ELSEVIER

Brachytherapy ■ (2017) ■

BRACHYTHERAPY

External pelvic and vaginal irradiation vs. vaginal irradiation alone as postoperative therapy in women with early stage uterine serous carcinoma: Results of a National Cancer Database analysis

Ankit Modh[1], Charlotte Burmeister[2], Adnan R. Munkarah[3], Mohamed A. Elshaikh[1,*]

[1]*Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI*
[2]*Department of Public Health Science, Henry Ford Hospital, Detroit, MI*
[3]*Division of Gynecologic Oncology, Department of Women's Health Services, Henry Ford Hospital, Detroit, MI*

ABSTRACT

PURPOSE: Adjuvant treatment in early stage uterine serous carcinoma (USC) usually consists of chemotherapy with vaginal brachytherapy (VB), pelvic external beam radiation therapy (EBRT), or combination. We compared survival outcomes across these various radiation treatment modalities using the National Cancer Database.

METHODS AND MATERIALS: The National Cancer Database was queried for adult females with histologically confirmed International Federation of Gynecology and Obstetrics 1988 Stage I–II USC diagnosed from 2003 to 2013 treated definitively with hysterectomy, adjuvant chemotherapy, and radiation therapy. χ^2 tests were used to assess differences by radiation type (VB, pelvic EBRT, and EBRT + VB) and various clinical variables. Kaplan–Meier and log-rank test methods were used to evaluate survival outcomes. Risk factors related to overall survival were identified by univariate and multivariate analysis.

RESULTS: We identified 1336 patients with USC who met our inclusion criteria. Most patients were treated with VB (66%) compared with EBRT (21%) or combination EBRT + VB (13%). The proportion of patients who received EBRT (including EBRT + VB) was higher for those who did not have a lymph node dissection or with fewer dissected lymph nodes. Patients treated with VB alone had longer 5-year survival rates (84% [95% confidence interval: 80, 90]) than those treated with EBRT (75% [95% confidence interval: 69, 80]) ($p < 0.001$). On multivariate analysis, the presence of lymphovascular space invasion (hazard ratio, 2.48; $p < 0.001$) and the absence of a lymph node dissection (hazard ratio, 2.24; $p = 0.047$) were independent predictors of overall survival.

CONCLUSIONS: This large hospital-based study suggests that VB alone may be sufficient for adjuvant radiation treatment in women with USC treated with adjuvant chemotherapy and who underwent an adequate surgical staging.

Keywords: Endometrial carcinoma; Uterine serous carcinoma; Brachytherapy; Radiation treatment; Chemotherapy; Survival

Introduction

Endometrial carcinoma (EC) is the fourth most common malignancy and the most common malignancy of the genital system of females in the United States (1). Although uterine serous carcinoma (USC) is a rare subtype of EC constituting less than 8% of all cancer (2), it is responsible for more than 39% of uterine cancer mortality (3) and portends a poorer prognosis, mostly because of its high propensity for extrauterine disease at presentation and high local and distant failure rates (4).

Received 3 February 2017; received in revised form 9 March 2017; accepted 6 April 2017.

Financial disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: None to report.

Presented as an oral presentation at the Annual meeting of American Brachytherapy Society, Boston, Massachusetts, April 2017.

* Corresponding author. Department of Radiation Oncology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202. Tel.: +1-313-916-1015; fax: +1-313-916-3664.

E-mail address: melshai1@hfhs.org (M.A. Elshaikh).

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2017.04.237

Given the higher tendency for distant failure, chemotherapy has been shown to improve outcomes in patients with early stage USC (5). A Phase II prospective study found favorable results when adding pelvic radiation treatment (RT) to chemotherapy in this subset of patients (6). Multiple randomized trials have confirmed the benefits of adjuvant pelvic RT in reducing pelvic recurrences in early stage EC (7–9), with a potential for improved overall survival (OS) in these patients with USC based on larger retrospective series (10).

Adjuvant RT modalities include pelvic external beam radiation therapy (EBRT) alone, vaginal brachytherapy (VB) alone, or their combination (EBRT + VB), yet selecting the optimal RT modality with regard to efficacy in women with EC is controversial. Two landmark prospective randomized studies compared effectiveness of different RT modalities in women with early stage EC. Nout *et al.* (11) compared VB with pelvic EBRT in patients with early stage EC, finding no significant difference in vaginal recurrence rates. Sorbe *et al.* (12) compared VB alone with EBRT + VB in a higher risk EC population and found a locoregional control benefit with the combination approach with no significant differences in OS; however, this came at the expense of increased toxicity and worse experienced quality of life favoring VB alone. Unfortunately, these two studies did not include patients with USC. Three retrospective studies have concluded that VB alone provides excellent disease outcomes for patients with specifically early stage USC, although these are single institution reports with limited sample sizes (13–15).

Owing to the rarity of USC, it is difficult to conduct a randomized study solely for this group of high-risk patients. We sought to use the National Cancer Database (NCDB) to compare survival outcomes across these various RT modalities in patients with early stage USC who underwent surgical staging and received adjuvant chemotherapy.

Methods and materials

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This is a clinical oncology database sourced from hospital registry data that are collected in more than 1500 Commission on Cancer–accredited facilities. Subjects included adult (age older than 18 years) females with a first primary of histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) 1988 Stage I–IIB corpus uteri serous carcinoma ([primary sites codes C54–C55.9] 8441, 8460, and 8461) diagnosed from 2004 to 2013. Patients with multiple primary malignancies, those who received adjuvant treatment before surgery, those who did not receive a hysterectomy, or those who did not have adjuvant chemotherapy or RT were excluded.

Differences in distribution of variables by type of adjuvant RT (VB, EBRT, and EBRT + VB) were assessed for statistical significance by χ^2 test, generating two-sided *p*-values. Findings were considered statistically significant at an α value of <0.05. Kaplan–Meier and log-rank test methods were used to evaluate OS. Univariate and multivariate modeling with Cox regression analysis was used to determine significant predictors of OS. Multivariable models were selected by first including any predictor with a univariate *p*-value of <0.2 and then using stepwise selection, with a *p*-value cutoff of 0.05 that used to remain in the model. Data from the NCDB were filtered, and all data analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Covariates included age, race (black, white, and other), lymph node dissection (performed or not), number of lymph nodes examined (continuous and categorical), surgical stage based on FIGO 1988 staging (IA, IB, IC, IIA, IIB, I—not otherwise specified, or II—not otherwise specified), the presence of lymphovascular space invasion (LVSI) (yes or no), number of para-aortic nodes dissected, performance of an omentectomy (yes or no), Charlson comorbidity score (0, 1, and ≥ 2), and the sequence of RT and chemotherapy (chemotherapy first and radiation first or concurrent). The difference between the time to initiation of chemotherapy and RT was used to determine the sequence. Therapy was considered concurrent if start days were within 10 days. The American Joint Committee on Cancer 6th edition stage grouping (based on FIGO 1988 surgical staging) was used for this analysis.

Results

A total of 1336 patients met the inclusion criteria. All patients received adjuvant chemotherapy and RT. Most patients received VB (65.8%), 20.1% of patients received pelvic EBRT, and 13.2% of patients received EBRT + VB. Table 1 details the patient demographics and clinical variables by radiation group (VB, EBRT, or EBRT + VB). The median ages were 65 in the EBRT and VB groups and 66 in the EBRT + VB group. Most patients were white. There were more women with Stage I (84.5%) in the VB group, compared with 74.4% in the EBRT and 55.5% in EBRT + VB groups. More women with Stage II (44.6%) were in the EBRT + VB group compared with only 15.5% in the VB group and 25.7% in the EBRT group.

Of those that received VB, only 5.7% of patients did not undergo a lymph node dissection, compared with 11% of patients who received any EBRT (including EBRT + VB, $p = 0.001$). The median number of examined lymph nodes was also larger in the VB group (17 nodes) compared with the EBRT and EBRT + VB (13 nodes) groups ($p < 0.0001$). Those that received any EBRT had a significantly larger proportion of patients with LVSI (36.6% vs. 23.0% VB; $p = 0.001$).

Figure 1 presents Kaplan–Meier estimates for OS stratified by adjuvant radiation modality. The log-rank test was