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Influence of treatment center and hospital volume on survival for locally advanced cervical cancer

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HIGHLIGHTS

- For locally advanced cervical cancer, hospital volume has a minimal impact on outcome.
- The specific center in which care is delivered is strongly associated with survival.

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ABSTRACT

Objective. Procedural volume is associated with outcomes for many surgical interventions. Little is known about the association between volume and outcomes of radiation. We examined the association between treatment center and hospital volume and outcomes for women with locally advanced cervical cancer treated with radiation.

Methods. Women with stage IIB–IVA cervical cancer treated with primary radiation from 1998 to 2011 and recorded in the National Cancer Database were examined. Hospital volume was estimated as the mean annualized volume, while center-specific effects on care were examined using a hospital-specific random effect. Multivariable regression models adjusted for metrics of treatment quality were used to estimate survival.

Results. 20,766 patients treated at 1115 hospitals were identified. The median follow-up was 24.2 months while 5-year survival was 36.5% (95% CI, 35.6–37.4%). Higher hospital volume was associated with receipt of brachytherapy ($P < 0.05$), but had no effect on use of chemotherapy. In a multivariable model accounting for clinical and demographic factors as well as quality of care, hospital volume was not associated with survival ($P = 0.25$). The specific hospital in which patients received care was the strongest predictor of survival ($P < 0.0001$) followed by stage, year of diagnosis and treatment quality ($P < 0.0001$ for all). The hospital-specific effect on mortality expressed as a hazard ratio, ranged from 0.66 to 1.53 across hospitals.

Conclusion. For locally advanced cervical cancer, hospital volume has a minimal impact on outcome; however, the specific center in which care is delivered is strongly associated with survival.

1. Introduction

Women with locally advanced cervical cancer (stages IIB–IVA) have tumors that have spread beyond the cervix to the adjacent pelvic structures. In the late 1990's, a series of studies demonstrated that chemotherapy combined with radiation therapy was superior to radiation alone for these neoplasms[1–4]. The magnitude and consistency of the survival benefit demonstrated in these studies prompted the National Cancer Institute to issue a clinical alert in 1999 recommending that chemoradiation should be considered the standard of care for patients with newly diagnosed, advanced stage cervical cancer [5].

The multimodal treatment of locally advanced cervical cancer is complex. External beam radiotherapy is typically administered every day with concurrent, weekly cisplatin. In addition, curative intent

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therapy requires intracavitary brachytherapy delivered through an apparatus placed directly into the cervix and vagina. Appropriate radiation planning is essential to ensure delivery of an adequate therapeutic dose to the pelvis while minimizing toxicity to surrounding tissues [6]. However, given the decreasing incidence of cervical cancer in the United States, many centers treat only a small number of patients each year.

For many complex medical interventions, procedural volume has been shown to have an association with treatment outcomes [7–12]. This paradigm has been demonstrated for high-risk oncologic and cardiovascular surgical procedures in which outcomes are superior when the operations are performed by high-volume surgeons at high-volume centers [7–12]. The improved outcomes for high-volume providers are likely due to a multitude of factors, including increased technical expertise, adherence to evidence-based treatment recommendations, and appropriate management of complications [13–15].

Despite the fact that delivery of therapeutic radiation is often technically demanding, there has been little prior data exploring the influence of the treating hospital on outcomes in patients treated with primary radiotherapy. We performed a population-based analysis to examine the influence of treatment center and hospital volume on quality of care and survival for women with locally advanced cervical cancer.

2. Methods

2.1. Data source and patient selection

Data from the National Cancer Data Base (NCDB) was utilized. NCDB is a nationwide oncology outcomes database sponsored by the American College of Surgeons and American Cancer Society [16,17]. NCDB captures data on approximately 70% of all newly diagnosed invasive cancers and includes over 1500 Commission on Cancer (CoC) affiliated hospitals from across the United States. NCDB collects data on patient demographics, tumor characteristics, staging data, treatment information, and survival [16,17]. Data are abstracted by trained cancer registrars and are regularly audited to ensure accuracy. The Columbia University Institutional Review Board deemed the study exempt.

Women with stage IIB–IVA cervical cancer diagnosed from 1998 to 2011 were included in the analysis. We included only those patients whose initial, primary treatment included radiation therapy. Patients treated with primary surgery and those who did not receive any treatment were excluded. As survival data in NCDB is only included for patients with at least 5 years of follow-up, we present data on the entire cohort (1998–2011) and analyzed survival outcomes in a limited survival cohort (1998–2006).

2.2. Treating hospital and hospital volume

The treating hospital was defined as the hospital in which radiation was administered. The primary analysis was limited to patients who received their entire course of radiotherapy at the institution in which treatment was initiated. A sensitivity analysis including patients who received radiation at multiple facilities was also performed. Prior studies have explored modeling volume in a variety of fashions [18]. The primary analysis of hospital volume was performed using annualized hospital volume [18]. For each hospital, we calculated the total number of patients treated and divided this by the number of years in which a hospital treated at least one patient with locally advanced cervical cancer. Exploratory analyses were performed modeling volume in several ways. First, we classified previous year volume as the number of cases treated at a given hospital in the calendar year prior to the index patient. Second, we defined current year volume as the number of cases treated at a given hospital in the same calendar year in which an index patient was treated.

The primary analysis was performed including hospital volume as a continuous variable [18]. We also explored the influence of classifying hospital volume as a categorical variable and dividing the cohort into patient-based quartiles: <2, 2–3.99, 4–5.99, and ≥6 cases per year.

2.3. Variables and outcomes

Clinical variables analyzed included age (<40, 40–49, 50–59, 60–6, ≥70 years), race (white, black, Hispanic, other), and insurance (commercial, Medicare, Medicaid, uninsured, other). Tumor characteristics included grade (1, 2, 3, or unknown), stage, and histology (squamous, adenocarcinoma, adenosquamous, or 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 [17].

A number of metrics of treatment quality were analyzed. For each patient, receipt of brachytherapy (either low or high dose rate) as well as chemotherapy was recorded. The primary outcome of the analysis was survival [16]. Survival is reported as all cause mortality and includes death from cancer and other causes.

2.4. Statistical analysis

Frequency distributions for categorical variables were analyzed across volume quartiles using χ^2 tests. Median volume for each quartile is reported along with interquartile ranges (IQR). Generalized linear mixed effects models using a Poisson distribution and a log link function were developed to examine predictors of treatment. These models included all of the clinical and demographic variables as well as a hospital-specific random effect to account for hospital-level clustering [19]. Multivariable models were developed to estimate factors associated with treatment at high-volume hospitals (annual volume ≥6 patients) and to explore factors associated with use of evidence-based treatments (brachytherapy and chemotherapy). To examine whether cluster size influenced outcomes, we performed sensitivity analyses using cluster weighted generalized estimating equations (CWGEE) that account for informative cluster size through inverse weighting [20].

Survival was assessed using mixed-effects Cox proportional hazards regression models [21]. Covariates for these models were chosen using purposeful selection [21,22]. We first included all variables that were significant at the $P < 0.02$ level in bivariate analysis, as well as all variables thought to be of clinical significance. We then removed variables that did not contribute to the multivariate fixed-effects model based on a P-value of >0.05 and a change in the coefficient of the remaining variables by >20% [21,23]. Based on this selection, we constructed a model (clinical model) including the following patient and hospital characteristics: age, year of diagnosis, tumor histology, tumor grade, stage, race, insurance status, hospital type, and hospital region. To account for differences in quality of treatment, a treatment-adjusted model was developed that included the above covariates as well as receipt of brachytherapy and chemotherapy.

The assumption of proportionality was assessed visually by plotting scaled Schoenfeld residuals [21,24]. A hospital-specific random effect was included in the Cox proportional hazards regression model to assess the center-specific effects on survival. The models assumed that the random effect followed a Gaussian distribution with a mean of 0. The proportional hazard assumption for the random effect was tested by fitting fixed-effect Cox models with the covariates of interest along with the random effect from the mixed-effects Cox model and visually inspecting the scaled Schoenfeld residuals.

The primary models included annualized hospital volume as a continuous variable. The linear relationship between annualized hospital volume and the log-hazard for death was assessed by Martingale residual plots. Sensitivity analyses were performed in which volume was modeled as a categorical variable; volume was estimated as the previous year volume, or current year volume. Additional models excluding