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Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: A national cancer data base analysis☆

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HIGHLIGHTS

- Adjuvant RT led to 4.1% improvement in 5-year OS in stage I HIR endometrial cancer.
- On MVA, surgery + adjuvant RT was independently associated with improved OS.
- This suggests improvement in local control with adjuvant RT leads to improved OS.

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ABSTRACT

Purpose. Adjuvant radiation therapy (RT) was shown to improve local control in patients with high-intermediate risk (HIR) stage I endometrial cancer (EC) in randomized trials. Overall survival (OS) was not significantly different with adjuvant RT in these trials or subsequent meta-analyses; however, they were underpowered to assess OS. We used the National Cancer Data Base (NCDB) to examine the impact of adjuvant RT on OS in HIR EC patients.

Methods. The NCDB was queried for patients diagnosed with FIGO (2009) Stage I endometrioid adenocarcinoma from 1998 to 2012 who underwent surgery ± adjuvant RT. Per ASTRO guidelines, HIR risk was defined as stage IB and/or grade 3. Patients were excluded if: non-surgical primary therapy, RT > 180 days after surgery, unknown stage/grade/RT status, or RT to targets outside pelvis/vagina. Kaplan-Meier plots and Cox proportional hazards regression were used.

Results. 33,600 patients met criteria. 18,070 patients (53.8%) received surgery alone, 15,530 patients (46.2%) received surgery + adjuvant RT. Of patients who received adjuvant RT, 42.2% received external beam RT, 44.7% brachytherapy, and 13.1% received both. 5-year OS was 79.2% for the surgery alone group and 83.3% for the surgery + adjuvant RT ($p < 0.0001$). On multivariate analysis, adjuvant RT was independently associated with improved OS vs. surgery alone (HR 0.7; 95% CI 0.8–0.9, $p < 0.0001$).

Conclusions. Our results show that surgery + adjuvant RT was associated with a statistically significant 4.1% improvement in 5-year OS vs. surgery alone in stage I HIR EC. This data along suggests that the improvement in local control with adjuvant RT leads to improved OS.

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1. Introduction

In the United States, endometrial cancer (EC) is the most common malignancy of the female reproductive tract with over 60,000 cases estimated to be diagnosed in 2016 [1]. The majority of cases present with early-stage disease and are treated with surgery alone; however, over 10,000 deaths are related to this disease annually. Adjuvant therapy is recommended based on several risk factors for recurrence including patient age, stage, tumor histology, grade, depth of myometrial invasion, and presence of lymphovascular invasion (LVI) [2]. Several randomized trials have demonstrated a benefit in local control with adjuvant radiation therapy (RT) in early-stage EC, particularly for subsets of patients classified as "high-intermediate risk" (HIR), although the criteria for this varied by trial [3–8]. Additionally, a 2012 Cochrane meta-analysis of eight trials examining adjuvant RT in stage I EC showed no significant difference in OS (HR 0.88, 95% CI 0.63–1.22) [9]. Though no differences in overall survival (OS) were found, the trials were not sufficiently powered to study this and the meta-analyses were underpowered in examining the impact of adjuvant RT on a specific high-intermediate or high-risk group.

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The definition of HIR EC was not consistent between these trials and it was not clear which patient population would derive the most benefit from adjuvant RT. Due to this discrepancy, the American Society for Radiation Oncology (ASTRO) published evidence-based recommendations for postoperative RT in HIR patients [10]. These recommendations were later endorsed by the American Society for Clinical Oncology (ASCO) [11]. In summary, for women with grade 1 or 2 endometrioid adenocarcinoma with ≥50% myometrial invasion or grade 3 cancer with <50% myometrial invasion, vaginal brachytherapy (VB) is the preferred adjuvant treatment. For patients with grade 3 cancer *and* ≥ 50% myometrial invasion (or cervical stroma invasion), external beam RT (EBRT) is recommended to prevent pelvic recurrence [11]. The randomized trials may not have demonstrated a survival advantage for adjuvant RT because they included lower risk patients who were not as likely to benefit from RT. We sought to examine the relationship between adjuvant RT and OS specifically in the HIR EC patient population by performing a retrospective analysis of the National Cancer Data Base (NCDB).

2. Methods and materials

2.1. Data source and study population

We used NCDB registry data from 1998 to 2012 to study OS in patients with FIGO (2009 Classification) Stage I endometrioid adenocarcinoma in a retrospective hospital-based analysis. The NCDB was established in 1989 and is a nationwide, facility-based, comprehensive data set that currently captures 70% of all newly diagnosed malignancies in the US each year [12]. The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The American College of Surgeons has a data use agreement with each of its Commission on Cancer accredited hospitals. Variables in the endometrial cancer database include patient demographics, stage, grade and other tumor characteristics, and treatments administered.

Records of patients with EC were obtained from the NCDB participant user file. Inclusion criteria were patients diagnosed with stage I HIR endometrioid adenocarcinoma from 1998 to 2012 who were treated with surgery as definitive therapy ± adjuvant RT. All patients were re-staged based on FIGO 2009 criteria. In accordance with the ASTRO/ASCO guidelines, HIR was defined as grade 3 and/or FIGO stage IB (≥50% invasion) [11]. We restricted the patients receiving RT to those who received a radiotherapy dose of at least 40 Gy for EBRT or at least 10 Gy for VB, to exclude patients given palliative doses, incomplete courses, and those patients with miscoded radiation details. Patients were excluded if: FIGO stages II-IV, non-surgical primary therapy, non-endometrioid histology, RT > 180 days after surgery, unknown stage or grade, any surgical operation other than a total hysterectomy, radical hysterectomy or modified radical hysterectomy, RT prior to surgery, unknown whether RT was given, any RT modalities other than EBRT or VB, or RT to targets outside the pelvis/vagina. Women were also excluded if survival and follow-up was <30 days to account for perioperative mortality and immortal time bias—an issue in observational cohort studies evaluating postoperative radiotherapy [13]. LVI was not included in our high-intermediate risk definition as this information is not available in the NCDB prior to 2010 and it is not included in the ASTRO/ASCO guidelines as a HIR feature. Patients were stratified on the basis of receiving surgery alone vs. surgery + adjuvant RT.

2.2. Variables

The variables examined were: age, race, Charlson-Deyo comorbidity score, facility type, geographic region, income, education, insurance type, receipt of adjuvant RT, receipt of adjuvant chemotherapy, and lymph node dissection. Patient demographics, tumor characteristics, and treatment details were dichotomized for analysis whenever possible. For instance, age was bracketed into <60 or ≥60 years. Charlson-Deyo comorbidity scores were 0, 1, and 2; since so few NCDB cases have a comorbidity score > 2, their data has been truncated in the database to 0, 1, 2 (>1). Treatment characteristics included receipt of adjuvant radiation therapy and receipt of adjuvant chemotherapy (yes/no).

2.3. Statistical analyses

Categorical variables were compared by the chi-squared test and continuous variables were compared using the *t*-test. Kaplan-Meier plots with log rank analyses were used to examine the impact of adjuvant RT on OS. OS was defined as the time from diagnosis until death or last contact. Last follow-up was recorded through December 2013. A multivariable Cox proportional hazards model was used to calculate adjusted hazard ratio (HR) and the 95% confidence intervals (CI) to determine association between RT—as well as other variables—and OS. In order to examine the effect of RT on survival outcome, a separate variable related to RT was formed with patients classified as having received RT or having not received RT. An identical variable for chemotherapy receipt was also created. This model determined the significance of RT as an independent predictor of survival after adjusting for the other covariates. A two-sided $P < 0.05$ was used to determine statistical significance. SAS version 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses.

3. Results

3.1. Study cohort characteristics

We identified 33,600 FIGO (2009 Classification) stage I HIR EC patients who were treated between 1998 and 2012 and met our inclusion criteria (see Fig. 1). Median follow-up was 61.2 months and mean follow-up was 66.1 months.

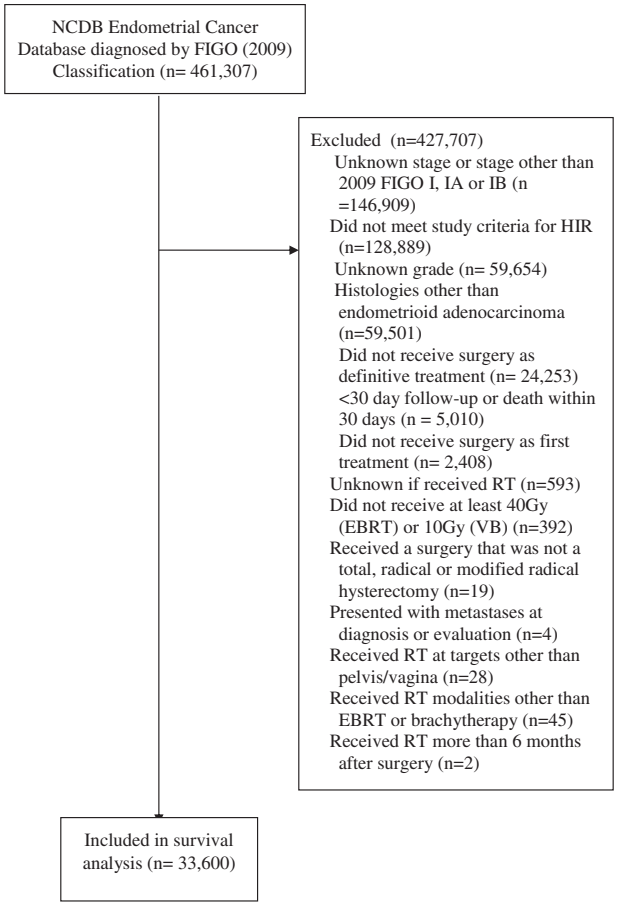

Fig. 1. Diagram of analytic cohort for survival analysis.

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