



Patterns of adjuvant radiation usage and survival outcomes for stage I endometrial carcinoma in a large hospital-based cohort



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HIGHLIGHTS

- The NCDB was analyzed for trends in adjuvant RT usage and survival for stage I endometrial cancer.
- Increasing stage and grade were associated with increased RT usage.
- Adjuvant EBRT and VB were each associated with improved survival for stage IB disease.

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ABSTRACT

Objective. Two randomized trials have demonstrated a local control advantage in the absence of a survival advantage for the addition of adjuvant radiation therapy (RT) to surgery in patients with stage I endometrial adenocarcinoma (EC). This study analyzed the National Cancer Data Base (NCDB) to evaluate the impact of adjuvant RT on overall survival (OS) for patients with stage I EC.

Methods. Patients with EC who underwent total hysterectomy/bilateral salpingo-oophorectomy between 2004 and 2011 were queried. Only those with AJCC stage pT1N0M0 were included. Patients surviving < 4 months excluded. Adjuvant RT included external beam RT (EBRT), brachytherapy, or external RT + brachytherapy. OS was analyzed using the Kaplan–Meier method. Multivariate Cox regression analysis and propensity matched analysis were performed to assess the impact of covariates on OS.

Results. There were 61,697 patients included. Most women (83.9%) did not receive adjuvant RT. Adjuvant RT usage increased with increasing stage/grade. Usage of brachytherapy alone decreased with increasing stage/grade (78.2% for IA/G1 to 36.1% for IB/G3) corresponding to an increase in the use of EBRT (21.8% for IA/G1 to 53.9% for IB/G3). On multivariable analysis, adjuvant EBRT (HR 0.83, 95%CI 0.74–0.93, $p = 0.002$) and brachytherapy (HR 0.82, 95%CI 0.74–0.93, $p = 0.002$) were each associated with improved survival for women with stage IB. In the propensity matched cohort, RT was associated with improved survival (0.85, 95% CI 0.78–0.92, $p < 0.001$).

Conclusion. The use of adjuvant RT for women with stage I EC is highly dependent on stage/grade and is associated with improved survival for stage IB.

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1. Introduction

Endometrial cancer is the most common gynecological malignancy and fourth most common overall malignancy in women in the United States [1]. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is recommended as the primary therapy for this disease. However, despite its high prevalence, the optimal adjuvant

therapy for stage I disease has yet to be established. Current national guidelines [2] recommend adjuvant radiation (either external beam radiation therapy or vaginal brachytherapy) depending on risk stratification considering the presence of adverse risk features including older age, lymphovascular invasion, higher grade, and deeper myometrial invasion. These recommendations have been based on the results of multiple randomized trials demonstrating a local control advantage in the absence of a survival advantage for adjuvant radiation over observation [3–8].

Two risk stratification schemes have been proposed based on the results of the Post Operative Radiation Therapy in Endometrial Carcinoma

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(PORTEC)-1 trial [3–6] and the Gynecologic Oncology Group (GOG)-99 trial [7]. The PORTEC-1 trial found that age >60 years old, grade 3, and >50% myometrial invasion were significant predictors of local recurrence. The presence of at least 2 of these factors resulted in a 23.1% risk of locoregional recurrence without radiation compared to 4.6% with pelvic radiation. The GOG-99 trial identified a high-intermediate risk group defined as women with 1) histologic grade 2 or 3, lymphovascular invasion, and outer third myometrial invasion; 2) age \geq 50 years old with 2 of the above risk features; or 3) age \geq 70 years old with 1 of the above risk features. In this high-intermediate risk subgroup, adjuvant pelvic radiation decreased locoregional recurrence from 26% to 6%. However, these significant improvements in locoregional control have failed to translate into a benefit in overall survival.

Prior studies using the Surveillance, Epidemiology, and End Results (SEER) database have reported an association between adjuvant radiation therapy and improved overall survival in higher-risk subgroups of women with stage I endometrial cancer [9–10]. The purpose of this study was to analyze the National Cancer Data Base (NCDB) to evaluate the impact of adjuvant radiation therapy on survival of patients with stage I endometrial cancer.

2. Methods

The NCDB is a hospital-based registry that is the joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is estimated that 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. Exemption was obtained from the New York Harbor Veterans Affairs Committee for Research and Development prior to the initiation of this study.

Women who were diagnosed with non-metastatic uterine adenocarcinoma and underwent total hysterectomy/bilateral salpingo-oophorectomy between 2004 and 2011 were included in this study. Based on the pathologic extent of invasion coding in by the NCDB, women were grouped into American Joint Committee on Cancer 7th edition TNM staging. Histologies included consisted only of endometroid adenocarcinoma (ICD-0-3 8380) and adenocarcinoma not otherwise specified (ICD-0-3 8140). All other histologies, such as clear cell, serous, and carcinosarcoma, were excluded. Those women staged as pT1N0M0 were included. Those who had no lymph nodes removed or those for whom it was unknown whether lymph node sampling or dissection was performed were excluded. All women had to have complete data regarding the grade of their disease as well as whether or not they were treated with radiation therapy. In addition, in order to account for immortal time bias [11], women who survived <4 months after diagnosis were excluded. Data regarding radiation usage were collected. Women were identified as having undergone no radiation therapy, postoperative external beam radiation therapy alone, postoperative brachytherapy alone, or postoperative external beam radiation therapy with brachytherapy boost. Those who were identified as receiving radiation to sites other than the pelvis or uterus were excluded.

Clinical, pathologic, and demographic details were compared between patients who received no further treatment and those who received postoperative radiation. Patient characteristics were compared via a Chi Square, Fisher's Exact test, and Mann Whitney test where appropriate. Kaplan Meier analyses of overall survival (OS) were performed comparing patients who received postoperative radiation with those who did not. Subgroup analysis was performed comparing different types of radiation therapy (external beam radiation or brachytherapy) by stage/grade of disease. For multiple subgroup comparisons between treatment cohorts, Bonferroni correction was utilized resulting

in an adjusted p-value < 0.0042. Chemotherapy was utilized in 1.6% of all patients, but 6.1% of those with IB grade 3 disease. Therefore, an additional subgroup analysis in IBG3 disease was performed in regards to the effect of chemotherapy on survival. Otherwise, chemotherapy use was not explicitly studied but was included as part of the multivariable analysis. Univariable and multivariable Cox regression were performed to determine their effects on survival. Due to the dramatic imbalances in treatment selection between T1a versus T1b disease, separate multivariable analysis were performed for pT1a and for pT1b disease. The variables measured included age (continuous), year of diagnosis (2004–2005, 2006–2007, 2008–2009, 2010–2011), race (white, black, other), receipt of radiation (none, external beam radiation, vaginal brachytherapy), receipt of chemotherapy (yes, no), pathologic grade of disease (1, 2, or 3), number of lymph nodes examined (1–9, \geq 10), modified Charlson/Deyo score (0, 1, \geq 2), and insurance status (no insurance, private insurance, Medicare, Medicaid, Other/Unknown). A secondary multivariable analysis was performed on a propensity score matched subpopulation, controlling for the variables noted above. A nearest neighbor matching algorithm was used with a caliper of 0.001. Data regarding local control and cause of death are not available in the NCDB. Significant values were defined as those with a p-value <0.05. Statistical analysis was performed using SPSS, Version 23 (IBM Inc., Armonk, NY).

3. Results

There were 61,697 women included in this study. The median age was 61 years (interquartile range 55–69 years) and the median follow-up was 48.7 months (interquartile range 28.8–71.4 months). The median number of lymph nodes removed was 12 (interquartile range 7–20). The most common pathologic stage was pT1a grade 1 (IAG1), consisting of 25,999 women (42.1%), followed by pT1a grade 2 (IAG2) with 17,721 women (28.7%). Most women (83.9%) did not receive adjuvant radiation. However, radiation utilization increased with increasing stage/grade ($p < 0.001$). Radiation therapy was utilized in less than 50% of women of all stage/grade groups except for those with IBG3 disease, for whom radiation was delivered 57% of the time. More recent year of diagnosis was associated with a small decrease in receipt of adjuvant radiation. A summary of the patient characteristics and comparisons between those who did or did not receive adjuvant radiation is available in Table 1.

For those who did receive adjuvant radiation, vaginal brachytherapy alone was utilized 78% of the time for those with stage IAG1–2 disease. The utilization of vaginal brachytherapy alone decreased with increasing stage, corresponding to an increase in the utilization of pelvic external beam radiotherapy \pm brachytherapy boost. However, vaginal brachytherapy alone remained the most commonly utilized treatment for all stages/grades except for IBG3, for whom it was only utilized 36.1% of the time. Table 2 includes radiation usage by stage and grade in more detail.

3.1. Overall survival

The impact of adjuvant radiation therapy was found to be highly dependent on the stage. There was no survival difference for those with stage IA disease whereas for those with stage IB disease the use of adjuvant radiation therapy was associated with increased overall survival, with an absolute improvement of 3.4–5.2% at 5 years (Fig. 1, Table 3).

Upon further breakdown by type of radiation received there was noted to be no significant differences in survival after Bonferroni correction for patients with stage IA disease. For those with IA grade 1 the 5-year OS was 94.7% for no radiation versus 89.7% for external beam radiation with or without vaginal brachytherapy ($p = 0.040$) and 95.0% for vaginal brachytherapy alone ($p = 0.52$). For IA grade 2 disease, the 5-year OS was 91.3% for no radiation versus 87.6% for external beam radiation \pm brachytherapy ($p = 0.017$) and 90.9% for vaginal brachytherapy alone ($p = 0.76$). For stage IA grade 3 disease the 5-year OS

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