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# A multicenter study of concurrent chemoradiotherapy-induced late toxicity and prognosis in locally advanced cervical cancer: The Gynecologic Oncology Trial and Investigation Consortium 008

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Aim: To identify concurrent chemoradiotherapy (CCRT)-related late toxicities in locally advanced cervical cancer treatment, and clarify their causal relationship with prognosis.

Methods: We conducted a retrospective study on Stage IB2 to IVA cervical cancer in patients who were diagnosed at facilities participating in the Gynecologic Oncology Trial and Investigation Consortium (GOTIC) and treated with CCRT between 2001 and 2010.

Results: In total, 304 eligible patients were enrolled. The median follow-up duration was 79.3 months (range, 1.2–162.9 months) for all patients. Overall late toxicities of G3 or more involved 32 cases (10.5%). The 5-year cumulative rates of Grade ≥ 3 late toxicities of the small bowel, rectum, and bladder were 3.7% (95% CI 1.9%–7.1%), 3.8% (95% CI 2.1%–7.0%), and 3.2% (95% CI 1.5%–6.7%), respectively. Multivariate analysis showed a statistically significant association between small bowel toxicities and histological type (Hazard ratio: 0.16, 95% CI: 0.04–0.68, *P*=.02) or chemotherapy (Hazard ratio: 0.17, 95% CI: 0.04–0.70, *P*=.02). The 5-year overall survival (OS) for all patients was 66.3% (95% CI 60.7%–71.9%). Age, Performance Status, clinical stage, Intracavity Brachytherapy, and late toxicities of the rectum showed a statistically significant impact on OS.

Conclusions: Regarding late toxicities, CCRT can be considered a standard treatment in the management of locally advanced cervical cancer.

The findings of this study provide a basis for comparison with current various radiation treatment methods and new chemotherapy strategies using immuno-checkpoint inhibitors.

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## Introduction

Cervical cancer is the fourth most common cancer among females. In 2024, an estimated 660,000 females were diagnosed with cervical cancer worldwide, and approximately 350,000 died from the disease [1]. Previously, radiation therapy (RT) was the primary treatment for locally advanced cervical cancer. However, since the 1990s, concurrent chemoradiation therapy (CCRT) has gradually been introduced and is now considered standard treatment. Large randomized controlled trials (RCTs) conducted during that period demonstrated significantly better progression-free survival (PFS) and overall survival (OS) with cisplatin-based CCRT than with RT alone. The current standard CCRT includes pelvic external beam radiation therapy (EBRT), either high-dose-rate or low-dose-rate intracavity brachytherapy (ICBT), and five to six weekly cycles of cisplatin (40 mg/m$^2$) administered concurrently with radiation.

Although acute toxicities associated with CCRT are well-documented[2], few studies have addressed late toxicities. Khoury et al. reported long-term follow-up outcomes for RT alone[3], identifying the small intestine, rectum, bladder, and vagina as the primary sites of late toxicity, most of which developed within 5 years. However, it remains unclear whether late toxicities follow a similar pattern with CCRT. Chung et al. reported severe late toxicities—including surgically managed ileus, intestinal perforation, and intestinal vesicointestinal fistula—in 6% of cases receiving CCRT[4]. Notably, their cisplatin dosage and administration schedule differed from current practice. Kato et al. examined long-term outcomes and late toxicities of CCRT in Eastern and Southeast Asia[5], presenting high-quality prospective multicenter data, although limited to approximately 120 cases. To better understand the nature of late toxicities following CCRT, larger studies are needed. This study aimed to identify late toxicities associated with CCRT through a large-scale multicenter study in Japan and to clarify their relationship with prognosis.

## Methods

Seven institutions affiliated with the Gynecologic Oncology Trial and Investigation Consortium (GOTIC) participated in this study. We reviewed medical records of patients with cervical cancer treated with CCRT. Eligible participants had stage IB2 to IVA cervical cancer according to the 1994 International Federation of Gynecology and Obstetrics (FIGO) classification and initiated CCRT between January 2001 and December 2010. RT at all sites was delivered following Japanese radiation therapy guidelines[6]. Medical record information was collected from January 2015 to March 2017. The study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (14-128). The other six sites were approved by their respective Institutional Review Boards.

The following variables were extracted from each patient's medical records: age, height, body weight, performance status at treatment initiation, presence of diabetes mellitus, major comorbidities, clinical stage, histological type, primary tumor size, and sites of enlarged lymph nodes. For radiation-related factors, we collected data on EBRT start and end dates, EBRT method and dose, ICBT start and end dates, and ICBT total dose. For chemotherapy-related factors, we recorded treatment dates, regimen, total dose, and number of cycles. Late toxicities were defined as symptoms developing ≥ 60 days after CCRT completion. The variables and severity of symptoms were categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For each late toxicity, the onset date, treatment, and outcome were recorded. Five-year cumulative rates were used to report the incidence of late toxicities. Prognostic data included recurrence status, site and date of recurrence, final survival confirmation date, and cause of death, if applicable.

The primary endpoint was the incidence of late toxicities. Secondary endpoints included the relationship between late toxicities and prognosis, the incidence of toxicities by chemotherapy regimen, associations between chemotherapy regimens and survival outcomes, the frequency of toxicities in relation to treatment for recurrence, and the relationship between ICBT and survival outcomes.

Statistical analysis was conducted using EXCELSTAT (EXCELSTAT ver. 23.3; USACO Corporation). Multivariate analysis was performed using JMP (JMP Student Edition, ver.18.2.1. SAS Institute). Survival curves were generated using the Kaplan–Meier method, and the log-rank test was used to evaluate significance. Multivariate survival analysis was conducted using multiple logistic regression. Considering previous reports and clinical importance, the variables were as follows: age, performance status, presence of diabetes mellitus, clinical stage, histological type, pelvic node metastasis, method of EBRT, presence of ICBT, chemotherapy, total dose of EBRT, total dose of ICBT, and hospitals. In addition, late toxicities of the small bowel, rectum, and bladder were added to the analysis of prognostic factors. Explanatory variables were selected based on those that were significant ($P$ value <.05) in univariate analysis and clinical stage. Additionally, factors with a variance influence factor >10 were excluded to eliminate multicollinearity. Adjusted hazard ratios and corresponding confidence intervals (CIs) were derived from the multivariate Cox model. A two-tailed $P$ value <.05 was considered statistically significant.

## Results

### Patient characteristics

A total of 304 eligible patients were included in the study. The median follow-up duration was 79.3 months (range, 1.2–162.9 months). Patient characteristics are summarized in Table 1. Of the enrolled patients, 271 (89.1%) had squamous cell carcinoma (SCC). Regarding EBRT, 187 patients (61.5%) received treatment using the 4-field box technique, while 117 patients (38.5%) were treated with anteroposterior–posteroanterior (AP-PA) parallel-opposed portals. ICBT was performed in 278 patients (91.4%). The most used chemotherapy regimen was weekly cisplatin (CDDP) in 250 patients (82.2%), followed by nedaplatin in 35 patients (11.5%), weekly carboplatin in 15 patients (4.9%), and paclitaxel plus carboplatin in 4 patients (1.3%).

**Table 1** Characteristics of the patients (N = 304)

| | | (%) |
|---|---|---|
| Age (y) | | |
| Mean | 55.3 | |
| Range | 28-87 | |
| FIGO (1994) Stage | | |
| IB2 | 8 | (2.6) |
| IIA | 12 | (3.9) |
| IIB | 94 | (30.9) |
| IIIA | 13 | (4.3) |
| IIIB | 144 | (47.4) |
| IVA | 33 | (10.9) |
| Histological Type | | |
| Squamous Cell Carcinoma | 271 | (89.1) |
| Adenocarcinoma | 27 | (8.9) |
| Others | 6 | (2.0) |
| Performance Status | | |
| 0 | 209 | (68.8) |
| 1 | 75 | (24.7) |
| 2 | 15 | (4.9) |
| 3 | 2 | (0.7) |
| Diabetes Mellitus | | |
| Yes | 24 | (7.9) |
| No | 280 | (92.1) |
| Overall treatment time (days) | | |
| Median | 42.5 | |
| Range | 18-96 | |
| External beam irradiation | | |
| AP-PA parallel opposed portals | 117 | (38.5) |
| 4-field box technique | 187 | (61.5) |
| Total dose of external beam irradiation | | |
| >50 Gy. | 153 | (50.3) |
| 50 Gy.≥ | 151 | (49.7) |
| Intracavity Brachytherapy | | |
| Yes | 278 | (91.4) |
| No | 26 | (8.6) |
| Total dose of intracavity brachytherapy | | |
| >18 Gy | 148 | (48.7) |
| 18 Gy.≥ | 25 | (51.3) |
| Chemotherapy | | |
| Weekly Cisplatin | 250 | (82.2) |
| Nedaplatin | 35 | (11.5) |
| Others | 19 | (6.3) |

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; AP-PA, anterior posterior and posterior anterior

### Late toxicities

Grade 3 or 4 late toxicities involving the small bowel, rectum, and bladder occurred in 9, 11, and 8 patients, respectively (Table 2). Among patients with Grade ≥ 3 small bowel complications, four developed stenosis or obstruction (Grade 3) three experienced fistula formation (Grade 4), and one died of small bowel obstruction. Regarding rectal complications, rectal bleeding (Grade 3) was most common (eight patients), and two patients developed rectovaginal fistula (Grade 4). Among patients with bladder complications, hematuria (Grade 3) occurred in five, and fistula (Grade 4) in one. Other Grade ≥ 3 toxicities included deep vein thrombosis, lumbar compression fracture, uterine infection, and leukemia in one case each. The overall incidence of Grade ≥ 3 late toxicities was 32 cases (10.5%).

The 5-year cumulative incidence rates of Grade ≥ 3 toxicities to organs were 3.7% (95% CI: 1.9%–7.1%) for the small bowel, 3.8% (95% CI: 2.1%–7.0%) for the rectum, and 3.2% (95% CI: 1.5%–6.7%) for the bladder (Table 3). For Grade ≥ 2 toxicities, the respective 5-year cumulative incidence rates were 4.4% (95% CI: 2.6%–7.4%), 8.5% (95% CI: 5.9%–12.2%), and 5.7% (95% CI: 3.6%–8.9%), respectively.

**Table 2** Late toxicities

| | Grade 3 (n) | Grade 4 (n) | Grade 5 (n) | Total (%) |
|---|---|---|---|---|
| **Small bowel** | Stenosis or obstruction (4)<br>Enteritis (1) | Fistula (3) | Obstruction (1) | 9 (3.0) |
| **Rectum** | Bleeding (8)<br>Stenosis (1) | Fistula (2) | 0 | 11 (3.6) |
| **Bladder** | Bleeding (5)<br>Cystitis (2) | Fistula (1) | 0 | 8 (2.6) |
| **Others** | Deep vein thrombosis (1)<br>Infection of uterus(1)<br>Compression fracture (1) | Leukemia (1) | 0 | 4 (1.3) |
| **Total (%)** | 24 (7.9) | 7 (2.3) | 1 (0.3) | 32 (10.5) |

**Table 3** Five-year cumulative rates

| | Grade2 or more | Cumulative rate | Grade3,4 | Cumulative rate |
|---|---|---|---|---|
| | Rate | (95% CI) | Rate | (95% CI) |
| **Small Bowel** | 4.4% | (2.6%-7.4%) | 3.2% | (1.7%-5.8%) |
| **Rectum** | 8.5% | (5.9%-12.2%) | 3.5% | (1.9%-6.2%) |
| **Bladder** | 5.7% | (3.6%-8.9%) | 2.2% | (1.1%-4.6%) |

Abbreviation: CI, confidence interval

**Table 4** Risk factors of late toxicity by univariate and multivariate analyses

| Risk factor | Small bowel | | | | | | Rectum | | | Bladder | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | | Univariate analysis | | | Univariate analysis | | |
| | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| **Age (≥60 y vs. <60 y)** | 0.27 | 0.04-1.15 | 0.08 | | | | 0.82 | 0.23-2.76 | 0.74 | 0.73 | 0.14-3.39 | 0.69 |
| **PS** | 0.79 | 0.12-3.39 | 0.78 | | | | 0.51 | 0.14-2.08 | 0.33 | 0.89 | 0.19-6.28 | 0.89 |
| **Diabetes Mellitus(yes or no)** | 1.48 | 0.08-8.58 | 0.73 | | | | 0 | 0.00-2.23 | 0.17 | 0 | 0.00-3.73 | 0.28 |
| **Stage** | 0.41 | 0.06-1.75 | 0.24 | | | | 0 | 0.00-5.67 | 0.37 | 0 | 0.00 | 0.40 |
| **Histological type(SCC vs. Others)** | 0.14 | 0.04-0.60 | 0.001* | 0.16 | 0.04-0.68 | 0.02* | 0.31 | 0.09-1.50 | 0.13 | 0.30 | 0.06-2.17 | 0.20 |
| **Pelvic node metastasis (yes or no)** | 2.50 | 0.59-17.0 | 0.22 | | | | 1.90 | 0.54-8.81 | 0.33 | 3.69 | 0.78-26.0 | 0.10 |
| **Overall treatment time** | 1.01 | 0.93-1.06 | 0.79 | 1.01 | 0.95-1.07 | 0.55 | 1.04 | 0.99-1.08 | 0.08 | 1.04 | 0.98-1.09 | 0.17 |
| **Method of EBRT (4 vs. 2 Portals)** | 1.26 | 0.32-6.06 | 0.74 | | | | 2.91 | 0.86-11.3 | 0.08 | 1.20 | 0.23-5.55 | 0.81 |
| **ICBT (yes or no)** | 1.29 | 0.07-7.46 | 0.81 | | | | 2.38 | 0.35-9.90 | 0.32 | 1.74 | 0.09-10.7 | 0.64 |
| **Total dose of EBRT (>50 Gy. vs 50 Gy≥)** | 2.07 | 0.54-9.95 | 0.30 | | | | 1.22 | 0.36-4.33 | 0.74 | 1.32 | 0.29-6.82 | 0.71 |
| **Total dose of ICBT (>18 Gy. vs 18 Gy≥)** | 1.93 | 0.50-9.29 | 0.34 | | | | 1.69 | 0.50-6.57 | 0.50 | 1.27 | 0.28-6.55 | 0.75 |
| **Chemotherapy (CDDP vs Others)** | 0.17 | 0.04-0.65 | 0.01* | 0.17 | 0.04-0.70 | 0.02* | 0.98 | 0.14-3.95 | 0.98 | 0.73 | 0.04-6.55 | 0.75 |
| **Hospitals** | 0.56 | 0.00-11.9 | 0.56 | | | | 8.78 | 0.00 | 1.00 | 2.40 | 0.00 | 1.00 |

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; SCC, squamous cell carcinoma; ICBT, intracavity brachytherapy; EBRT, extra beam radiotherapy; CDDP, cisplatin.

Multivariate analysis identified histological type and chemotherapy as significant predictors of small bowel toxicity (Table 4). No significant associations were found for rectal or bladder toxicities.

**Survival outcome**

The 5-year PFS for all patients was 58.1% (95% CI: 52.3%–63.9%). By stage, the 5-year PFS was 77.9% (95% CI: 50.2%–100%) for Stage I, 67.2% (95% CI: 57.8%–76.6%) for Stage II, 55.0% (95% CI: 37.2%–72.8%) for Stage III, and 48.7% (95% CI: 32.2%–65.3%)for Stage IV. A statistically significant difference was observed between Stages II and III ($P$=0.009), but not between Stages I and II ($P$=0.75) or III and IV ($P$=0.64). (Fig. 1).

The 5-year OS was 66.3% (95% CI: 60.7%–71.9%). By stage, the 5-year OS was 90.0% (95% CI: 71.4%–100%) for Stage I, 78.8% (95% CI: 70.6%–87.1%) for Stage II, 58.7% (95% CI: 50.6%–66.8%) for Stage III, and 56.4% (95% CI: 40.0%–72.9%) for stage IV. A statistically significant difference was found between Stages II and III ($P$=0.002), while no significant differences were observed between Stages I and II ($P$=0.90) or III and IV ($P$=0.96) (Fig. 2).

Univariate analysis suggested that age, histological type, ICBT, and chemotherapy may have an influence on PFS; however, multivariate analysis revealed that only age affected PFS (Table 5). Regarding OS, age, PS, clinical stage, ICBT, and late toxicities of the rectum were statistically significant predictors (Table 6). OS was higher in patients who underwent ICBT than in those who did not. Neither total EBRT dose nor ICBT was associated with PFS or OS.

**Discussion**

CCRT is considered a standard treatment for managing locally advanced cervical cancer[7]. This large-scale multicenter study in Japan aimed to identify the incidence of late toxicities associated with CCRT and clarify their potential relationship with prognosis. Grade ≥ 3 late toxicities occurred in 32 of 304 cases (10.5%). This incidence aligns with previous reports. However, because the definitions of late toxicities vary from report to report, simple comparisons may not be appropriate. In the GOG 85 study published in 1999, the 3-year rate of major late toxicities was 16.2% among patients treated with CCRT[8]. Similarly, the Radiation Therapy Oncology Group study 90-01 reported a 5-year incidence of major late toxicities of 14% for both the CCRT and RT groups[9]. In 2013, Kudaka et al. reported a 2.0% (2/99) incidence of Grade ≥ 3 small or large intestine late adverse effects and no bladder toxicities[10]. During the same year, Kato et al. reported a 5-year cumulative

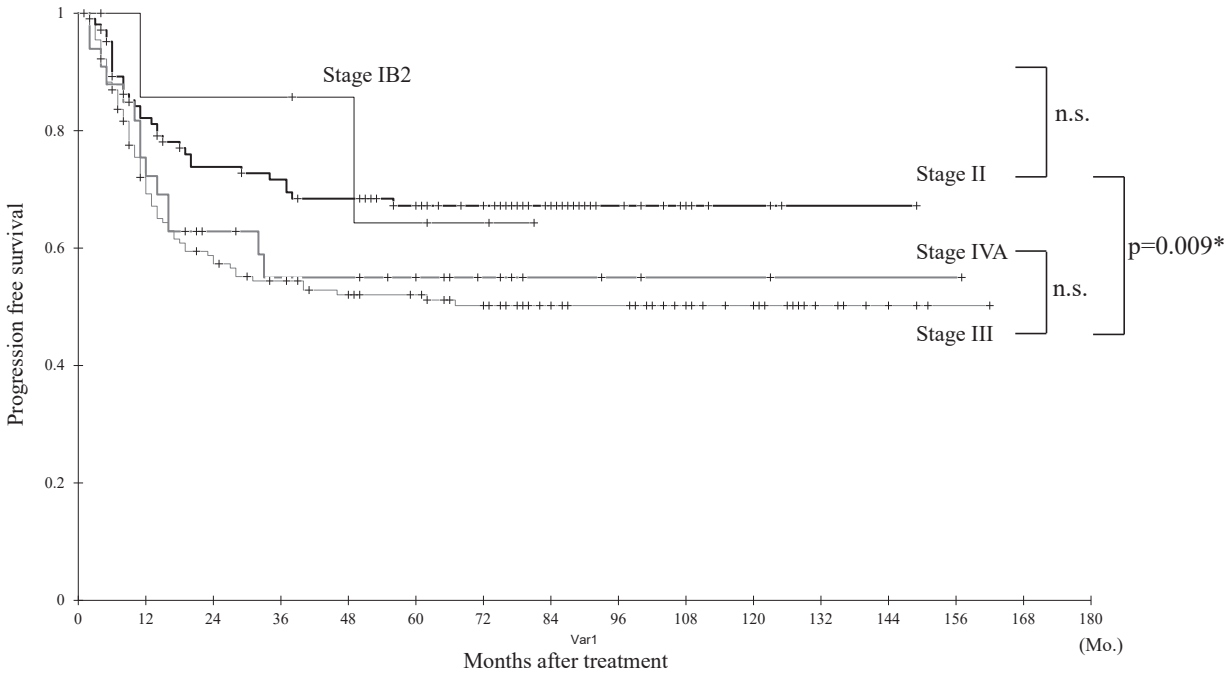


**Fig. 1** Progression free survival (PFS) by clinical stage

Kaplan–Meier curves of the PFS of all patients by clinical stage. A statistically significant difference was observed between Stages II and III (*P*=0.009).

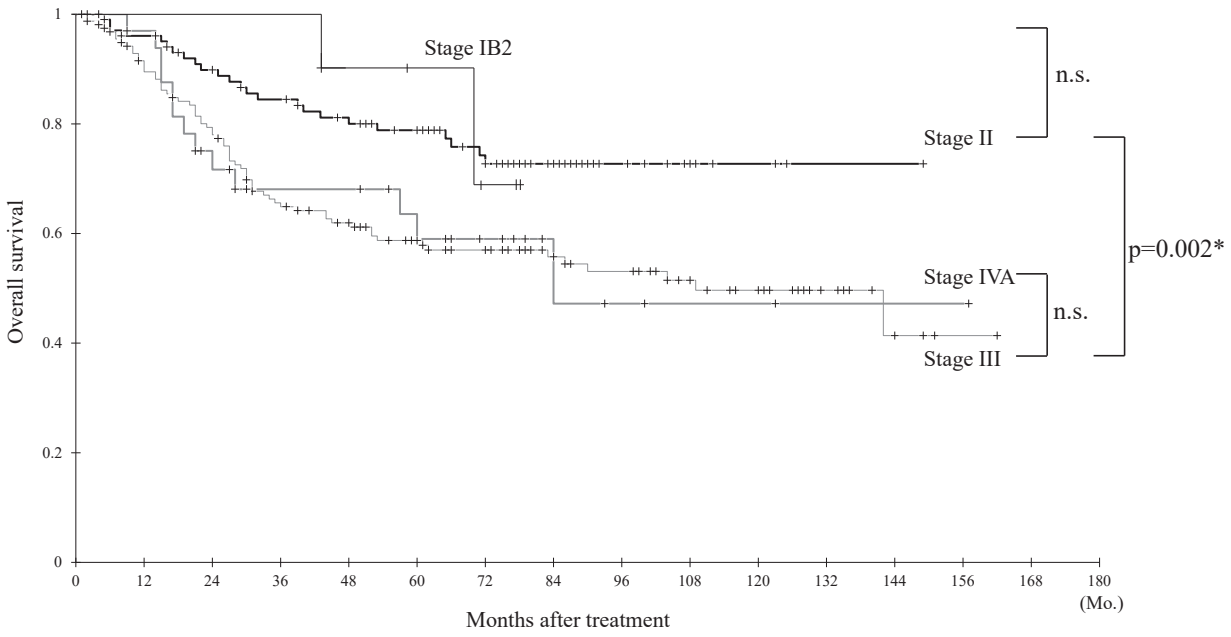


**Fig. 2** Overall survival (OS) by clinical stage

Kaplan–Meier curves the OS of all patients by clinical stage. A statistically significant difference was observed between Stages II and III (*P*=0.002).

incidence of Grade ≥3 rectal toxicities of 7.8% (95% CI: 0.2–15.5%) (5). In 2014, Jakubowicz et al. reported Grade 3 or 4 late toxicities in 1.6% (2/120) of patients, including large intestine narrowing requiring surgery and recto-vaginal fistula[11]. These data suggest that the incidence of late adverse events has declined since the 2010s.

Previous studies demonstrated associations between total radiation dose, overall treatment time, and the development of late toxicities[2]. Specifically, the frequency of late toxicities increased with extended treatment time. Pathy et al. compared two groups with differing treatment durations and found a numerically higher rate of Grade ≥3 toxicity in the longer-

**Table 5** Risk factors of progression free survival by univariate and multivariate analyses

| | Univariate Analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Risk factor** | HR | 95% CI | p-value | HR | 95% CI | p-value |
| **Age (<60 y vs. ≥60 y)** | 0.06 | 0.04-0.09 | 0.0001* | 0.06 | 0.04-0.09 | <0.0001* |
| **PS** | 1.14 | 0.68-1.94 | 0.61 | | | |
| **Diabetes Mellitus(yes or no)** | 1.41 | 0.93-2.15 | 0.14 | | | |
| **Stage** | 0.72 | 0.36-1.49 | 0.36 | 0.65 | 0.32-1.35 | 0.24 |
| **Histological type(SCC vs. Others)** | 0.63 | 0.44-0.91 | 0.01* | 0.98 | 0.68-1.41 | 0.91 |
| **Pelvic node metastasis (negative vs. positive)** | 0.88 | 0.70-1.11 | 0.28 | | | |
| **Method of EBRT (4 vs. 2 Portals)** | 0.82 | 0.65-1.04 | 0.10 | | | |
| **ICBT (yes or no)** | 0.45 | 0.30-0.68 | 0.0001* | 0.79 | 0.51-1.21 | 0.28 |
| **Chemotherapy (CDDP vs Others)** | 0.75 | 0.56-0.99 | 0.05* | 0.84 | 0.62-1.14 | 0.27 |
| **Total dose of EBRT (>50 Gy. vs. 50 Gy.≥)** | 0.93 | 0.74-1.17 | 0.55 | | | |
| **Total dose of ICBT(>18 Gy. vs. 18 Gy.≥)** | 0.98 | 0.78-1.23 | 0.85 | | | |
| **Hospitals** | 1.58 | 0.81-2.24 | 0.69 | | | |
| **Late toxicities of Small Bowel (G3,4 vs. No or G1,2)** | 1.49 | 0.76-2.91 | 0.24 | | | |
| **Late toxicities of Rectum (G3,4 vs. No or G1,2)** | 1.66 | 0.90-3.06 | 0.10 | | | |
| **Late toxicities of Bladder (G3,4 vs. No or G1,2)** | 1.51 | 0.71-3.22 | 0.28 | | | |

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; SCC, squamous cell carcinoma; EBRT, extra beam radiotherapy; ICBT, intracavity brachytherapy; CDDP, cisplatin.

**Table 6** Risk factors of overall survival by univariate and multivariate analyses

| | Univariate Analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Risk factor** | HR | 95% CI | p-value | HR | 95% CI | p-value |
| **Age (<60 y vs. ≥60 y)** | 0.007 | 0.002-0.02 | <0.0001* | 0.005 | 0.002-0.02 | <0.0001* |
| **PS** | 0.11 | 0.02-0.48 | 0.003* | 0.19 | 0.04-0.82 | 0.03* |
| **Diabetes Mellitus(yes or no)** | 1.46 | 0.96-2.21 | 0.08 | | | |
| **Stage** | 1.41 | 0.69-2.89 | 0.34 | 2.32 | 1.11-4.83 | 0.02* |
| **Histological type(SCC vs. Others)** | 0.55 | 0.39-0380 | 0.001* | 0.79 | 0.54-1.15 | 0.22 |
| **Pelvic node metastasis (negative vs. positive)** | 0.84 | 0.67-1.06 | 0.14 | | | |
| **Method of EBRT (4 vs. 2 Portals)** | 0.87 | 0.69-1.11 | 0.26 | | | |
| **ICBT (yes or no)** | 0.34 | 0.23-0.51 | <0.0001* | 0.53 | 0.34-0.82 | 0.005* |
| **Chemotherapy (CDDP vs Others)** | 0.67 | 0.50-0.90 | 0.007* | 0.78 | 0.57-1.06 | 0.11 |
| **Total dose of EBRT (>50 Gy. vs. 50 Gy.≥)** | 0.86 | 0.69-1.08 | 0.20 | | | |
| **Total dose of ICBT(>18 Gy. vs. 18 Gy.≥)** | 0.93 | 0.74-1.17 | 0.56 | | | |
| **Hospitals** | 1.02 | 0.11-9.35 | 0.99 | | | |
| **Late toxicities of Small Bowel (G3,4 vs. No or G1,2)** | 1.83 | 0.94-3.58 | 0.07 | | | |
| **Late toxicities of Rectum (G3,4 vs. No or G1,2)** | 1.88 | 1.02-3.47 | 0.04* | 2.04 | 1.19-3.82 | 0.03* |
| **Late toxicities of Bladder (G3,4 vs. No or G1,2)** | 1.53 | 0.72-3.27 | 0.26 | | | |

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; SCC, squamous cell carcinoma; EBRT, extra beam radiotherapy; ICBT, intracavity brachytherapy; CDDP, cisplatin.

treatment group, although statistical significance was not achieved[12]. In the present study, longer treatment duration was not significantly associated with small bowel toxicity.

Regarding histological type, patients with SCC experienced fewer late toxicities of the small bowel than those with other histological types. We compared SCC with non-SCC cases, and examined potential contributing factors, such as total EBRT dose and lymph node metastasis, but no clear associations were identified. Although some reports suggested the relationship between overall treatment time and the occurrence of late toxicities[5,10], herein, no correlation between them was observed. This may be because of central shield use, which reduces adverse events particularly in the bladder and rectum.

No significant association was found between bladder or rectal late toxicities and known risk factors. Additionally, late toxicities were not associated with survival outcomes (both

PFS and OS), except for rectal toxicities. Rectal toxicities may have shown a significant impact on prognosis possibly due to the relatively low incidence of toxicities.

Initially, we hypothesized that a weekly cisplatin regimen would yield a better prognosis than other regimens; however, no association was observed between chemotherapy and survival outcomes. Kagabu et al. previously reported that nedaplatin and weekly cisplatin produced comparable prognoses when used in CCRT[13]. The ongoing TACO trial by Korean investigators aims to demonstrate the noninferiority of a triweekly cisplatin regimen to the standard weekly regimen, with results expected soon.

Although previous studies suggested improved prognosis with the addition of ICBT compared to EBRT alone, our study found significant associations between ICBT use and survival outcomes. No difference was observed in the specific methods of ICBT probably because ICBT was administered in over 90% of cases.

One limitation of this study is the lack of detailed evaluation of EBRT and ICBT dosing. Considering organ-specific radiation doses may help identify more precise factors contributing to late toxicities.

Overall, this study reported the incidence of late toxicities in patients treated with CCRT from 2001 to 2010. During this period, EBRT was administered to the whole pelvis using anterior–posterior parallel-opposed portals or the four-field box technique, while ICBT was delivered using x-ray-based two-dimensional planning. In current practice, ICBT is administered via three-dimensional image-guided interstitial–intracavitary brachytherapy, allowing for more accurate dose estimation. Additionally, technologies such as intensity-modulated radiation therapy have emerged, which are expected to further reduce the risk of late toxicities. Therefore, future studies should assess whether these modern modalities reduce radiation-related toxicities compared with our current findings.

## Conclusion

This study reported the incidence of late toxicities and prognosis in patients treated with CCRT from 2001 to 2010. Regarding both late toxicities and prognosis, CCRT can be considered a standard treatment in the management of locally advanced cervical cancer.

These findings provide a basis for comparison with various current radiation treatment methods and new chemotherapy strategies such as the use of immuno-checkpoint inhibitors.

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## Disclosure

None.

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## 局所進行子宮頸癌に対する同時化学放射線療法の晩期毒性と予後に関する多施設共同研究：婦人科腫瘍臨床試験コンソーシアム（GOTIC）008 試験

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目的：局所進行子宮頸癌に対する同時化学放射線療法（CCRT）の晩期毒性を明らかにし，晩期毒性と予後との因果関係を明らかにすること．
方法：2001 年から 2010 年の間に，婦人科腫瘍臨床試験コンソーシアム（GOTIC）参加施設で診断され，同時化学放射線療法（CCRT）を受けた Stage IB2～ IVA の子宮頸癌患者を対象に，後ろ向き研究を実施した．
結果：対象患者は合計 304 名であった．全患者の追跡期間の中央値は 79.3 か月（範囲：1.2～162.9 か月）であった．グレード 3 以上の晩期毒性は全体で 32 例（10.5%）であった．小腸，直腸，膀胱におけるグレード 3 以上の晩期毒性の 5 年累積発現率は，それぞれ 3.7%（95% 信頼区間 1.9%～7.1%），3.8%（95% 信頼区間 2.1%～7.0%），3.2%（95% 信頼区間 1.5%～6.7%）であった．多変量解析の結果，小腸毒性と組織型（ハザード比 0.16，95% 信頼区間 0.04～0.68，*P*=.02）および小腸毒性と化学療法（ハザード比 0.17，95% 信頼区間 0.04～0.70，*P*=.02）の間に統計的に有意な関連が認められた．全患者の 5 年全生存率は 66.3%（95% 信頼区間 60.7% ～71.9%）であった．年齢，パフォーマンス・ステイタス（PS），臨床進行期，腔内照射の有無，および直腸障害の有無は，全生存期間（OS）との間に統計的に有意な関連が見られた．
結論：晩期毒性の観点から，CCRT は局所進行子宮頸癌の治療における標準治療と考えられ，本研究は，現在の多様な照射方法や免疫チェックポイント阻害薬を用いた新たな化学療法と比較するための資料となる．

 