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High versus low-dose rate brachytherapy for cervical cancer

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HIGHLIGHTS

- The use of HDR therapy has increased rapidly.
- Overall survival is similar for LDR and HDR brachytherapy.

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ABSTRACT

Objectives. Brachytherapy plays an important role in the treatment of cervical cancer. While small trials have shown comparable survival outcomes between high (HDR) and low-dose rate (LDR) brachytherapy, little data is available in the US. We examined the utilization of HDR brachytherapy and analyzed the impact of type of brachytherapy on survival for cervical cancer.

Methods. Women with stages IB2–IVA cervical cancer treated with primary (external beam and brachytherapy) radiotherapy between 2003–2011 and recorded in the National Cancer Database (NCDB) were analyzed. Generalized linear mixed models and Cox proportional hazards regression were used to examine predictors of HDR brachytherapy use and the association between HDR use and survival.

Results. A total of 10,564 women including 2681 (25.4%) who received LDR and 7883 (74.6%) that received HDR were identified. Use of HDR increased from 50.2% in 2003 to 83.9% in 2011 ($P < 0.0001$). In a multivariable model, year of diagnosis was the strongest predictor of use of HDR. While patients in the Northeast were more likely to receive HDR therapy, there were no other clinical or socioeconomic characteristics associated with receipt of HDR. In a multivariable Cox model, survival was similar between the HDR and LDR groups (HR = 0.93; 95% CI 0.83–1.03). Similar findings were noted in analyses stratified by stage and histology. Kaplan–Meier analyses demonstrated no difference in survival based on type of brachytherapy for stage IIB ($P = 0.68$), IIIB ($P = 0.17$), or IVA ($P = 0.16$) tumors.

Conclusions. The use of HDR therapy has increased rapidly. Overall survival is similar for LDR and HDR brachytherapy.

Introduction

Radiation therapy has long been the mainstay of treatment for advanced stage cervical cancer. Radiation is delivered in the form of external beam therapy in combination with intracavitary brachytherapy. Brachytherapy allows dose escalation to the cervix and surrounding tissues and is critical in improving local control and decreasing the risk of pelvic relapse [1,2].

Intracavitary radiation typically relies on low-dose rate (LDR) brachytherapy which delivers radiation at a dose of 0.4–2 Gray (Gy)/h [3]. The radiation sources are loaded into an intrauterine tandem and vaginal ovoid delivery system that is placed while the patient is under anesthesia in the operating room. Patients are typically hospitalized after placement of the applicator for 24–72 h to allow radiation delivery of LDR treatments. The source positions and dosing of LDR brachytherapy have been well defined for several decades.

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More recently, high-dose rate (HDR) brachytherapy has been explored for the treatment of cervical cancer. HDR brachytherapy delivers a dose >12 Gy/h, and is typically delivered in the outpatient setting through multiple applicator placements that are left in place for a short duration. Advantages of HDR brachytherapy include greater patient convenience and ease of administration, as well as the ability to optimize dosing to normal tissues.

Outcomes after LDR and HDR brachytherapy have been compared in a number of retrospective, institutional studies as well as in four prospective randomized trials [2,4–11]. The randomized trials noted similar survival outcomes for the two brachytherapy techniques, however, all four studies were conducted outside of the U.S. and have been criticized for a number of methodologic limitations including the inclusion of diverse patient populations and the utilization of a variety of different radiation techniques [2,7]. Given the limited data describing the safety and use of HDR brachytherapy in the U.S., we performed a population-based analysis to examine the patterns of brachytherapy use and outcomes for women with cervical cancer undergoing primary radiation therapy.

Materials and methods

Data source and patient selection

The National Cancer Data Base (NCDB) was used for analysis. NCDB is a nationwide registry developed and sponsored by the American College of Surgeons and American Cancer Society [12,13]. The database records all patients with newly diagnosed invasive cancers from over 1500 Commission on Cancer (CoC) affiliated hospitals located throughout the United States. The NCDB catalogs data on patient demographic factors, tumor characteristics and treatment data, staging, and survival [12,13]. Data are abstracted by trained registrars and is audited regularly to ensure accuracy. It is estimated that nearly 78% of women with invasive cervical cancer in the U.S. are recorded in NCDB [14]. The Columbia University Institutional Review Board deemed the study exempt.

Women with stages IB2–IVA cervical cancer diagnosed from 2003–2011 were included. Only patients who underwent primary radiotherapy with combination external beam radiation and intracavitary brachytherapy were included in the analysis. Further, the cohort was limited to those women with specific documentation of receipt of either LDR or HDR brachytherapy. NCDB only reports survival data on patients with at least five years of follow-up. Therefore, all survival analyses were limited to patients treated from 2003–2006.

Clinical and demographic characteristics

Demographic data analyzed included age (<40, 40–49, 50–59, 60–69, ≥70 years), race (white, black, Hispanic, other or unknown), income (median household income in a patient's zip code), education (percentage of adults in a patient's zip code that did not graduate high school; <14%, 14–19.9%, 20–28.9%, ≥29%, unknown) and insurance status (commercial, Medicare, Medicaid, uninsured and unknown). Comorbidity was measured using the Deyo classification of the Charlson comorbidity score (0, 1, ≥2) [15,16]. Tumor stage (stages IB2–IVA) and grade (1, 2, 3, unknown) were noted for each patient. Tumor histology was classified as squamous, adenosquamous, adenocarcinoma and other.

Hospital characteristics analyzed included region (Northeast, Midwest, South, or West) and location (metropolitan, urban, rural). Based on the ACS CoC criteria, hospitals are also classified as academic/research cancer centers or community cancer centers [13]. Hospital volume was estimated as annualized volume. We calculated the total number of patients treated at a given hospital divided by the number of years in which a given hospital treated at least one patient [17,18]. Patients were then stratified into four approximately equal volume quartiles: lowest (<2 cases/year), second (2.00–3.25 cases/year), third (3.26–5.37 cases per year), and highest (≥5.37 cases/year).

Treatment quality was captured through measurement of use of chemotherapy (yes, no and unknown) and through duration of radiation therapy [19]. Radiation therapy encompassed prior radiation treatment and was grouped as: <6 weeks, 6–10 weeks, 10 weeks–6 months, >6 months, and unknown.

Statistical analysis

Frequency distributions between categorical variables were compared using χ [2] tests and trends analyzed using Mantel–Haenszel tests. The association between the clinical and demographic characteristics and use of HDR brachytherapy was examined using multivariable mixed effects log-linear regression models. To account for hospital-level clustering, these models included a random-intercept for the hospital in which the radiation was administered. The models included all clinically relevant demographic, clinical, and oncologic variables. Results are reported as risk ratios (RR) with 95% confidence intervals (CI).

Overall survival was estimated as the number of months from diagnosis until death from any cause. Patients who were alive at the last follow-up were censored. Stage-specific Kaplan–Meier curves were developed to compare survival between women who received LDR

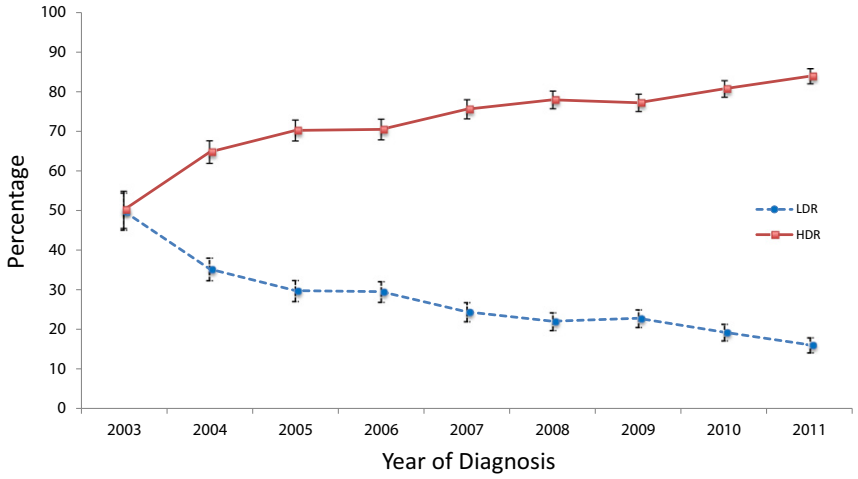

Fig. 1. Trends in the use of low-dose rate (LDR) and high-dose rate (HDR) brachytherapy from 2003–2011.