Abstract.  Aim: To identify predictive factors for locoregional recurrence in patients with FIGO stage IB-IIB cervical cancer treated with concurrent chemoradiotherapy (CCRT). Patients and Methods: Data were analyzed for 123 patients with FIGO stage IB-IIB squamous cell carcinoma of the cervix between 1997 and 2007. Eligibility for CCRT included tumor size >4 cm and/or lymph node enlargement over a minimum diameter of 1 cm. Results: Tumor size (≥5.2 cm) and age (<48 years) were independent predictive factors for locoregional recurrence by multivariate analysis. Based on these two factors, the patients were divided into low-risk (n=91) and high-risk (n=32) groups for locoregional recurrence. The 5-year disease-free survival for the low-risk group was 95.3%, which was significantly better than 65.5% for the high-risk group (p<0.0001). Locoregional recurrence was noted in 10 out of the 32 patients in the high-risk group compared to only 3 out of the 91 patients in the low-risk group. Conclusion: To improve locoregional control in the high-risk group, it may be worthwhile to consider CCRT using new radiosensitizing agents, adjuvant hysterectomy or adjuvant chemotherapy.

Carcinoma of the uterine cervix is a significant cause of death from cancer in women. The US National Cancer Institute released a clinical alert for practicing oncologists based on research showing significant improvement in survival when locally advanced carcinoma of the uterine cervix is treated with concurrent chemoradiotherapy (CCRT) (1). Five clinical trials have shown a 30%-50% improvement in survival with a local control rate of approximately 90% (2-6). In addition, several reports describing the results of long-term follow-up and late adverse effects have been published (7-9).

CCRT can be performed for a wide range of patients with different stages of cancer, ranging from the relatively good prognosis of International Federation of Gynecology and Obstetrics (FIGO) stage IB to poor prognosis of stage IVA. For the subset of patients with favorable prognosis, regular follow-up may be a suitable choice, however, for patients with unfavorable prognosis, consolidation chemotherapy or another novel therapeutic modality may be a suitable choice after CCRT. In a retrospective analysis of 106 patients with stage IB-IIB cervical cancer treated with CCRT (10), Kim et al. reported that a large tumor volume, uterine body invasion, and pelvic lymph node enlargement showed significantly unfavorable influence on overall survival (OS). Tseng et al. recently generated a nomogram for stage IIB-IV A cervical cancer treated by CCRT which can be used as a predictive tool to counsel patients in predicting outcomes (11). The results of another report on advanced cervical cancer treated with CCRT were in agreement with our findings that tumor size and lymph node metastases are important risk factors (12). However, given the heterogeneous nature of the disease, it is very difficult to develop a predictive tool suitable for all patient subgroups.

In this study, we focused on identifying predictive factors for locoregional recurrence in patients with stage IB1-IIB cervical cancer treated with CCRT.

Patients and Methods

Data were retrospectively analyzed for 123 patients with stage IB-IIB squamous cell carcinoma of the uterine cervix who were treated with CCRT between 1997 and 2007 at the University of the Ryukyus Hospital. Patient charts were reviewed for clinicopathological and serological data. CCRT was administered to patients with local tumors of 4 cm or more as assessed by pretreatment magnetic resonance imaging (MRI), or pelvic lymph node enlargement over a minimum diameter of 1 cm assessed by pretreatment computed tomography (CT) or MRI. Patients with para-aortic lymph node enlargement were
Studies have reported on the prognostic factors in cervical cancer patients treated with various treatment modalities. Several risk factors associated with poor survival have been identified in patients with cervical cancer. These factors include advanced stage, large tumor size, poor performance status, and high serum SCC-Ag levels. The identification of these risk factors allows for better patient selection and management, leading to improved outcomes and survival rates.

**Results**

Patient characteristics are given in Table I. The median age was 47 years (range: 25-70 years). The median follow-up period was 51 months (range: 8-125 months). Disease stage was determined according to the FIGO 1994 classification. Most patients had stage IIB disease. Clinically and pathologically complete response was achieved in 107 out of 123 patients (87.0%). The 5-year OS and DFS of all patients treated with CCRT were 82.7% and 74.3%, respectively. The 5-year local and distant DFS of all patients were 89.1% and 85.3%, respectively. Thirty of the 123 patients (24.4%) experienced recurrence (Table II). Fifteen patients experienced locoregional recurrence (of whom 13 experienced locoregional recurrence alone, and 2 patients experienced both distant and locoregional recurrence), and the remaining 15 patients showed distant metastasis. Sites of distant and locoregional recurrence are given in Table II.

The cut-offs of serum SCC-Ag level, pretreatment hemoglobin level, tumor size, and patient age at the time of treatment were determined as 2.6 ng/ml, 8.9 g/dl, 5.2 cm, and 48 years, respectively, by ROC curve (data not shown). Tumor size (≥5.2 cm), pretreatment hemoglobin (≤8.9 g/dl), and patient age (<48 years) were significantly correlated with locoregional recurrence by univariate analysis (Table III).

When all these variables were assessed by the Cox proportional regression analysis, tumor size (≥5.2 cm) (p=0.01) and patient age (<48 years) (p=0.002) were identified as factors correlating significantly with locoregional recurrence (Table IV). The locoregional DFS curve shown in Figure 1 stratifies the patients according to both factors of tumor size and patient age. Based on these two factors, the patients were divided into low-risk (n=91) and high-risk (n=32) groups for locoregional recurrence. Ten of the 32 patients with both factors had locoregional recurrence. The 5-year locoregional DFS in the high-risk group was 65.5%, which was significantly worse than 95.3% in the low-risk group (p<0.001). Locoregional recurrence developed within 12 months in all 10 patients.

**Discussion**

Studies have reported on the prognostic factors in cervical cancer patients treated with various treatment modalities. Several risk factors associated with poor survival have been identified in...
cervical cancer patients; these include high pretreatment SCC-Ag levels, advanced stage, positive pelvic/para-aortic lymph nodes on imaging, histology, tumor size, FIGO stage, and initial hemoglobin level (11-14). However, a few studies have described the prognostic factors in patients treated with CCRT. Kim et al. reported that a large tumor volume (≥30 ml; \( p = 0.012 \)), uterine body invasion (\( p = 0.020 \)) and positive pelvic lymph node enlargement (\( p = 0.040 \)) had a significantly unfavorable influence on OS in a retrospective analysis of 106 patients with stage IB-IIIB cervical carcinoma treated with CCRT (10). Tseng et al. generated a nomogram for predicting 5-year OS based on the Cox regression model from 7 parameters, including age, serum SCC-Ag, tumor size, parametrium invasion, hydronephrosis, bladder/rectum invasion, and lymph node metastases among patients with stage IIB-IV A squamous cell carcinoma of the uterine cervix who underwent CCRT (11). The results of another study on advanced cervical cancer treated with CCRT were in agreement with our findings that tumor size and lymph node metastasis are important risk factors (12). In our study population, tumor size (≥5.2 cm) and patient age (<48 years) were found to be independent predictors of locoregional recurrence by multivariate analysis.

Tumor size (or volume) is one of the most important predictive factors in patients treated with irradiation. Perez et al. conducted a retrospective analysis of 1178 patients with histologically proven invasive carcinoma of the uterine cervix treated with irradiation alone, and concluded that clinical stage and tumor size are critical factors for prognosis (15). In a French cooperative study from 1970 to 1993 on a group of 1875 patients with invasive carcinoma of the cervix treated with radiotherapy alone, Barillot et al. stressed that tumor size is a very important prognostic factor, and that tumor size per stage and nodal status should be systematically recorded to allow a better prediction of failure rates and compare literature reports (16). Perez et al. also demonstrated that clinical stage and tumor size were critical factors for prognosis, efficacy of therapy, and evaluation of results in carcinoma of the uterine cervix in 1499 patients (stages IA-IV A) treated with definitive irradiation (17). Toita et al. also reported that anterior-posterior tumor diameter assessed by MRI was a significant prognostic factor in uterine cervical cancer treated with irradiation and predominantly affected the incidence of distant metastasis (18). Thus, there is a consensus that tumor size is crucial in cervical cancer patients treated with irradiation, which is consistent with our results.

On the other hand, whether patient age at the time of treatment is a prognostic factor in cervical cancer patients undergoing radiation is unclear. Meanwell et al. demonstrated that for women presenting with the common characteristics associated with stage IB disease and treated with radical radiotherapy, the 5-year survival rate decreased non-linearly from 71% in the 25- to 29-year group to 65% in the 65- to 69-year group. They concluded that young age alone is not a reason to alter existing policies for treatment of patients with invasive cervical cancer (19). To evaluate the prognostic importance of age in patients with stage IB

Table III. Univariate analysis for locoregional recurrence.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off</th>
<th>No. of patients (n=123)</th>
<th>LRR cases</th>
<th>5-year PFS (%)</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum SCCAg (ng/ml)</td>
<td>≥2.6</td>
<td>80</td>
<td>6</td>
<td>91.2</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>&lt;2.6</td>
<td>43</td>
<td>8</td>
<td>81.3</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>≥5.2</td>
<td>53</td>
<td>11</td>
<td>77.3</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>&lt;5.2</td>
<td>70</td>
<td>3</td>
<td>95.3</td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>&lt;8.9</td>
<td>14</td>
<td>4</td>
<td>70.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Hb level</td>
<td>≥8.9</td>
<td>109</td>
<td>10</td>
<td>89.8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;48</td>
<td>66</td>
<td>13</td>
<td>78.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Yes</td>
<td>42</td>
<td>6</td>
<td>85.0</td>
<td>0.5</td>
</tr>
<tr>
<td>PLN enlargement</td>
<td>Positive</td>
<td>44</td>
<td>5</td>
<td>87.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>79</td>
<td>9</td>
<td>87.7</td>
<td></td>
</tr>
</tbody>
</table>

LRR, Locoregional recurrence; PLN, pelvic lymph node.

Table IV. Multivariate analysis for locoregional recurrence.

<table>
<thead>
<tr>
<th>Locoregional recurrence</th>
<th>Cut-off</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>&lt;8.9</td>
<td>1.7</td>
<td>–0.23-0.96</td>
<td>0.1</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>≥5.2</td>
<td>5.8</td>
<td>0.12-1.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;48</td>
<td>9.3</td>
<td>0.34-2.60</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Hb, Hemoglobin; CI, confidence interval.
cervical cancer, Dattoli et al. reviewed the results of 131 patients treated between 1974 and 1985. In their subset analysis, the 5-year survival rate for patients treated with curative radiation was 65% and that for patients aged 40 or younger and patients older than 40 years were 42% and 90%, respectively (p=0.005), indicating that age has a profound influence on survival in women with stage IB cervical cancer (20). Grigien et al. reported that age had no significant relationship in an analysis of 162 patients with FIGO stage IIA-IIIB cervical carcinoma treated with irradiation (21). Kim et al. noticed that age was an independent risk factor in their analysis of older patients with an unfavorable OS compared with those who were younger (11). Therefore, the effect of age on survival in cervical cancer patients treated with radiation is not fully known. Furthermore, it is also unclear whether age can affect prognosis in cervical cancer treated with CCRT. The explanation for these contradictory results may stem from the inconsistent treatment protocols and regimens used in these studies.

In our study population of patient with stage IB1-IIB squamous cell carcinoma of the cervix undergoing CCRT, tumor size and patient age at the time of treatment were found to be independent predictors of locoregional recurrence by multivariate analysis. The 5-year locoregional DFS of the high-risk group was significantly worse than that of the low-risk group. In addition, it should be noted that the locoregional recurrence developed within 12 months in all 10 patients. Therefore, new treatment strategies for locoregional recurrence should be considered. A reasonable approach is to use new radiosensitizing agents combined with cisplatin. A Gynecologic Oncology Group (GOG) study of CCRT with new radiosensitizing agents combined with cisplatin is currently underway (GOG-0240; a phase III randomized study of paclitaxel in combination with cisplatin or topotecan hydrochloride with/without bevacizumab in patients with stage IVB, recurrent, or persistent carcinoma of the cervix). Consolidation chemotherapy or adjuvant treatment using a molecular targeting agent (i.e., bevacizumab and cetuximab,) after CCRT, or neoadjuvant chemotherapy before CCRT are other possible treatment options, for which trials are now underway (GOG-0240; use of bevacizumab as a consolidation therapy; and UCLCTC-BRD/05/22-CERVIX; a phase II study of neoadjuvant chemotherapy comprising dose-dense paclitaxel and carboplatin followed by cisplatin and radiotherapy in patients with stage IB2-IVA cervical cancer). We are awaiting the results of these trials for new treatment modalities in our high-risk group of patients.

Furthermore, adjunctive hysterectomy after CCRT is a potential option. Classe et al. demonstrated that surgery after CCRT for advanced cervical cancer (stages IB2-IVA) leads to an acceptable morbidity and improves local control in cases of partial pathological responses (22). Houvenaeghel et al. also stressed in their study that adjuvant surgery may increase survival as it reduces the risk of local relapse in stage IB2-IVA cervical cancer, allowing a 10-year DFS of 56.7% (23). Huguet et al. treated 92 patients with operable bulky stage IB2, IIA, and IIB cervical carcinomas without pelvic or para-aortic nodes on pretreatment imaging in which all patients underwent class II modified radical hysterectomy with bilateral pelvic lymphadenectomy after CCRT. They concluded that this strategy can be used with acceptable toxicity and that pathological complete response increases the probability of DFS (24). Morice et al. also analyzed the results of hysterectomy after CCRT, concluding that it has a place in the multimodality management of stage IB2 or II cervical cancer, particularly in cases of bulky residual disease (25). Adjuvant hysterectomy may be indicated for the high-risk group of patients in our study, as well as for those with residual disease after CCRT.

In conclusion, our study shows that tumor size ≥5 cm and patient age <48 years are significant predictors of locoregional recurrence in patients with FIGO stage IB1-IIB squamous cell carcinoma of the cervix treated with CCRT and would be helpful in identifying patients who are at high-risk of locoregional recurrence.

**Conflict of Interest**

We have no conflict of interest in regard to this article.

**References**

Hirakawa et al.: Local Recurrence in CC Treated with CCRT


