Volume 20, No 3 | International Journal of Radiation Research, July 2022

Effectiveness of postoperative radiotherapy excluding the common iliac lymph nodes in patients with node-negative cervical carcinoma

T. Saito-Zama[1], R. Mikami[1*], T. Itonaga[1], M. Okubo[2], S. Sugahara[3], K. Saito[1]

[1]Department of Radiology, Tokyo Medical University, 6-7-1, Nishi-shinjuku, Shinjuku-Ku, Tokyo, Japan
[2]Department of Radiology, Tokyo Medical University Hachioji Medical Center, 1163 Tatemachi, Hachioji, Tokyo, Japan
[3]Department of Radiology, Tokyo Medical University Ibaraki Medical Center, 3-20-1 Chuo, Ami-machi, Inashiki-gun, Ibaraki, Japan

► ***Original article***

***Corresponding author:**
Ryuji Mikami, Ph.D.,
E-mail:
mikami-r@tokyo-med.ac.jp

Received: December 2020
Final revised: December 2021
Accepted: December 2021

Int. J. Radiat. Res., July 2022; 20(3): 537-541

DOI: 10.52547/ijrr.20.3.3

Keywords: *Clinical target volume, postoperative radiotherapy, cervical carcinoma, common iliac lymph nodes, treatment outcome.*

ABSTRACT

***Background*:** To evaluate whether excluding the common iliac lymph nodes from the clinical target volume (CTV) during radiotherapy is effective in node-negative patients after cervical cancer surgery. ***Materials and Methods*:** Between January 2014 and December 2017, 29 patients who underwent radiotherapy after curative surgery for cervical carcinoma were included in this study. We included 19 and 10 patients in the CTV group with common iliac lymph nodes (CTV_L) and those without (CTVs), respectively. We retrospectively investigated the correlation among CTV, treatment outcome, and adverse events. ***Results*:** The median follow-up period was 30.4 (range, 2–55) months. The 3-year overall survival (OS) and progression-free survival (PFS) rates of the CTV_L group were 95.0% and 85.0%, respectively, and those of the CTVs group were 100% and 88.9%, respectively. The 3-year OS and PFS rates were not significantly different between both groups (log-rank; P=0.414 and 0.657, respectively). Three CTV_L patients and 1 CTVs patient had recurrences. However, there was no significant difference in the recurrence rate between both groups (P=1.0). ***Conclusion*:** CTV excluding the common iliac lymph nodes in postoperative radiotherapy may be effective in patients with node-negative postoperative cervical cancer.

INTRODUCTION

Cervical cancer is often treated with surgery as part of the standard treatment in staging without distant metastasis. If postoperative pathological findings indicate an intermediate risk (large cervical mass, deep cervical interstitial invasion, or positive vascular invasion) or high risk (positive pelvic lymph node metastasis, parametrial invasion), radiotherapy (RT) and chemotherapy are performed as postoperative adjuvant therapies [(1)].

Postoperative RT significantly reduces recurrence rates and prolongs overall survival (OS) [(2-4)] because a positive lymph node status favors recurrence and extrapelvic metastasis [(4)]. The National Comprehensive Cancer Network (NCCN) ver1.2021 Cervical Cancer guideline recommends that, for patients with negative lymph nodes, the radiation field should include the external and internal iliac, obturator, and presacral nodes, and for patients with high risk of lymph node metastasis, the radiation field should be enlarged to cover the common iliac node as well [(2)]. However, there are few existing reports on the association between clinical target volume (CTV) and treatment outcomes in patients undergoing postoperative RT. In addition, it is useful to set an appropriate CTV because clinical adverse events can be reduced by reducing the dose of surrounding organs such as the intestinal tract and bone marrow [(5-7)].

In our institution, when lymph nodes are negative after surgery, we systematically treat only the CTV, excluding the common iliac (CILN) and presacral lymph nodes (PLN) in order to reduce the dose to the bowels, which is organs at risk (OAR).

This is the first study to examine the relationship between CTV volume and treatment outcomes in patients who underwent postoperative three-dimensional conformal RT (3D-CRT).

This study aimed to evaluate whether excluding the CLIN and PLN from the CTV during RT is effective in node-negative patients after cervical cancer surgery. We retrospectively investigated the correlation between CTV, treatment outcomes, and adverse events.

[DOI: 10.52547/ijrr.20.3.3]

MATERIALS AND METHODS

Patients

This retrospective study was approved by the ethics committee of our institution (IRB No. SH4107), and informed consent was obtained in the form of an opt-out on the hospital website.

Eligible candidates for this study were those with postoperative intermediate risk (lymphovascular space invasion, more than one-third stromal invasion, and tumor diameter >4 cm), high risk (parametrial extension or positive nodes), or others (surgical margin-positive, etc.).

A total number of 29 patients with cervical cancer who were treated with postoperative RT after primary radical hysterectomy with bilateral pelvic lymph node dissection from January 2014 to December 2017 were enrolled in our study.

The numbers of patients with postoperative intermediate risk, high risk, or others were 12, 15, and 2, respectively.

Data on patient characteristics, including age, pathological/histological finding, and metastatic lymph nodes, grade of risk factors, chemotherapy, and intracavitary irradiation in each CTV group were obtained from patients' medical records and are shown in table 1.

Table 1. Patients' characteristics.

Patients (n = 29)	CTV_L (n= 19)	CTV_S (n =10)	P-value
Age (years)	41(30-71)	55(31-78)	0.142
Pathologic-T category T1 : T2	8:11	6:4	0.555
Histology			0.070
Squamous	16	8	
Adenosquamous	3	0	
Adenocarcinoma	0	1	
Mixed carcinoma	0	1	
Metastatic lymph node + : −	10:9	0:10	0.005
Risk factors intermediate: high: other	7:11:1	5:4:1	0.499
Chemotherapy + : −	17:2	6:4	0.086
Intracavitary irradiation + : −	2:17	2:8	0.429

Chemotherapy

Twenty-four patients received three to six cycles of weekly cisplatin (40 mg/m^2) concurrently during RT.

Positioning

All patients were lying flat in the supine position with their hands folded around their forehead. A non-contrast planning computed tomography (CT) scan was obtained with 5.0-mm slice thickness using a 16-multislice CT system (Aquilion LB, Toshiba Medical Systems, Tokyo, Japan).

Target delineation

Treatment planning was performed using Xio (Elekta, Stockholm, Sweden) and Pinnacle (Philips, Amsterdam, Netherlands).

A CTV including the internal iliac, external iliac, and obturator lymph nodes and tumor bed was defined as a small CTV (CTV_S). A large CTV (CTV_L) was defined as a CTV_S, including the CILN. Some cases included the PLN node and some did not, based on the judgment of the physicians at that time.

There were 19 (10 positive-node and 9 negative-node) and 10 (all negative-node) patients included in the CTV_L and CTV_S groups, respectively.

In the CTV_L group, 13 patients had the PLN included and 6 did not. The planned target volume (PTV) was determined by enlarging all around 0.5 cm to the CTV_S or CTV_L.

Planning of radiation treatment

The whole pelvic field (WPF) was used in the CTV_L group, and the small pelvic field (SPF) was used in the CTV_S group (figure 1). In the SPF group, collimation was rotated 90°, and the multileaf collimator (MLC) was lowered to the central part of the head to reduce the intestinal dose. Radiation was delivered with anteroposterior, posteroanterior, and opposed lateral X-ray beams of 10 MV. The beam field was determined by adding 0.5 cm to the PTV. The reference point was set within the PTV.

All patients received a total dose of 45.0–50.4 Gy in five fractions per week at 1.8 Gy per fraction. Four patients had additional intracavitary irradiation (total dose of 10–12 Gy at 5–6 Gy per fraction, once a week, with reference point 5 mm from the submucosa).

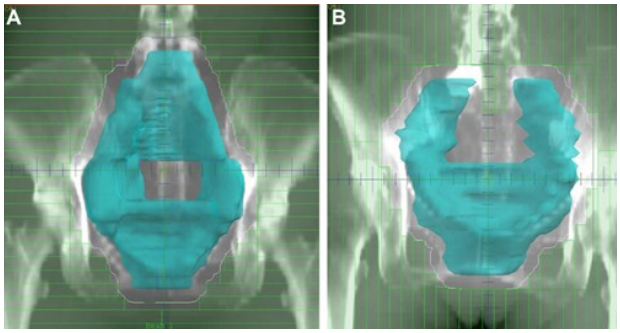

Figure 1. Front beam view of CTV_L group **(A)** and CTV_S group **(B)**.

Analysis of adverse events

The definition of adverse events was that acute events occurred during RT and late events occurred after RT. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) fifth edition and were determined by reviewing the electronic medical records. Complete blood counts (CBCs) were performed during RT and a week after RT.

Statistical analysis

Patient characteristics and adverse events were

[DOI: 10.52547/ijrr.20.3.3]

analyzed using Student's t-test or the chi-squared test. The time to progression-free survival (PFS) and OS were calculated based on the start date of RT until the date of last follow-up or event. Rates of OS and PFS were estimated using the Kaplan–Meier method and compared between the CTV_L and CTV_S groups using the log-rank test. The correlations between CTV and recurrence and that between CTV and adverse events were analyzed using Fisher's exact test. The SPSS Statistics (ver. 22.0, IBM, Armonk, NY) was used for all statistical analysis. A *P*-value of less than 0.05 was defined as indicating statistical significance.

RESULTS

Clinical outcomes

The median follow-up period was 30.4 (range, 2–55) months. The three-year OS and PFS rates were 96.6% and 86.2%, respectively. The 3-year OS rates of the CTV_L and CTV_S groups were 95.0% and 100%, respectively, and the 3-year PFS rates were 85.0% and 88.9%, respectively. There were no significant differences in the 3-year OS or PFS rates between the CTV_L and CTV_S groups (*P*=0.414 and 0.657, respectively) (figure 2).

Among the node-negative patients, 9 CTV_L patients and 10 CTV_S patients survived until the end of the study. The results showed that PFS rates for patients with negative lymph nodes in both groups were not significantly different (P=0.495) (figure 3).

Three patients in the CTV_L group and one patient in the CTV_S relapsed, and one patient in the CTV_L group died due to exacerbation of the primary disease. Two patients in the CTV_L group and one in the CTV_S group had out-of-field recurrences, including lung, liver, spleen, peritoneal and mediastinal lymph node metastases. One patient in the CTV_L group had in-field recurrences, including left external and right internal iliac lymph node metastases. The rate of recurrence in the CTV_L and CTV_S groups was not significantly different (*P*=1.0).

Adverse events

Acute diarrhea of grades 0, 1, 2, and 3 was observed in 14, 6, 3, and 6 patients, respectively (table 2). No grade 4 diarrhea was observed. Diarrhea of grade ≤2 was observed in 6 patients in the CTV_L group and 3 patients in the CTV_S, without significant difference between the groups.

Leukopenia of grades 0, 1, 2, and 3 was observed in 2, 6, 14, and 6 patients, respectively (table 3). CBC was not performed in one patient. Fifteen patients in the CTV_L group and 5 in the CTV_S had grade ≤2 leukopenia, but there was no significant difference between the CTV groups or between patients with and without chemotherapy or intracavitary irradiation. The occurrences of grade ≤2 neutropenia, anemia, and thrombocytopenia were also not significantly different between the CTV_L and CTV_S groups. Patients in both the CTV_L and CTV_S groups had no late adverse events during the follow-up period.

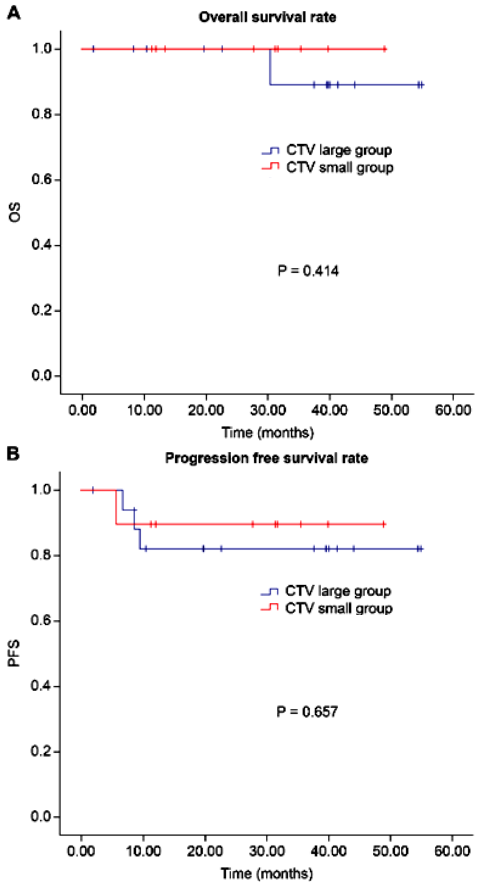

Figure 2. Overall survival (OS) and progression-free survival (PFS) rates were estimated using the Kaplan–Meier method and compared between CTV_L and CTV_S groups using the log-rank test.

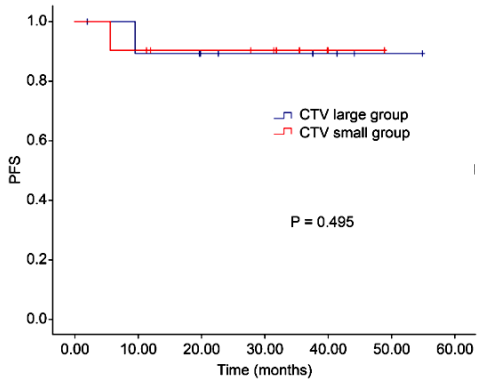

Figure 3. The progression-free survival (PFS) rate in node-negative patients was calculated using the Kaplan–Meier method and compared between CTV_L and CTV_S groups using the log-rank test.

Table 2. CTCAE (Common Terminology Criteria for Adverse Events) Grade of diarrhea in the CTV_L and CTV_S groups.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CTV_L (n=19)	9	4	1	5	0
CTV_S (n=10)	5	2	2	1	0

CTCAE: Common Terminology Criteria for Adverse Events. CTV_L: Clinical Target Volume Large. CTV_S: Clinical Target Volume Small.

[DOI: 10.52547/ijrr.20.3.3]

Table 3. CTCAE (Common Terminology Criteria for Adverse Events) Grade of leukopenia in the CTVL and CTVS group

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CTV_L (n=18)	1	2	10	5	0
CTV_S (n=10)	1	4	4	1	0

CTCAE: Common Terminology Criteria for Adverse Events. CTV_L: Clinical Target Volume Large. CTV_S: Clinical Target Volume Small.

DISCUSSION

If there is no lymph node metastasis on postoperative pathological findings, there is no difference in treatment outcome even with a CTV without the CILN, and it may be possible to reduce adverse events.

Ohara *et al*. showed that the 5-year OS and disease control rates were significantly higher in node-negative patients treated with a SPF than in node-positive patients treated with a WPF on postoperative RT (P = 0.005 and 0.0005, respectively) [4]. In this study, the 3-year OS and PFS rates were not significantly different between the CTV_L and CTV_S groups treated with 3D-CRT in the node-negative patients, which was similar to previous studies.

The Oncology/Radiation Therapy Oncology Group Consensus Guidelines recommend that PLN should be included for patients with postoperative cervical cancer patients [8]. In this study, no patients in the CTVs group had presacral recurrence, and all had good pelvic control within the irradiation field. Previous study reported that PLN metastasis is less common in cervical cancer [9]. Therefore, if postoperative lymph node metastasis is negative, the treatment results are considered sufficiently acceptable even if the CTV did not include the CILN and PLN.

Reducing the lymph node area covered in the CTV helps reduce adverse events.

The bone marrow responds to an increase in the population of progenitor cells in small, exposed areas so that the unexposed bone marrow can meet hematopoietic needs [10]. The lumbar vertebrae, sacrum, iliac bones, and femurs, which are included in the area of pelvic irradiation, contain approximately half of the active bone marrow in the human body [5, 10–13]. Ohara *et al.* reported that grade ≤3 of leukopenia was significantly more common in patients who received WPF than SPF (P=0.0032) [4]. In this study, the CTV_L group (15 patients) had more patients with grade ≤2 leukopenia than the CTV_S group (5 patients). Although without statistical significance (P=0.091), the results suggest that the range of CTV affects leukopenia.

Ohara *et al.* reported that grades 2 or 3 diarrhea was also significantly more common in the WPF group than SPF group (P=0.0031) [14]. In this study, diarrhea grade ≤2 occurred in 6 CTV_L patients (31.6%) and 3 CTV_S patients (30.0%), with no significant difference (p=1.0). All cases of CTV_S and 6 cases (31.6%) of CTV_L did not include the PLN, which may have reduced the dose to the intestine in this study.

This study had some limitations. This was a small non-randomized controlled retrospective study. Therefore, an increase number of patients and randomized controlled trial are desirable to investigate the relationship between the extent of CTV, treatment effects and adverse events.

CONCLUSION

In conclusion, we demonstrated that a CTV excluding the CILN might be more effective than one including them for postoperative RT in patients with node-negative cervical cancer.

ACKNOWLEDGMENTS

We thank Yukinori Okada, Ph.D., for his help in checking for plagiarism.

***Funding*:** None

***Conflicts of interest*:** The authors declare that they have no conflict of interest.

***Ethical Statement*:** This study was approved by the appropriate institutional review board (No. SH4107) and was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived owing to the retrospective nature of the study.

***Author contribution*:** RM and TS-Z conceived of the study, and participated in its design and coordination. RM and TS-Z carried out the statistical analyses. TS-Z, RM, TI, MO, SS and KS carried out the manuscript drafting or revising for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. Li X, Yin Y, Sheng X (2015) Distribution pattern of lymph node metastases and its implication in individualized radiotherapeutic clinical target volume delineation of regional lymph nodes in patients with stage IA to IIA cervical cancer. *Radiat Oncol, **10**: 40.*
2. Abu-Rustum NR and Yashar CM (2021) National comprehensive cancer network. NCCN Clinical Practice Guidelines in Oncology Cervical Cancer. version 1. 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed [October 2, 2020].
3. Rotman M, Sedlis A, Piedmonte MR (2006) A Phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys*, ***65**:169–176*.
4. Ohara K, Tsunoda H, Nishida M (2003) Use of small pelvic field instead of whole pelvic field in postoperative radiotherapy for node-negative, high-risk stages I and II cervical squamous cell carcinoma. *Int J Gynecol Cancer, **13:** 170–176.*
5. Rose BS, Aydogan B, Liang Y (2011) Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys, **79**(3): 800-807.*

[DOI: 10.52547/ijrr.20.3.3]

6. Mell LK, Tiryaki H, Ahn KH (2008) Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys,* ***71****(5): 1504-1510.*
7. Chen MF, Tseng CJ, Tseng CC (2007) Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys,* ***67****: 1438–1444.*
8. Small W Jr, Bosch WR, Harkenrider MM (2021) NRG Oncology/RTOG consensus guidelines for delineation of clinical target volume for intensity modulated pelvic radiation therapy in postoperative treatment of endometrial and cervical cancer: An update. *Int J Radiat Oncol Biol Phys,* ***109****: 413–424.*
9. Kasuya G, Toita T, Furutani K (2013) Distribution patterns of metastatic pelvic lymph nodes assessed by CT/MRI in patients with uterine cervical cancer. *Radiat Oncol,* ***8****: 139.*
10. Mauch P, Constine L, Greenberger J (1995) Hematopoietic stem cell compartment: Acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys,* ***31****: 1319–1339.*
11. Mell LK, Kochanski JD, Roeske JC (2006) Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys,* ***66****: 1356–1365.*
12. Lewis S, Chopra S, Naga P (2018) Acute hematological toxicity during post-operative bowel sparing image-guided intensity modulated radiation with concurrent cisplatin. *Br J Radiol,* ***91****: 20180005.*
13. Hayman JA, Callahan JW, Herschtal A (2011) Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. *Int J Radiat Oncol Biol Phys,* ***79****: 847–852.*
14. Ohara K, Tsunoda H, Satoh T (2004) Use of the small pelvic field instead of the classic whole pelvic field in postoperative radiotherapy for cervical cancer: reduction of adverse events. *Int J Radiat Oncol Biol Phys,* ***60****: 258–264.*

[DOI: 10.52547/ijrr.20.3.3]