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Prognostic significance of residual lymph node status after definitive chemoradiotherapy in patients with node-positive cervical cancer

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HIGHLIGHTS

- Residual lymph node after chemoradiotherapy was associated with worse survival.
- Lymph node response had a greater prognostic significance than primary tumor response.
- Central necrosis of lymph node was associated with worse survival.

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ABSTRACT

Objective. Lymph node involvement is an important prognostic factor in patients with cervical cancer. However, the prognostic significance of lymph node response to chemoradiotherapy remains unclear. We retrospectively analyzed the relationship between residual lymph node status after definitive chemoradiotherapy and survival.

Methods. We enrolled 117 patients with node-positive cervical cancer. All patients were treated with definitive chemoradiotherapy in our institution, from 2006 to 2016. The median follow-up period was 41 months (range, 6–128 months). The criterion for a positive lymph node was defined as a maximum short axis diameter of ≥8 mm on pretreatment magnetic resonance imaging (MRI)/computed tomography (CT) scans. Posttreatment pelvic MRI was obtained 3 months after the completion of chemoradiotherapy. Residual primary tumor was defined as any residual lesion identified upon clinical examination and/or MRI. Residual lymph node was defined as any lymph node with a short axis diameter of ≥8 mm posttreatment, according to MRI/CT.

Results. At follow-up, 3 months after chemoradiotherapy, we observed residual primary tumor in 30 patients (25.6%), and residual lymph node in 31 patients (26.5%). The presence of residual lymph node was associated with worse overall survival according to multivariate analysis (hazard ratio, 3.04; 95% confidence interval, 1.43–6.44; $p = 0.004$). In the 5-year time-dependent ROC analysis of survival prediction, the presence of residual lymph node showed an AUC value of 0.72.

Conclusions. The presence of residual lymph node after chemoradiotherapy was associated with worse survival in patients with node-positive cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide [1]. Lymph node involvement is one of the most important prognostic factors in cervical cancer patients [2–4]. Although the International Federation of Gynecology and Obstetrics' (FIGO) current staging system for cervical cancer does not account for lymph node involvement, the initial workup of patients usually includes lymph

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node assessment. The incidence of lymph node involvement has been reported as 20–60% among patients with cervical cancer [3,5–7].

The primary treatment option for patients with node-positive cervical cancer is definitive concurrent chemoradiotherapy with cisplatin. The impact of the response to chemoradiotherapy on survival is known, but previous studies have mainly focused on the evaluation of primary tumor response to predict clinical outcome [8–10]. Given that the significance of lymph node response after chemoradiation is not well understood, we retrospectively analyzed the prognostic relevance of residual lymph node after definitive chemoradiotherapy with survival in patients with node-positive cervical cancer.

2. Materials and methods

2.1. Patient selection

We reviewed the medical records of 238 consecutive patients, after approval from the institutional review board. These patients were treated in our institution with concurrent chemoradiotherapy with cisplatin for pathologically proven cervical cancer, between 2006 and 2016. Of these patients, 39 were excluded for the following reasons: 6 patients had distant metastases other than at the para-aortic node at diagnosis (before receiving chemoradiotherapy); 1 patient received chemoradiotherapy for salvage aim; 1 patient was diagnosed with vaginal stump cancer; 2 patients refused intracavitary brachytherapy; 1 patient was not evaluated by any imaging modality at the staging work-up; and 28 patients were followed up for a short period (<3 months from the completion of chemoradiotherapy). Of the 199 patients remaining, 117 patients with pelvic and/or para-aortic lymph node involvement were included in this analysis (Supplementary Fig. 1).

2.2. Image analysis

A positive lymph node was defined as a lymph node with a maximum short axis diameter of ≥8 mm, according to pretreatment magnetic resonance imaging (MRI) and/or computed tomography (CT) [11–16]. Lymph node size was measured by one radiologist, using the axial T2-weighted MRI image and the abdominal contrast-enhanced axial CT (CECT) scan, using a measurement tool on the Picture Archiving and Communications System (PACS). For patients with multiple lymphadenopathies, the short-axis diameter of the largest lymph node was used for the analysis. Regarding morphologic appearance, the radiologist identified lymph nodes with central necrosis or perinodal infiltration, using pelvic MRI and/or abdominal CECT [16].

2.3. Concurrent chemoradiotherapy

All patients were treated with definitive concurrent chemoradiotherapy. Radiotherapy consisted of external beam radiotherapy (EBRT) and high-dose rate intracavitary brachytherapy. EBRT was delivered to the whole pelvis using 10 MV photons with customized shielding, in 1.8 Gy daily fractions, five times a week, for a total dose of 45 Gy. A four-field box technique was used. The superior border was the L4–L5 vertebral level. The inferior border was at the bottom of the obturator foramen, or 2–3 cm below the lowest extent of the cervical or vaginal disease. The lateral borders were placed 2 cm lateral to the inner bony margins of the true pelvis. For the lateral fields, the anterior border included the symphysis pubis, and the posterior border was the S2–3 interspace. For patients with para-aortic lymph node involvement, the superior border extended to the T12–L1 interspace. A parametrial boost was irradiated to patients with parametrial involvement (delivered in 5 fractions for a total of 10 Gy). Intracavitary brachytherapy was initiated after delivery of an EBRT dose of 39.6 Gy. Intracavitary brachytherapy was delivered twice a week in 5 fractions, with a fractional dose of 6 Gy at point A. At the end of parametrial boost, CT scans were performed. In cases where residual lymph node was identified, an additional boost of EBRT was irradiated (4–10 Gy) at the discretion of the treating radiation oncologist. The involved lymph nodes were contoured on brachytherapy planning system, and the total dose delivered to the lymph nodes was calculated from the sum of the doses of the EBRT and the intracavitary brachytherapy. Also, the biologic effective dose 10 (BED_{10}) was calculated from the sum of the BED_{10} from the sum of the BED_{10} of the EBRT and the intracavitary brachytherapy, using an α/β ratio of 10 Gy for tumor cell kill. Six cycles of weekly cisplatin were administered during radiotherapy, at a dose of 40 mg/m^2. The first course of cisplatin was administered on day 1 of radiotherapy.

2.4. Response evaluation

After completion of chemoradiotherapy, patients were followed up every 3 months during the first year, and every 6 months thereafter. Follow-up consisted of clinical examination and Papanicolaou smears, with other imaging modalities used at the physician's discretion (chest x-ray, CT, MRI, and/or ^{18}F-Fluorodeoxyglucose-positron emission tomography (PET)/CT). Post-treatment pelvic MRI scans were routinely obtained 3 months after the completion of chemoradiation. For patients with para-aortic lymph node involvement, abdominal CT scans were also obtained. A radiologist performed a retrospective review of the first post-treatment MRI and CT scans. Primary tumor response and lymph node response were evaluated separately. Residual primary tumor was defined as any residual lesion identified upon clinical examination and/or MRI. Residual lymph node was defined as any lymph node with a short axis diameter of ≥8 mm.

2.5. Statistical analysis

The primary endpoint was overall survival (OS) and the secondary endpoints were local control (LC), regional control (RC), distant metastasis-free survival (DMFS), and disease-free survival (DFS). These endpoints were reached at the first observation of a defined event, and all events were measured from the initiation of definitive chemoradiotherapy. For OS, the event was death due to any cause. For LC, the event could present as persistent disease, or as recurrence in the cervix or an adjacent pelvic organ. For RC, the event was defined as either recurrence in the pelvic or para-aortic lymph nodes or an increase from the initially involved nodes after treatment. For DMFS and DFS, the events were metastasis to distant sites (including distant lymph nodes e.g. mediastinal, supraclavicular regions), and disease recurrence or any cause of death, respectively.

The OS, LC, RC, DMFS, and DFS endpoints were estimated using the Kaplan-Meier method, and the differences were compared using log-rank tests in univariate analysis. Multivariate analysis using the Cox proportional hazards model was performed to identify independent predictors among the prognostic factors. Correlation between treatment response and other variables was evaluated using logistic regression analysis. Time-dependent receiver-operating characteristic (ROC) curves were drawn to evaluate survival or recurrence, according to the prognostic factors that had statistical significance in multivariate analysis. The area under the curve (AUC) with a 95% confidence interval (CI) was used to evaluate the influence of prognostic factors [17]. p values of <0.05 were considered statistically significant. All statistical analysis was performed using the R statistical language (Version 3.4.1, The R Project) (http://www.R-project.org).

3. Results

The patient and treatment characteristics are summarized in Table 1. The median age at diagnosis was 52 years (range, 23–80). The FIGO stage was IIB, IIIA, IIIB, and IVA, in 88 (75.2%), 7 (6.0%), 13 (11.1%), and 9 (7.7%) patients, respectively. The median primary cervical tumor size was 53 mm (range, 20–115 mm), and the median lymph

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