

Analysis of late adverse events and their chronological changes after radiation therapy for cervical cancer

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ABSTRACT

Several late adverse events occur after radiation therapy (RT) for cervical cancer. However, there has been little reported about their chronological changes. It is still unclear whether concurrent chemoradiotherapy (CCRT) increases late complications. We aimed to evaluate the late adverse events and their chronological changes and whether CCRT increases their incidence and severity. For this purpose, we retrospectively analyzed 157 women with histologically proven cervical cancer. We reviewed all late adverse events and compared the frequency and severity between the patients who underwent CCRT and those who underwent RT alone. We calculated the cumulative occurrence rates of late adverse events stratified by the site and severity, and determined the chronological changes. With survivors' median follow-up time of 74.3 months, late adverse events occurred in 49.0% and serious complications developed in 24.2% of all patients. There was no significant difference in the cumulative incidence rate of all late adverse events between the CCRT and RT-alone groups ($p = 0.720$). The incidence rate of rectal bleeding was 25.5%. Serious rectal bleeding developed in 5 patients, all within 20 months from the start of RT. Importantly, the symptoms of rectal bleeding disappeared or were relieved in most patients during follow-up. In conclusion, we evaluated the late adverse events and their chronological changes after RT for cervical cancer and showed that adding chemotherapy to RT did not affect the frequency and severity of late complications, and the symptoms of rectal bleeding were relieved over time.

Keywords: cervical cancer, radiation therapy, concurrent chemoradiotherapy, late adverse event, chronological changes.

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INTRODUCTION

Worldwide, cervical cancer is one of the leading causes of cancer death among women, and the fourth most frequency occurring malignancy in women.¹⁾

Radiation therapy (RT) is one of the most curative therapeutic methods for treating cervical cancer, and a combination of external beam RT (EBRT) and intracavitary brachytherapy (ICBT)

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is considered the standard method.²⁾ For locally advanced cervical cancer, treatment outcome has been shown to be improved by concurrent chemoradiotherapy (CCRT) with cisplatin-based chemotherapy compared with RT alone.³⁾ However, several late adverse events represented by rectal bleeding, small intestinal obstruction, and cystitis occur after RT,²⁾ because a wide pelvic area is irradiated and high doses are administered locally by ICBT. Regarding these late adverse events, there has been little reported about their chronological changes, whereas their frequency and severity have been described.⁴⁾ In addition, it is still unclear whether CCRT increases the incidence and severity of late complications.⁵⁻⁶⁾

The purpose of this study was to evaluate the late adverse events and their chronological changes after RT in cervical cancer patients and to reveal whether CCRT increases the incidence and severity of late complications.

MATERIALS AND METHODS

We retrospectively analyzed patients with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix who were treated with RT as part of their primary treatment at the Toyohashi Municipal Hospital between January 2007 and December 2013. We excluded patients who received adjuvant or neoadjuvant chemotherapy and who underwent postoperative radiotherapy, radiotherapy for postoperative local recurrence and for distant metastasis. The clinical stages of all patients were determined according to the Union for International Cancer Control (UICC) 7th edition and the International Federation of Gynecology and Obstetrics (FIGO) 2008 staging system before treatment. We also obtained information about comorbidities such as diabetes, collagen disease, cirrhosis and anticoagulant use, which have been reported as risk factors for the late adverse events. This retrospective, observational, single-center study was approved by the ethics committee of Toyohashi Municipal Hospital (No. 321) and Nagoya University Graduate School of Medicine (No. 2017-0299). Survival study participants were asked to give their informed consent when they came to Toyohashi Municipal Hospital for follow up, but when consent could not be obtained, participants were assured they could opt out by phone using the Toyohashi Municipal Hospital website.

We relied on medical records for identification of late complications, and, for some patients, we also confirmed them by phone or letter. Late complications were defined as occurring more than 3 months after the start of RT, and their severity was evaluated at the first occurrence and at the worst time based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Further, we defined a serious complication as a complication of grade 3 or more. In addition to the risks of late adverse events, we also determined their chronological changes by continuing observation. We then evaluated the latest severity of rectal bleeding (that is, last grade), and defined grade 0 as a symptom that had disappeared for more than 6 months since its last occurrence.

RT was performed using a combination of EBRT and ICBT for most patients.

EBRT was performed with 10 MV X-rays or 6 MV X-rays, with a total dose of approximately 50 Gy (median, 50.4 Gy) administered to the whole pelvis. Five fractions of 1.7–2.0 Gy (median, 1.8 Gy) per fraction, were delivered weekly. The first ICBT was delivered after 20–50 Gy of whole pelvis irradiation (WP) and additional external beam therapy was delivered with center shielding (CS).

WP was enforced using the 4 fields (anteroposterior, posteroanterior, and 2 lateral fields) technique for most patients. The anterior posterior parallel opposing field was used as CS, and a shield that was approximately 4 cm wide was inserted to the height of the uterus floor on

the isocenter surface. The timing of the change to CS was determined taking into consideration the size of the primary tumor and its reduction.

ICBT was performed by a remote after-loading system using ^{60}Co sources, and a combination of tandem and ovoid applicators was used. Point A was defined using the Manchester system as 2 cm above and 2 cm lateral from the external uterine orifice. One fraction of 5.0–6.0 Gy (median, 6.0 Gy) per fraction, was delivered weekly to Point A. The median total dose of ICBT was 24 Gy in 4 fractions (range, 6.0–28 Gy). If ICBT was impossible (for reasons that, the reduction of tumor was insufficient, cervical canal was running on the edge of tumor, dilatation of cervical canal was impossible), we substituted the additional EBRT for it (median dose, 12.6 Gy; range, 8.0–18.9 Gy).

The prescribed doses of EBRT and ICBT were evaluated using the biological equivalent dose in 2 Gy (EQD2) assuming $\alpha/\beta = 3$. We calculated the EQD2 using the linear quadratic model, and we assumed that rectum was not irradiated at the CS.

For chemotherapy, cisplatin-based regimens were mainly used. Most patients in the CCRT group received cisplatin (CDDP) + 5-fluorouracil (5-FU) regimen, and patients usually received CDDP at a dose of 70 mg/m² of body-surface area on day 1 and 5-FU at a dose of 700 mg/m² on days 1–4 every 3 weeks.

We reviewed all late adverse events, and compared their frequency and severity between the patients who underwent CCRT and those who underwent RT alone. We compared clinical and pathological factors between the two groups with t-test for continuous data, and Fisher's exact test for categorical data. We compared the ratios of late complications using Fisher's exact test between the 2 treatment arms stratified by the site and severity. Further, we calculated the cumulative occurrence rates of all late adverse events, including rectal bleeding, small intestinal obstruction/perforation, and urinary tract obstruction/bleeding using the Kaplan-Meier method, and assessed age (<60 versus ≥ 60 years), size of primary tumor (<50 versus ≥ 50 mm), FIGO stage ($\leq \text{II}$ versus $\geq \text{III}$), and combination of ICBT as the factors that could affect the cumulative occurrence rate stratified by severity (all grades and grade 3 or more). We then evaluated the cumulative occurrence rates of rectal bleeding and the irradiation dose for rectum (EQD2 <70 versus ≥ 70 Gy). When calculating the cumulative incidence rates, deaths before events were treated as competitive risks, and trends over time were evaluated in competing-risk models. The factors affecting the cumulative incidence of late adverse events were assessed using univariate analysis by Gray's test and multivariable Fine-Gray proportional hazards regression analysis. All reported p-values were 2-sided, and we considered that p-values of <0.05 indicated statistical significance. For all analyses, we used free statistical software (EZR; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We followed 157 patients, all of whom were included in the analysis. Patient characteristics are presented in Table 1. A total of 104 patients (66.2%) received CCRT. Of these patients, 86 (82.7%) received CDDP + 5-FU, 7 (6.7%) received weekly CDDP, 8 (7.7%) received nedaplatin (NDP) + 5-FU, and 2 received other regimens. The median age of all patients was 58 (range, 24–92) years. In the CCRT group, the median age was 21 years younger and their performance status was better than the RT-alone group. The UICC stages were I in 12, II in 58, III in 62, and IV in 25 patients, and the FIGO stages were IA in 1, IB in 15, IIA in 5, IIB in 82, IIIA in 6, IIIB in 33, and IVA in 15 patients. The patients with FIGO stage II and III mainly received

CCRT, and the ones with FIGO stage I and IV mainly received RT alone. Regarding tumor histopathology, 137 patients had squamous cell carcinoma, 19 had adenocarcinoma, and 1 had adenosquamous carcinoma. Regarding the comorbidities, 5 patients (4.8%) had diabetes, 2 (1.9%)

Table 1 Characteristics of 157 patients with cervical cancer

Characteristic	CCRT (n = 104)	RT alone (n = 53)	p-value
Age at the start of RT (years)	58 (24–92)		
	52 (24–78)	73 (36–92)	< 0.05
Performance status			< 0.05
0	63 (60.6)	15 (28.3)	
1	39 (37.5)	29 (54.7)	
2–4	2 (1.9)	9 (17.0)	
Clinical stage (UICC 2009)			< 0.05
I	2 (1.9)	10 (18.9)	
II	43 (41.3)	15 (28.3)	
III	46 (44.2)	16 (30.2)	
IV	13 (12.5)	12 (22.6)	
FIGO stage			< 0.05
IA	0 (0.0)	1 (1.9)	
IB	5 (4.8)	10 (18.9)	
IIA	3 (2.9)	2 (3.8)	
IIB	65 (62.5)	17 (32.1)	
IIIA	4 (3.8)	2 (3.8)	
IIIB	23 (22.1)	10 (18.9)	
IVA	4 (3.8)	11 (20.8)	
Size of primary tumor (mm)	53 (0–157)		
	55 (15–157)	51 (0–95)	NS
≤40 mm	19 (18.3)	19 (35.8)	< 0.05
>40 mm	85 (81.7)	34 (64.2)	
Histologic type			NS
Squamous cell carcinoma	94 (90.4)	43 (81.1)	
Adeno or adenosquamous carcinoma	10 (9.6)	10 (18.9)	
Comorbidities			
Diabetes	5 (4.8)	6 (11.3)	NS
Anticoagulant use	2 (1.9)	3 (5.7)	NS
Cirrhosis	0 (0.0)	1 (1.9)	NS
Ulcerative colitis	1 (1.0)	0 (0.0)	NS

a) Values are presented as median (range) or number (%).

b) CCRT, concurrent chemoradiotherapy; RT, radiation therapy; UICC, Union for International Cancer Control; NS, not significant.

c) The p-value shows the results of comparison by t-test (for continuous data) or Fisher's exact test (for categorical data) between the patients who underwent CCRT and those who underwent RT alone.

had anticoagulant use, and 1 had ulcerative colitis in the CCRT group, 6 patients (11.3%) had diabetes, 3 (5.7%) had anticoagulant use, and 1 had cirrhosis in the RT-alone group.

The median follow-up time for survivors was 74.3 (range, 41.0–122.3) months. Late adverse events occurred in 77 patients (49.0% of all patients), and serious complications developed in 38 patients (24.2%). Tables 2 and 3 summarize these late complications.

Most of the late complications occurred within the first 2 years, and the incidence rate subsequently decreased (Fig. 1A, B). Regarding the late complications that occurred for the first time, the rates of grade 1, 2, 3, and 4 (that is, the first grade) were 11.5%, 19.1%, 15.3%, and 3.2%, respectively. Fisher's exact test revealed no significant differences in the incidence rates between the CCRT and RT-alone group (Table 2).

Gray's test indicated that the cumulative incidence rate of all late adverse events was significantly higher when the size of the primary tumor was >50 mm than when its size was ≤50 mm ($p = 0.043$) (Fig. 1C) and that there was no significant difference between the CCRT and

Table 2 Summary of late complications stratified by site and severity

Late complications	All (n = 157)	CCRT (n = 104)	RT alone (n = 53)	p-value
All	77 (49.0)	54 (51.9)	23 (43.4)	NS
Rectal bleeding	40 (25.5)	26 (25.0)	14 (26.4)	NS
Small intestinal obstruction/perforation	23 (14.6)	16 (15.4)	7 (13.2)	NS
Urinary tract obstruction/bleeding	27 (17.2)	21 (20.2)	6 (11.3)	NS
Severity (First grade; CTCAE version 4.0)	All (n = 77)	CCRT (n = 54)	RT alone (n = 23)	
1	18 (23.4)	11 (20.4)	7 (30.4)	NS
2	30 (39.0)	25 (46.3)	5 (21.7)	NS
3	24 (31.2)	15 (27.8)	9 (39.1)	NS
4	5 (6.5)	3 (5.6)	2 (8.7)	NS

a) Values are presented as number (%).

b) CCRT, concurrent chemoradiotherapy; RT, radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events; NS, not significant.

c) The p-value shows the results of comparison of ratios of late complications by Fisher's exact test between the patients who underwent CCRT and those who underwent RT alone.

Table 3 Summary of serious late complications stratified by site

Site	All (n = 157)	CCRT (n = 104)	RT alone (n = 53)	p-value
All	38 (24.2)	25 (24.0)	13 (24.5)	NS
Rectum	5 (3.2)	1 (1.0)	4 (7.5)	0.0447
Small intestine	17 (10.8)	12 (11.5)	5 (9.4)	NS
Urinary tract	16 (10.2)	12 (11.5)	4 (7.5)	NS
Others	4 (2.5)	3 (2.9)	1 (1.9)	NS

a) Values are presented as number (%).

b) CCRT, concurrent chemoradiotherapy; RT, radiation therapy; NS, not significant.

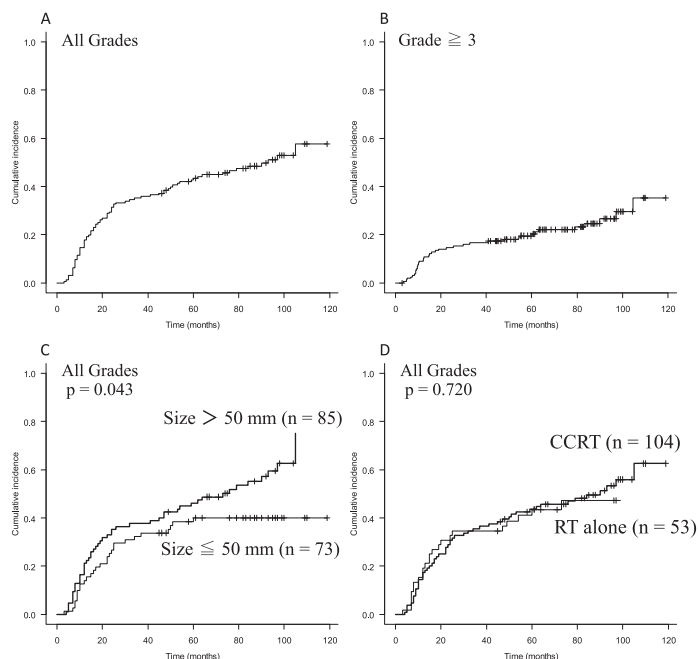


Fig. 1 Cumulative incidence rates of late adverse events

Cumulative incidence rates of late adverse events of all grades (A), and grade ≥ 3 (B) using the Kaplan-Meier method. Comparison of cumulative incidence rates of late adverse events for primary tumors <50 versus ≥ 50 mm (C) and for patients who underwent CCRT and RT alone (D). CCRT, concurrent chemoradiotherapy; RT, radiation therapy.

RT-alone group ($p = 0.720$) (Fig. 1D). Multivariate analysis using Fine-Gray proportional hazards regression considering age, size of primary tumor, FIGO stage, and combination ICBT detected none of these factors significantly affected the cumulative occurrence rate.

The incidence rate of rectal bleeding, small intestinal obstruction/perforation, urinary tract obstruction/bleeding for any grade was 25.5%, 14.6%, and 17.2%, respectively, and that for grade 3 or more was 3.2%, 10.8%, and 10.2%, respectively. Fig. 2 shows their probabilities.

Gray's test indicated that the cumulative incidence rate of rectal bleeding was significantly higher when combination ICBT was used than when it was not used ($p = 0.037$) (Fig. 3A). Further, the cumulative incidence rate of rectal bleeding was considerably higher when the EQD2 for the rectum was >70 Gy than when EQD2 was ≤ 70 Gy, although the difference was not statistically significant ($p = 0.089$) (Fig. 3B).

Grade 3 rectal bleeding developed in 5 patients (3.2%), all within 20 months from the start of RT (Fig. 2B). We detected no significant risk factor for the cumulative incidence rate of serious (grade 3) rectal bleeding using Gray's test and Fine-Gray proportional hazards regression analysis. Grade 4 and 5 rectal bleeding did not occur. In the patients who developed rectal bleeding, the disappearance of symptoms (grade 0) was confirmed in 18 patients (45.0%), and 32 patients (80.0%) required no treatment (grade ≤ 1) during follow-up.

In contrast, the risks of serious late complications in the small intestine and urinary tract were still elevated 100 months after treatment (Fig. 2D, F). Univariate analysis (Gray's test) revealed that the cumulative incidence rate of serious small intestinal obstruction/perforation was significantly higher for patient >60 years of age than for those ≤ 60 years of age ($p = 0.016$)

Toxicities after RT for cervical cancer

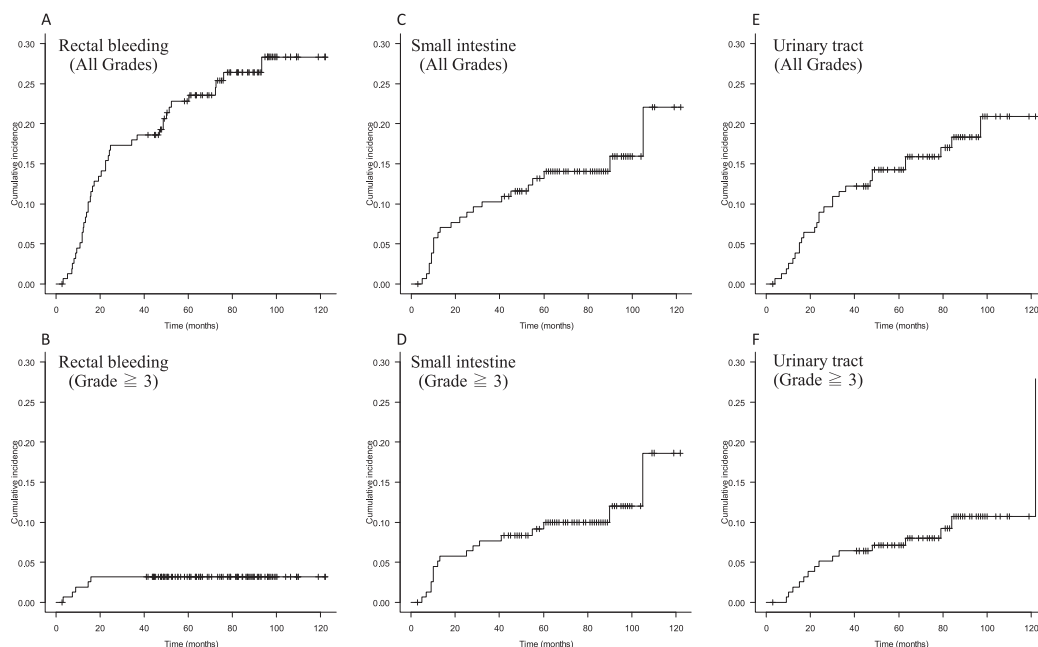


Fig. 2 Summary of the cumulative incidence rates of late adverse events stratified by site and severity
The cumulative incidence rates of rectal bleeding, small intestinal obstruction/perforation, and urinary tract obstruction/bleeding stratified by severity: all grades (A, C, E) or grade 3 or more (B, D, F).

Table 4 Summary of rectal bleeding

Severity	All (n = 40)	CCRT (n = 26)	RT alone (n = 14)	p-value
First grade				
1	20 (50.0)	12 (46.2)	8 (57.1)	NS
2	16 (40.0)	13 (50.0)	3 (21.4)	NS
3	4 (10.0)	1 (3.8)	3 (21.4)	NS
Last grade				
0	18 (45.0)	13 (50.0)	5 (35.7)	NS
1	14 (35.0)	8 (30.8)	6 (42.9)	NS
2	5 (12.5)	4 (15.4)	1 (7.1)	NS
3	3 (7.5)	1 (3.8)	2 (14.3)	NS

a) Values are presented as number (%).

b) CCRT, concurrent chemoradiotherapy; RT, radiation therapy; NS, not significant.

c) The p-value shows the results of comparison of ratios of late complications by Fisher's exact test between the patients who underwent CCRT and those who underwent RT alone.

(Fig. 3D). We detected no significant risk factor for the cumulative incidence rate of urinary tract obstruction/bleeding using Gray's test and Fine-Gray proportional hazards regression analysis.

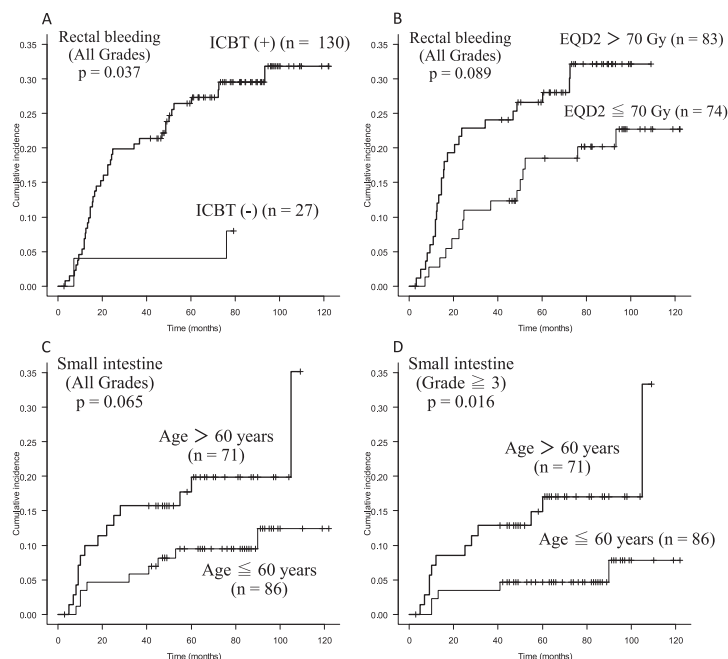


Fig. 3 Comparison of the cumulative incidence rates of rectal bleeding
Comparison of the cumulative incidence rates of rectal bleeding stratified by combination of ICBT and radiation therapy (A) and irradiation dose (B).

The Cumulative incidence rates of late complications in small intestine of all grades (C) and grade ≥ 3 (D) stratified by age.

ICBT, intracavitary brachytherapy; EQD2, equivalent dose in 2 Gy.

DISCUSSION

Our study indicated that the incidence rate and severity of late adverse events after RT for cervical cancer was not significantly different between the patients treated with CCRT and those treated with RT alone. Further, we showed the outline of chronological changes of rectal bleeding, and, to our knowledge, this is the first study to evaluate these changes. We think that the number of patients and the follow-up time in our study were sufficient for the analysis. However, because small intestinal obstruction/perforation and urinary tract obstruction/bleeding often occur a long time after treatment, the follow-up time of this study may not be long enough to observe their chronological changes.

Nakano *et al.* followed 1148 patients with cervical cancer after RT alone for over 20 years and reported that the actuarial rates of late complications in the rectum, small intestine, and bladder at 10 years were 22%, 9%, and 18%, respectively, and those of the major late complications (grades 3–5; Radiation Toxicity Grading/European Organization for Research and Treatment of Cancer (RTOG/EORTC)) were 4.4%, 3.3%, and 0.9%, respectively.²⁾ Compared with the results of Nakano *et al.*, we obtained a similar incidence rate of late adverse events in the rectum (especially for serious late complications), although our follow-up time was slightly shorter. Further, Kato *et al.* reported that the 5-year overall actuarial rate of late rectal complications in patients with cervical cancer treated with RT alone was 26.4%,⁷⁾ also similar to our results. However, the incidence rates we found in the small intestine were extremely higher (particularly

for serious late complications) than the results of Nakano *et al.* The incidence of serious small intestinal complications in our analysis was significantly higher for patients >60 years of age than for patients ≤60 years of age, although the patient characteristics of our study, including age, were similar to those of Nakano *et al.* (Table 5). Therefore, although the exact reason for this difference is unclear, the combination of chemotherapy and RT may affect serious small intestinal complications. Regarding the bladder (urinary tract), although the incidence rates of all grades were similar, we observed higher rates of serious late complications. We suspected that the classification of macroscopic hematuria as grade 3 in CTCAE version 4.0 may have led to this difference in rates. Excluding macroscopic hematuria from the present study would decrease the incidence rate of serious urinary complications to 3.8%, which would considerably narrow the difference. In addition, Nakano *et al.* targeted only the bladder, whereas we targeted the entire urinary tract, which also may affect this difference. Further, Nakano *et al.* suggested in their study that late adverse events occurred even 10 years or more after RT in the small intestine and bladder. Therefore, the follow-up time of our study may not be sufficient for the analysis of the late radiation complications in the small intestine and urinary tract and their chronological changes.

Toita *et al.* followed 71 patients after CCRT for locally advanced cervical cancer (Table 5) and reported that the 2-year cumulative late complication rates for all grades, grade 1, grade 2, and grade 3 were 24%, 9%, 12%, and 3%, respectively.⁴⁾ In our study, the 2-year cumulative late complication rate for all grades and grade 3 were 29% and 15%, respectively. Compared with Toita *et al.*, the late complication rates of our study were high and particularly higher for grade 3. We think that one reason for this difference is that the number (rate) of the patients over 71 years of age in our study was high (22.3%). Further, in Toita *et al.*, all patients received a weekly CDDP regimen as the concurrent chemotherapy, whereas a CDDP + 5-FU regimen was mainly used in our study. Kong *et al.* suggested that, after CCRT for cervical cancer, the severe acute hematologic and gastrointestinal toxicity was more often observed when a CDDP + 5-FU regimen was used than when CDDP alone was used.⁸⁾ Although the late complications were not analyzed sufficiently in their study, the results of our study suggest that the high incidence rates of the serious late complications may be related to this regimen.

Our study has some limitations. First, to identify late complications, we relied mostly on medical records and patients' complaints of symptoms. With this method, the presence or absence of adverse events will depend largely on each patient's self-assessment, and objectivity may be low. Second, our study design may not be appropriate to evaluate the effect of the combination of chemotherapy and RT on the risk of late complications, because the regimens of chemotherapy were not unified, and the patient background in each group was different. Third, though we tried to evaluate the comorbidities that described in the medical reports, there were some cases of insufficient description. Finally, the incidence rates of late adverse events in our study were high compared with those of previous reports, which may be because we noted all minor events, and therefore, we think that the incidence rate of our study reflects the true incidence rate of

Table 5 Comparison of patient characteristics with previous reports

Study	Combination of chemotherapy	Number of patients	Age (years) median (range)	Follow-up time (years)
Nakano <i>et al.</i> ²⁾	None	1148	60 (25–92)	22
Toita <i>et al.</i> ⁴⁾	All	71	57 (32–70)	2.3
Present study	66.2%	157	58 (24–92)	6.2 (median)

late adverse events.

Importantly, when we observed the chronological changes of rectal bleeding, the symptoms disappeared or were relieved in most of the patients during follow-up. However, further long-term follow-up is still required to completely evaluate the chronological changes of late complications, especially in the small intestine and urinary tract.

In conclusion, we evaluated the late adverse events and their chronological changes after RT for cervical cancer patients and showed that adding chemotherapy to RT did not affect the frequency and severity of late complications, and the symptoms of rectal bleeding were relieved over time.

Author contributions

Initial draft of manuscript and study design: T.Y.; Data acquisition and critical revision of the manuscript for important intellectual content: T.Y., S.I., M.K., Y.I., S.N., and M.I.; Approval of final version of the manuscript: T.Y., S.I., M.K., Y.I., S.N., and M.I.

CONFLICT OF INTEREST

None declared.

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