Original Article

Intensity-Modulated Radiotherapy with Concurrent Chemotherapy for Elder Cervical Cancers: A Comparison of Clinical Outcomes with Conventional Radiotherapy

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S U M M A R Y

Background: The goal of this report was to compare clinical outcomes for elderly patients with cervical cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy (IM-CCRT) or two-dimensional radiotherapy (2D-CCRT).

Methods: Sixty patients older than 75 years were treated with CCRT (30 with 2D-CCRT, and 30 with IM-CCRT) in Mackay Memorial Hospital, Taipei, Taiwan with Eastern Cooperative Oncology Group performance status 0–1. Retrospectively, treatment toxicities were graded weekly according to the NCI (National Cancer Institute) Common Toxicity Criteria version 3.0 and RTOG (Radiation Therapy Oncology Group) criteria. The Kaplan and Meier method compared with the log-rank test was used for disease-free survival (DFS) and overall survival (OS).

Results: The median follow up duration of all patients was 41.7 months (range, 1–101 months). There were no statistical differences in histological type, The International Federation of Gynecology and Obstetrics stage, performance status, and cycles of chemotherapy between these two groups (p = 0.554, p = 0.793, p = 0.796, and p = 0.161, respectively). The mean treatment duration was significantly longer for the IM-CCRT-group (66.1 days vs. 51.7 days, p < 0.05). The local recurrence and distant metastasis were significantly lower for the IM-CCRT-group (p = 0.023 and p = 0.006, respectively). Acute gastrointestinal toxicities tended to be more significant in patients who received IM-CCRT (2D-CCRT vs. IM-CCRT: Grade 2 = 23% vs. 27%, Grade 3 = 23% vs. 37%, p = 0.001, respectively). The 3-year actuarial OS of the 2D-CCRT-group and IM-CCRT-group were 70.2% and 78.8%, respectively (p = 0.689). The 3-year DFS of the 2D-CCRT-group and IM-CCRT-group were 73.4% and 100%, respectively (p = 0.014).

Conclusion: The use of IM-CCRT was associated with equivalent compliance and encouraging preliminary clinical results compared to 2D-CCRT.

1. Introduction

The efficacy of cisplatin-based concurrent chemo-radiotherapy (CCRT) over radiotherapy alone in cervical cancers has been well documented for more than 15 years.¹ CCRT was suggested for women who have locoregionally advanced cervical cancer that is confined to the pelvis and for women who require post-hysterectomy radiotherapy for high-risk disease.²

Cervical cancer typically occurs in the 5th and 6th decades of life; < 20% of patients are older than 75 years.³ Old aged patients’ tolerance may be compromised because of their general performance status, comorbidities, and general concepts about short residual life. Therefore, administration of concurrent chemotherapy may increase the cost and complexity of treatment for elderly patients.

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From our previous report and a report from Goodheart et al., it is suggested that chemoradiation should be considered in elderly patients with invasive cervical cancer with decreased mortality compared with conventional radiotherapy alone.1

Recently, standard radiotherapy treatment planning for cervical cancer has been shifting from conventional two-dimensional (2D) planning to 3D planning in order to achieve appropriate coverage of the target within sufficient dose and optimal sparing of organs at risk.1

Intensity-modulated radiotherapy (IMRT) is a promising form of 3D-conforming radiotherapy that produces a highly conformal dose closer to the target volumes and normal pelvic tissues (i.e., small bowel, bladder, rectum) are relatively spared. Treatment related toxicities might be reduced in patients with uterine cervical cancer by using IMRT alone6,7. At the present time, there is not enough data to support routine use of IMRT for cervical cancer with CCRT, especially for the elderly.

Therefore, we reviewed our experience in elderly patients (aged ≥ 75 years) with good performance status treated in Mackay Memorial Hospital, Taipei, Taiwan from January 1, 2000 to June 6, 2013, and analyzed their survivals and compliance after CCRT with conventional 2D (2D-CCRT-group) versus IMRT (IM-CCRT-group), retrospectively.

2. Materials and Methods

From January 2000 to June 2013, there were 1250 cervical cancers treated with radiotherapy in Mackay Memorial Hospital. Sixty biopsy proven cervical cancers in patients aged ≤ 75 years with Eastern Cooperative Oncology Group performance status 0—1 after complete history, physical examination including cystoscopy and proctoscopy, and laboratory studies had received concurrent chemoradiotherapy (CCRT) with weekly intravenous cisplatin, retrospectively. The Institute Review Board of Mackay Memorial Hospital (MMH-I-S-157 and MMH-I-S-434) approved this study.

2D Radiotherapy was planned by using a Pinnacle Treatment Planning System (Philips Healthcare, Madison, WI, USA) or Eclipse IMX Planning System (Varian Associates, Inc., Palo Alto, CA, USA) and delivered by a linear accelerator (Clinac1800 or IX, Varian Associates, Inc., Palo Alto, CA, USA; Precise, Elekta Inc., Stockholm, Sweden) to target volumes including the primary lesion, the pelvic nodes and the common iliac lymph nodes. Paraaortic lymph nodes were included if metastases were detected in image examination. 2D Radiotherapy was delivered by an initial four-field box technique followed by a parallel-opposed technique at the time brachytherapy was begun. Margins of the anterior-posterior fields were the upper margin of L4—5 (superiorly), the lower margin of the obturator foramen or the lowest extension of the disease (inferiorly), and 1.5—2.0 cm beyond lateral margins of true bony pelvis. For the lateral fields, the anterior margin was the anterior edge of the pubic symphysis. The posterior margins at the S2—S3 interspaces were used.

A total of 45—50.4 Gy to the isocenter was prescribed in 25—28 fractions by 10—15 MV X-ray at 320 cGy/min. A supplemental dose of 5.4—9 Gy was given to the parametrium area when necessary. For patients with positive paraaortic lymph node metastasis, periarteric node irradiation was irradiated with 45 Gy of extended ante-roposterior and posteroanterior fields in conjunction with whole pelvic radiation. High dose intracavitary brachytherapy was given following the initial 30—40 Gy of whole pelvis irradiation. Meanwhile, the RT plan was changed in anteroposterior/posteroanterior fields to achieve the intended prescription dose of 45—59.4 Gy. The designed prescription dose was delivered at 1.8—2.0 Gy daily fraction, five fractions per week.

IMRT was delivered by a 6—10 MV linear accelerator (Precise, or VMAT, Elekta Inc.) after CT (computed tomography) simulation in a supine position with customized immobilization devices to decrease variability in the daily setup. The planning target volumes and clinical target volumes were defined and contoured on the individual axial CT slices according to the guideline report from Small et al. for vaginal and nodal areas. A seven field equally spaced co-planner IMRT plan was generated using the dose-volume constraints described by RTOG 0413. A patient whose disease was limited to ≤IB2 received 50.4 Gy in 28 fractions over 5.5 weeks to the vaginal planning-target-volume (PTV) and nodal PTV. Patients with locally advanced diseases received 60 Gy in 30 fractions over 6 weeks to the gross tumor volume defined by the computed tomographic simulation after discussion with the radiologist, and 50.4 Gy in 30 fractions to the vaginal PTV and nodal PTV at the same time by using the simultaneous integrated boost technique. The prescription dose was the isodose which encompassed at least 97% of the PTV.

After completion of treatment, patients received regular follow-up every 1—2 months in the 1st year, then every 3 months.
subsequently. Overall survival (OS) and disease-free survival (DFS) were calculated from the date of treatment. Surviving patients were censored on the date of last follow-up. We confirmed the cause of death by correspondence, telephone, or medical record review.

All data were analyzed with the SPSS program for Windows (version 13; IBM, Armonk, NY, USA). We used Pearson Chi-square test to find the significance of between-group differences in treatment groups and t tests for finding the significance of mean between groups. The Kaplan-Meier method compared by the log-rank test was used for OS and DFS. A p value ≤ 0.05 was considered significant, and only two-sided results with assumed equal variance were used.

3. Results

The patient and tumor characteristics of these groups are summarized in Table 1. Conventional 2D radiotherapy was received in 30 patients (2D-CCRT-group) and intensity-modulated radiotherapy was received in 30 patients (IM-CCRT-group). The median and mean follow-up durations of all patients were 41.7 months and 42.6 months (range, 1–101 months). The median age of patients in the IM-CCRT group was greater (80.5 years vs. 77.8 years, p = 0.0044). There was no statistical difference in combined medical problems such as diabetes, hypertension, atherosclerosis, and chronic renal failure between the two groups. There was no statistical difference in histological type, The International Federation of Gynecology and Obstetrics (FIGO) stage, and performance status between the two groups. About 30% patients had diabetes, hypertension, atherosclerosis, and chronic renal failure between the two groups. There was no statistical difference in combined medical problems such as diabetes, hypertension, atherosclerosis, and chronic renal failure between the two groups. There was no statistical difference in histological type, FIGO stage, and performance status between the two groups. About 30% patients had diabetes, hypertension, or both. There were fewer patients with medical problems in the IM-CCRT-group, but not significantly. Only two cases with adenocarcinoma were noted in the IM-CCRT-group in this analysis. Around 60% patients had performance status one in both groups (p = 0.793). The clinical stage distribution was identical in both groups (p = 0.796) and about half of patients were staged as having locally advanced disease.

There was no statistical difference in receiving cycles of chemotherapy between the two groups (p = 0.161). More cycles of chemotherapy were given in the 2D-CCRT-group than in the IM-CCRT-group.

Only two cases in IM-CCRT completed their treatment in 8 weeks, but 24 cases in 2D-CCRT completed their treatment in 56 days (p < 0.05). The mean treatment duration was significantly longer for IM-CCRT patients than for 2D-CCRT patients (66.1 days vs. 51.7 days, p < 0.05).

Up to December 2014, eight patients in the 2D-CCRT-group were lost, and none were lost in the IM-CCRT-group. The mean follow-up durations were the same in these groups (41.4 months vs. 43.7 months, p = 0.729). One case in the IM-CCRT group had local recurrence with distant metastasis. The local recurrence and distant metastasis were significantly lower for the IM-CCRT-group than for the 2D-CCRT-group (local recurrence = 1/30 vs. 7/30, p = 0.023; distant recurrence = 1/30 vs. 9/30, p = 0.006). About 30% of cases died and the incidences were identical for these two groups (8/30 vs. 11/30, p = 0.405). No cancer related death was noted in the IM-CCRT-group (0/30 vs. 6/30).

Table 2 summarizes the frequency and severity of acute complication rates. Acute toxicities such as diarrhea, abdominal cramping, nausea, anemia, leukocytopenia, urinary tract infection, and dysuria were observed in this study. The chronic toxicities were mainly proctitis and cystitis. Acute Grade 2 and Grade 3 gastrointestinal toxicities tended to be more significant in the IM-CCRT-group (2D-CCRT vs. IM-CCRT: Grade 2 = 23% vs. 27%, Grade 3 = 23% vs. 37%, p = 0.011). Acute genitourinary and hematologic toxicities were common with no differences in both groups (p = 0.502, p = 0.338).

The chronic toxicities in these two groups are summarized in Table 3. Higher chronic gastrointestinal toxicity was noted in the IM-CCRT-group, but the p value was not significant (2D-CCRT vs. IM-CCRT: Grade 2 = 17% vs. 23.3%, Grade 3 = 0% vs. 13.3%, p = 0.054). Chronic genitourinary toxicity was higher in patients receiving 2D-CCRT, but the p value was not significant (2D-CCRT vs. IM-CCRT: Grade 2 = 13.3% vs. 6.7%, Grade 3 = 3.3% vs. 0%, respectively, p = 0.083).

The DFS and OS of the entire group are shown in Figure 1. The 3-year OS of the 2D-CCRT-group and IM-CCRT-group were 70.2% and 78.8%, respectively. The 3-year DFS of the 2D-CCRT-group and IM-CCRT-group were 73.4% and 100%, respectively. The mean OS for patients in the 2D-CCRT-group and in the IM-CCRT-group were 69 months and 66 months, respectively. The mean DFS for patients in the 2D-CCRT-group and in the IM-CCRT-group were 79.86 months and 78.64 months, respectively. Patients who had IM-CCRT had better DFS than 2D-CCRT cases (p = 0.014). The OS is identical in both groups (p = 0.689).

4. Discussion

Optimal cancer treatment among the elderly is controversial. Currently, those patients with cervical and ovarian cancer are reported to receive less aggressive treatment when general performance, comorbidity, and treatment tolerance are taken into consideration 10. Our previous study revealed 2D radiotherapy with concurrent cisplatin chemotherapy was well tolerated in elderly patients with good performance. Although higher treatment related acute and chronic toxicities were noted, elderly patients with cervical cancer had a better overall outcome following chemoradiotherapy than radiation alone or incomplete radiotherapy.

IMRT alone has been documented with lower treatment related toxicity and better tumor control than conventional radiotherapy alone 12,13. There are many dosimetric studies that show a reduction of dose delivered to the pelvic organs-at-risk with IMRT compared with conventional RT in the treatment of cervical cancer 12,14.
However, whole pelvis IMRT is still associated with considerable rectal and cystic toxicity. In the present study, acute gastrointestinal toxicity and chronic gastrointestinal toxicity seemed higher in the IM-CCRT group. By reviewing IMRT planning, “hot spots” with high rectum and bladder volumes were sometimes unavoidable. This uncertain high dose would elevate the highest dose to the rectum and bladder. The difference in acute and chronic genitourinary toxicities between the groups was not significant (acute: 10% vs. 3%, *p* = 0.52; chronic: 16.6% vs. 6.7%, *p* = 0.083). For the bladder, the high dose volume ratio might not be high enough to produce a higher incidence of toxicity. However, for the rectum, this might be the cause of higher toxicity. This phenomenon might be exaggerated in the elderly because of more complex comorbidity and the combination of CCRT. Therefore, the guideline related to dose-volume constrains might need to be modified for the elderly. Further dose-volume study will be needed to address this question.

Hasselle et al. reported the results of 111 patients with Stage I–IVA cervical carcinoma treated with IMRT. The 3-year OS was 78%. Du et al. reported their comparison results of 122 patients with IMRT and conventional radiotherapy and the 3-year OS was 82.5% for patients treated with IMRT and concurrent chemotherapy and the complete response rate was 88% for IMRT cases. In the present study, the 3-year actuarial OS of the IM-CCRT group was 78.8%. That means for the elderly patients with cervical cancer, aggressive treatment did not shorten their survival by comparing with the general population, even though higher gastrointestinal toxicity had been noted in our study.

A population-based study from Taiwan concluded that three-dimensional conformal radiotherapy had better OS than 2D radiotherapy after adjustment for age, diabetes mellitus, hypertension, coronary heart disease, hyperlipidemia, side effects, urbanization level, geographic region, and enrollment category (5-year survival rate: 82.3% vs. 73%, *p* = 0.007, the hazard ratio = 1.82 with CI, 1.16–2.85). In our study, the 3-year progression-free survival of the IM-CCRT group was 100%. IM-CCRT did provide better 3-year DFS than 2D-CCRT, but the OS did not conclude in significant improvement by using IM-CCRT. Five deaths in the IM-CCRT group were not related to their cancers (1 with pneumonia, 2 with severe anemia, 2 with urosepsis). Causes of the other three deaths in the IM-CCRT group were unknown, but two patients developed other cancers during follow-up.

Prolonged treatment times in cervical cancer treated with conventional radiotherapy were reported with poor pelvic control and cancer-specific survival in several retrospective studies. Song et al. reported that total treatment time over 56 days was not significantly affected by pelvic failure, distant failure, and disease specific mortality for cervical cancers treated with concurrent chemoradiotherapy. Reasons for treatment prolongation were multifactorial. The incidence of Grade 3+ acute toxicities and delayed time with brachytherapy were reported in analysis by Song et al. The incidence of Grade 3+ acute gastrointestinal toxicities was significantly higher in the IM-CCRT group in our study and the fact that we started brachytherapy after the completion of IMRT might be the major reason for a prolonged treatment time. In our study, 93.3% of patients who received IM-CCRT had a prolonged treatment time over 56 days. The disease specific survival and OS were not affected by this factor, most likely because there were other modulating factors that affect outcome, such as more adequate tumor coverage with higher dose by IMRT than 2D, benefits of concurrent chemotherapy, and a physician’s threshold for giving RT breaks for toxicities. The study published by Peter et al. which mentioned a treatment range of 43–80 days yielded a significant difference in cell kill, particularly with shorter tumor doubling time; in addition, repopulation of proliferating tumor clonogens in cervical cancer may partially be negated by higher radiation doses. Therefore, in the IM-CCRT group, prolonged treatment time might

### Table 2
Incidence of acute toxicities in both groups.

<table>
<thead>
<tr>
<th>Grade</th>
<th>2D-CCRT</th>
<th>IM-CCRT</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (No.)</td>
<td>0–1</td>
<td>17 (57)</td>
<td>11 (37)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6 (20)</td>
<td>8 (27)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7 (23)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Genitourinary (No.)</td>
<td>0–1</td>
<td>27 (90)</td>
<td>29 (96.7)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (10)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Hematologic (No.)</td>
<td>0–1</td>
<td>20 (67)</td>
<td>25 (83)</td>
</tr>
<tr>
<td></td>
<td>2–3</td>
<td>10 (33)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

2D-CCRT = two-dimensional concurrent chemo-radiotherapy; IM-CCRT = intensity-modulated concurrent chemo-radiotherapy.

### Table 3
Incidence of chronic toxicities in both groups.

<table>
<thead>
<tr>
<th>Grade</th>
<th>2D-CCRT</th>
<th>IM-CCRT</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (No.)</td>
<td>0–1</td>
<td>25 (83)</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 (17)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0 (0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Genitourinary (No.)</td>
<td>0–1</td>
<td>25 (83)</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (13.3)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

2D-CCRT = two-dimensional concurrent chemo-radiotherapy; IM-CCRT = intensity-modulated concurrent chemo-radiotherapy.
not be an important issue related to tumor control. Further randomized trials will be arranged to address these results.

We acknowledge that this study has several limitations. First, the patient sample size is small in this retrospective study and the mean follow-up period is short. Reasons for the short follow-ups were multifactorial. Old age, family care, and comorbidity may be related to the short follow-up. However, in this study the mean follow-ups in both groups were > 36 months, therefore we felt that the relatively short follow-up does not compromise the analysis for DFS. Second, the comorbid conditions influencing survival may be underestimated, such as diabetes may be a pretreatment prognostic factor in survival of cervical cancer.16

Our study suggested that IM-CCRT is feasible for elderly patients with cervical cancer but there should be caution in its application. IM-CCRT significantly increased acute gastrointestinal toxicities with encouraging preliminary clinical results compared with 2D-CCRT. Prolonged treatment time had no negative impact on tumor control in the IM-CCRT group. Large sample prospective clinical trials are needed to evaluate the benefits of IM-CCRT for cervical cancers.

References