

## External beam boost irradiation for clinically positive pelvic nodes in patients with uterine cervical cancer

Takuro ARIGA<sup>1</sup>, Takafumi TOITA<sup>1,\*</sup>, Goro KASUYA<sup>1</sup>, Yutaka NAGAI<sup>2</sup>, Morihiko INAMINE<sup>2</sup>, Wataru KUDAKA<sup>2</sup>, Yasumasa KAKINOHANA<sup>1</sup>, Youichi AOKI<sup>2</sup> and Sadayuki MURAYAMA<sup>1</sup>

<sup>1</sup>Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan

<sup>2</sup>Department of Obstetrics and Gynecology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan

\*Corresponding author. Tel: +81-98-895-1162; Fax: +81-98-895-1420; E-mail: b983255@med.u-ryukyu.ac.jp

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The purpose of this study was to retrospectively analyze the treatment results of boost external beam radiotherapy (EBRT) to clinically positive pelvic nodes in patients with uterine cervical cancer. The study population comprised 174 patients with FIGO stages 1B1–4A cervical cancer who were treated with definitive radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT). Patients with positive para-aortic or common iliac nodes ( $\geq 10$  mm in the shortest diameter, as evaluated by CT/MRI) were ineligible for the study. Fifty-seven patients (33%) had clinically positive pelvic nodes. The median maximum diameter of the nodes was 15 mm (range, 10–60 mm) and the median number of positive lymph nodes was two (range, one to four). Fifty-two of 57 patients (91%) with positive nodes were treated with boost EBRT (6–10 Gy in three to five fractions). The median prescribed dose of EBRT for nodes was 56 Gy. The median follow-up time for all patients was 66 months (range, 3–142 months). The 5-year overall survival rate, disease-free survival rate and pelvic control rate for patients with positive and negative nodes were 73% and 92% ( $P=0.001$ ), 58% and 84% ( $P<0.001$ ), and 83% and 92% ( $P=0.082$ ), respectively. Five of 57 node-positive patients (9%) developed pelvic node recurrences. All five patients with nodal failure had concomitant cervical failure and/or distant metastases. No significant difference was observed with respect to the incidence or severity of late complications by application of boost EBRT. The current retrospective study demonstrated that boost EBRT to positive pelvic nodes achieves favorable nodal control without increasing late complications.

**Keywords:** boost; cervical cancer; lymph node; radiotherapy

### INTRODUCTION

Pelvic lymph node status is considered to be one of the important prognostic factors for patients with uterine cervical cancer treated with surgery [1, 2] and definitive radiotherapy (RT) [3, 4]. Several authors have reported the treatment results of surgical debulking or dissection of metastatic pelvic nodes before definitive RT or concurrent chemoradiotherapy (CCRT) [5–7]. In contrast, limited clinical data are available for boost external beam RT (EBRT) to the metastatic nodes [8]. Since 1998 we have delivered boost EBRT to clinically metastatic pelvic nodes ( $\geq 10$  mm in the shortest diameter, as evaluated by computed tomography

(CT)/magnetic resonance imaging (MRI)) for patients with cervical cancer who were treated with definitive RT/CCRT. In this paper, we retrospectively reviewed our experience with boost EBRT to assess the efficacy and toxicity in patients with cervical cancer.

### MATERIALS AND METHODS

We retrospectively analyzed 174 patients with uterine cervical cancer who were treated with definitive RT alone or CCRT in the Department of Radiology of the University of the Ryukyus Hospital between January 1998 and December 2005. Patients who had para-aortic or common iliac lymph

**Table 1.** Patient characteristics ( $n = 174$ )

Characteristics	Total ( $n = 174$ )	LN negative ( $n = 117$ )	LN positive ( $n = 57$ )	<i>P</i> value
Median age (range in years)	51 (24–89)	52 (24–89)	48 (29–80)	0.086
FIGO stage (%)				
IB1	15 (8)	14 (12)	1 (2)	0.26
IB2	6 (3)	3 (2)	3 (5)	
IIA	4 (2)	4 (3)	0	
IIB	76 (44)	52 (45)	24 (42)	
IIIA	1 (1)	1 (1)	0	
IIIB	69 (40)	41 (35)	28 (49)	
IVA	3 (2)	2 (2)	1 (2)	
Pathology (%)				
SqCC	168 (96)	113 (96)	55 (96)	0.74
Adeno	5 (3)	3 (3)	2 (4)	
Adenosq	1 (1)	1 (1)	0	
Median tumor diameter <sup>a</sup> (mm) (range)	55 (24–95)	59 (24–80)	57 (30–95)	0.055
Treatment				
RT alone	24	19	5	0.48
CCRT	150	98	52	

<sup>a</sup>Assessed by MRI-T2WI (three patients without pretreatment MRI are not included). SqCC, squamous cell carcinoma; Adeno, adenocarcinoma; Adenosq, adenosquamous cell carcinoma; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

node enlargement were excluded from this study because at our institution such patients are usually treated with extended field CCRT. The patient characteristics are shown in Table 1. During the study period, we did not routinely perform (18) F-fluorodeoxyglucose-positron emission tomography as part of the pre-treatment work-up for patients with cervical cancer. Therefore, pelvic lymph node status was assessed by CT/MRI. Lymph nodes  $\geq 10$  mm in minimum diameter were interpreted as clinically positive [9, 10]. There were 57 patients (33%) who were considered to have node metastases, with a total of 95 positive nodes. The maximum diameter of the nodes ranged from 10–60 mm (median, 15 mm) and the number of lymph nodes ranged from one to four (median, two) for each patient. The cervical tumor diameter was measured by MRI (T2 weighted image). The maximum tumor diameter ranged from 24–95 mm (median, 55 mm). The tumor diameter could not be evaluated in three patients because of an absence of pre-treatment MRI. Twenty-four patients were treated with RT alone, and the remaining 150 patients were treated with CCRT.

### Irradiation technique

All patients were treated with a combination of EBRT and high-dose-rate intracavitary brachytherapy (HDR-ICBT).

The details of EBRT and HDR-ICBT as delivered in our department have been described in previous reports [11, 12]. Briefly, EBRT was delivered to a total dose of 50 Gy in 25 fractions over 5–6 weeks. The initial 40 Gy was delivered to the whole pelvis (WP) through anterior–posterior and posterior–anterior (AP–PA) ports or four-box fields using a high-energy photon beam (15 MV). Then, 10 Gy was administered through the same WP field with a midline block (MB), 4 cm in width (WP–MB), delivered through AP–PA ports. The doses were prescribed at the isocenter for the WP. For the WP–MB, we shifted out the reference point from the MB. HDR-ICBT was applied after 40 Gy of EBRT. Total doses of HDR-ICBT were 18–24 Gy and administered in three or four fractions as prescribed at point A (median, 18 Gy administered in three fractions). Fifty-two of 57 patients (91%) with positive pelvic nodes were treated with boost EBRT to the nodes. The boost EBRT was omitted in five patients at the discretion of the treating physicians (i.e. complete response was achieved after 40 Gy of EBRT). Treatment planning CT was performed again for nodal boost irradiation at the end of EBRT of 50 Gy. We defined the remaining visible nodes as persistent nodal CTV (pn CTV). The persistent nodal planning target volume (pn PTV) was created by expanding a 5–10 mm margin around

the pn CTV. Finally, a 5-mm leaf margin was attached to the pn PTV with adjustment of doses for organs at risk (e.g. small intestine). When the pn PTV overlapped bowel loops, the overlapped volume was deleted from the pn PTV. The fields were chiefly expanded laterally if the field size was  $<4 \times 4$  cm. A total dose of 6–10 Gy administered in three to five fractions (median, 6 Gy in three fractions) was delivered through three or four ports (Fig. 1a–b). The prescribed

doses were calculated at the center of the pn PTV or within pn PTV where there is no steep dose gradient. The total prescribed doses of EBRT for the positive lymph nodes ranged from 50–60 Gy (median, 56 Gy).

### Chemotherapy

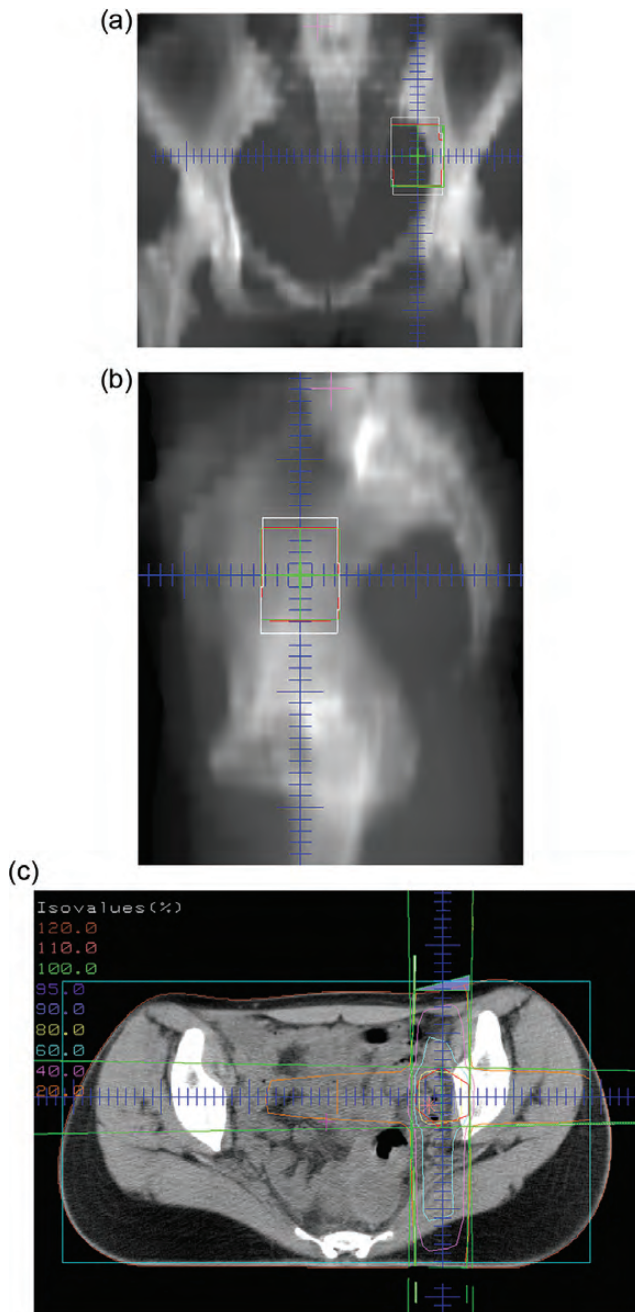
One hundred and fifty patients (86%) were treated with CCRT. The details of the CCRT used in our institution have been described in a previous report [12]. Cisplatin (CDDP) at a dose of  $20 \text{ mg/m}^2$  was administered intravenously for 2 h/day for 5 days concomitantly with EBRT; this schedule was repeated every third week. The median number of cycles per patient was two (range, one to six).

### Statistical analysis

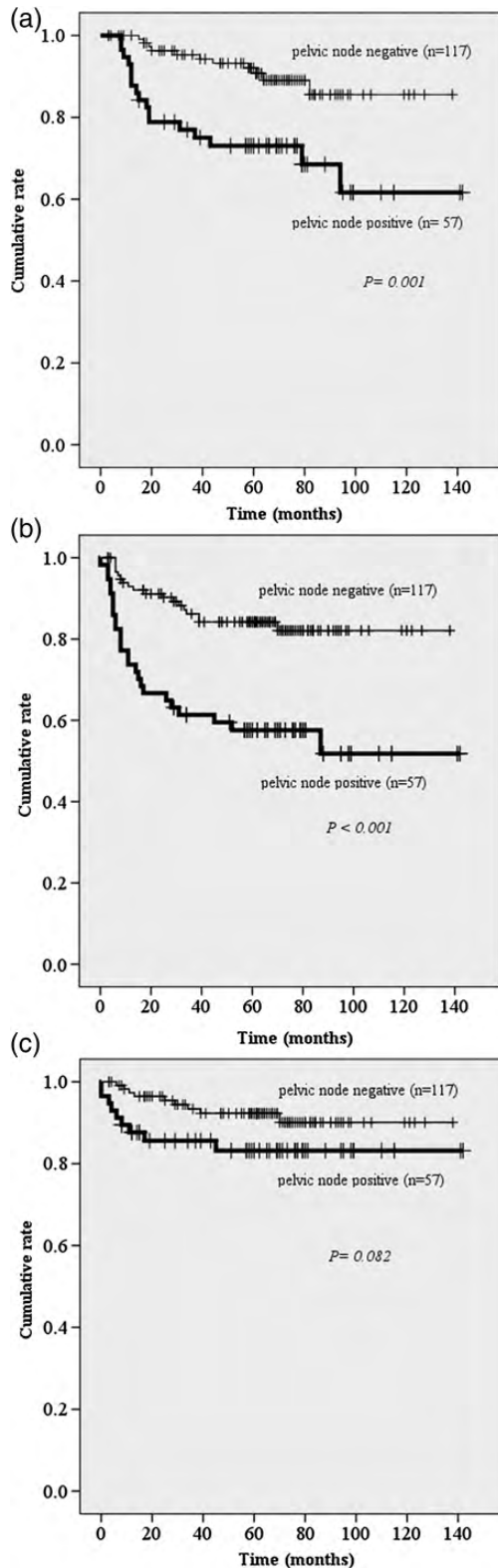
Continuous variables that were not normally distributed (e.g. age) were compared using the Mann–Whitney *U* test. Categorical variables (e.g. stage) were compared using a chi-squared test. For small numbers of variables, Fisher's exact test was used. For all tests, *P* values  $\leq 0.05$  were considered statistically significant. The Kaplan–Meier method was used to derive estimates of the overall survival rate (OS), disease-free survival rate (DFS) and pelvic control rate (PC). The tests for equivalence of the estimates of OS, DFS and PC were performed using the Breslow and log-rank statistic. Doses resulting from HDR-ICBT were not added to the EBRT prescribed dose administered to the lymph nodes. Toxicity was documented according to the Radiation Therapy Oncology Group acute and late morbidity scoring criteria [13]. The duration of follow-up ranged from 3–142 months (median, 66 months). Statistical analyses were performed using SPSS software (version 19.0; IBM, Inc., New York, USA).

## RESULTS

The 5-year OS, DFS and PC for all 174 patients were 85%, 75% and 89%, respectively. Patients with positive nodes had significantly poorer outcomes than patients with no positive nodes, except when determining the PC. The 5-year OS, DFS and PC for patients with positive and negative nodes were 73% and 92% ( $P=0.001$ ), 58% and 84% ( $P<0.001$ ), and 83% and 92% ( $P=0.082$ ), respectively (Fig. 2a–c). Table 2 shows the patterns of recurrence according to pelvic node status. Twenty-five of 57 patients (44%) with positive nodes had recurrences, as follows: cervix in 8 patients (14%); pelvic lymph nodes in 5 patients (9%); and distant metastases in 20 patients (35%). All pelvic nodal recurrences developed in the area where boost EBRT was delivered, but one patient also had multiple nodal failures in a non-boosted area. All patients with nodal failure had concomitant cervical failure and/or distant metastases. Of 20 patients with distant metastases, 13 had para-aortic lymph node (PAN) recurrences. There were no



**Fig. 1.** Boost irradiation ports and dose distribution at the isocenter. (a) Anterior–posterior/posterior–anterior port, (b) lateral port and (c) dose distribution at the isocenter.



**Fig. 2.** Cumulative rates according to pelvic node status. (a) Overall survival rate, (b) disease-free survival rate and (c) pelvic control rate.

**Table 2.** Patterns of recurrence according to pelvic node status assessed by CT/MRI

Recurrence site	Total (n = 174)	LN negative (n = 117)	LN positive (n = 57)
<i>Pelvis alone</i>			
Primary	10	6	4
Pelvic LN	0	0	0
Both	2	1	1
Total	12	7	5
<i>Distant alone</i>			
PAN	6	2	4
Other	13	8	5
PAN + other	7	0	7
Total	26	10	16
<i>Pelvis and distant</i>			
Primary + PAN	0	0	0
Primary + other	1	1	0
Pelvic node + PAN	1	0	1
Primary + pelvic LN + PAN	1	1	0
Primary + pelvic LN + other	2	0	2
Primary + pelvic LN + PAN + other	1	0	1
Total	6	2	4
<i>Total recurrences</i>	44	19	25

LN, lymph node; PAN, para-aortic node.

tumor, patient or treatment-related factors that significantly affected the incidence of PAN recurrences. Of the five patients who did not receive boost EBRT despite having positive nodes, none had nodal recurrences. Table 3 shows the lymph node control rate based on the size of the lymph node. No significant difference was observed in the control rate based on nodal diameter.

For patients with positive nodes, outcomes were analyzed according to some node- and treatment-related factors. Node-related factors included maximum diameter (10–19 vs. 20–29 vs. ≥30 mm), and the number of positive nodes (single vs. multiple). Treatment-related factors included the prescribed dose to the positive nodes (56 Gy vs. 60 Gy). No significant differences in the OS, DFS or PC were observed for these factors.

Thirty-five patients had late complications (Table 4). Delivery and dose of boost EBRT had no significant effects on the incidence or grades of late complications.

## DISCUSSION

The present retrospective analysis demonstrated that boost EBRT achieves favorable pelvic nodal control without increasing late complications for cervical cancer patients with clinically positive nodes treated by definitive RT or CCRT.

Several investigators have reported the clinical outcomes of cervical cancer patients who underwent surgical node debulking. Hacker *et al.* [5] performed surgical debulking in 34 patients who had lymph node enlargement with a maximum diameter >1.5 cm, and reported pelvic recurrences in 10 patients (29%), as follows: pelvic side wall recurrences in five patients; central pelvis recurrences in four patients; and pelvic side wall and central pelvis recurrences in one patient. Cosin *et al.* [6] also reported the outcomes of 266 patients who underwent surgical debulking; specifically 4 of 39 patients (11%) with microscopic metastases and 9 of 79 patients (13%) with macroscopic metastases developed pelvic recurrences. They concluded that surgical debulking was beneficial because no prognostic difference was observed between the two groups; however, the number of patients who developed pelvic recurrences after surgical node debulking was not small in these series [6].

**Table 3.** Pelvic node failure according to size of lymph nodes

Size of node (mm) <sup>a</sup>	n	Node failure
10–19	34	4 (12%)
20–29	14	0
≥30	9	1 (11%)
		P = 0.76

<sup>a</sup>Maximum diameter assessed by CT/MRI.

**Table 4.** Late complications

		Total (n = 174)	Boost (n = 52)	No boost (n = 122)	P value
Small intestine	All grade	25 (14%)	7 (13%)	18 (15%)	0.82
	≥grade 3	3 (2%)	2 (4%)	1 (1%)	0.16
Rectum	All grade	7 (4%)	1 (2%)	6 (5%)	0.35
	≥grade 3	0	0	0	NA
Bladder	All grade	4 (2%)	2 (4%)	2 (2%)	0.37
	≥grade 3	0	0	0	NA
Others <sup>a</sup>	All grade	5 (3%)	2 (4%)	3 (2%)	0.38
	≥grade 3	0	0	0	NA

<sup>a</sup>including lower extremity edema in two, leg pain in one, cellulitis in one and deep vein thrombosis in one.

NA, not available.

In contrast, few reports are available regarding the outcomes after boost EBRT administered to pelvic node metastases. Grigsby *et al.* [8] reported the clinical outcomes of 132 patients treated with boost EBRT administered to pelvic nodes who were assessed by PET and/or CT. They demonstrated that only five patients (4%) developed lymph node recurrences [8]. Similar findings were observed in the present study. Pelvic node failure occurred in only 9% of patients with positive nodes after receiving boost EBRT. Based on these findings, we suggest that boost EBRT can achieve favorable nodal control without surgical debulking.

Grigsby *et al.* [8] demonstrated that dose escalation had no effect on improving the PC; the prescribed dose to lymph nodes was high (66.8–74.1 Gy) compared with ours. In the current series, favorable nodal control was achieved within 56–60 Gy with no dose–response relationship. Niibe *et al.* [14] demonstrated that patients who received >51 Gy to PAN had improved survival compared with those who received <50 Gy. They also showed that a dose ≤60 Gy produced no severe late complications, and recommended that patients with PAN recurrences should be treated with 51–60 Gy. Fletcher *et al.* [15] indicated that 90% of a tumor with a diameter <2 cm could be eradicated by a prescribed dose of 60 Gy. According to NCCN guidelines, highly conformal boosts of an additional 10–15 Gy (total dose, 55–60 Gy) are recommended for limited volumes of unresected gross adenopathy. The present results support the NCCN recommendations. In the current study, the maximum diameter of the nodes had no significant effect on nodal control. Only one patient with a node diameter ≥30 mm had a nodal recurrence. Despite the limited number of patients, the possibility exists that boost EBRT with prescribed doses of 56–60 Gy can achieve favorable nodal control regardless of a node diameter <3 cm.

The present study demonstrated that patients with positive pelvic nodes treated with boost EBRT had a

significantly worse DFS and OS compared with node-negative patients, despite the good PC. Grigsby *et al.* [8] also showed that patients with a positive node oversized by  $\geq 2$  cm had a worse OS and DFS. In the present study, the predominant failure for node-positive patients was distant metastases, especially in PANs. Marana *et al.* [16] reported that surgical debulking achieved significantly improved OS (surgical debulking, 80.6%; non-surgical treatment, 51.1%;  $P=0.001$ ). In contrast, Cheung *et al.* [7] and Kupet *et al.* [17] indicated that surgical debulking did not have a positive effect on the OS. Several authors have concluded that pelvic lymph node metastasis is a significant prognostic indicator for developing distant metastasis [3, 5, 8, 17, 20]. Surgical debulking and boost EBRT are local treatment strategies. Thus, additional systemic chemotherapy with or without prophylactic PAN irradiation might be appropriate treatment options to further improve outcomes for patients with positive pelvic nodes.

We showed that the delivery and dose of the boost EBRT had no significant effect on the incidence of late complications. In contrast, several investigators have reported a high incidence of late complications in surgical debulking series. Hacker *et al.* [5] reported that severe late complications occurred in six patients (18%); five of these complications were small bowel obstructions, and one patient developed ischemic bowel in the distribution of the superior mesenteric artery necessitating resection of the small bowel and a duodenocolic anastomosis. Marana *et al.* [16] also indicated that 9 of 36 patients (25%) had late complications.

There were four potential limitations in this study. First, this study was based on a small number of retrospective cases from a single institution. Some bias (e.g. indication of boost EBRT and dose) cannot be avoided. A prospective study is needed to determine the appropriate boost EBRT method, including appropriate target volumes and doses for positive pelvic nodes. Second, the current study did not include patients with positive common iliac and para-aortic nodes because these patients received different treatments. In our institution, such patients received another treatment strategy involving concurrent chemotherapy using prophylactic extended field EBRT. Unfortunately, the exclusion of the patients might have brought unexpected bias affecting the outcome of the study. Third, the dose contribution to the pelvic nodes resulting from HDR-ICBT was not accounted for in the current study. Lee *et al.* [20] reported that there is an approximate 1.4 Gy contribution from HDR-ICBT when 5.0–5.5 Gy is prescribed at point A. Our prescribed HDR-ICBT dose was 18 Gy in three fractions in nearly all of the patients. Although most patients were treated using the same radiotherapy protocol, there might be some uncertainty regarding doses administered to the nodes due to anatomic variations between patients. In a future study investigating optimal dosing, an adequate calculation of the dose contribution from HDR-ICBT is

mandated, along with the use of three-dimensional image-guided brachytherapy (3D-IGBT). Finally, evaluation of nodal status was based solely on morphologic findings on CT/MRI in the current study. Several investigators demonstrated superior sensitivity and specificity of FDG-PET to CT/MRI in the evaluation of lymph node metastases [21]. Application of FDG-PET for lymph node evaluation is needed in future studies.

The present results showed that boost EBRT for the treatment of pelvic lymph nodes in definitive radiotherapy for uterine cervical cancer yielded a favorable nodal control with a low incidence and grades of late complications. Based on these results, debulking surgery is not always essential for patients with pelvic node metastases. To investigate the optimal methods for using boost EBRT, a prospective study incorporating the dose contribution from ICBT using 3D treatment planning (image-guided brachytherapy) is necessary. Additional treatments, such as adjuvant chemotherapy and prophylactic PAN irradiation, are needed to improve survival in patients with uterine cervical cancer with clinically positive pelvic nodes.

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