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# Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer

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## HIGHLIGHTS

- Less than half of patients with locally advanced cervix cancer receive SOC therapy despite a substantial OS benefit.
- Management per SOC guidelines was associated with private insurance, higher income, and higher volume centers.
- Patients with lower incomes and those treated at low volume centers were more likely to receive no radiotherapy boost.

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## ABSTRACT

*Purpose.* Standard of care (SOC) treatment for locally advanced cervical cancer includes pelvic external beam radiation (EBRT) with chemotherapy and interdigitated brachytherapy. We evaluated national utilization trends and factors associated with receiving SOC therapy.

*Materials and methods.* We utilized the National Cancer Database (NCDB) to identify women with locally advanced cervical cancer treated with definitive radiation or chemoradiation therapy and stratified these patients by treatment received.

*Results.* We identified 15,194 patients. Only 44.3% of patients received SOC treatment and this group had significantly improved OS. High volume centers, academic centers, comprehensive community cancer centers, private insurance, and higher income, were all associated with an increased likelihood of receiving SOC, whereas Black patients were less likely to receive SOC. We found 26.8% of patients received no radiation boost, 23.8% received an EBRT boost only, and 49.5% of patients received EBRT with brachytherapy. Although an EBRT boost was advantageous over no boost at all (HR 0.720, $p < 0.001$), OS was superior in patients who received brachytherapy (HR 0.554, $p < 0.001$). Patients were more likely to receive no radiotherapy boost if they had lower incomes, Medicaid, were treated at low volume centers, or were treated at non-comprehensive community cancer centers.

*Conclusions.* SOC for locally advanced cervical cancer offers superior outcomes, yet less than half of patients receive SOC and there are disparities in which patients receive SOC treatment. No additional treatment, including sophisticated EBRT techniques including IMRT or SBRT, can make up for the survival decrement from lack of brachytherapy as a component of definitive care.



## 1. Introduction

Brachytherapy has historically been shown to increase survival when added to external beam radiation [1–4] and this was again demonstrated in more modern series [5,6]. In fact, the American Brachytherapy Society (ABS) states that all patients being treated with radiation for cervical cancer should receive brachytherapy as a component of their care unless they have a documented medical contraindication [7]. Nevertheless, it was recently shown that brachytherapy use is significantly declining in recent years [5,8].

In addition to the importance of brachytherapy use in treating these patients, the value of chemotherapy should not go understated. In 1999 formal recommendations were issued in support of concurrent chemotherapy with external beam radiation therapy (EBRT) plus brachytherapy [9] based on large randomized clinical trials [10–14].

We used the National Cancer Database (NCDB) to compile a large cohort of locally advanced cervical cancer patients that were treated with definitive intent radiation. We set out to address lingering fundamental questions. Prior large national database studies have shown that

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patients who received brachytherapy over EBRT alone have superior survival [5], and that a brachytherapy boost is advantageous over an intensity modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) boost [8]. It remained unclear, however, if there is a group that is not receiving a radiotherapy boost at all, and if so how this group compares to patients receiving EBRT boosts and brachytherapy boosts, and what patient characteristics are associated with boost omission. Our second goal was to take advantage of chemotherapy data provided by the NCDB to compare outcomes for patients that received SOC treatment with concurrent chemoradiation therapy including brachytherapy versus those patients that received alternate treatment. Prior studies have shown survival advantages for brachytherapy or chemotherapy, analyzed individually [5,6,8,15], but in our study we focused specifically on patients that received complete SOC treatment including concurrent chemoradiation therapy with a brachytherapy boost, and assessed overall survival as well as factors predictive of receiving SOC treatment.

## 2. Material and methods

We utilized the de-identified NCDB for this study. The NCDB collects data from over 1500 community and academic cancer centers and has been reported to represent about 70% of all cancer cases in the United States. The NCDB is the result of a collaboration between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. The NCDB has established criteria to ensure the data submitted meet specific quality benchmarks. The following NCDB analysis was performed with the approval of our local institutional review board.

We queried the de-identified NCDB file for all primary cervical cancer patients diagnosed between 2004 and 2012 based on primary site codes C530, C531, C538, and C539. In order to select for patients that were managed with primary radiation therapy we excluded all patients with primary site surgery listed as hysterectomy (site specific surgery code "30") or greater. For staging, we first utilized the coded International Federation of Gynecology and Obstetrics (FIGO) stage. Where FIGO stage was unknown we next relied on the American Joint Committee on Cancer (AJCC) staging. We next excluded all patients listed as stages 0, I NOS, IA NOS, IA1, IA2, IB NOS, IB1, IV NOS, and IVB. This resulted in patients with FIGO and AJCC clinical stage IB2 to IVA cervical cancer (locally advanced) who received radiation therapy as their primary cancer treatment. The additional variables accounted for in our primary analysis included age, race, Charlson/Deyo combined comorbidity score (CDCC) [16,17], histology, stage, location of radiation treatment, EBRT with or without chemotherapy, and radiation boost modality. We excluded all patients with unknown values for these variables or unknown vital status or date of last contact. This yielded a total of 15,194 patients available for primary analysis. Concurrent chemotherapy was defined as a chemotherapy start date within 14 days of the radiation start date. For our secondary analysis of factors associated with likelihood of receiving either SOC therapy or of receiving therapy where a radiotherapy boost was omitted, we utilized the following additional variables: insurance status, median household income, county population, distance to the hospital, facility volume, facility type, and facility location. After excluding for unknowns in these additional variables we identified a total of 11,948 patients available for secondary analysis. Objective tumor size data was only available for 6989 of these patients but was included in our logistic regression analysis.

Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). We performed Kaplan-Meier survival analysis with log-rank comparison. Multivariate Cox regression analysis was performed using OS as outcomes with a significance level of $p < 0.05$. Logistic regression models were used to assess the association between patient characteristics and treatment. GraphPad Prism version 5.03 (GraphPad Software Inc., La Jolla, CA) was used for creation of Kaplan-Meier curves presented in our figures.

## 3. Results

We identified 15,194 patients with FIGO/AJCC stage IB2 through IVA cervical cancer diagnosed between 2004 and 2012, and treated with definitive intent radiation or chemoradiation therapy. Patient characteristics are highlighted in Table 1. We found that 6972 (45.9%) patients were treated with EBRT alone, whereas 8222 (54.1%) patients received EBRT and brachytherapy. Of the 6972 patients that received EBRT alone, we identified 4067 patients that were treated with EBRT without a documented boost. The other 3609 patients that were treated without brachytherapy received an EBRT boost including treatment with IMRT or SBRT. We next stratified patients by chemotherapy. We found that 2350 patients (15.5%) received EBRT alone, 4622 (30.4%) patients received EBRT with chemotherapy, 1498 (9.9%) patients received EBRT with brachytherapy, but without chemotherapy, and 6724 (44.3%) patients received full SOC therapy with EBRT, chemotherapy, and brachytherapy (Table 1).

We then looked at Kaplan-Meier survival curves for patients stratified by radiation and chemotherapy treatment. Patients who received brachytherapy had significantly improved overall survival compared to patients treated with EBRT alone (median survival 93.04 months versus 32.95 months, $p < 0.001$) (Fig. 1A). We next stratified the patients who did not receive a boost versus patients who received an EBRT only boost. We found improved overall survival for patients who received an EBRT only boost compared to patients who did not receive a radiotherapy boost at all, but both groups had substantially inferior overall survival compared with the group that received brachytherapy (median survival 27.63 months versus 47.05 months, versus 94.03 months, $p < 0.001$) (Fig. 1B). Finally, we used Kaplan-Meier curves and log-rank comparison to evaluate the role of chemotherapy in these patients. We stratified patients by EBRT alone, EBRT with concurrent chemotherapy, EBRT with brachytherapy without concurrent chemotherapy, and EBRT with concurrent chemotherapy and brachytherapy (SOC). We found the median survival was 20.34 months, 43.74 months, 56.18 months, and 105.23 months, respectively (Fig. 1C).

We next assessed the importance of brachytherapy and chemotherapy in the context of additional relevant variables including age, race, CDCC, histology, stage, and location of radiation. In our first multivariate analysis we compared these variables for patients who received EBRT alone versus patients who received EBRT and brachytherapy. In multivariate analysis we found that brachytherapy remained associated with improved survival (HR 0.625, $p < 0.001$). We found that increasing age was associated with worse overall survival (HR 1.012, $p < 0.001$). We also found that Hispanic patients had significantly improved overall survival (HR 0.700, $p < 0.001$) whereas Black patients had worse overall survival (HR 1.080, $p = 0.010$). CDCC score was associated with worse overall survival (CDCC = 1, HR 1.326, $p < 0.001$; CDCC = 2, HR 1.630, $p < 0.001$). Importantly, CDCC scores for Caucasian and Black patients were relatively well balanced. 85.4%, 11.3%, and 3.3% of Caucasian patients had CDCC scores of 0, 1, and 2, respectively, and 82.6%, 12.5%, and 4.8% of Black patients had CDCC scores of 0, 1, and 2, respectively. Non-squamous histology was associated with worse prognosis as well. Compared with pure squamous cell cancer, adenocarcinoma and adenosquamous cancers were associated with worse overall survival (HR 1.236, $p < 0.001$ and HR 1.306, $p < 0.001$, respectively). Increasing stage was associated with worse overall survival (stage II, HR 1.267, $p < 0.001$; stage III, HR 2.326, $p < 0.001$; stage IVA, HR 3.600, $p < 0.001$). We were interested in whether patients that received treatment split between multiple centers had worse overall survival than patients that received treatment at one center, but did not see a correlation in this study (HR 1.043, CI 0.960–1.132, $p = 0.319$). Finally in this

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