Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Utilization of adjuvant therapies and their impact on survival for women with stage IIIC endometrial adenocarcinoma

Andrew T. Wong [a,b,*], Justin Rineer [c], Yi-Chun Lee [b], David Schwartz [a,b], Joseph Safdieh [a,b], Joseph Weiner [a,b], Kwang Choi [b], David Schreiber [a,b]

[a] Department of Veterans Affairs, New York Harbor Healthcare, Brooklyn, NY, USA
[b] SUNY Downstate Medical Center, Brooklyn, NY, USA
[c] UF Health Cancer Center - Orlando Health, Orlando, FL, USA

HIGHLIGHTS

- >20% of women with stage IIIC uterine adenocarcinoma did not receive adjuvant therapy.
- 37% of women were treated with both adjuvant chemo and RT.
- Women treated with both adjuvant chemo and RT had significantly higher survival.

ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 27 June 2016
Accepted 6 July 2016
Available online xxxx

Keywords:
Uterine adenocarcinoma
Endometrial adenocarcinoma
Combined modality therapy
Chemotherapy
Radiation therapy

ABSTRACT

Purpose/objectives. Adjuvant treatment options following surgical staging for women with stage IIIC endometrial carcinoma include chemotherapy (CT) with or without radiation therapy (RT). We utilized the National Cancer Database (NCDB) to investigate utilization of adjuvant CT and RT for this group of patients and assess their impact on overall survival (OS).

Materials/methods. The NCDB was queried for patients diagnosed with non-metastatic surgically staged uterine adenocarcinoma between 2004 and 2011 with at least one pathologically positive lymph node. Overall survival (OS) was analyzed using the Kaplan-Meier method. Comparison was made between patients receiving no additional therapy, RT alone, CT alone, or a combination of CT and RT (CMT). Multivariable cox regression analysis (MVA) was performed to evaluate the effect of covariates on OS.

Results. A total of 6720 patients were included in this study. Of whom, 1409 received no adjuvant treatment, 1533 received CT only, 1265 received RT only, and 2522 received CMT. The 5-year OS for patients receiving no adjuvant therapy, RT alone, CT alone, and CMT were 54.9%, 63.9%, 64.4%, and 72.6%, respectively. On pairwise analysis, CMT was associated with improved survival compared to all other subgroups ($p < 0.001$). On MVA, CMT (HR 0.58, 95% CI 0.52–0.66, $p < 0.001$) was the strongest predictor for improved OS compared to RT alone (HR 0.79, 95% CI 0.69–0.89, $p < 0.001$) or CT alone (HR 0.75, 95% CI 0.66–0.85, $p < 0.001$).

Conclusions. Both adjuvant CT and adjuvant RT were associated with improved OS for women with stage IIIC endometrial adenocarcinoma, but CMT was associated with the largest improvement in OS.

1. Introduction

Endometrial cancer is the fourth most common malignancy in women with an estimated 60,000 new cases annually in the United States [1]. Approximately 15% of these women will present with locally advanced disease including women with positive lymph node involvement as the most common subgroup [2–6]. For those with regional lymph node involvement (2009 FIGO stage IIIC), the primary treatment consists of extirpative surgery with total hysterectomy/bilateral salpingo-oophorectomy and lymphadenectomy. This procedure is therapeutic and also provides essential pathologic prognostic information.

Patients with stage IIIC disease are at an increased risk of recurrence with 5-year disease-free survival rates ranging from 30 to 70% [2–6]. Adjuvant therapy is unquestionably needed, but the optimal form of adjuvant therapy has yet to be defined. The role of chemotherapy over whole abdominal irradiation was established by the Gynecologic Oncology Group (GOG) 122 trial, which demonstrated significant progression-free and overall survival benefits for chemotherapy in

* Corresponding author at: SUNY Downstate Medical Center, Department of Radiation Oncology, 450 Clarkson Ave, Box 1211, Brooklyn, NY 11203, USA.
E-mail address: andrew.wong@downstate.edu (A.T. Wong).

http://dx.doi.org/10.1016/j.ygyno.2016.07.091
0090-8258/

patients with stage III-IV disease [7]. However, due to its broad inclusion criteria, this trial included a heterogeneous group of patients with 51.5% having stage IIIC disease, and hence was underpowered to perform a meaningful analysis of this subgroup. Furthermore, adjuvant chemotherapy alone is associated with a high risk of pelvic relapse ranging from 19 to 50% [7–11]. A multimodality approach comprised of chemotherapy and tumor-directed radiation therapy has therefore been advocated by national guidelines [12,13] and is supported by non-randomized data.

The purpose of this study was to evaluate the patterns of adjuvant therapy usage for patients with stage IIIC endometrial carcinoma using the National Cancer Database (NCDB). Additionally, the impact of these adjuvant therapies on overall survival was assessed.

2. Methods

The NCDB is a hospital-based registry that is the joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is estimated that 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. Exemption was obtained from the New York Harbor Veterans Affairs Committee for Research and Development prior to the initiation of this study.

Women who were diagnosed with non-metastatic uterine adenocarcinoma between 2004 and 2011 and underwent total hysterectomy/bilateral salpingo-oophorectomy with a minimum of one pathologically confirmed positive lymph node were included in this study (TNM classification pT1-4 N1-2 M0). The ICD-O-3 histologic codes included were 8140 (adenocarcinoma not otherwise specified) and 8380 (endometrioid adenocarcinoma). Based on the pathologic extent of invasion coding in the NCDB, women were grouped into American Joint Committee on Cancer 7th edition TNM staging. All women had to have complete data regarding the grade of their disease, extent of their disease invasion as well as whether or not they were treated with radiation therapy and/or chemotherapy. In addition, in order to account for immortal time bias [14], women who survived <-6 months after diagnosis were excluded. Data regarding radiation usage were collected, and only those who were identified as having received treatment to the pelvis or uterus/cervix regions were included. Chemotherapy data were also collected. Those for whom it was unknown whether or not chemotherapy was received were excluded, as well as those who received neoadjuvant chemotherapy. This resulted in a cohort of 7199 women with pathologically confirmed node positive disease who met the study inclusion criteria. However, there were 470 women who were identified in one NCDB variable as having pathologically positive nodes but were staged by NCDB in a separate variable as pNX or pN0. In order to reduce the effect of potential database coding errors influencing this analysis, these women were excluded as well. Therefore, the final cohort consisted of 6720 women.

The sequence of chemotherapy and radiation therapy in relation to each other was derived from the NCDB data based on the number of days from diagnosis to receipt of chemotherapy and radiation therapy. Patients were identified as receiving their chemotherapy followed by radiation, radiation followed by chemotherapy, or concurrent chemoradiation (if the chemotherapy and radiation were initiated within 14 days of each other).

Clinical, pathologic, and demographic details were compared between patients based on whether they received no adjuvant treatment, adjuvant radiation alone, adjuvant chemotherapy alone or both adjuvant radiation and concurrent chemotherapy. Patient characteristics were compared via a Chi Square, Fisher's Exact test, and Mann Whitney test where appropriate. Kaplan Meier analyses of overall survival (OS) were performed comparing patients who received postoperative radiation with those who did not. Further Kaplan Meier analyses were also performed based on the receipt of any adjuvant treatment. The variables analyzed were those who received no adjuvant chemotherapy or radiation, those who received adjuvant radiation only, those who received adjuvant chemotherapy only, and those who received both adjuvant chemotherapy and radiation. Univariate and multivariate Cox regression were performed to determine the influence of covariates on survival. The variables that were significant on univariate analysis were included in the multivariate analysis. Variables measured in the univariate analysis included age (continuous), receipt of adjuvant treatment (no adjuvant treatment, adjuvant radiation only, adjuvant chemotherapy only, or adjuvant chemotherapy and radiation), grade of disease (1,2 or 3), modified Charlson/Deyo score (0, 1, or ≥2), number of nodes examined (≤10, >10, unknown), number of positive lymph nodes (1, 2–5, >5), FIGO invasion (IA, IB, II, IIIA, IIIB, IV), FIGO nodal status (IIIC1, IIIC2), year of diagnosis (2004–2011 in yearly increments), facility type (community cancer program, comprehensive community cancer program, academic program) and race (White, Black, Other). For the use of facility type variable, only those treated at one center were included, as otherwise we cannot determine which treatments were received at each facility type. All variables except for facility type were also utilized in the multivariate analysis. Data regarding local control and cause of death are not available in the National Cancer Database. Significant values were defined as those with a p-value < 0.05. Statistical analysis was performed using SPSS, Version 23 (IBM Inc., Armonk, NY).

3. Results

3.1. Patient characteristics

There were 6720 women included in this study, with a median age of 62 years (interquartile range 55–70 years). The median follow up for all women was 38.9 months (interquartile range 23.2–63.6 months) and the median follow up for living women was 47.6 months (interquartile range 28.6–71.5 months). The breakdown of adjuvant treatment was as follows: 1409 (20.9%) received no adjuvant treatment, 1533 (22.8%) received CT only, 1265 (18.8%) received RT only, and 2522 (37.5%) received CMT.

Of the 3787 women noted above who received adjuvant radiation, 2110 women (55.7%) received external beam radiation alone, 498 (13.2%) received brachytherapy alone, and 1182 (31.2%) received external beam radiation plus brachytherapy boost.

Information regarding the sequencing of chemotherapy with radiation was available for 2268 women. For 1536 women (67.8%), chemotherapy was delivered prior to the radiation treatments. An additional 328 women (14.5%) received chemoradiation and 404 women (17.8%) received their radiation prior to chemotherapy. Table 1 lists several characteristics among the groups.

3.2. Overall survival

There was a significant improvement in overall survival associated with adjuvant radiation. Those who received adjuvant radiation had a 5-year overall survival of 69.2% compared to 59.6% for those who did not receive adjuvant radiation ($p < 0.001$) (Fig. 1). There was a similar survival benefit noted in those who received chemotherapy (69.5% versus 59.2%, $p < 0.001$). We also compared overall survival among women who received no adjuvant therapy, adjuvant radiation alone, adjuvant chemotherapy alone, or both chemotherapy and radiation (Fig. 2). The 5-year overall survival was 72.6% for those who received both chemotherapy and radiation, which was superior to all other groups on pairwise analysis ($p < 0.001$). The 5-year overall survival for those who received no adjuvant therapy, adjuvant radiation alone, and adjuvant chemotherapy alone were 54.9%, 63.9%, and 64.4%, respectively. On pairwise analysis, there was no difference in survival between

Please cite this article as: A.T. Wong, et al., Utilization of adjuvant therapies and their impact on survival for women with stage IIIC endometrial adenocarcinoma, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.07.091