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ORIGINAL ARTICLE

Does postoperative prophylactic irradiation of para-aortic lymph nodes reduce the risk of recurrence in uterine cervical cancer with positive pelvic lymph nodes?

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Abstract

Background In cervical cancer, para-aortic lymph nodes are common sites of metastasis. The purpose of the study was to evaluate the clinical benefits of prophylactic irradiation as postoperative therapy.

Methods A retrospective cohort study was conducted during 2001–2015 at a single institution. Patients with a high risk of para-aortic lymph nodes recurrence were eligible for this study, and we identified patients who had pelvic lymph node metastasis and underwent radical surgery and concurrent chemo-radiotherapy. As a result, 33 and 46 patients were included in the treatment (prophylactic irradiation) and non-treatment groups, respectively. Baseline differences between the two groups were adjusted with the inverse probability of treatment weighting using propensity scores composed of the independent variables including age, stage, tumor size, pathological findings, lymph node status, and pathological subtypes.

Results In the 68-month median follow-up period (range 6–178 months), 25 patients experienced recurrence, and 17 patients were dead. After adjustment with the inverse probability of treatment weighting, the recurrence rates tended to decrease in the treatment group, but there was no significant difference between the two groups [treatment vs. non-treatment, 29.4% and 44.3%, respectively; hazard ratio, 0.593 (95% CI 0.320–1.099); $P=0.097$]. However, adjusted para-aortic lymph nodes recurrence rates were not significantly different [treatment vs. non-treatment, 7.8% and 11.4%, respectively; odds ratio, 0.660 (95% CI 0.187–2.322); $P=0.558$]. Moreover, Kaplan–Meier curves showing post-recurrence survival revealed no significant difference between the two groups ($P=0.141$).

Conclusions Prophylactic para-aortic lymph nodes irradiation did not reduce the risk of recurrence.

Keywords Inverse probability of treatment weighting · Propensity score · Prophylactic irradiation of para-aortic lymph nodes · Uterine cervical cancer

Introduction

Cervical cancer is a common malignancy among females worldwide. Mortality rates associated with uterine cervical cancer have declined due to the widespread use of cancer screening for the prevention and early detection of cervical cancer [1]. However, approximately one-third of patients experience recurrence within 5 years [2], with a median survival period after recurrence of 15 months [3] and less than 5% of them surviving for 5 years [4]. Therefore, the oncologic outcome is far from satisfactory. Moreover, in particular, prognosis of patients with para-aortic lymph nodes (PAN) metastasis has been reported to be worse than that of those with pelvic node (PLN) metastasis [5–7].

Treatment options for patients with cervical cancer depend mainly on the International Federation of Gynecology and Obstetrics (FIGO) stage and lymph node status. Two major treatment options are radical surgery and concurrent chemoradiation (CCRT), and radical hysterectomy (RH) with pelvic node dissection (PLND) is an option in patients with early-stage disease [4]. Surgical specimens reveal factors indicating a poor prognosis including lymph node metastasis, large tumor size, deep cervical stromal

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invasion, lymphovascular space invasion, and positive margins [4]. Adjuvant pelvic CCRT has been applied and has shown clinical benefits [8]. Thus, the impact of extended-field radiotherapy including the pelvis and the para-aortic area has been explored. Regarding PAN metastasis, cervical cancer cells are considered to spread along the direction of lymph flow [9], and therefore metastasis to the bilateral PLNs and common iliac lymph nodes is considered a risk factor in PAN metastasis [7, 10]. Considering the undetected presence of micrometastasis in the PAN due to inaccuracy of radiological evaluation [11], a preventive effect of PAN irradiation can be expected, and a randomized study showed that DFS rates were significantly improved due to extended-field CCRT [12]. However, there were some reports that showed no significant improvement [13–15]. Therefore, survival benefits of prophylactic PAN irradiation have not been consistent. Moreover, its impact on postoperative status is even less clear because most patients included in previous studies did not receive surgical treatment.

In the present study, we introduced inverse probability of treatment weighting (IPTW) using propensity scores to reduce background selection bias. An advantage of using propensity score methods is that they allow observational studies to be designed similarly to randomized experiments [16], and the use of IPTW has increased rapidly in recent years [17]. This is the first study that evaluated the clinical impact of prophylactic irradiation of PAN as postoperative therapy using IPTW.

Patients and methods

Patients

We retrospectively reviewed all the records of 886 patients with cervical cancer who were initially treated in our hospital from 2001 to 2015. Written informed consent was obtained from all patients. This study was approved by the ethics committee of our institute (Approval no.: 2013-0078).

Patients with a high risk of PAN recurrence were eligible for this study, and 163 patients who had PLN metastasis but no extra-pelvic metastasis were identified. Lymph node and distant metastasis were evaluated using computed tomography, and lymph nodes larger than 1 cm in the shorter axis were considered to indicate metastasis. We focused on the patients who were surgically treated. Two patients who refused treatment and 72 patients who were treated without surgery were excluded. Next, seven patients who did not undergo adjuvant whole pelvis CCRT were excluded, because these patients were thought to be at low risk for PAN recurrence. Three patients with a residual tumor soon after initial treatment were also excluded. Finally, 79 patients who had PLN metastasis and were treated with both surgery and CCRT were included. The ECOG performance status (PS) of the 79 patients was 0 or 1. Then, we compared 33 patients who underwent prophylactic irradiation of PAN (PI group) with 46 patients who did not (non-PI group). For adverse event analysis, after excluding 10 patients with insufficient clinical information about regarding adverse events, we compared 28 patients in the PI group with 41 patients in the non-PI group. A flowchart showing patient selection is presented in Fig. 1.

Treatment

Treatment strategies for each patient were determined by several gynecologic oncologists and clinical radiologists in our hospital depending on patient age, PS, and spread of the disease. For example, patients who were in the early stage and had a good PS (The ECOG PS = 0 or 1) were indicated for RH with PLND. All patients received laparotomy, and the uterus, cervix, upper part of the vagina, and parametrium were removed. Moreover, the following PLNs were also removed: external iliac, internal iliac, obturator and common iliac lymph nodes. None of them were treated with PAN dissection or sampling. Moreover, adjuvant pelvic CCRT was performed for patients with a high risk of recurrence such as lymph node metastasis, lymphovascular space invasion, or parametrial invasion in our institute. On the other hand, patients who were not indicated for surgery were treated with pelvic CCRT or radiotherapy. Further, as was the practice in our institute, prophylactic irradiation of PAN was considered for patients with a good PS and more than two PLN metastases but no apparent residual disease after initial treatment. Extended-field ERBT was not performed in any of the patients. All patients in PI group received prophylactic irradiation of PAN after pelvic CCRT. As initial chemotherapy, a cisplatin (70 mg/m^2, on day 1) and 5-fluorouracil (700 mg/m^2, 24-h continuous intravenous infusion, on days 1–4) combination regimen was followed. When creatinine clearance was below 60 mL/min, nedaplatin or carboplatin was considered instead of cisplatin.

Radiotherapy involved a combination of external beam radiotherapy (ERBT) and vaginal brachytherapy. ERBT was performed at 1.8 Gy once per day (total dose of 45 Gy in 25 fractions). Vaginal brachytherapy was performed during external beam radiation therapy via remote afterloading the system with a Co 60 source. The total dose delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 8–10 Gy in two fractions. Prophylactic irradiation of PAN was performed at 2.0 Gy once per day (total dose of 46 Gy in 23 fractions).

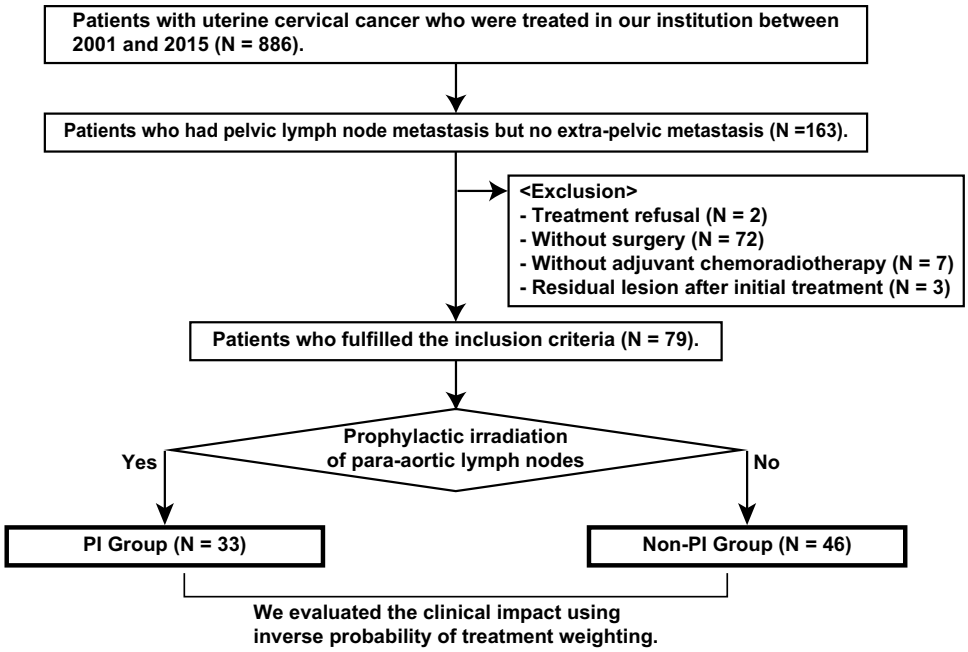

Fig. 1 Patient selection flowchart

Follow-up

Post-treatment follow-up was performed monthly at the beginning, and then the interval was extended. Recurrence was determined via physical examination, trans-vaginal ultrasound examination, vaginal stump cytology, laboratory tests, and computed tomography.

Outcomes

The primary end points were the PAN recurrence rate, progression-free survival (PFS), and post-recurrence survival (PRS). The secondary end points were adverse events. PFS is defined as the time elapsed between treatment initiation and tumor progression or death from any cause. PRS is defined as the time elapsed between recurrence diagnosis and death from any cause. Adverse events were differentiated into acute and chronic toxicities. The acute period was defined as the duration from the start of treatment to four weeks after treatment, and the remaining duration was considered the chronic period. Common Terminology Criteria for Adverse Events Version 4.0 was used for the adverse event grading system.

Statistics

Statistical analyses for IPTW using propensity scores were performed with SPSS version 25. Baseline differences between patients who underwent prophylactic PAN irradiation and those who did not were adjusted with IPTW using propensity scores composed of the following independent variables: age, pT/N, tumor size, surgical margin, parametrial/vaginal invasion, preoperative LN swelling, number of LNs resected in surgery, number of LN metastases, pathological subtypes, neoadjuvant therapy and hemoglobin level. Kaplan–Meier curves were used for the analysis of PFS. Differences at $P < 0.05$ were considered significant.

Results

We first compared the 33 patients in the PI group with the 46 patients in the non-PI group, and evaluated the efficacy of prophylactic PAN irradiation as an adjuvant treatment. Baseline differences were seen in patient's age, pN, number of LN metastases, histological type, and neoadjuvant therapy (Table 1). This was mainly because the criteria for prophylactic PAN irradiation in our institute were a good performance status and more than two PLN metastases. Therefore, the baseline difference between the two groups was adjusted with IPTW using the propensity scores described above.

Median follow-up periods of the PI and the non-PI groups were 64 (range 11–150 months) and 67 months (range 6–178 months), respectively (Table 1). During these periods, 25 patients experienced recurrence [PI vs. non-PI, $n = 11$ (33.3%) and $n = 14$ (30.4%), respectively; hazard ratio, 1.077 (95% CI, 0.489–2.374); $P = 0.853$] (Table 2), and there was no significant difference between the two groups. Similarly, Kaplan–Meier curves showing PFS revealed no significant difference between the two groups ($P = 0.905$) (Fig. 2a). Then, we adjusted baseline imbalances using IPTW. As a result, the recurrence rates tended to decrease in the PI group, but there was no significant difference between the two groups [PI vs. non-PI, 29.4% and 44.3%, respectively;

Table 1 Patient characteristics

Characteristics	Non-PI group ($N=46$)	PI group ($N=33$)	P value
Follow-up periods (months)			
Median (range)	67 (6-178)	64 (11–150)	0.056
Age			
Median (range)	49.5 (25–67)	37 (20–67)	< 0.001
pT			
pT1	23 (50%)	11 (33%)	0.143
pT2	23 (50%)	22 (67%)	
Tumor size			
< 4 cm	22 (48%)	22 (67%)	0.099
≥ 4 cm	24 (52%)	11 (33%)	
Surgical margin			
Negative	44 (96%)	32 (97%)	0.764
Positive	2 (4%)	1 (3%)	
Parametrial/vaginal invasion			
No	25 (54%)	12 (36%)	0.116
Yes	21 (46%)	21 (64%)	
Preoperative LN swelling			
No	20 (43%)	15 (45%)	0.862
Yes	26 (57%)	18 (55%)	
Number of LNs resected in surgery			
< 25	19 (41%)	20 (61%)	0.093
≥ 25	27 (59%)	13 (39%)	
pN			
0	10 (22%)	0 (0%)	0.004
1	36 (78%)	33 (100%)	
Number of LN metastases			
1	33 (72%)	9 (27%)	< 0.001
≥ 2	13 (28%)	24 (73%)	
Histological type			
SCC	27 (59%)	27 (82%)	0.030
Non-SCC	19 (41%)	6 (18%)	
Neoadjuvant therapy			
No	23 (50%)	30 (91%)	< 0.001
Yes	23 (50%)	3 (9%)	
Hb			
≥ 10	31 (67%)	23 (70%)	0.829
< 10	15 (33%)	10 (30%)	

PI prophylactic irradiation, *SCC* squamous cell carcinoma, *LN* lymph node, *Hb* hemoglobin

hazard ratio, 0.593 (95% CI 0.320–1.099); $P=0.097$] (Table 2; Fig. 3a). These results indicate that the prophylactic PAN irradiation might improve PFS.

Next, we closely evaluated recurrence sites. Although isolated PAN recurrence was only seen in the non-PI group, the recurrence pattern was not apparently affected by prophylactic PAN irradiation. Four patients (12.1%) in the PI group and six patients (13.0%) in the non-PI group experienced PAN recurrence, with no significant difference ($P=1.000$). Moreover, even after adjustment, PAN recurrence rates were not significantly different [PI vs. non-PI, 7.8% and 11.4%, respectively; odds ratio, 0.660 (95% CI 0.187–2.322); $P=0.558$] (Table 2). These results indicate that prophylactic PAN irradiation has no preventive effect against PAN recurrence.

Then, we focused on 25 patients who experienced recurrence, and evaluated survival after recurrence. During these periods, 17 patients died [PI vs. non-PI, $n=7$ (63.6%) and $n=10$ (71.4%)]. The 1-, 2-, 3-year PRS rates in PI group were 60.0%, 40.0%, and 26.7%, respectively, and those in non-PI groups were 78.6%, 63.5%, and 24.2%, respectively. Kaplan–Meier curves showing PRS revealed no significant difference between the two groups ($P=0.821$) (Fig. 2b). Moreover, even after IPTW adjustment, Kaplan–Meier curves showing PRS revealed no significant difference between the two groups ($P=0.141$) (Fig. 3b). Therefore, prognosis of patients with recurrent cervical cancer was poor, and prophylactic PAN irradiation might not contribute to their survival.

Finally, we evaluated adverse events (Table 3). No patients died during the treatment period or discontinued treatment because of adverse events. Grade 3–4 neutropenia was seen in approximately 50% of all patients, and febrile neutropenia was noted in one patient of the PI group. Nausea and vomiting were more frequently seen in the PI group, but there were no significant differences. After adjustment using IPTW, nausea and vomiting were not significantly increased in the PI group compared to the non-PI group ($P=0.306$ and 0.570, respectively). In terms of chronic adverse events, intestinal obstruction rate was not significantly different between the two groups, even after IPTW adjustment. One patient in PI group showed grade 3 of bladder perforation. Therefore, adverse events caused due to additional PAN irradiation were mostly tolerable.

Discussion

Cervical cancer cells are thought to spread to PAN via PLN, and two risk factors for PAN metastasis have been indicated: metastasis to bilateral PLNs and to the common iliac lymph nodes [7]. However, it is still unclear whether PAN metastasis can be prevented with prophylactic PAN irradiation. In the present study, we focused on postoperative therapy and investigated the clinical efficacy of prophylactic PAN irradiation using IPTW; to the best of our knowledge, this is the first such study.

An advantage of using propensity score methods is that they allow observational studies to be designed similarly to randomized experiments [16], and the use of IPTW has increased rapidly in recent years [17]. In the present study, baseline characteristics were significantly different

Table 2 Recurrence pattern

Recurrence pattern	Non-PI group ($N=46$)	PI group ($N=33$)	HR or OR (95% CI)	P value
Patients who had PAN recurrence				
PAN	3			
PAN + pelvic	1			
PAN + pelvic + distant	1	1		
PAN + distant	1	3		
Patients who had no PAN recurrence				
Pelvic	3	2		
Pelvic + distant	1	1		
Distant	4	4		
PAN recurrence rates	13.0%	12.1%	OR: 0.920 (0.238–3.556)	1.000
Total recurrence rates	30.4%	33.3%	HR: 1.077 (0.489–2.374)	0.853
IPTW-adjusted PAN recurrence rates	11.4%	7.8%	OR: 0.660 (0.187–2.322)	0.558
IPTW-adjusted total recurrence rates	44.3%	29.4%	HR: 0.593 (0.320–1.099)	0.097

PI prophylactic irradiation, *PAN* para-aortic lymph nodes, *HR* hazard ratio, *OD* odds ratio

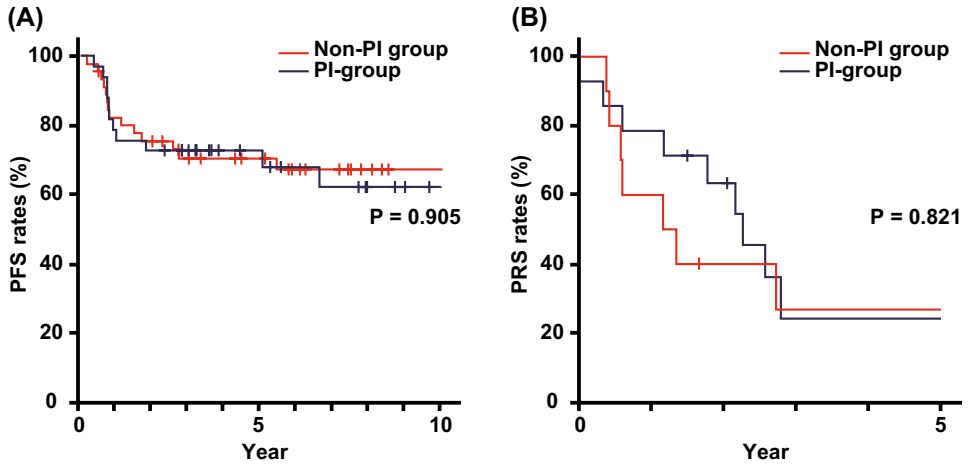

Fig. 2 Kaplan–Meier curves showing progression-free survival (PFS) and post-recurrence survival (PRS). **a** PFS of the PI group (blue) and the non-PI group (red), and there was no significant difference ($P=0.905$). **b** PRS of the two groups, and there was no significant difference ($P=0.821$)

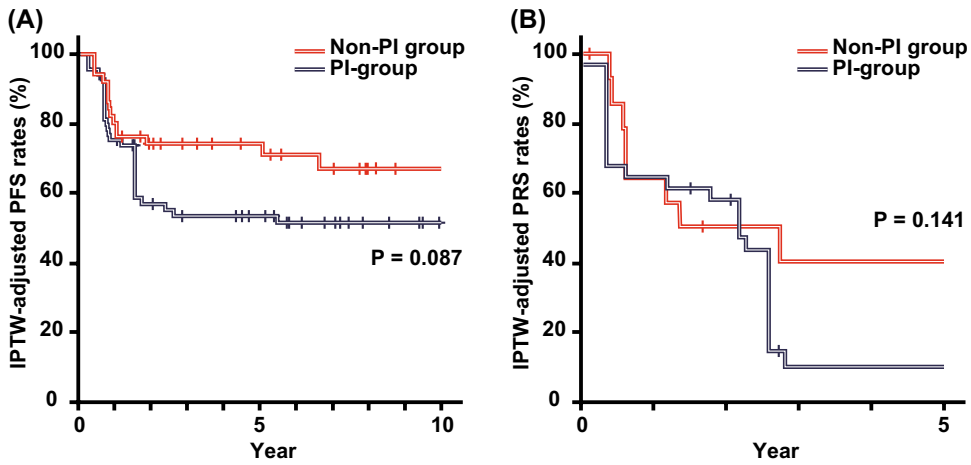

Fig. 3 Kaplan–Meier curves showing IPTW-adjusted progression-free survival (PFS) and post-recurrence survival (PRS). **a** PFS of the PI group (blue) and the non-PI group (red), and there was no significant difference ($P=0.087$). **b** PRS of the two groups, and there was no significant difference ($P=0.141$)

Table 3 Adverse events (Grade 3 or 4)

	Non-PI group ($N=41$)	PI group ($N=28$)	Odds ratios (95% CI)	P value
Non-adjusted				
Acute				
Neutropenia	18 (43.9%)	14 (50.0%)	1.278 (0.487–3.350)	0.633
Febrile neutropenia	0	1 (3.6%)		
Anemia	8 (19.5%)	3 (10.7%)	0.495 (0.119–2.058)	0.505
Thrombocytopenia	0	0		
Creatinine	0	0		
AST or ALT	1 (2.4%)	0		
Nausea	1 (2.4%)	3 (10.7%)	4.800 (0.473–48.730)	0.296
Vomiting	1 (2.4%)	2 (7.1%)	3.077 (0.265–35.682)	0.562
Diarrhea	2 (4.9%)	1 (3.6%)	0.722 (0.062–8.370)	1.000
Dermatitis	0	0		
Peripheral neuropathy	0	1 (3.6%)		
Chronic				
Intestinal obstruction	3 (7.3%)	2 (7.1%)	0.974 (0.152–6.243)	1.000
Bladder perforation	0	1 (3.6%)		
IPTW-adjusted				
Acute				
Neutropenia	45.6%	61.0%	1.863 (0.824–4.212)	0.155
Anemia	17.5%	9.8%	0.508 (0.147–1.750)	0.383
Nausea	1.8%	7.3%	4.421 (0.443–44.112)	0.306
Vomiting	1.8%	4.9%	2.872 (0.252–32.784)	0.570
Diarrhea	8.8%	2.4%	0.260 (0.029–2.314)	0.396
Chronic				
Intestinal obstruction	7.0%	7.3%	1.046 (0.221–4.947)	1.000

PI PROPHYLACTIC irradiation, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

between the two groups due to the use of prophylactic PAN irradiation as a criterion in our institution. Therefore, we used IPTW with a propensity score, and as a result, baseline differences due to components of the propensity score were eliminated.

Initially, we evaluated the impact of prophylactic PAN irradiation on PFS. The recurrence rate was found to be 31.6% and was almost the same as that in a previous study [18]. After adjustment for baseline imbalances, PFS was slightly improved due to prophylactic PAN irradiation, but there was no significant difference. According to previous reports, survival benefits of prophylactic PAN irradiation have not been consistent. While randomized studies and a systematic review including four randomized clinical trials indicated that disease-free survival (DFS) rates was not significantly altered due to extended-field irradiation [13–15, 19], a randomized study showed that DFS rates were significantly improved due to extended-field CCRT [12]. A similar tendency was also seen in overall survival [12–15]. Therefore, we thought that different inclusion criteria of each study may affect the results. In the present study, we only evaluated patients who were at high risk of PAN metastasis after surgical treatment, and found that prophylactic PAN irradiation tended to improve PFS.

Next, we evaluated recurrence sites. According to a previous report, among clinically PAN-negative cases at surgery, PAN recurrence rate was 4.2% [10]. Considering the undetected presence of micrometastasis in the PAN due to inaccuracy of radiological evaluation [11], a preventive effect of PAN irradiation can be expected. However, in the present study, the recurrence pattern was not apparently affected due to prophylactic PAN irradiation although isolated PAN recurrence was not seen in the PI group. This finding might reflect the therapeutic effect of micrometastasis elimination. However, total PAN recurrence rates were not significantly different between the two groups. This is similar to a previous report showing that among patients who had PLN metastasis but did not undergo PAN dissection at RH, prophylactic PAN irradiation did not significantly decrease PAN recurrence [10]. However, there were other reports that showed contrasting results, finding that PAN metastasis was significantly decreased in patients treated with PAN irradiation [12, 13, 15, 19]. Therefore, the preventive effect of PAN recurrence due to prophylactic irradiation was also

not consistent. In addition, considering the fact that pelvic recurrence after whole pelvis radiotherapy is not rare, PAN recurrence after PAN irradiation is not surprising. Moreover, about pelvic or distant organ recurrence, it was difficult to evaluate the impact of prophylactic PAN irradiation. Therefore, the preventive effect of prophylactic PAN irradiation may be limited. In addition, prognosis of patients with recurrent cervical cancer was poor, and IPTW-adjusted PRS was not significantly different between the two groups. Therefore, we considered that routine prophylactic PAN irradiation for all high-risk patients with cervical cancer has limited value.

Finally, we evaluated adverse events. After adjustment using IPTW, the frequency of acute severe adverse events (Grade 3 or 4) was not significantly increased due to the prophylactic irradiation. Even though the frequency and severity of adverse events were equivalent, patients in the PI group might suffer from longer-term symptoms due to the longer duration of radiotherapy in this group. However, taking this point into consideration, all patients completed the treatment in this study and the acute adverse events were thought to be almost tolerable. This is the same trend as that seen in previous studies reporting that acute toxicity was tolerable and grade 3 or 4 toxicity was not increased due to extended-field CCRT [12, 15, 20]. On the other hand, in the chronic period, intestinal obstruction rate was not altered between two groups after adjustment using IPTW in the present study. However, some reports have shown that the number of patients with severe late complications, especially digestive complications, was increased due to PAN irradiation [13, 21]. Therefore, patient selection for prophylactic PAN irradiation should be done carefully, considering the possibility of severe digestive complications.

There were several limitations to the present study. First, it was a small-scale, non-randomized study. Therefore, potential bias might have existed even though we used the IPTW method to reduce bias. Therefore, an additional large-scale study is desirable by accumulating more patients. In addition, it is possible that the results of studies using propensity scores are different from those of randomized controlled trials (RCTs) [22]. Therefore, the efficacy of prophylactic PAN irradiation should be evaluated in RCTs. Second, it was difficult for a retrospective study to investigate mild complications precisely. Therefore, further prospective studies are essential about adverse events. Third, we only evaluated additional effects of prophylactic PAN irradiation in patients who were treated with RH plus pelvic CCRT. Therefore, its effect on patients who received only pelvic CCRT remains unknown.

In conclusion, prophylactic PAN irradiation resulted in no significant improvement in PFS, PAN failure rates, and PRS after adjustment using the IPTW method. The efficacy of such prophylactic irradiation in postoperative settings needs to be evaluated and verified in large-scale RCTs. This would enable the development of effective treatment for patients with a high risk of recurrence.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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