Concurrent Radiotherapy and Intra-arterial Infusion Chemotherapy for Locally Advanced Cervical Cancer

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Abstract

Purpose: We investigated the toxicity and efficacy of concurrent chemoradiotherapy (CCRT) with intra-arterial infusion chemotherapy (IAIC) and definitive radiotherapy for locally advanced cervical cancer to evaluate the feasibility and effectiveness of our treatment.

Materials and Methods: We analyzed 15 patients of pathologically confirmed locally advanced cervical cancer treated with CCRT with IAIC and radiotherapy between 2003 and 2006 in our hospital. The patients with primary tumor ≥ 4 cm in diameter accessed by MRI were enrolled in this study. The numbers of patients with Stage II, III, and IVA were 3, 10, and 2, respectively. Patients received definitive radiotherapy consisting of pelvic external beam therapy and high-dose-rate intracavitary brachytherapy. IAIC using combination of Cisplatin, 5FU, and MMC (or BLM) was given concurrently. Two courses with 3-week interval were performed in 10 patients. Weekly 3 or more courses were performed in 5 patients. We evaluated local control (LC), overall survival (OAS), cause-specific survival (CSS), patterns of failure, and toxicity.

Results: The 5-year LC was 80%. The 5-year OAS and CSS were 56%. The rate of distant metastasis at initial recurrence was 47%.

Acute Grade 3 hematologic toxicity was observed in 27%, but severe acute non hematologic toxicity (Grade ≥ 3) was not observed. No patient developed severe late toxicity (Grade ≥ 3).

Conclusion: The results suggested that CCRT with IAIC and radiotherapy is feasible and effective for locally advanced cervical cancer except for high rate of distant metastasis. To further improve treatment outcomes, a combination of IAIC for local tumor control and intravenous administration of chemotherapy for distant metastasis control should be considered.

Key words

Uterine cervical cancer, Concurrent chemoradiotherapy (CCRT), Intra-arterial infusion chemotherapy (IAIC)

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Introduction

Radiotherapy has long been established as a treatment for uterine cervical cancer, and while good outcomes have been achieved, outcomes in locally advanced cervical cancer remain less than satisfactory.¹⁻² A combination of chemotherapy and radiotherapy is now being widely used to improve these outcomes. Several large-scale, randomized clinical trials (RCTs) and a meta-analysis have been conducted since the 1990s, and cisplatin (CDDP)-based concurrent chemoradiotherapy (CCRT) has been shown to significantly improve clinical outcomes compared to definitive radiotherapy alone.³⁻¹¹ Therefore, CCRT with chemotherapy including CDDP is now being recommended for locally advanced cervi-
CDDP alone or in combination with 5-Fluorouracil (5FU) has often been used as the drug regimen in many of these studies. This regimen is usually administered intravenously (IV), but intra-arterial (IA) infusion has also been used. Local concentration of drugs with IA infusion provides excellent local control while reducing systemic adverse events. IA infusion chemotherapy (IAIC) has often been used preoperatively in cervical cancer. Considering these beneficial effects, it was decided to use IA infusion to administer concurrent chemotherapy with radiotherapy. The purpose of this study was to investigate the toxicity and efficacy of CCRT with IAIC and radiotherapy.

**Materials and Methods**

**Patients**

This study evaluated clinical outcomes in 15 patients with locally advanced cervical cancer who met the following enrollment criteria and received CCRT with IAIC and radiotherapy between March 2003 and August 2006. The patients with pathologically confirmed cervical cancer, a primary tumor size of $\geq 4$ cm in diameter by MRI, and no serious complications were included in the study. Para-aortic lymph nodes (PAN) $\geq 1$ cm in shortest diameter by CT were considered positive, and patients with these or other distant metastasis were excluded.

Table 1 summarizes the patient characteristics.

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range in years)</td>
<td>55 (25–78)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>squamous cell carcinoma</td>
<td>13</td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Stage (FIGO)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>3</td>
</tr>
<tr>
<td>IIB</td>
<td>10</td>
</tr>
<tr>
<td>IIIB</td>
<td>2</td>
</tr>
<tr>
<td>Primary tumor size*</td>
<td>mean 6 cm (range 4–9 cm)</td>
</tr>
<tr>
<td>&lt;6 cm</td>
<td>7</td>
</tr>
<tr>
<td>6 cm ≤</td>
<td>8</td>
</tr>
<tr>
<td>Pelvic lymph node status #</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>12</td>
</tr>
<tr>
<td>negative</td>
<td>3</td>
</tr>
<tr>
<td>PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Assessed by MRI
# $\geq 10$ mm in shortest diameter by CT

Mean patient age was 55 years (range 25–78 years). There were 13 patients with squamous cell carcinoma and 2 patients with adenocarcinoma. All patients were staged with the International Federation of Gynecology and Obstetrics (FIGO) criteria. The numbers of patients with Stage IIA, IIB, IIIB, and IVA were 1, 2, 10, and 2, respectively. Primary tumor size by MRI ranged from 4 to 9 cm, with a mean of 6 cm. The size was 4–6 cm in 7 patients, and 6–9 cm in 8 patients. Pelvic lymph nodes (PN) were positive, based on a size of $\geq 1$ cm in shortest diameter by CT, in 12 patients. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 5 patients and 1 in 10 patients.

**Method of Treatment**

Standard definitive radiotherapy as recommended in Japan was given concurrently with IAIC. Figure 1 shows the treatment schedule. Radiotherapy was started immediately after initial IAIC.

**Radiotherapy**

Radiotherapy consists of whole pelvic external beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT). EBRT was delivered with a photon beam of 10 MV using an anteroposterior-posteroanterior technique. In general, fractionated doses of 1.8 Gy per day, 5 days per week, were given for a total dose of 50.4 Gy. If there was bulky parametrial tumor or gross pelvic lymph node metastases, additional local irradiation, up to 54 Gy, was given at that site. After 30 to 40 Gy with
EBRT, a central shield (width: 4 cm) was inserted for EBRT field.

HDR-ICBT was started after inserting a central shield for EBRT. HDR-ICBT using $^{192}$Ir, one fraction weekly, with a dose of 4–6 Gy at point A, in 3–4 fractions, was given for a total dose of 12–24 Gy.

### Intra-arterial infusion chemotherapy (IAIC)

Intra-arterial implantation of port-catheter system was performed by interventional radiologists, after alteration of the feeding artery by the coil embolization of the branches of internal iliac arteries except the uterine artery. The infusion catheter was placed in the internal iliac artery, and infusion chemotherapy was performed through the implanted reservoir port.

Usually, the initial infusion was given just before the start of EBRT, and the second infusion was given 3 weeks later (Method A). However, 5 patients received more frequent infusions of smaller doses at 1-week intervals (Method B). Selection of these methods was not based on specific criteria, but was left to the discretion of the treating physician.

The drugs given were regimens used previously for IAIC in cervical cancer at our hospital. In Method A, each infusion included CDDP 100 mg/body, 5FU 1000 mg/body, and Bleomycin (BLM) 20 mg/body. This was switched in 2005 to BLM 20 mg/body and MitomycinC (MMC) 10 mg/body. In Method B, CDDP 20 mg/body, 5FU 500 mg/body, and MMC 10 mg/body were given.
cluded primary tumor and pelvic lymph nodes recurrence. The endpoints of this study were local control (LC) rate, overall survival (OAS) rate, cause-specific survival (CSS) rate, patterns of failure, and toxicity. LC was measured from the date of initiation of treatment to the date of the first recurrence of primary tumor or pelvic lymph nodes recurrence or the most recent follow-up visit. Survival was measured from the date of initiation of treatment to the date of death or the most recent follow-up visit. These probabilities were calculated by the Kaplan-Meier method. The significance of differences was examined by the Wilcoxon test.

This study was approved by the Ethics Committee of St. Marianna University School of Medicine (Approval No. 2267).

Results

Feasibility

Radiotherapy

EBRT was completed in all patients, and ICBT was performed in 14 of the 15 patients. ICBT could not be performed in one patient with stage IIIB cancer because of severe cervical flexion that made a tandem applicator technically impossible to insert. This patient received 50.4 Gy of EBRT only and was carefully followed-up. She has survived for more than 6 years without recurrence or any adverse events.

Intra-arterial infusion chemotherapy

Among the 10 patients in the Method A group, 8 had two courses of IAIC, and 2 had one course of IAIC.

One of the 2 patients with only one course of IAIC had a stage IVA tumor measuring 6 cm. However, she had a good response to initial IAIC, with rapid tumor shrinkage and uterine atrophy, so IAIC was given only once. This same patient completed radiotherapy. She has survived for 102 months without recurrence or any adverse events.

The other patient had a stage IIIB tumor that measured 6 cm, but because of mild vulva ulceration after IAIC, this was limited to one course. The vulva ulcer healed in about 2 weeks. This patient completed radiotherapy and achieved local control, but PAN metastasis was found at 19 months, distant metastasis was found at 25 months, and she died. At the time of death, local control was maintained, and no adverse events had occurred.

With Method B, weekly IAIC was given 3 times in two patients, and 4 times, 6 times, and 7 times in one patient each.

Outcomes

Local control

The 5-year LC rate was 80%. (Fig. 2)

Survival

Seven patients died during follow-up, and all were cause-specific deaths. In other words, OAS and CSS were the same. The 5-year OAS rate was 56%. (Fig. 3) Analysis of the relationship between LC and OAS showed significantly better survival in patients with LC (P = 0.039) (Fig. 4).

Patterns of failure

The numbers of patients with initial local recur-
rence, distant metastasis, and both were 2, 6, and 1, respectively. The rate of distant metastasis at initial recurrence site was 47% (7 of 15 patients). The most common site of distant metastasis was PAN (5 patients), followed by lung (2 patients). Among the 5 patients with PAN recurrence, radiotherapy for the PAN region was given in 4 patients, but all had distant metastases and died. The 2 patients with lung metastases at initial recurrence received chemotherapy. One patient improved and has survived 78 months. The other had a cause-specific death due to distant metastasis. Patients with distant metastasis generally had a poor prognosis.

Table 2 shows the results of univariate analysis for prognostic factors that might affect LC and OAS. These prognostic factors were categorized by clinical stage (II or III–IV), tumor diameter (<6 cm or ≥6 cm), pelvic lymph nodes (negative or positive), pathology (squamous cell carcinoma or adenocarcinoma), and IAIC method (A or B). There were no significant differences for any of these prognostic factors. However, clinical stage tended to affect OAS (p = 0.0789), and tumor diameter tended to affect LC (p = 0.081) and OAS (p = 0.061).
Table 3 summarizes the acute adverse events. Grade 3 leukopenia was observed in 4 patients (27%), anemia in 2 patients (13%), and thrombocytopenia in 1 patient (7%). There were no severe (Grade ⩾ 3) non-hematologic acute adverse events. No patient failed complete radiotherapy because of acute adverse events.

Only one patient developed Grade 2 late bladder complication. No other patient developed Grade ⩾ 2 late adverse events.

In terms of acute adverse events with IAIC, mild vulva ulceration occurred in one patient, but this healed in about 2 weeks. Leg numbness also occurred in another patient, but this resolved in about 4 weeks. (Table 3)

Discussion

In CCRT, chemotherapy is usually administered IV, but local concentration of drugs by IA infusion may provide better local control while reducing systemic adverse events. However, IAIC requires more specialized technical skills than IV administration, and safety when given concurrently with radiotherapy must be evaluated. Therefore, the present study investigated treatment outcomes of CCRT with IAIC. Although a few adverse events specific to IAIC occurred, treatment was generally safe in all patients.

Comparison of outcomes with radiotherapy alone

The National Institute of Radiological Sciences (NIRS) in Japan, has published results on outcomes in cervical cancer when treated with standard definitive radiotherapy alone. This was one of the most reliable studies in Japan with stringent long-term evaluation of treatment. The 5-year LC rates in stage II and III were 84% and 76%, respectively. The
5-year OAS rates in stage II, III, and IVA were 69%, 56%, and 21%, respectively. On the other hand, in the present study, the 5-year LC rate for stage II-IV was 80% and the 5-year OAS rate for this stage range was 56%.

Although the outcomes were similar compared to radiotherapy alone, the primary tumor diameter was 4–9 cm in the present series of patients, and exceeded 6 cm in more than half of patients. In contrast, in the NIRS patients, relatively smaller tumors measuring ≤5 cm, as assessed by palpation, accounted for 90% of stage II, 78% of stage III, and 66% of stage IV lesions. Thus, concurrent chemotherapy probably contributed to the present outcomes. In the NIRS study, late adverse events grade ≥3 involved the colon in 3.8%, bladder in 0.8%, and small intestine in 2.6% of patients. In the present series, there were no grade ≥3 late adverse events. Therefore, adverse events were not increased by concurrent IAIC.

The present outcomes of CCRT with IAIC are not inferior to other reported outcomes with radiotherapy alone in Japan with standard radiotherapy regimens. Furthermore, considering that the present results were only in patients with larger tumor diameters, concurrent IAIC probably contributed positively to treatment.

### Comparison of outcomes with intravenous CCRT

Concurrent radiotherapy and IV chemotherapy including CDDP has also recently been used in Japan, but long-term outcomes have seldom been reported. Therefore, treatment outcomes in 4 large-scale RCTs conducted in Western countries since the 1990s were reviewed. Table 4 summarizes the results in these study treatment arms.3–8)

There are some differences in diagnosis and treatment methods between Japan and Western countries. One is regarding the assessment of PAN. In Western countries, PAN are assessed by pathologic examination of biopsy specimens from exploratory laparotomy, whereas in Japan, PAN are often assessed based on CT imaging. In addition, although EBRT and ICBT are used for radiotherapy in both the West and Japan, a central shield is usually inserted during treatment with EBRT in Japan, but it is seldom used in Western countries. Furthermore, HDR-ICBT is widely used in Japan, whereas low-dose-rate ICBT is generally used in Western countries. The above differences must be taken into consideration when comparing outcomes between Japan and Western countries.

### Table 4. Prospective Randomized 4 Major Trials of Concurrent Chemoradiotherapy for locally Advanced Cervical Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Regimen of chemotherapy</th>
<th>no Sy.LC</th>
<th>Sy.PFS</th>
<th>Sy.OAS</th>
<th>Hem.</th>
<th>GI</th>
<th>All region</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTG001</td>
<td>II B III IVA</td>
<td>C75mg+F1g x4days</td>
<td>194</td>
<td>82%</td>
<td>68%</td>
<td>73%</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>1999, 2004</td>
<td>or I B A(≥5cm or PN+)</td>
<td>every 3w 3course</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG85</td>
<td>II B III IVA</td>
<td>C50mg+F1g x4days</td>
<td>177</td>
<td>75%</td>
<td>65%</td>
<td>65%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td>every 3w 2course</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG120</td>
<td>II B III IVA</td>
<td>1 C40mg weekly 6course</td>
<td>176</td>
<td>78%</td>
<td>58%</td>
<td>60%</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>1999, 2007</td>
<td></td>
<td>2 C50mg+F1g x4days+HU</td>
<td>173</td>
<td>79%</td>
<td>57%</td>
<td>61%</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>NCIC</td>
<td>II B III IVA</td>
<td>C40mg weekly 5course</td>
<td>127</td>
<td>73%</td>
<td>62%</td>
<td>5%</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>2002</td>
<td>or I B A(≥5cm or PN+)</td>
<td>every 4w 2course</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C=cisplatin; F=5-Fluorouracil; G3=Grade3; GI=gastrointestinal; GOG=Gynecologic Oncology Group; GI=Gastrointestinal; GU=Genitourinary; Hem.=Hematologic; HU=Hydroxyurea; LC= Local control; NCIC=National Cancer Institute of Canada; OAS=Overall survival; PFS=Progression-free survival; RTG=Radiation Therapy Oncology Group.

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Toita et al.14 evaluated the effect of tumor diameter as measured by MRI on treatment outcomes with radiotherapy alone. The 5-year survival rates were 74% for tumors <4 cm but only 24% for tumors ≥4 cm. In the present series with tumors ≥4 cm in all patients, the 5-year survival rate was 56%. This indeed suggests that concurrent IAIC had a contributing effect.

The present outcomes of CCRT with IAIC are not inferior to other reported outcomes with radiotherapy alone in Japan with standard radiotherapy regimens. Furthermore, considering that the present results were only in patients with larger tumor diameters, concurrent IAIC probably contributed positively to treatment.
The eligibility criteria in these studies were similar to those in Japan. Chemotherapy consisted of CDDP alone or combinations including CDDP and 5FU. Intravenous treatment was given at 3- to 4-week intervals or once a week. The 5-year LC rates were 57–80%, and the 5-year survival (including OAS or Progression-free survival) rates were 57–73%. The outcomes were similar to the present local control and survival rates.

A comparison of adverse events showed similar rates of acute hematologic toxicity, but other events tended to be fewer in the present patients. In addition, the incidence of grade ≥3 late adverse events with IV administration ranged from 1–16% in previous studies, but no grade ≥3 late adverse events occurred in the present patients. Therefore, the present treatment outcomes with IAIC were similar to outcomes in these major RCTs in Western countries, but the present incidence of adverse events was lower.

The Japanese Gynecologic Oncology Group (JGOG) 1066, 15) a multicenter study conducted at major institutions in Japan, evaluated the toxicity and efficacy of standard radiotherapy and concurrent chemotheraphy including CDDP. An interim report analyzed results over a short time with median follow-up of 28 months. That study targeted patients with stage III-IV A tumors, and standard radiotherapy and concurrent chemotherapy with intravenous CDDP 40 mg/m²/weekly was given. The 2-year OAS rate was 90%, the 2-year LC rate was 73%, and the 2-year distant metastasis rate was 25%. The rate of grade ≥3 late adverse events was 3%. As compared to those short-term results, the outcomes and incidence of adverse events in the present patients were not inferior.

Comparison of outcomes with other studies of CCRT with IAIC

Neoadjuvant IAIC before radical surgery has been used for down-staging of cervical cancer. Similar treatment before definitive radiotherapy in locally advanced cervical cancer has also been reported, but its effectiveness was limited.

CCRT with IAIC was also previously reported from foreign countries like the United States, but there have been almost no recent reports other than from Japan. Table 5 summarizes the outcomes from study arms in 4 major studies from Japan. These patients generally had locally advanced stage III or stage III-IVA tumors, but in some studies, large tumors on MRI, even if stage II, were included. Patients with distant metastasis on imaging or who had positive PAN, defined as ≥1 cm on CT imaging, were excluded.

A study by Ohnishi et al. was the only RCT

Table 5. Clinical Data of Concurrent Radiotherapy and Intra-arterial Chemotherapy for Locally Advanced Cervical Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Regimen of chemotherapy</th>
<th>No.</th>
<th>Pelvic control</th>
<th>survival</th>
<th>Acute toxicity</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kokubo 1998: III (IVA)</td>
<td>C60mg/A30mg every 3 week, 2course</td>
<td>24</td>
<td>3y 80%</td>
<td>3y CSS 67%</td>
<td>H: &gt; G3 70%</td>
<td>≥G3 0%</td>
<td></td>
</tr>
<tr>
<td>Ohnishi 2000: III (IVA)</td>
<td>1 C100mg every 3 week, 2 course</td>
<td>8</td>
<td>5y 33%</td>
<td>5yOAS 44%</td>
<td>5yDFS30% 5yDMFS40%</td>
<td>H: ≥G3=4 33%</td>
<td>Gl: ≥G3=4 44%</td>
</tr>
<tr>
<td>Kawase 2008: III (IVA)</td>
<td>C70mg +i.v. F700mgx4days every 3 week, 2course</td>
<td>45</td>
<td>5y OAS80.6%</td>
<td>Rectum: G4 2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaneyasu 2009: III</td>
<td>C100~120mg or CB300mg every 4 week 2course</td>
<td>29</td>
<td>5y 89%</td>
<td>5y OAS62% 5yCSS72%</td>
<td>H: ≥G3 24%</td>
<td>Rectum: ≥G3 3%</td>
<td>small bowel: G3 10%</td>
</tr>
<tr>
<td>Present study</td>
<td>III (IVA)</td>
<td>1 C100mg+F1g=100mg</td>
<td>10</td>
<td>5y 80%</td>
<td>5y OAS-CSS58%</td>
<td>H: ≥G3 27%</td>
<td>≥ G3 0%</td>
</tr>
</tbody>
</table>

Abbreviations: A=pirarubicin B=Bleomycin C=Cisplatin: CB =Carboplatin: DFS=Disease- free survival : CSS=cause-specific survival: DMFS=Distant metastasis- free survival: F=5-Flourouracil: G3=Grade3 : Gl=Gastrointestinal: Hem = Hematologic: M=Mitomycin C : OAS=Overall survival : PFS=Progression- free survival
with comparison to radiotherapy alone. Studies by Kokubo et al.\(^2\) and Kawase et al.\(^2\) included comparisons with historical controls. A study by Kaneyasu et al.\(^2\) included one arm with IAIC. Radiotherapy consisted of a standard regimen in Japan, with both EBRT and HDR-ICBT. The chemotherapy was CDDP alone or CDDP in combination with other drugs. Treatment was usually given at 3- to 4-week intervals. Ohnishi et al. compared 3 types of regimens.

The treatment outcomes, except those of Ohnishi et al., were the LC rates of ≥80% and the OAS rates of 60–80%. In the studies of Kokubo et al. and Kawase et al. with historical control comparisons, CCRT with IAIC was better than radiotherapy alone, but in Ohnishi et al., it was poorer, perhaps due to a large number of patients with large-diameter tumors in the study arm.

In the present series of patients, the LC rate was 80%, and the OAS rate was 56%. These were similar to the above studies, with the exception of Ohnishi et al. With regard to the incidence of distant metastasis, Kaneyasu et al. reported distant metastasis as the initial recurrence site in 47% of patients. Our result was also 47%, and Ohnishi et al. reported the 5-year distant metastasis-free survival rate of 40%. The distant metastasis sites often included PAN metastases, but assessment was by imaging diagnosis, and there may have been many patients who already had micro PAN metastases at the time of initial diagnosis.

There were acceptable levels of adverse events, both acute and late, except in the Ohnishi et al. study. Adverse events associated with IAIC included numbness due to lower extremity neuropathy and skin ulcerations.\(^2\) Kaneyasu et al. also reported one patient with lower extremity neuropathy. In the present patients, leg numbness and vulva ulceration occurred as acute events in one patient each. Both were mild in severity, improved within a few weeks, and did not recur.

In conclusion, CCRT with IAIC was safe for treatment of locally advanced cervical cancer, and there was an acceptable level of adverse events, with a lower incidence compared to IV treatment regimens. Treatment outcomes of CCRT with IAIC were superior to those of radiotherapy alone, but there was no clear superiority over CCRT with IV chemotherapy. LC was good, with satisfactory outcomes, but the rate of distant metastasis, primarily PAN metastasis, was high. To further improve treatment outcomes, a combination of IAIC for local tumor control and IV administration of chemotherapy for distant metastasis control should be considered.

**Acknowledgements**

The authors are grateful to the patients who participated in this study, and to Dr. Kenji Takizawa, Department of Radiology, St. Marianna University School of Medicine, who contributed greatly to treatment with intra-arterial infusions.

**References**


23) Chaney AW, Eifel PJ, Lodsdon MD, Morris M, Wharton T; Mature results of a pilot study of


