Effect of pelvic radiotherapy on patients with stage IB-IIA cervical cancer after radical hysterectomy: A single-center retrospective study

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Abstract. The effects of post-operative adjuvant radiotherapy (RT) on intermediate-risk patients with cervical cancer have not been fully elucidated. Therefore, the present study aimed to investigate the impact of RT on intermediate-risk cervical cancer. The data of 112 patients with stage IB and IIA cervical cancer treated with radical hysterectomy between January 2009 and December 2018 were retrospectively reviewed. Overall survival (OS), progression-free survival (PFS), and the frequency of adverse events were compared between patients with and without adjuvant RT (RT^+ and RT^-, respectively). Subgroup analyses of PFS based on tumor size, cervical stromal invasion, lymphovascular space invasion and histology [squamous cell carcinoma (SCC) vs. non-SCC] were performed. Among the 112 patients, 41 received adjuvant RT. Although there were no significant differences in OS or PFS between the RT^+ and RT^- groups, the frequency of adverse events was much higher in the RT^+ group. Patients in the RT^+ group also had more recurrent risk factors than those in the RT^- group. Based on the subgroup analyses, although no significant differences were observed between any of the groups, RT demonstrated a different impact on PFS between SCC and non-SCC: No difference was observed in the SCC group, whereas patients in the RT^+ group tended to have poorer prognoses compared to those in the RT^- group of the non-SCC group. These results suggest that the impact of post-operative RT on stage IB and IIA cervical cancer is limited and is accompanied by increased adverse events. The eligibility of patients for post-operative RT should be carefully determined based on the therapeutic effect of RT in each subgroup.

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Abbreviations: RT, radiotherapy; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma; LNM, lymph node metastasis; SI, stromal invasion; LVSI, lymphovascular space invasion; CCRT, concurrent chemoradiotherapy; AC, adenocarcinoma

Key words: adjuvant radiotherapy, cervical cancer, hysterectomy, intermediate-risk group

Introduction

Cervical cancer is one of the leading causes of cancer-related death among women. Worldwide, cervical cancer is the fourth most frequently occurring malignancy in women, resulting in 530,000 new cases annually and 270,000 deaths (1). The 5-year survival rate depends on the stage of primary cancer: 91.3% for stage I; 76.6% for stage II; 62.2% for stage III; and 28.3% for stage IV (2). Standard treatment strategies for stage IB-IIA cervical cancer are surgery and radiation-based therapy.

Based on the post-operative pathological diagnosis, patients are divided into three groups according to the recurrence risk: i) High-risk, with lymph node metastasis (LNM) or parametrium invasion; ii) intermediate-risk, with a deep cervical stromal invasion (SI), large size or lymphovascular space invasion (LVSI); and iii) low-risk, with no recurrence risk (3). For patients in the high-risk group, adjuvant concurrent chemoradiotherapy (CCRT) is recommended to prevent recurrence (4,5), and in the low-risk group, patients are usually followed-up without additional therapies (3).

In contrast to adjuvant therapy for patients in the high-risk group, the effect of adjuvant therapy for patients in the intermediate-risk group has not yet been fully elucidated. Worldwide, for intermediate-risk patients, adjuvant radiotherapy (RT) or CCRT is considered. However, the effect of adjuvant RT/CCRT is controversial. Certain reports have demonstrated that adjuvant RT improves progression-free survival (PFS), whereas others indicate no significant effect on overall survival (OS) (6-10). According to a Gynecological Oncology Group Trial, which was a randomized clinical trial of pelvic RT vs. no further therapy for post-operative intermediate-risk patients, pelvic RT significantly improved PFS, although severe life-threatening adverse effects were frequently observed in the RT group (9). Another meta-analysis indicated that no significant difference was observed in OS between the RT and

non-RT groups (10). In this report, increased severe adverse effects were also reported in the RT group.

The effect of adjuvant RT on intermediate-risk patients has not been fully elucidated. In the present study, the aim was to evaluate the impact of adjuvant RT on PFS for patients with stage IB-IIA cervical cancer.

Materials and methods

Patient selection and clinicopathological findings. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine of University of Tokyo [Tokyo, Japan; approval no. 3084-(7)] and was conducted following the Declaration of Helsinki (11). A total of 232 cases of patients with Stage IB and IIA cervical cancer [diagnosed using the International Federation of Gynecology and Obstetrics 2008 staging system (12)], initially treated with extended/radical hysterectomy and pelvic lymphadenectomy between January 2009 and December 2018 at the University of Tokyo Hospital (Tokyo, Japan) were retrospectively reviewed. All cases were identified on the basis of pathological evidence. The histological types were divided into two groups: Squamous cell carcinoma (SCC) and non-SCC, which included adenocarcinoma (AC) and adenosquamous cell carcinoma. Other clinicopathological data [e.g., age at diagnosis, body mass index, tumor size, SI of cancer, LVSI, the presence of LNM, post-operative adjuvant therapies (RT or not) and adverse events] were obtained from the electronic medical record. Post-operative adjuvant RT was administered at a daily fraction of 1.8 Gy (50.4 Gy/28 fractions in total) and none of the patients received CCRT. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events (v.5.0) (13). Patients were excluded if they met any of the following criteria: i) Histologic cancer type was neuroendocrine carcinoma; ii) pathological T stage (pT)1a; iii) pT2b; iv) presence of LNM; or v) a positive surgical margin.

Risk factors for recurrence. The intermediate-risk group was defined according to the Japan Society of Gynecologic Oncology guidelines (14). Large tumor size (≥4 cm in diameter), deep SI (≥1/3) and positivity for LVSI were considered risk factors for recurrence (9,14). In addition to these three risk factors, the study focused on histology, as several reports have demonstrated that the non-SCC histological type is a risk factor for poor prognosis (15-17).

Statistical analysis. Patients were divided into two groups according to the post-operative adjuvant RT: Patients with adjuvant RT (RT^+) and without (RT^-). The clinicopathological characteristics of the two groups were compared using an unpaired Student's t-test and the χ^2 test. PFS and OS were estimated using the Kaplan-Meier method and analyzed by the log-rank test and the univariate Cox-proportional hazard regression model to calculate hazard ratios (HRs) for each factor. PFS was assessed from the date of diagnosis to the date of first documentation of disease progression or death from any cause. The effect of RT was analyzed in each of the following subgroups: i) Tumor size ≥4 or <4 cm; ii) SI ≥1/3 or <1/3; iii) $LVSI^+$ or $LVSI^-$; and iv) SCC or non-SCC. A forest plot was created to visualize the HRs. Based on all clinicopathological characteristics, propensity scores and conditional probabilities of receiving adjuvant RT were calculated via logistic regression analysis. In order to reduce the bias due to confounding variables between the RT^+ and RT^- groups, propensity score matching was performed with 'EZR (64-bit)' in R software (version R4.2.2). Standardized differences for the covariates were calculated to assess the comparability of the matched cohorts and a normalized difference of <0.1 was considered to indicate a balance between the cohorts. Other statistical analyses, including the χ^2 test, log-rank test, Cox-proportional hazard model and Student's t-test, were performed using JMP software (version 15.0; SAS Institute, Inc.). P<0.05 was considered to indicate a statistically significant difference.

Table I. Patients' clinicopathological characteristics.

Characteristic	RT^+ (n=41)	RT^- (n=71)	P-value
Age, years	46 (28-74)	45 (22-74)	0.839[a]
FIGO stage			0.883[b]
IB	36 (88)	63 (89)	
IIA	5 (12)	8 (11)	
Histology			0.203[b]
Non-SCC	14 (34)	33 (47)	
SCC	27 (66)	38 (54)	
Tumor size, cm			<0.001[b]
<4	13 (32)	56 (79)	
≥4	28 (68)	15 (21)	
SI			<0.001[b]
<1/3	2 (4.9)	37 (52)	
≥1/3	39 (95)	34 (48)	
LVSI			<0.001[b]
Positive	25 (61)	23 (32)	
Negative	16 (39)	48 (68)	

[a]Calculated using unpaired t-test, [b]calculated using χ^2 test. Values are expressed as n (%) or median (interquartile range). FIGO, International Federation of Obstetrics and Gynecology; SCC, squamous cell carcinoma; SI, stromal invasion; LVSI, lymphovascular space invasion; RT^+, patients with adjuvant radiotherapy; RT^-, patients without adjuvant RT.

Results

Patient characteristics. Of the 232 patients reviewed, 120 were excluded due to the following reasons: 3 patients had neuroendocrine carcinoma; 20 had pT1a; and 97 had pT2b or were LNM^+. None of the patients presented with positive surgical margins. The remaining 112 patients were included in the subsequent analyses. Among them, 103 patients underwent Okabayashi radical hysterectomy, which corresponds to a Gynecologic Cancer Group type III hysterectomy (18), while 9 patients with small tumor sizes underwent modified radical hysterectomy (19). In the Okabayashi radical hysterectomies, the cardinal ligaments and anterior layers of the vesicouterine ligaments were cut and ligated. After mobilization of the ureters, the posterior layers of the vesicouterine ligaments

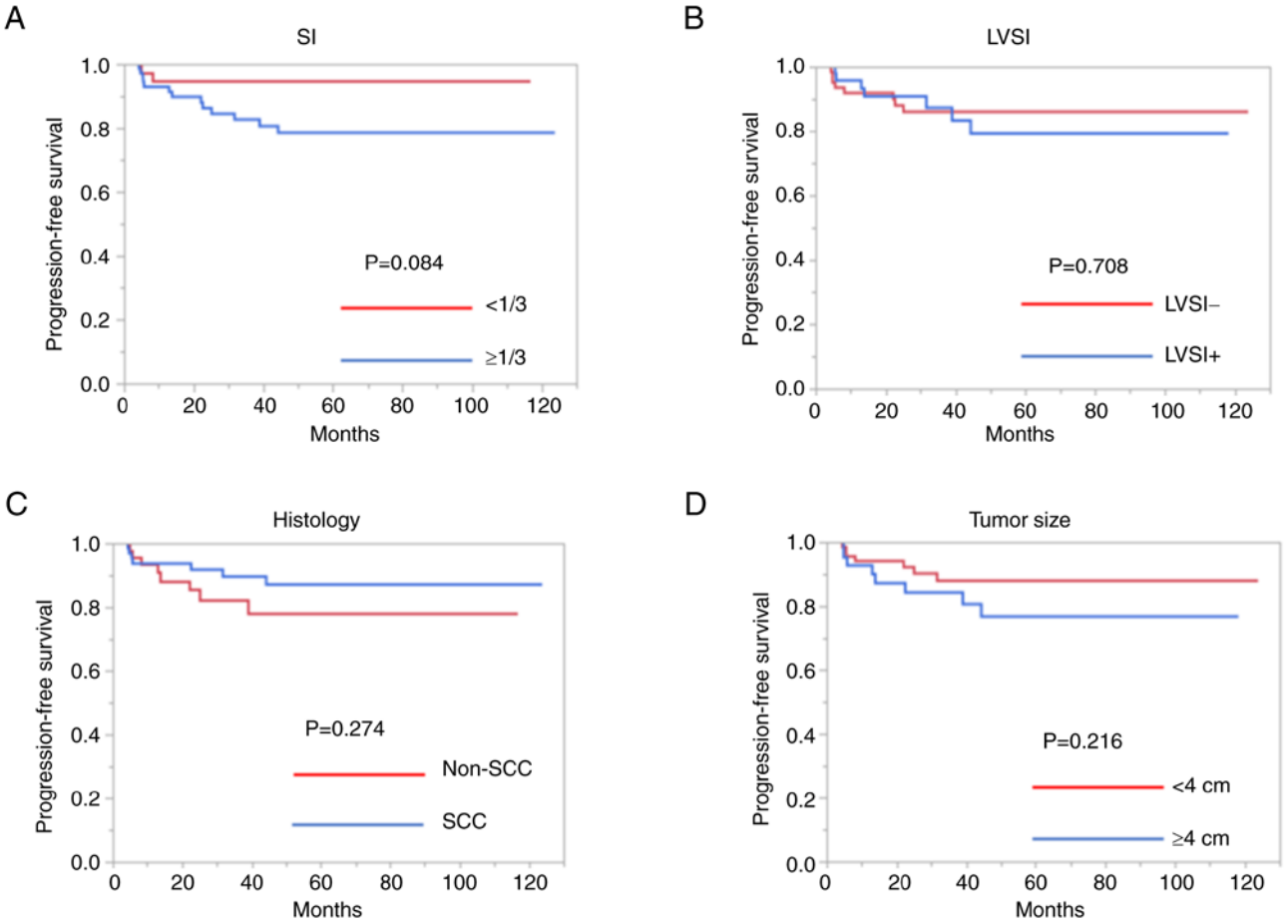


Figure 1. Progression-free survival rate according to (A) SI, (B) LVSI, (C) histology and (D) tumor size. The log-rank test was used to calculate the P-values. LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma; SI, stromal invasion.

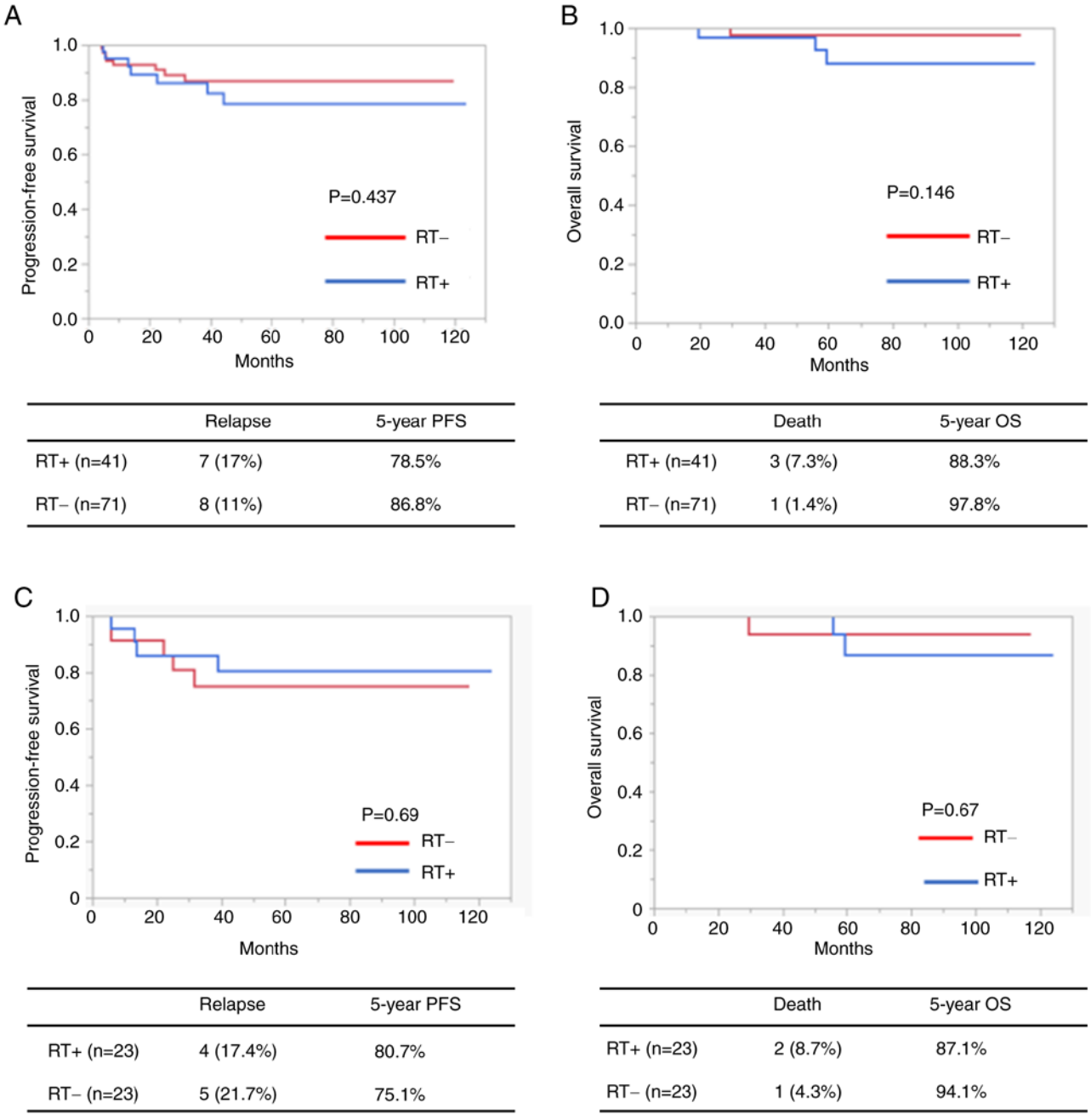
were cut and ligated (20). In the modified radical hysterectomy, the posterior layers of the vesicouterine ligaments were preserved to protect pelvic nerves (19). The median number of resected lymph nodes was 39 (interquartile range [IQR], 11-106), and there were no differences in the number of lymph nodes by surgical procedure. The patients' clinicopathological characteristics according to adjuvant RT are summarized in Table I. Patients in the RT^+ group had significantly larger tumors, higher incidence of deep SI and/or higher frequency of LVSI than those in the RT^- group. There was no difference in the age of the patients between the groups; the median ages were 46 years old (IQR, 28-74) and 45 years old (IQR, 22-74) in the RT^+ and RT^- groups, respectively.

Prognosis. Among the 112 patients, 15 (13.4%) relapsed and 4 (3.6%) died. First, the PFS according to the four risk factors for recurrence was compared. As presented in Fig. 1, although patients with deep SI tended to have a poorer PFS, no significant differences were observed among these groups (SI, P=0.084; tumor size, P=0.216; LVSI, P=0.708; histology, P=0.274).

The overall prognoses were also compared between the RT^+ and RT^- groups. There was no significant difference either in the OS or PFS between the RT^+ and RT^- groups (5-year OS rate, 88.3 vs. 97.8%, respectively; 5-year PFS rate, 78.5 vs. 86.8%, respectively; Fig. 2A and B).

Since the patients in the RT^+ group had more recurrence risk factors compared to those in the RT^- group, the PFS and OS in a propensity score-matched cohort were subsequently compared. Of the 112 patients with intermediate risks, 23 RT^- patients were matched with 23 RT^+ patients. For all covariates except for the age of patients, the absolute standardized difference was <0.1 after matching, implying sufficiently balanced treatment and non-treatment groups (Table SI). Kaplan-Meier curves based on adjuvant RT after propensity score matching are depicted in Fig. 2C and D. No significant differences were recorded between the groups. The 5-year PFS rates were 75.1 and 80.7% in the non-treatment and treatment groups, respectively (P=0.69; Fig. 2C).

The effect of RT in each of the following subgroups was subsequently evaluated: i) Tumor size ≥4 or <4 cm; ii) SI ≥1/3 or <1/3; iii) $LVSI^+$ or $LVSI^-$; and iv) SCC or non-SCC by the univariate Cox-proportional hazard regression model (Fig. 3A). Although no significant differences were observed between RT^+ and RT^- groups in each subgroup, RT had a different impact on HR for PFS between the SCC and non-SCC groups (Fig. 3A). In the SCC group, no difference was observed in the RT^+ and RT^- groups. In the non-SCC group, although no significant difference could be observed, patients in the RT^+ group exhibited a slight trend toward poorer prognosis compared to those in the RT^- group (SCC, P=0.986; non-SCC, P=0.17; Fig. 3B). The clinicopathological



	Relapse	5-year PFS
RT+ (n=41)	7 (17%)	78.5%
RT– (n=71)	8 (11%)	86.8%

	Death	5-year OS
RT+ (n=41)	3 (7.3%)	88.3%
RT– (n=71)	1 (1.4%)	97.8%

	Relapse	5-year PFS
RT+ (n=23)	4 (17.4%)	80.7%
RT– (n=23)	5 (21.7%)	75.1%

	Death	5-year OS
RT+ (n=23)	2 (8.7%)	87.1%
RT– (n=23)	1 (4.3%)	94.1%

Figure 2. OS and PFS according to adjuvant RT. (A) PFS and (B) OS according to adjuvant RT. (C) PFS and (D) OS according to adjuvant RT after propensity score matching. The log-rank test was used to calculate the P-values. OS, overall survival; PFS, progression-free survival; RT^+, patients with adjuvant radiotherapy; RT^-, patients without adjuvant RT.

characteristics of each pathology according to adjuvant RT are provided in Table II. In both the SCC and non-SCC groups, patients with RT had more risk factors of recurrence, such as large tumor size, deep MI and LVS, than those without RT.

Adverse events. The adverse events between the RT^+ and RT^- groups were compared. The number of adverse events, including gastrointestinal disorders, bowel obstruction, lymphedema and dysuria, tended to be higher in the RT^+ group. In particular, gastrointestinal disorders and lymphedema were observed significantly more frequent in the RT^+ group compared to the RT^- group (P<0.001 and P=0.0001, respectively; Table III). In addition, it is noteworthy that, although there were no significant differences between the two groups, RT tended to increase grade 3 and 4 adverse events, including bowel obstruction, dysuria and lymphedema.

Discussion

From the overall analysis, post-operative adjuvant RT did not improve the survival outcomes of patients with cervical cancer in the intermediate-risk group. In addition, survival analyses using a propensity score-matched cohort did not demonstrate any differences between PFS and OS. However, the positivity for risk factors of recurrence was much higher in the RT^+ group than that in the RT^- group, suggesting that the

Table II. Patients' clinicopathological characteristics for each pathology type.

	SCC (n=65)			Non-SCC (n=47)		
Characteristic	RT^+ (n=27)	RT^- (n=38)	P-value	RT^+ (n=14)	RT^- (n=33)	P-value
Age, years	47 (28-74)	45.5 (22-74)	0.642[a]	44 (32-68)	44 (31-71)	0.474[a]
FIGO stage			0.471[b]			0.472[b]
IB	21 (78)	31 (82)		12 (86)	30 (91)	
IIA	6 (22)	7 (18)		2 (4.3)	3 (9.1)	
Tumor size, cm			<0.001[c]			0.0044[c]
<4	8 (30)	30 (79)		5 (58)	26 (79)	
≥4	19 (70)	8 (21)		9 (64)	7 (21)	
SI			0.011[c]			<0.001[c]
<1/3	2 (7.4)	13 (34)		0 (0)	24 (73)	
≥1/3	25 (93)	25 (66)		14 (100)	9 (27)	
LVSI			0.080[b]			0.016[c]
Positive	17 (63)	16 (42)		8 (57)	7 (21)	
Negative	10 (37)	22 (58)		6 (43)	26 (79)	

[a]Calculated using unpaired t-test, [b]calculated using Fisher's test, [c]calculated using χ^2 test. Values are expressed as n (%) or median (interquartile range). FIGO, International Federation of Obstetrics and Gynecology; SCC, squamous cell carcinoma; SI, stromal invasion; LVSI, lymphovascular space invasion; RT^+, patients with adjuvant radiotherapy; RT^-, patients without adjuvant RT.

Table III. Adverse events according to adjuvant RT.

	RT^+ (n=41)		RT^- (n=71)		P-value	
Adverse events	All grades	Grade 3 and 4	All grades	Grade 3 and 4	All grades	Grade 3 and 4
Gastrointestinal disorders	12 (29)	0	0	0	<0.001	-
Bowel obstruction	3 (7.3)	3 (7.3)	1 (1.4)	1 (1.4)	0.14	0.14
Dysuria	8 (20)	2 (4.9)	14 (20)	0	0.59	0.13
Lymphedema	27 (66)	5 (12)	19 (27)	3 (4.2)	0.0001	0.12

Values are expressed as n (%). RT^+, patients with adjuvant radiotherapy; RT^-, patients without adjuvant RT.

prognosis of relatively higher-risk patients may be improved by adjuvant RT. Further research to compare the prognosis between RT^+ and RT^- groups in patients with cervical cancer in the intermediate-risk group with relatively higher risks is warranted to confirm the hypothesis.

In the present study, it was investigated which patients may benefit from adjuvant RT based on subgroup analyses. Due to the small sample size, statistically significant findings were not achieved. However, the results suggested that the effect of adjuvant RT may be dependent on histology. For the patients with SCC, there was no difference in relapse rate or PFS between the RT^+ and RT^- groups. By contrast, for the patients with non-SCC, those who received adjuvant RT tended to have poorer prognoses compared to those without adjuvant RT. The results suggest that, in terms of reducing recurrent risk after surgery, patients with SCC may benefit from adjuvant RT, whereas the effect of adjuvant RT may be limited in patients with non-SCC. In general, sensitivity to RT depends on cancer histology, as SCC is more sensitive to RT than AC (21). Several reports have demonstrated that, in the case of initial treatment by definitive RT, AC is relatively resistant to RT compared to SCC (22-24). The differential effect of adjuvant RT on SCC and non-SCC may be due to the differences in radiosensitivity between SCC and AC.

In the present analysis, the frequency of adverse events was much higher in the RT^+ group than in the RT^- group, which concurs with previous studies (8,10). In order to prevent harmful effects from treatment, it is important to select patients who are likely to benefit from post-operative RT. Although the results suggest a differential effect of RT according to histology type, further research is required to prove this hypothesis.

The present study has certain limitations. First, the retrospective design of the present study may be linked to potential treatment bias. Herein, patients in the RT^+ group had markedly higher recurrence risks than those in the RT^- group. Even in a propensity score-matched cohort, there were only a small number of patients with deep SI, which made it difficult to compare those patients. Although a clear

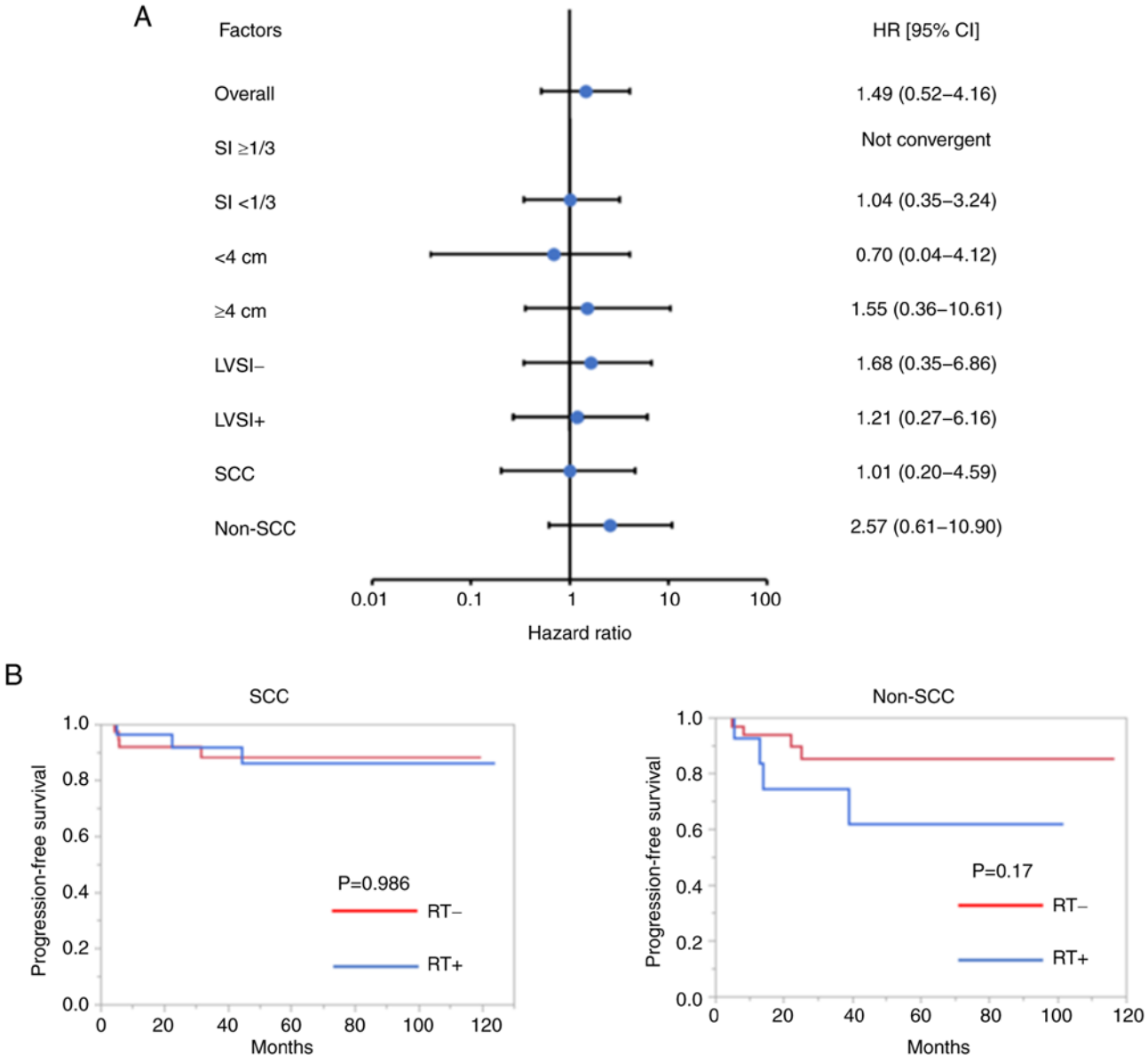


Figure 3. Subgroup analysis according to adjuvant RT. (A) Forest plot of HR of progression-free survival in each group according to adjuvant RT. The Cox-proportional hazards model was used to estimate the HR. (B) Progression-free survival of patients with SCC and non-SCC according to RT. The log-rank test was used to calculate the P-values. LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma; RT^{+}, patients with adjuvant radiotherapy; RT^{-}, patients without adjuvant RT; SI, stromal invasion; HR, hazard ratio, CI, confidence interval.

treatment effect of RT in intermediate-risk patients was not apparent, the results should be interpreted with caution, as an increase in the number of risk factors is known to be associated with a worse prognosis (7,25). Further research with multi-center or nationwide data is warranted to validate the findings. As another limitation, only one institution was involved in the present study, which led to a relatively small sample size. Further studies in a larger population are warranted to confirm the findings.

In conclusion, the present study has demonstrated that the impact of post-operative RT for stage IB and IIA cervical cancer is limited and is accompanied by increased adverse events. Although there were no statistically significant differences, the findings suggested that histology may influence the effects of post-operative RT for intermediate-risk patients with cervical cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AT and MT conceptualized the study. CI, HH, AN, SE and YM obtained the data. CI and AT analyzed the data. CI, AT, TT, KS, MM, MT and YO interpreted the data. CI and AT wrote the original draft. TT, MT, KS, MM and YO reviewed and edited the manuscript. CI and AT confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript. YO supervised the study.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine of University of Tokyo [Tokyo, Japan; approval no. 3084-(7)] and all methods were performed in accordance with relevant guidelines and regulations. The Research Ethics Committee of the Faculty of Medicine of the University of Tokyo (Tokyo, Japan) waived the requirement to obtain informed consent due to the retrospective nature of the study. This study was performed by the opt-out method on the hospital website.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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