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Original Article

Treatment outcomes of locally advanced cervical cancer by histopathological types in a single institution: A propensity score matching study

Kuang-Cheng Yin [a], Chien-Hsing Lu [b], Jin-Ching Lin [a], Chiann-Yi Hsu [c], Lily Wang [a,*]

[a] *Department of Radiation Oncology, Taichung Veterans General Hospital, 40705, Taichung, Taiwan*
[b] *Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, 40705, Taichung, Taiwan*
[c] *Biostatics Task Force, Taichung Veterans General Hospital, 40705, Taichung, Taiwan*

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Background: In the current National Comprehensive Cancer Network (NCCN) guidelines, the standard treatment methods revealed no difference between locally advanced cervical (LAC) adenocarcinoma/adenosquamous carcinoma (AC/ASC) and LAC squamous cell carcinoma (SCC). The aim of this study was to compare the treatment outcomes of LAC AC/ASC with LAC SCC through the propensity score matching (PSM) analysis.
Methods: This retrospective study enrolled 181 LAC cancer patients who were treated with intensity modulated radiotherapy/volumetric modulated arc therapy and concurrent weekly cisplatin 30–40 mg/m^2. In total, there were 151 LAC SCC patients and 30 LAC AC/ASC patients. The endpoints were overall survival (OS), disease-free survival (DFS), locoregional failure-free survival (LRFFS), and distant metastasis-free survival (DMFS). A 1:1 ratio PSM analysis was performed using the nearest neighbor method with a caliper of 0.20. Treatment outcomes were compared between 30 matched LAC SCC patients and 30 LAC AC/ASC patients.
Results: Before a 1:1 ratio PSM, the 5-year OS, DFS, LRFFS, and DMFS in the LAC SCC group were 78.6%, 71.3%, 88.2%, and 76.2%, respectively. After a 1:1 ratio PSM, the 5-year OS, DFS, LRFFS, and DMFS in the LAC AC/ASC group were 46.0%, 43.3%, 70.0%, and 45.4%, respectively, which were all significantly inferior than the rates of 90.0%, 75.8%, 96.6%, and 78.8% in the matched LAC SCC group, respectively ($p < 0.05$).

* Corresponding author. Department of Radiation Oncology, 1650 Taiwan Boulevard Sect. 4, Taichung 40705, Taiwan, ROC. Fax: +886 423741316.
E-mail address: llwang1212@gmail.com (L. Wang).

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Conclusion: LAC AC/ASC carries a poorer prognosis than LAC SCC. LAC AC/ASC needs more aggressive treatment in order to achieve higher OS and DFS.

Introduction

From 1991 to 2007, approximately 1800–3000 patients annually were newly diagnosed with invasive cervical cancer annually in Taiwan.[1] In 2012, research into worldwide cancer incidence manifested cancer of the uterine cervix to become the fourth most common cancer in women with estimated 528,000 new cases and 266,000 deaths.[2] In the 1950s and 1960s, squamous cell carcinoma (SCC) constituted 90% of invasive cervical cancer, while adenocarcinoma (AC) or adenosquamous carcinoma (ASC) accounted for 5%–10% of invasive cervical cancer.[3] Recent studies have demonstrated an increased proportion of cervical adenocarcinoma, not only in Western countries but also in Taiwan.[1,4] Regardless of histopathological types, cisplatin-based concurrent chemoradiotherapy (CCRT) has been established as the cornerstone in which to engage locally advanced cervical (LAC) cancer through previously prospective randomized control studies.[5–7] In cervical cancer stage IB to IIA randomized study, cervical AC seemed less effective to radiotherapy.[8] Additionally, more evidence has revealed that cervical AC behaved differently from cervical SCC.[3,9] However, owing to the rare number of cases of cervical AC, few prospective studies were designed to evaluate the prognostic distinction between cervical AC/ASC and cervical SCC. To the authors' knowledge, the most recent understanding of the prognostic impacts of LAC AC/ASC came primarily from retrospective studies. Some retrospective articles have suggested that patients with cervical AC/ASC possessed poorer prognostic outcomes,[10–14] while others have revealed contradictory evidence.[12,15]

In our preceding study, we reported on 125 patients diagnosed with LAC cancer from January 2004 to November 2010.[16] AC histology was an independently poor prognostic factor for overall survival, local failure-free survival, and disease-free survival. The aim of this study was to compare the treatment outcomes of LAC AC/ASC with LAC SCC under similar treatment intensities, pre-treatment condition, and initial clinical status through the propensity score matching (PSM) analysis.

Materials and methods

Patients

From January 2004 to April 2016, 181 new cases of LAC cancer were documented at the radiation oncology department of Taichung Veterans General Hospital (TC-VGH), Taiwan, Republic of China. The inclusion criteria included (1) age $\geq$ 18 years old; (2) International Federation of Gynecology and Obstetrics (FIGO) stage: IB2, IIA2, IIB, IIIA, IIIB, and IVA; (3) histopathological-proven SCC, AC, or ASC; (4) no evidence of distant metastasis except para-aortic (PA) lymph node (LN) metastasis; and (5) receiving chemotherapy with a single concurrent weekly cisplatin. The exclusion criteria included (1) pregnant women; (2) histopathological types except SCC, AC, and ASC; (3) an incomplete treatment course of radiotherapy; (4) patients with the second primary cervical cancer; (5) those who had received neoadjuvant chemotherapy or surgical intervention before CCRT. The flowchart (Fig. 1) demonstrated the inclusion criteria and exclusion of the patients. In total, the 181 LAC cancer cases composed of four LAC ASC patients, 26 LAC AC patients, and 151 LAC SC patients were used in this study.

Initial tumor staging workup included comprehensive history information, a clinical physical examination, bimanual pelvic and rectal examinations, a cervical biopsy, a chest X-ray, whole body bone scan, a diagnostic abdomen and pelvic computed tomography (CT) scan, complete blood cell count, serologic chemistry profiles (including liver and renal function tests), and tumor markers (including SCC antigen, carcinoembryonic antigen, and cancer antigen 125). If bladder or rectal invasion was clinically suspected, cystoscopy or proctoscopy was indicated. A Positron Emission Tomography (PET)-CT scan was elective if clinically indicated. Tumor staging was defined in accordance with FIGO staging system. Before the CCRT, each patient signed an informed consent. This retrospective study was approved by the TC-VGH Clinical Research Ethics Committee (Institutional Review Board number: CE17233A).

Radiotherapy

All 181 patients were scheduled to undergo intensity-modulated radiotherapy (IMRT)/volumetric-modulated arc therapy (VMAT) and high-dose rate intracavitary brachytherapy (HDR-ICBT). Of all the 181 LAC cancer patients, 146 received IMRT, and 35 received VMAT. The IMRT treatment planning was delivered using a dynamic multileaf accelerator with a 10-MV photon (400 MU/min). The VMAT treatment planning was delivered using a dynamic multileaf accelerator with a 10-MV photon (0–600 MU/min).

The gross tumor volume (GTV) delineation included the cervix, cervical tumor, and uterus. GTV-N delineation contained gross pelvic LN(s) $\geq$ 0.8 cm. The clinical target volume (CTV) delineation stretched a 0.5–1.0 cm margin from GTV radially and covered the upper half vagina, parametria, and regional LNs. The regional LNs included the common iliac, external iliac, internal iliac, and presacral regions. The CTV field extended from the L4-5 interspace to 3 cm below the most distal cervical site of disease. The planned target volume (PTV) expanded a 0.7–1.0 cm margin from CTV superiorly, inferiorly, and radially. A total

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