survival analyses were performed. Based on these analyses, we propose a new classification of unfavorable risk. We then analyzed the association of adjuvant radiation with survival, stratified by this classification.

Results We identified 117,272 patients with stage I endometrial cancer. Of these, 11,207 patients met GOG-99 criteria only and 5,920 patients met PORTEC-1 criteria only. After propensity score matching, adjuvant radiation therapy improved survival (HR=0.73; 95% CI 0.60 to 0.89; p=0.002) in the GOG-99 only cohort. However, there was no benefit of adjuvant radiation (HR=0.89; 95% CI 0.69 to 1.14; p=0.355) in the PORTEC-1 only cohort. We, therefore, defined unfavorable risk stage I endometrial cancer as two or more of the following risk factors: lymphovascular invasion, age ≥70, grade 2–3 disease, and FIGO stage IB. Adjuvant radiation improved survival in stage I patients with adverse risk factors (HR=0.74; 95% CI 0.68 to 0.80; p<0.001), but not in other stage I patients (HR=1.02; 95% CI 0.91 to 1.15; p=0.710; p interaction <0.001).

Conclusion Our study showed that adjuvant radiation was associated with an overall survival benefit in patients meeting GOG-99 criteria only; however, no survival benefit was seen in patients meeting PORTEC-1 criteria only. We propose a definition of unfavorable risk stage I endometrial cancer: ≥2 risk factors from among lymphovascular invasion, age ≥70, grade 2–3 disease, and FIGO stage IB disease.

IINTRODUCTION

Endometrial cancer is the most commonly diagnosed cancer of the female reproductive system in North America and Europe, affecting 63,000 women in the United States and an estimated 319,600 women globally each year.[1 2] Stage I endometrial cancer has a favorable prognosis, and surgical resection with hysterectomy is considered the standard of care.[3–5] Several clinical trials have investigated the role of adjuvant radiation therapy after hysterectomy, demonstrating improved loco-regional control in stage I patients with adverse risk factors.[6–8] Both the Gynecologic Oncology Group (GOG)–99 and Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)–1 trials defined a 'high–intermediate risk' group. However, there are differences between these two trials in the specific risk factors used. GOG-99 uses three risk factors: lymphovascular space invasion, outer third myometrial invasion, and grade 2–3 histology. High–intermediate risk was defined as age ≥70 years with one risk factor, age 50–69 with two risk factors, or any age with three risk factors.[9] The PORTEC-1 definition is two of the following three factors: age >60, more than one half myometrial invasion, and grade 3 disease.[10]

Owing to the inconsistent definition of high–intermediate risk, consensus guidelines have varying recommendations for patient selection for adjuvant radiation. In general, guidelines recommend consideration of adjuvant brachytherapy in stage I disease based on the depth of myometrial invasion, grade, and additional risk factors. The National Comprehensive Cancer Network (NCCN) includes lymphovascular space invasion, age, tumor size, and lower uterine segment invasion as additional risk factors.[3] The American Society for Therapeutic Radiation Oncology

(ASTRO) guideline specify age >60 and lymphovascular invasion as adverse risk factors.[11 12] However, there is no single standard for risk criteria used in guidelines.

Although these GOG-99 and PORTEC-1 risk definitions have considerable overlap, a significant proportion of patients qualify as high–intermediate risk under one set of criteria but not the other. To our knowledge, no published studies have investigated adjuvant radiation in these subsets of patients. Therefore, we used the National Cancer Database to define two cohorts for survival analysis: (1) patients meeting the GOG-99 but not the PORTEC-1 high–intermediate risk criteria, and (2) patients meeting the PORTEC-1 but not the GOG-99 criteria. We used the results of this analysis to elucidate limitations of current criteria and form the basis of a set of unified criteria for classifying unfavorable risk stage I endometrial cancer.

METHODS

The National Cancer Database is a national oncology database sponsored by the American College of Surgeons and the American Cancer Society. It includes patient data from over 1,500 accredited facilities and captures >70% of newly diagnosed cancer cases in the United States.[13] The data used in the study are derived from a de-identified file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the methodology used or the conclusions drawn from these data by the investigators.

Using the National Cancer Database, a total of 242,172 patients diagnosed with endometrial cancer between January 2010 and December 2014 were identified. Patients were excluded if they did not undergo hysterectomy, had metastatic disease at presentation, non-endometrioid histology, or stage II–IV disease under the international Federation of Gynecology and Obstetrics (FIGO) 2009 staging system.[14] Additionally, patients with high-risk stage I disease (both grade 3 and FIGO stage IB) were excluded from all analyses, as these patients were excluded from the PORTEC trials and may be offered systemic therapy based on contemporary guidelines.[8 10] Additional exclusion criteria included metastatic or nodal disease, positive margins, unknown receipt of radiation/chemotherapy/surgery, neoadjuvant therapy, and <3 months' follow-up. Lymphovascular invasion was recorded in the National Cancer Database starting in 2010.

PORTEC-1 and GOG-99 high–intermediate risk cohorts were defined according to the original published risk factors. Of note, we use a modified set of GOG-99 criteria for analysis in this study. The original GOG-99 criteria specify outer one-third myometrial invasion, but exact depth of myometrial invasion is not available in the National Cancer Database. Instead, we use FIGO stage IB disease (myometrial invasion ≥50%) similar to GOG-249. These criteria were applied to patients regardless of receipt of lymphadenectomy, and those with pathologic nodal disease were excluded; this results in a prognostic stratification effect[15] and differs from the original PORTEC-1 trial which disallowed lymph node dissection,[10] but is felt to more accurately reflect contemporary practice.

We then defined two cohorts: (1) patients meeting only the modified GOG-99 definition and (2) patients meeting only the PORTEC-1 definition. Figure 1 depicts a diagram summarizing the exclusion criteria and selection of cohorts, which were then stratified by receipt of radiation. Patients receiving any radiation, including brachytherapy, external beam radiation therapy, or both, were considered as receiving radiation, given non-inferiority of vaginal brachytherapy in PORTEC-2.[8] All variables were selected *a priori*. Demographic variables, including age, year of diagnosis, race/ethnicity, insurance status, facility type, and region, were defined according to the data dictionary.[16 17]

For pathologic factors, FIGO stage was defined according to the site-specific factor FIGO stage, extension, and pathologic tumor node metastasis (TNM) fields. Lymphovascular invasion and grade were coded according to the corresponding site-specific factors. Non-endometrioid histologies were excluded using the International Classification of Diseases for Oncology, third edition codes.[18] Missing values for the key risk factors were imputed using multiple imputation with chained equations.[19] For treatment variables, receipt of external beam radiation and brachytherapy were defined by the corresponding codes found under regional or boost modality. Sequencing of treatment was determined according to the corresponding codes of surgery and radiation sequence.

Statistical Analysis

Descriptive statistics were calculated for each patient cohort. Overall survival was plotted using the Kaplan-Meier method with differences across groups assessed using the log-rank statistic. Survival time was calculated from the date of diagnosis until the date of death or last contact if alive. Living patients were censored at the last contact date. Survival analyses were performed using the log-rank test and Cox proportional hazards regression. The final parsimonious multivariate Cox model was formed using hierarchical backwards selection at a significance level of $p<0.10$. The proportional hazards assumption was assessed for the final variables and was not violated.[20] Within each cohort, logistic regression was performed using receipt of adjuvant radiation as the outcome variable, with all factors included regardless of statistical significance. This was used to generate propensity scores. Propensity score-matched analysis was performed to compare survival for patients receiving versus not receiving adjuvant radiation. One-to-one nearest neighbor matching without replacement, using caliper width 0.10, was performed to form the final propensity-matched cohort. The propensity score was stratified into quintiles and a standardized difference between the treatment groups of <0.10 was validated. Statistical analyses were performed using the R statistical environment (version 3.4.2; R Core Team 2017).

Based on the results of the propensity score-matched analyses, we proposed a unifying definition of high–intermediate risk criteria—namely, at least two of the following four risk factors: lymphovascular invasion, age ≥70, grade 2 or 3 disease, and FIGO stage IB disease. Using the same exclusion criteria described previously, we divided stage I patients (excluding high-risk patients both FIGO IB and grade 3) into unfavorable risk and favorable risk subsets and performed Cox proportional hazards regression in each subset. Concordance indices were estimated by generating separate Cox models for each risk definition and using bootstrapping with 200 re-samples.

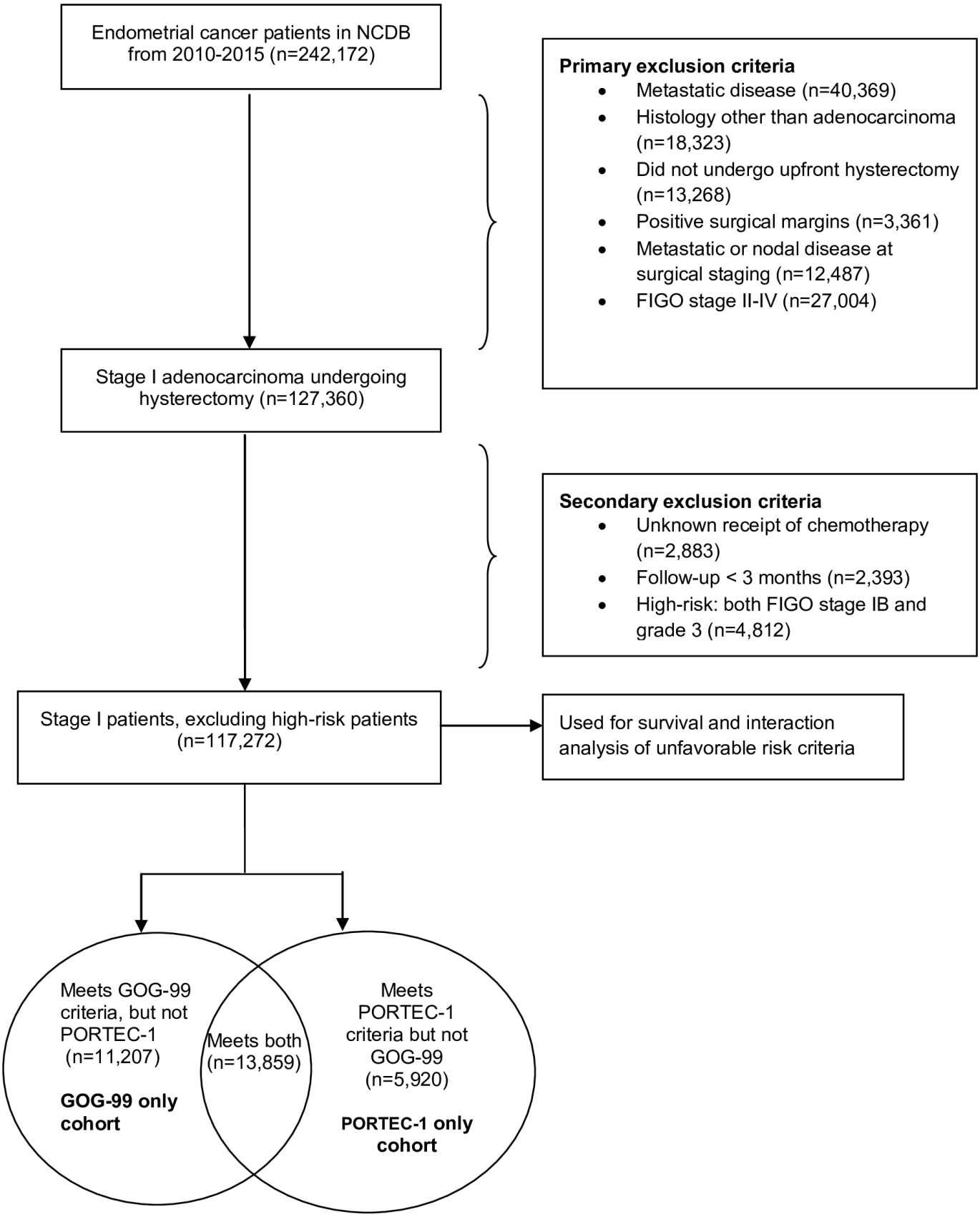

Figure 1 Diagram illustrating exclusion criteria and case selection for patient cohort. GOG-99, Gynecologic Oncology Group trial 99; HIR, high–intermediate risk; LVSI, lymphovascular space invasion; NCDB, National Cancer Database; PORTEC-1, Post-Operative Radiation Therapy in Endometrial Carcinoma study 1.

Table 1 Baseline characteristics of patients in the two analytic cohorts. GOG-99 only indicates patients meeting only the GOG-99 high–intermediate risk criteria; PORTEC-1 indicates patients meeting only the PORTEC-1 high–intermediate risk criteria.

	GOG-99 only (n=11,207) No. (%)	PORTEC-1 only (n=5,920) No. (%)
Sociodemographic factors		
Year of diagnosis		
2010	1589 (14.2)	804 (13.6)
2011	1653 (14.7)	883 (14.9)
2012	1870 (16.7)	964 (16.3)
2013	1950 (17.4)	1004 (17.0)
2014	2040 (18.2)	1128 (19.1)
2015	2105 (18.8)	1137 (19.2)
Age		
≤60 years	3755 (33.5)	0 (0.0)
>60 years	7452 (66.5)	5920 (100.0)
Charlson-Deyo co-morbidity score		
0	8092 (72.2)	4332 (73.2)
1	2473 (22.1)	1275 (21.5)
≥2	642 (5.7)	313 (5.3)
Race/ethnicity		
Non-black	10266 (91.6)	5062 (85.5)
Black	862 (7.7)	784 (13.2)
Unknown	79 (0.7)	74 (1.3)
Insurance status		
Government	7029 (62.7)	3173 (53.6)
Private	3807 (34.0)	2517 (42.5)
Uninsured	265 (2.4)	156 (2.6)
Unknown	106 (0.9)	74 (1.3)
Facility type		
Academic	6288 (56.1)	3335 (56.3)
Community/ comprehensive community	4901 (43.7)	2585 (43.7)
Unknown	18 (0.2)	0 (0.0)
Facility location		
Midwest	3004 (26.8)	1608 (27.2)
Northeast	5201 (46.4)	2780 (47.0)
South	1405 (12.5)	656 (11.1)
West	1579 (14.1)	876 (14.8)
Unknown	18 (0.2)	0 (0.0)
Pathological factors		
FIGO stage		
IA	8733 (77.9)	3611 (61.0)
IB	2474 (22.1)	2309 (39.0)
Lymphovascular invasion		
No	7138 (63.7)	5920 (100.0)
Yes	4069 (36.3)	0 (0.0)
Histologic grade		
Grade 1	721 (6.4)	2309 (39.0)
Grade 2	10007 (89.3)	0 (0.0)
Grade 3	479 (4.3)	3611 (61.0)
Treatment factors		
Received radiation therapy		
No	7414 (66.2)	3382 (57.1)
Yes	3793 (33.8)	2538 (42.9)
Radiation therapy modality		
Brachytherapy alone	2981 (26.6)	2115 (35.7)
External beam therapy alone	532 (4.7)	282 (4.8)
External beam and brachytherapy	280 (2.5)	141 (2.4)
No radiation	7414 (66.2)	3382 (57.1)
Received chemotherapy		
No	10302 (91.9)	4340 (73.3)
Yes	905 (8.1)	1580 (26.7)
Received lymph node dissection		
No	2376 (21.2)	995 (16.8)
Yes	8820 (78.7)	4916 (83.0)
Unknown	11 (0.1)	9 (0.2)

RESULTS

A total of 11,207 patients at a median follow-up of 42 months (IQR 25–54) were identified who met modified GOG-99 criteria only, and 5,920 patients at a median follow-up of 41 months (IQR 26–55) who met PORTEC-1 criteria only. The demographic, pathologic, and treatment characteristics of these patient cohorts are summarized in Table 1. The modified GOG-99 only cohort contains predominantly patients with grade 2 disease (89.3%) with other risk factors such as lymphovascular invasion, age, and myometrial invasion. The PORTEC-1 only cohort comprised patients in the age 60–70 range with a single risk factor (100%).

Survival Analysis in the GOG-99 Only Cohort

In the modified GOG-99 only cohort, 33.8% of patients received radiation therapy. The 5-year overall survival was 87.6% in patients receiving radiation compared with 83.3% in patients not receiving radiation (log-rank p<0.001; Figure 2A). We then performed multivariate survival analysis using Cox proportional hazards regression (Table 2). After adjustment in multivariate analysis, receipt of adjuvant radiation remained a statistically significant predictor of overall survival (HR=0.85; 95% CI 0.72 to 1.00; p=0.048). Charleson-Deyo co-morbidity score, age >60, race other than white, treatment at a community center, government insurance, and lack of lymph node

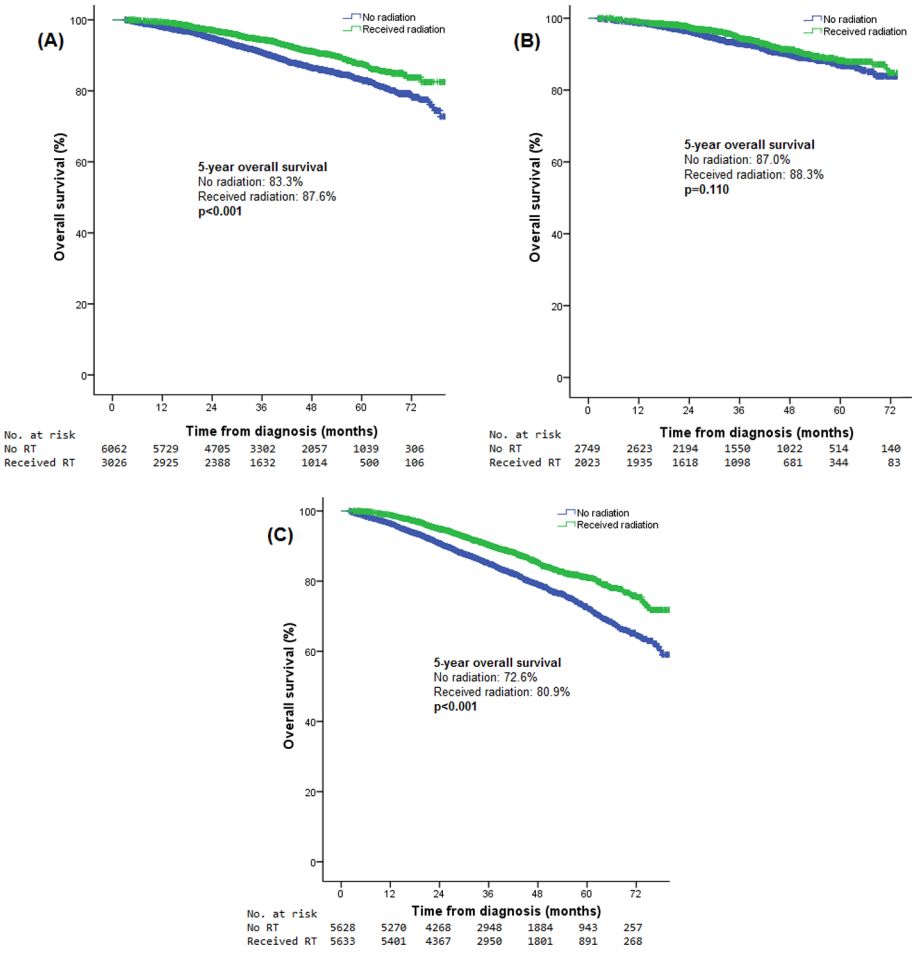

Figure 2 Survival analysis of patients treated with or without adjuvant radiation therapy. (A) Kaplan-Meier curves in the GOG-99 only cohort. (B) Kaplan-Meier curves in the PORTEC-1 only cohort. (C) Kaplan-Meier curves in patients meeting both GOG-99 and PORTEC-1 criteria. GOG-99, Gynecologic Oncology Group trial 99; PORTEC-1, Post-Operative Radiation Therapy in Endometrial Carcinoma study 1; RT, radiation therapy.

dissection were associated with worse survival. Propensity score matching was performed, adjusting for use of radiation. In the final matched cohort, the receipt of adjuvant radiation was associated with improved overall survival compared with hysterectomy alone by log-rank test (p<0.001) and on univariate Cox regression (HR=0.73; 95% CI 0.60 to 0.89; p=0.002). We additionally performed a sensitivity analysis using inclusion criteria more closely approximating the original GOG-99 study: we included patients with FIGO stage IB and grade 3 disease and required all patients to have undergone nodal staging. In 8,809 such patients, radiation therapy was similarly associated with a survival benefit (HR=0.83; 95% CI 0.71 to 0.98; p=0.029).

Survival Analysis in the PORTEC-1 Only Cohort

We then repeated the analysis with similar methodology in the PORTEC-1 only cohort. Of 5,920 patients, 42.9% received adjuvant radiation. There was no significant difference in survival; the 5-year overall survival was 88.3% in patients receiving radiation compared with 87.0% in patients not receiving radiation (log-rank p=0.110, Figure 2B). Table 3 demonstrates the results of Cox proportional hazards regression. Similar factors were associated with survival in this cohort; however, there was no statistically significant survival benefit associated with receipt of adjuvant radiation (HR=0.86; 95% CI 0.70–1.06; p=0.166). There was no significant survival benefit seen after propensity score matching with either log-rank test (p=0.110) or univariate Cox regression (HR=0.89; 95% CI 0.69 to 1.14; p=0.355). In 13,859 patients meeting both PORTEC-1 and GOG-99 criteria, 6,779 patients (48.9%) received adjuvant radiation. The 5-year overall survival was 80.9% with adjuvant radiation versus 72.6% without radiation (log-rank p<0.001; Figure 2C).

Unified Classification of Stage I High–Intermediate Risk

We summarize the results of the two propensity score-matched analyses as follows. In the modified GOG-99 only cohort, comprising predominantly higher-risk grade 2 patients, adjuvant radiation was associated with a survival benefit. In the PORTEC-1 only cohort, composed of patients age 60–70 with a single risk factor, adjuvant radiation was not associated with survival benefit. We thus use the principles of (1) including higher-risk grade 2 patients and (2) excluding lower risk patients age 60–70 as the basis for a set of unifying risk criteria. Our proposed definition of unfavorable risk stage I endometrial cancer is at least two risk factors from among lymphovascular invasion, age ≥70, grade 2–3 disease, and FIGO stage IB disease (online supplementary table 1). We applied this definition to a cohort of 117,272 patients with stage I endometrial adenocarcinoma. Of these, 25,691 patients (21.9%) met our

Table 2 Multivariable COX proportional hazards model in patients meeting Gynecologic Oncology Group trial 99 (GOG-99) criteria only.

Significant factors	Hazard of death (95% CI)	P value
Age		
≤60 years	Reference	<0.001*
>60 years	1.57 (1.27 to 1.94)	
Charlson-Deyo co-morbidity score		
0	Reference	<0.001*
1	1.38 (1.19 to 1.60)	<0.001*
≥2	1.85 (1.47 to 2.32)	
Race		
Non-black	Reference	<0.001*
Black	1.65 (1.35 to 2.01)	0.804
Unknown	1.11 (0.50 to 2.47)	
Insurance status		
Government	Reference	0.001*
Private	0.72 (0.59 to 0.88)	0.543
Uninsured	0.86 (0.53 to 1.39)	0.468
Unknown	0.76 (0.36 to 1.60)	
Facility type		
Academic	Reference	0.016*
Community	1.17 (1.03 to 1.34)	
Lymphovascular space invasion		
No	Reference	0.030*
Yes	1.18 (1.02 to 1.38)	
Lymph node dissection performed		
No	Reference	<0.001*
Yes	0.62 (0.54 to 0.72)	
Radiation therapy received		
No	Reference	0.048*
Yes	0.85 (0.72 to 1.00)	

Table 3 Multivariable COX proportional hazards model in patients meeting Post-Operative Radiation Therapy in Endometrial Carcinoma study 1 (PORTEC-1) criteria only

Significant factors	Hazard of death (95% CI)	P value
Charlson-Deyo co-morbidity score		
0	Reference	0.157
1	1.19 (0.94 to 1.50)	0.003*
≥2	1.74 (1.21 to 2.50)	
Race		
Non-black	Reference	<0.001*
Black	1.71 (1.33 to 2.19)	0.050*
Unknown	2.02 (1.00 to 4.09)	
Insurance status		
Government	Reference	0.018*
Private	0.77 (0.62 to 0.96)	0.690
Uninsured	0.89 (0.51 to 1.56)	0.714
Unknown	1.16 (0.52 to 2.62)	
Facility type		
Academic	Reference	0.005*
Community	1.33 (1.09 to 1.63)	
Histologic grade		
Grade 1	Reference	<0.001*
Grade 3	2.36 (1.84 to 3.02)	
Lymph node dissection performed		
No	Reference	0.005*
Yes	0.69 (0.53 to 0.89)	
Radiation therapy received		
No	Reference	0.166
Yes	0.86 (0.70 to 1.06)	

proposed unfavorable risk criteria (online supplementary table 1), compared with 25,066 patients (21.4%) meeting modified GOG-99 criteria and 19,779 patients (16.9%) meeting PORTEC-1 criteria.

We then performed multivariate survival analysis on a subset of stage I patients meeting our unfavorable risk definition, and a separate subset of other stage I patients (online supplementary table 2). For the 25,691 patients meeting the unfavorable risk criteria, adjuvant radiation was associated with improved survival (HR=0.74; 95% CI 0.68 to 0.80; p<0.001). For the remaining 91,581 favorable risk patients, adjuvant radiation was not associated with improved survival (HR=1.02; 95% CI 0.91 to 1.15; p=0.710; online supplementary figure 1). The interaction term between adjuvant radiation and unfavorable risk classification was statistically significant (p<0.001).

DISCUSSION

We found that adjuvant radiation was associated with an overall survival benefit in patients meeting GOG-99 criteria only; however, no survival benefit was seen in patients meeting PORTEC-1 criteria only. We therefore proposed a set of unifying risk criteria that would better encompass the subset of higher-risk grade 2 patients. Our definition of unfavorable risk stage I endometrial cancer is two or more risk factors from among lymphovascular invasion, age ≥70, grade 2–3 disease, and FIGO stage IB disease. Our proposed unfavorable risk definition deals with several limitations in the existing classifications. The PORTEC-1 criteria do not incorporate lymphovascular invasion, which has been identified as an independent prognostic factor in numerous studies.[21–24] Bendifallah et al found that incorporation of lymphovascular invasion significantly improved prognostic accuracy; this was later validated by Korkmaz et al.[25 26] Our criteria also include higher-risk grade 2 patients who are omitted by the PORTEC-1 criteria. In comparison with the GOG-99 criteria, our proposed criteria facilitate ease of use and practical application owing to more straightforward age groupings and use of modern FIGO staging.

We noted low rates of use of adjuvant radiation therapy, with only 43.5% of patients at unfavorable risk receiving adjuvant radiation. This is concordant with several published analyses of use in endometrial cancer.[27–31] We hypothesize that inconsistent description of risk factors among guidelines may contribute to low rates of adjuvant therapy. Our definition provides a more concrete set of risk criteria compared with current guidelines. In the absence of

further randomized trials, these criteria may help to guide clinicians in selecting patients for adjuvant therapy.

Importantly, we note that our unfavorable risk definition captures a heterogeneous population, and some subsets may derive reduced or negligible benefit from adjuvant radiation. For example, patients aged >70 with grade 2 disease meet inclusion criteria for a previous trial of low-risk patients, showing similar vaginal recurrence rates with adjuvant brachytherapy versus observation.[32] Individualized, multidisciplinary discussion about adjuvant therapy will be crucial for patients with unfavorable risk criteria. One consequential point of discussion is the use of overall survival as the primary endpoint. The National Cancer Database unfortunately does not include data on loco-regional control or distant metastasis rate. Prior trials have demonstrated decreased loco-regional recurrence rates but no difference in overall survival with the addition of radiation.[9 10 15 33] However, we note that GOG-99 included only 132 patients and PORTEC-1 included only 366 patients meeting their respective definitions of high–intermediate risk,[9 10] and therefore these studies were under-powered to detect survival differences. A 2012 Cochrane meta-analysis similarly concluded that "meta-analyses of these subgroups were under-powered".[6] Our findings of a survival benefit for radiation in selected populations are consistent with multiple prior studies in stage I endometrial cancer.[30 34 35]

Our analysis is subject to the standard limitations of retrospective database studies, including inability to control for confounding factors such as lower uterine segment involvement. Additionally, lymphovascular invasion was recorded only for year of diagnosis 2010 onwards, limiting the length of follow-up. Systematic patterns in the missing data may introduce bias, which we try to mitigate using multiple imputations. Our findings are subject to immortal time bias, as patients undergoing adjuvant therapy by definition recover from hysterectomy, whereas patients who undergo surgery alone may be lost to follow-up or die during the immediate post-operative recovery period. We attempt to mitigate this using conditional landmark analysis. There is no central review mechanism within the National Cancer Database for factors such as tumor grading. Finally, our proposed unfavorable risk classification requires prospective validation in independent datasets.

In conclusion, we performed an analysis of patients meeting either only GOG-99 or only PORTEC-1 criteria for high–intermediate risk. We found that adjuvant radiation was associated with improved survival in patients meeting GOG-99 criteria only, but not in patients meeting PORTEC-1 criteria only. Based on this analysis, we proposed a unified definition of unfavorable risk stage I endometrial cancer—namely, two or more of the following four risk factors: lymphovascular invasion, age ≥70, grade 2–3 disease, and FIGO stage IB disease. We found a significant interaction between the survival impact of adjuvant radiation and unfavorable risk classification. Further studies are needed for independent validation.

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