Concurrent Chemoradiotherapy for Non-bulky Stage IB/II Cervical Cancer Without Pelvic Node Enlargement

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Abstract. Background: Concurrent chemoradiotherapy (CCRT) has not been extensively studied in patients with small cervical cancer tumors with no pelvic node enlargement. Patients and Methods: We retrospectively analyzed 55 patients with stage IB1-IIB cervical cancer and tumors of ≤40 mm with no pelvic node enlargement treated with radiotherapy (RT)-alone. Results: Cancer recurred in seven patients. Patient age (≤63 years) was identified as an independent factor for better disease-free survival (DFS) (p=0.027), and tumor size (≥25 mm) had a tendency to correlate with reduced locoregional DFS (p=0.089) by the Cox hazard model. Among patients aged 63 years or less, cancer recurred in five out of 18 patients with tumors of ≥25 mm, but in only one of 10 patients with tumors of ≤24 mm. Conclusion: In patients with stage IB1-IIB cervical cancer and small tumors with no node enlargement, CCRT may provide a better disease control for the group aged 63 years or less and with tumor size of 25 mm or more.

Carcinoma of the uterine cervix is a significant cause of cancer-related mortality in women. A clinical alert released by the National Cancer Institute reported significantly higher survival after treatment of locally advanced cervical cancer with concurrent chemoradiotherapy (CCRT) (1). CCRT can be performed in patients with a variety of cancer types at different stages, ranging from stage IB1, with a relatively good prognosis according to the International Federation of Gynecology and Obstetrics (FIGO), stage IVA with poor prognosis. CCRT has proven effective in the definitive treatment of more advanced-stage disease (2-6). However, this approach has not been extensively studied in patients with stage IB1 or IIA1 disease. The risk-benefit ratio should be considered in patients with small tumors.

In a randomized Italian study comparing radiotherapy (RT) alone versus radical hysterectomy and lymph node dissection for stage IB-IIA cervical cancer, outcomes were identical in patients treated with RT and those treated with surgery (7). For patients with stage IB1 or IIA1 cancer for whom hysterectomy is not indicated, RT without concurrent chemotherapy was chosen due to possible adverse effects. A prospective study conducted in Japan showed that definitive RT is an effective and safe treatment for stage I and II cervical cancer patients with small (<40 mm) tumors, however, cancer recurred in four out of 22 patients with tumors ≥30 mm (8). Analysis of two trials conducted by the Gynecologic Oncology Group (GOG) after long-term follow-up demonstrated better overall (OS) and disease-free (DFS) survival in patients with stage IB-IIIB disease treated with CCRT compared to those treated with RT-alone (9). For the subset of patients with favorable prognosis, RT-alone may be a suitable choice. However, CCRT may be a better choice for patients with unfavorable prognosis.

In the present study, predictive factors for recurrence were identified in patients with stage IB1-IIB cervical cancer and small tumors with no pelvic lymph node enlargement treated with RT-alone to select candidates for CCRT.

Patients and Methods

We retrospectively analyzed 55 patients with FIGO stage IB1-IIB cervical cancer with local tumors of 40 mm or less who were treated with RT between 1997 and 2009 at the University Hospital of Ryukyus. Patients’ charts were reviewed for clinicopathological and serological data. RT was administered to patients with FIGO stage IB1-IIB cancer with local tumors of 40 mm or less assessed by pretreatment magnetic resonance imaging (MRI). Patients with pelvic or para-aortic lymph node enlargement greater than a minimum diameter of 10 mm assessed by pretreatment computed tomography (CT) or MRI were excluded. The eligibility criteria for patients were as follows: Eastern Cooperative Oncology Group performance status of 0, 1, or 2, and adequate hematological (white blood cell count, 3,000–10,000/μl; hemoglobin, 9.0 g/dl, and platelet count, 100,000/μl).
100,000/μl), hepatic (bilirubin level, 1.5 mg/dl and aspartate aminotransferase/alanine aminotransferase, 2.5× the upper limit of normal), renal (creatinine clearance, 60 ml/min), and cardiac function (normal electrocardiographic findings).

RT was performed as previously described elsewhere (10). In brief, patients were treated with anteroposterior and posteroanterior parallel-opposed ports or four-box fields of external beam radiotherapy (EBRT). A 50-Gy dose of EBRT was delivered in 25 fractions. The center shield (4 cm width at the midline) was set up after delivery of 20-40 Gy. High-dose rate intracavitary brachytherapy (HDR-ICBT) was delivered once per week at a fraction dose of 6 Gy administered three or four times at point A.

Follow-up examinations were conducted every month for the first year, every two months for the second year, and then subsequently every 3-6 months. OS, DFS, and locoregional DFS curves were estimated by the Kaplan–Meier method and differences were tested using the log-rank test. The Cox proportional hazard model was used to analyze prognostic factors for recurrence. A p-value of less than 0.05 was considered significant. All patients provided written informed consent. This retrospective study was conducted according to the principles stated in the Declaration of Helsinki (1964) and all subsequent revisions, and approved by the Institutional Review Board of our university (#2011-366).

Results

Patients' characteristics are presented in Table I. The median age was 63 years (range, 37-75 years). Disease stage was determined according to the FIGO classification of 1994 (11). Squamous cell carcinoma was diagnosed in the majority of patients (96%). Median tumor size was 29 mm (range, 10-38 mm). The median follow-up period was 57 months (range: 7-157 months).

Discussion

The National Cancer Comprehensive Network Guidelines for Cervical Cancer stressed out that the risk/benefit ratio should be carefully considered when evaluating indications for CCRT in patients with small tumors (12). Although CCRT has proven effective for the treatment of more advanced disease, this approach has not been specifically studied in patients with stage IB1 or IIA1 cervical cancer (2-6). In our study, 55 patients with stage IB1-IIA cervical cancer and local tumors of 40 mm or less were treated with RT-alone. The 5-year OS and DFS rates of all patients were excellent, despite recurrence in seven patients. In the analysis of prognostic factors, patient age of 63 years or less and tumor size of 25 mm or more were identified as factors positively-influencing recurrence.

A significant correlation with better DFS was found for patient age of 63 years or less by univariate (p=0.042) analysis (Table III). When assessed by the Cox proportional regression analysis, patient age of 63 years or less was identified as a factor significantly correlating with better DFS (p=0.027) (Table IV), and tumor size of 25 mm or more had a tendency to correlate with reduced locoregional DFS (p=0.089). With regards to recurrence by primary tumor size, recurrence occurred in only one patient with a primary tumor of less than 25 mm in diameter. Analysis of initial recurrences by age group revealed only one recurrence in patients greater than 63 years old outside the previously irradiated field. Among patients 63 years or younger, cancer recurred in five out of 18 patients with tumors of 25 mm or more and in only one out of 10 patients with tumors of 24 mm or less (Figure 1).

Complete response was defined as no clinically or pathologically-viable cancer cells three months after completion of RT. Clinically- and pathologically-complete response was achieved in all 55 patients. The 5-year OS, DFS, and locoregional DFS of all patients treated with RT were 96.1%, 86.4%, and 92.5%, respectively. Cancer recurred in seven out of 55 (12.7%) patients. Locoregional recurrence was recorded in four patients. Sites of distant and locoregional recurrence are mentioned in Table II.

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The influence of patient age as a prognostic factor in patients with cervical cancer treated with RT is unclear.
Meanwell et al. demonstrated that for women with stage IB disease treated with RT alone, the 5-year survival rate non-linearly decreased from 71% in the 25- to 29-year-old group to 65% in the 65- to 69-year-old group (13). To evaluate the prognostic importance of age in patients with stage IB cervical cancer treated with curative RT, Dattoli et al. reviewed the results of 131 patients treated between 1974 and 1985. The 5-year OS rate in that study was 65%, and survival rates in patients aged 40 years or less and more than 40 years were 42% and 90%, respectively ($p=0.005$), indicating that age had a profound influence on survival in women with stage IB cervical cancer (14). Grigien et al. found no significant relationship between age and survival in an analysis of 162 patients with FIGO stage IIA-IIIB cervical cancer treated with RT (15). In our study, older age was found to be an independent factor predictive of recurrence. The results of our study conflicted with those of previous studies, possibly because of differences in patient population and RT prescription. The effect of age on survival of patients with cervical cancer treated with RT is still not fully understood.

Eifel et al. proposed a subclassification of stages I and II cervical cancer based on tumor diameter. They found that tumor size was one of the most important parameters affecting local control in RT for cervical cancer and that tumor size varied widely even within patients with the same FIGO stage. However, in the specific study, data for patients with tumors of 40 mm or more were not investigated in detail (16). A long-term follow-up study from Japan was performed to evaluate the efficacy of and late toxicity resulting from high-dose rate intracavitary brachytherapy (HDR-ICBT) for stage IB-III cervical cancer. The 10-year cancer-specific survival rates in patients with stage IB disease and tumors of less than 30 mm and 30-50 mm were 90.2% and 86.4%, respectively. These rates in stage II patients with tumors less than 30 mm, 30-50 mm, and greater than 50 mm were 79.3%, 75.0%, and 53.3%, respectively, and in stage III patients, they were 76.9%, 61.1%, and 46.4%, respectively. A significant relationship between tumor size and treatment outcome was noted for patients with stage II and III disease, but no such relationship was found between these parameters in stage I disease in the specific study (17). Results of a prospective Japanese study demonstrated that definitive RT is an effective treatment for patients with stage I and II cervical cancer with small tumors (<40 mm). Although the median age was 73 years in that study, cancer recurred in four out of 22 patients with tumors of 30 mm or more, and no pelvic recurrences occurred in 30 patients with tumors less than 30 mm in diameter. The incidence of distant metastasis increased with an increase in tumor diameter (8). Therefore, tumor size may also be an important prognostic factor in patients with cervical cancer and smaller tumors treated with RT alone.

Furthermore, several differences have been described in standard RT treatment for cervical cancer in Japan compared to Western countries (18, 19). In Japan, the prescribed RT dose for treatment of cervical cancer is lower, EBRT is performed using a central shield during the latter half of treatment using the anteroposterior parallel opposing technique, and HDR-ICBT is usually performed as brachytherapy. However, results from retrospective and prospective studies conducted in Japan have proven that these lower RT doses combined with HDR-ICBT are sufficient to eradicate cervical cancer cells (8, 10, 19).

Table III. Univariate analysis of 5-year disease-free and locoregional disease-free survival (n=55).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>DFS (%)</th>
<th>p-value*</th>
<th>LDFS (%)</th>
<th>p-value*</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>&gt;63</td>
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<td>96.2</td>
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<td>≤63</td>
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<td>0.000</td>
<td>88.9</td>
<td>0.000</td>
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<tr>
<td>Tumor size (cm)</td>
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<tr>
<td>≥2.5</td>
<td>40</td>
<td>84.4</td>
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<td>89.7</td>
<td>0.217</td>
</tr>
<tr>
<td>&lt;2.5</td>
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<td>IB1, IIA</td>
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<td>96.3</td>
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<tr>
<td>IIB</td>
<td>26</td>
<td>80.4</td>
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<td>88.5</td>
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</table>

LDFS: Locoregional disease-free survival, DFS: Disease-free survival, FIGO: International Federation of Gynecology and Obstetrics; *log-rank test.

Table IV. Multivariate analysis for disease-free survival (n=55).

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
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<tr>
<td>Stage IIB</td>
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<td>Tumor size ≥2.5 cm</td>
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<tr>
<td>Age ≤63 years</td>
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DFS: Disease-free survival, HR: hazards ratio, CI: confidence interval.

Figure 1. Recurrence by tumor size in patients aged 63 years or less (n=28).


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