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Isolated para-aortic lymph node metastasis in FIGO stage IA2-IB2 carcinoma of the cervix: Revisiting the role of surgical assessment

Marcela G. del Carmen [a,*], Rene Pareja [b], Alexander Melamed [a], Juliana Rodriguez [b], Anna Greer [a], Rachel M. Clark [a], Laurel W. Rice [c]

[a] Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States of America
[b] Gynecologic Oncology Department, National Cancer Institute, Bogota, Colombia
[c] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States of America

HIGHLIGHTS

- Isolated para-aortic lymph node metastases are rare in cervical cancer.
- Para-aortic nodal metastases are more common when pelvic nodes are involved.
- Surgical assessment of the para-aortic lymph nodes in patients with early-stage cervical cancer may be safely omitted.
- Para-aortic lymphadenectomy does not confer survival advantage.

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ABSTRACT

Objectives. To investigate the utility of para-aortic lymph node dissection among women undergoing radical hysterectomy and pelvic lymph adenectomy for FIGO Stage IA2-IB2 cervical cancer using the National Cancer Database (NCDB).

Methods. We identified patients with stage IA2-IB2 squamous cell, adenosquamous, or adenocarcinoma of the cervix diagnosed 2011–2014 in the NCDB. The primary outcome was the negative predictive value of histologically assessed pelvic lymph node status for para-aortic lymph node status among women undergoing pelvic and para-aortic lymph node dissection. We calculated probability of para-aortic lymph node metastasis conditional on pelvic lymph node status. Finally, we compared overall survival between patients undergoing para-aortic lymph node dissection and those in whom this procedure was omitted.

Results. A total of 3212 patients met study inclusion criteria, of whom 994 (30.9%) underwent para-aortic lymph node dissection. In this group, the risk of isolated para-aortic metastasis was 0.11%. The negative predictive value of surgically assessed pelvic lymph nodes to predict para-aortic lymph node status was 99.9% (95% CI 99.9–99.9). Among 93 patients with pelvic lymph node metastasis, 18 (19.4%) had concurrent para-aortic lymph node metastasis. There was no difference in overall survival between women undergoing pelvic and para-aortic lymph node dissection compared with those undergoing pelvic lymphadenectomy only ($p = 0.69$).

Conclusions. In patients undergoing radical hysterectomy and pelvic lymphadenectomy for stage IA2-IB2 cervical cancer, para-aortic lymph node dissection is not warranted based on the low risk of isolated metastatic disease, and lack of survival benefit associated with the procedure.

1. Introduction

The International Federation of Gynecology and Obstetrics (FIGO) has established a clinical staging system for cancer of the uterine cervix [1]. Although not included in the FIGO staging system, lymph nodal status remains one of the most important independent prognostic indicators for patients with early stage cervical cancer [2,3]. When compared to survival in patients with pathologically negative lymph nodes, survival rates in patients with patients with metastatic lymph nodal disease are much lower [4,5]. Median 5-year survival rates in patients with cervical cancer and without lymph nodal metastases are estimated to be of 80–100%, in contrast to 47–78% for patients with metastatic disease to the para-aortic lymph nodes [4,5].

* Corresponding author at: Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, United States of America.
E-mail address: mdelcarmen@mgh.harvard.edu (M.G. del Carmen).

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Lymph nodal involvement also influences designation of radiation treatment fields [5]. The presence of lymph node metastases also influences delivery of primary and/or adjuvant therapy. Although pelvic lymph node dissection is generally recommended in patients with early-stage, and operable cervical cancer, the role of para-aortic lymph node dissections in these cases is less clear and has remained elusive [6]. Recognition of metastatic para-aortic lymph node disease is critical since patients with metastatic para-aortic lymph nodes have a much more guarded prognosis and their treatment requires chemotherapy with extended-field radiation. Para-aortic lymph node dissection is generally a safe procedure when carried out by an expert surgeon. However, it requires additional surgical time and some related morbidity is to be expected [7–17]. Surgical complications from lymph nodal dissection include vascular, ureteral, nerve injury, as well as risk of infection, lymphocyst formation, lymphedema, and thrombophlebitis.

Although radiologic studies can be utilized to assess lymph nodal involvement in early-stage cervical cancer, imaging modalities have poor sensitivity for detecting small metastases, which could be diagnosed histologically following surgical resection of relevant nodal beds. Imaging by integrated 18-fluoro-2-deoxy-D-glucose positron emission tomography (PET)/computed tomography (CT) may have a higher sensitivity for detection of lymph nodal metastasis [18,19]. In a prospective study of 153 patients with advanced-stage cervical cancer, conducted by the American College of Radiology Imaging Network, imaging by PET/CT was associated with a modest increase in sensitivity for detection of lymph nodal metastases [20]. In a review of the peer-reviewed literature, inclusive of 15 studies, pooled estimates of PET imaging sensitivity and specificity for detection of para-aortic lymph node metastasis was reported to be 84% and 95%, respectively. These estimates were higher than for PET detection of pelvic lymph nodes (sensitivity: 79%; specificity: 99%) [21].

Several studies have identified limitations of PET/CT imaging in detection of para-aortic metastasis, with reported higher false-negative rates than previously noted [22–24]. Ramirez et al. reported on 60 patients with stage IB2-IVA cervical cancer undergoing para-aortic lymph node dissection following pre-operative PET/CT imaging [22]. Twelve percent of patients with negative PET/CT imaging of the para-aortic nodes were found to have occult histologically confirmed metastasis at the time of surgery [22]. In 22% of patients, pathologically positive para-aortic lymph nodes were encountered surgically, and in the setting of positive pelvic lymph nodes and negative para-aortic lymph nodes by pre-operative PET/CT imaging [22]. Uzan and colleagues compared rates of para-aortic nodal metastasis by PET/CT and pathologic evaluation and found that patients with positive pelvic lymph nodes by imaging were more likely to have para-aortic lymph nodal involvement than patients with PET-negative pelvic lymph nodes (24% vs 3%, respectively) [24]. Use of PET/CT imaging to assess lymph nodal involvement in early-stage cervical cancer is further limited by its cost and availability in resource-challenged settings, where the largest burden of cervical cancer is seen. The most appropriate use of PET/CT imaging for the evaluation of lymph nodes may be in the assessment of patients with locally-advanced cervical cancer, FIGO Stages IB2-IV, triaged for treatment with chemoradiation therapy.

Most available studies show that the incidence of para-aortic lymph node metastasis is highest, estimated to be 2–14%, among patients who also have metastatic disease in pelvic lymph nodes [7–17]. Isolated para-aortic lymph nodal metastases are rare, occurring in fewer than 1.5% of patients with early-stage cervical cancer [7–17]. In this study, we investigate the use and utility of para-aortic lymph node dissection among patients undergoing radical hysterectomy and pelvic lymphadenectomy for FIGO Stage IA2-IB2 cervical cancer in included in the National Cancer Database (NCDB). Specifically we describe the frequency of para-aortic lymph node dissection and factors associated with its use, evaluate whether the absence of pelvic lymph node metastasis can reliably exclude the presence of para-aortic lymph node metastasis, and assess whether para-aortic lymph node dissection is associated with overall survival.

2. Methods

We conducted a retrospective cohort study using data from NCDB, a joint program of the American Cancer Society and the American College of Surgeons [25]. This registry collects data from >1500 hospitals, and includes over 70% of all new cancer diagnoses in the United States (US). Data including demographic and clinical characteristics, histology, staging, cancer directed treatment, hospital characteristics, perioperative outcomes, and overall survival are reported by trained cancer registrars. This investigation was exempt from Institutional Review Board oversight by the Partners Healthcare Committee.

We identified patients diagnosed with FIGO stage IA2-IB2 carcinoma of the cervix and included squamous (International Classification of Disease for Oncology, 3rd Edition [ICD-O-3] codes: 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8078) adeno-squamous (ICD-O-3 codes: 8560, 8570) and adenocarcinoma (ICD-O-3 codes: 8140, 8144, 8255, 8384, 8480, 8481, 8482) histologic sub-types, diagnosed 2011–2014, utilizing the 2016 release of NCDB participant file [26]. Fig. 1 depicts the cohort diagram. We excluded patients who did not undergo radical hysterectomy (site-specific surgery codes other than 50–62) and pelvic lymphadenectomy (collaborative stage site-specific factor 3 code other than 40), and those who received no treatment at the reporting facility (case class 0).

We categorized patient age at diagnosis as <40, 40–49, 50–59, 60–69, 70–79 and 80 years or older. Race-ethnicity was defined as Asian, Black, Hispanic, White, or Other/Unknown. Tumor grade was classified using a three-point scale. We categorized tumor size as ≤2 cm, >2 cm, or unknown. We report the Charlson co morbidity index using the Deyo classification, categorized in the NCDB as 0, 1, and >2 [27–29]. Treating facility location was categorized by US Census Region (Northeast, South, Midwest, and West). We categorized insurance type as privately insured, Medicaid, Medicare, other government insurance, or uninsured.

The primary study outcome of interest was the negative predictive value of pelvic lymph node status for paraaortic lymph node status. We also calculated the proportion of patients with pelvic and paraaortic lymph node metastasis. Lastly, we compared overall survival between patients who underwent para-aortic lymph node dissection and those among whom this procedure was omitted.

Univariate analyses to determine variables associated with para-aortic lymph node dissection were conducted using t- and χ^2-tests. We plotted survival functions using the Kaplan-Meier method, and compared them using the log-rank test. We estimated unadjusted hazard ratios using a univariate Cox proportional hazard model. To adjust for measured confounders, we constructed a Cox model that included variables which were a priori considered to be potential confounders of the relationship between treatment and survival including: patient age, tumor size, grade, histologic subtype, Charlson comorbidity index, year of diagnosis, insurance status, and region. All analyses were performed in STATA 14.2 [30].

3. Results

A total of 3212 women had FIGO Stage IA2-IB2 between 2011 and 2014. Sixty-nine percent (2218 of 3212 patients) underwent pelvic lymph node dissection only at the time of radical hysterectomy. A total of 994 of 3212 patients (30.9%) underwent a concurrent para-aortic lymph node dissection at the time of radical hysterectomy and pelvic lymph node dissection. Table 1 summarizes the patient demographic and tumor characteristics of the study population. There were no age-, race/ethnicity-, comorbidity-, regional- or tumor histology-related differences when comparing patients undergoing assessment of para-aortic lymph nodes to those where the procedure was omitted. Out of 994 patients who underwent surgical assessment of their para-

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