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# Intensity-modulated Radiation Therapy Versus Para-aortic Field Radiotherapy to Treat Para-aortic Lymph Node Metastasis in Cervical Cancer: Prospective Study

Xue-lian Du, Xiu-gui Sheng, Tao Jiang, Hao Yu, Yu-feng Yan, Rong Gao, Chun-hua Lu, Qing-shui Li

Department of Gynecologic Oncology, Shandong Tumor Hospital and Institute, Jinan, People's Republic of China

**Aim** To compare dosimetry, efficacy, and toxicity of intensity-modulated radiation therapy (IMRT) with para-aortic field radiotherapy in patients with para-aortic lymph node (PALN) metastasis of cervical cancer.

**Methods** This prospective study examined 60 patients with cervical cancer with PALN metastasis who underwent whole-pelvis radiotherapy followed by brachytherapy between November 1, 2004 and May 31, 2008. After 3 cycles of chemotherapy, patients were serially allocated into two groups and treated with IMRT or para-aortic field RT at doses of 58-68 Gy and 45-50 Gy, respectively. Treatment response was evaluated and toxicities were assessed. Patients in the IMRT group were treated with both para-aortic field RT and IMRT in order to compare the exposure dose of organs at risk.

**Results** In the IMRT group, the mean dose delivered to the planning target volume was 67.5 Gy. At least 99% of the gross tumor volume received effective coverage and radical dose (median, 63.5 Gy; range, 54.5-66) during treatment. IMRT plans yielded better dose conformity to the target and better sparing of the spinal cord and small intestine than para-aortic field RT. The IMRT patients experienced less acute and chronic toxicities. The IMRT group also had higher 2- and 3-year survival rates than the para-aortic RT group (2-year, 58.8% vs 25.0%,  $P = 0.019$ ; 3-year, 36.4% vs 15.6%,  $P = 0.016$ ). However, no significant difference was found in 1-year survival (67.7% vs 51.3%,  $P = 0.201$ ). The median survival in the IMRT group was 25 months (range, 3 to 37 months). The actuarial overall survival, disease-free survival, and locoregional control rates at 2 years were 67%, 77%, and 88%, respectively, in the IMRT group.

**Conclusions** IMRT provides better clinical outcomes than para-aortic field radiotherapy in patients with PALN metastasis. However, cervical local and distal recurrence remain a problem. Long-term follow-up and studies involving more patients are needed to confirm our results.

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**Correspondence to:**

Xiu-gui Sheng  
Department of Gynecologic  
Oncology  
Shandong Tumor Hospital and  
Institute  
Jinan 250117, People's Republic of  
China  
[jnsd2000@yahoo.cn](mailto:jnsd2000@yahoo.cn)

Cervical cancer can metastasize to para-aortic lymph nodes (PALN), which are not covered in the conventional exposure field (1,2). According to Fletcher (3), some patients with positive PALNs show better long-term survival when treated with radiation therapy (RT) of the abdominal para-aortic lymph nodes in a procedure known as para-aortic field RT. However, this technique features an excessively high incidence of complications in the digestive tract.

Intensity-modulated radiation therapy (IMRT) is a novel approach to planning and delivery of radiation therapy. Numerous investigators have demonstrated the benefits of IMRT for a variety of tumor sites in terms of normal tissue sparing (4,5) and delivery of radiation doses higher than conventional doses (6,7). IMRT can provide almost ideal dose distribution to the clinical target volume (CTV) while reducing the dose to normal tissue, thereby enhancing the effects and decreasing complications (8-10). Another advantage of IMRT is its ability to deliver differentiated doses to various structures during the same fraction dose irradiation, thus allowing delivery of a higher dose to gross tumor and lower dose to subclinical disease during the same treatment session.

The aim of the current study was to compare the therapeutic response and toxicity of IMRT and para-aortic field RT in patients with cervical cancer with PALN metastasis following conventional RT or surgery in order to develop an optimal treatment modality for this recurrent disease.

## METHODS

### Patient population

Between November 1, 2004 and May 31, 2008, 60 patients were selected according to the following inclusion criteria: newly diagnosed PALN metastasis of cervical cancer, previously received conventional RT or surgery, a Karnofsky performance status score  $\geq 70$ , and definitive IMRT or para-aortic field RT received at Shandong Tumor Hospital and Institute (Jinan, China). Exclusion criterion was the presence of distant metastasis. Patients were serially assigned to one of two groups: the first patient in the series was assigned to group 1, the second patient to group 2, and so on. Patients in the group 1 received IMRT and patients in the group 2 received para-aortic field RT.

The study was approved by the hospital's Institutional Review Board and all patients gave their informed consent for radiation therapy.

### Chemotherapy

All patients were treated with 3 cycles of chemotherapy before RT. Patients with squamous cell carcinoma received either a combination of cisplatin (25 mg/m<sup>2</sup>, d1-3), vincristine (1.25 mg/m<sup>2</sup>, d1, d8), and bleomycin (20 mg/m<sup>2</sup>, d1-3) (combination PVB), or a combination of cisplatin (25 mg/m<sup>2</sup>, d1-3), etoposide (70 mg/m<sup>2</sup>, d1-5), and bleomycin (20 mg/m<sup>2</sup>, d1-3) (combination PEB). Patients with adenocarcinoma received a combination of cisplatin (25 mg/m<sup>2</sup>, d1-3), etoposide (70 mg/m<sup>2</sup>, d1-5), and adriamycin (40 mg/m<sup>2</sup>, d1) (combination PEA). Ureteral stent placement was done in 3 of 14 IMRT patients and 2 of 10 para-aortic field RT patients with hydronephrosis caused by tumor pressure before RT.

### Radiotherapy

All patients underwent computed tomography (CT) scanning in a supine position with their arms by their sides; the CT images were taken with a Panasonic CTX100 scanner (Beijing, China) at a 3-mm thickness throughout the entire abdomen and pelvic region.

IMRT plans to deliver the intended dose of 58-68 Gy with 15 MV X-rays were developed for 28 patients. Para-aortic field RT was performed in the other 32 patients with an intended dose of 45-50 Gy.

For IMRT, the RT was planned using the ADAC Pinnacle 3 Treatment Planning System (Philips Radiation Oncology Systems, Milpitas, CA, USA) and treatment was delivered with 15-MV X-rays using a Varian 21EX. To reconstruct the GTV, we scanned the patient from the epigastrium to pelvic floor in order to locate the PALN metastasis. The GTV, CTV, planning target volume (PTV), the kidney, spinal cord, and small intestine were outlined on each image. The GTV was defined as any visible tumor on the image. The CTV was defined as the GTV plus a 2- to 5-cm margin above the highest extension of the tumor and a 4- to 5-cm margin below the lowest extension of the tumor with a 2-cm radial margin. Uninvolved bony structure was kept outside the CTV. The PTV was defined as the CTV plus a 5-mm margin. The mean dose, dose range, and standard deviation (SD) of the PTV (for GTV boost and CTV) were calculated.

### Dosimetric considerations

A 6- to 10-field, equally spaced, coplanar IMRT plan was generated for each patient using an identical starting set

of dose-volume constraints. Dose distribution was calculated by the 3D treatment planning system to include the target area with a 90% isodose curve. IMRT planning used dynamic multileaf collimators to shape the fields. In order to compare the exposure dose of organs at risk in patients who received IMRT, we designed a para-aortic 4-fields box plan for IMRT group using the ADAC system and planned to deliver the same prescription dose.

For para-aortic field RT planning we used the anteroposterior and posteroanterior-field box plan. After the initial tumor dose of 40 Gy was given in 20 fractions, the RT plan was changed into 2 anterior fields to achieve the intended prescription dose of 45-50 Gy, delivered as 2 Gy/fraction and 5 fractions/week.

### Toxicity assessment

Acute toxicity levels were assessed weekly using complete blood cell counts and examinations for enteritis and skin reactions during the chemo-radiotherapy. Acute and late toxicities (occurring >90 days after the beginning of RT) were defined and graded according to Radiation Therapy Oncology Group criteria (11). Radiotherapy was interrupted if there was uncontrolled diarrhea or other acute complications. In cases of grade 4 hematologic or non-hematologic toxicity, radiotherapy was stopped until toxicity resolved to at least grade 3.

### Response assessment

The response of the metastatic lymph nodes was assessed by ultrasound, CT, or positron emission tomography-CT scanning after 1-3 months of treatment. A complete response was defined as the complete disappearance of all measurable and assessable disease in  $\geq 4$  weeks. A 50% or more decrease in tumor size constituted a partial response.

### Follow-up evaluation

Upon treatment completion, patients were evaluated every 3 months for the first year, every 6 months during the following two years, and annually thereafter. At each visit, a physical and pelvic examination, blood counts, clinical chemistry, and chest X-rays were performed. Scans of the abdomen and pelvic region were conducted by ultrasound, CT scan, and/or positron emission tomography-CT.

Overall survival was calculated from the date of diagnosis. Surviving patients were censored on the date of the last

follow-up. We confirmed the cause of death by mail, telephone, or medical record review.

### Statistical analysis

The overall survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Clinical characteristics of patients, local control, survival rates, toxicities, and the dosimetric parameter were compared between the two groups using *t*-test and  $\chi^2$  test. Statistical significance level was set at  $P < 0.05$ . All analyses were performed using SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA).

### RESULTS

Patient characteristics are summarized in Table 1. There was no statistical difference in age, previously determined pathologic type, grade, and previous treatment modality between the two groups ( $P=0.282$ ,  $P=0.068$ , and  $P=0.303$ , respectively). Patients who were lost to follow-up were excluded. In 3 of 32 (9.4%) patients from the para-aortic field RT group, therapy was stopped for a median of 11 days (range, 6 to 15 days) due to grade 3/4 acute enteritis. All of the patients in the study ultimately completed their radiotherapy and received the full intended dose of RT.

### Outcome of follow-up

The median time of follow-up was 28 months (range, 3-45 months). Up to May 2008, 4 of 28 (14%) patients from the

**TABLE 1.** Clinicopathologic characteristics of intensity-modulated radiation therapy (IMRT) and para-aortic field radiotherapy (RT) patients

Factor	Para-aortic	
	IMRT group (n = 28)	field RT group (n = 32)
Age (years, median [range])	48.5 (38-62)	50.0 (32-70)
<b>Previous histopathologic grade*</b>		
Good or moderate	19	25
Poor	9	7
<b>Previous histological type (No.)</b>		
Squamous cell carcinoma	20	25
Adenocarcinoma	8	7
<b>Previous treatment (No.)</b>		
Surgery and RT	17	11
RT	11	21
Cycles of chemotherapy	3	3
Intended RT dose (Gy)	60	45-50
Delivered RT dose (Gy, mean $\pm$ standard deviation)	59.2 $\pm$ 5.8	48.9 $\pm$ 5.3

\*Based on Gauthier et al (12).

IMRT group and 6 of 32 (19%) patients from the para-aortic field RT group were lost, with follow-up rates of 86% and 81%, respectively. Of the 10 lost patients, 6 were out of contact and 4 did not appear at the reexamination. Their responses were not included in the data analysis. They also showed no significant differences from the patients who remained in the study in age ( $P=0.513$ ), previously determined pathologic type and grade ( $P = 0.086$ ), previous treatment modality ( $P = 0.144$ ), or complications ( $P = 0.137$ ).

### Dosimetric considerations

The intended prescribed dose in the IMRT group was 58-68 Gy (median, 63.5 Gy). The PTV received a total dose of 67.5 Gy at 1.8-2.3 Gy/fraction, 5 fractions per week. Patients in the para-aortic field RT group received a total dose of 45-50 Gy (median, 47.5 Gy) at 1.8-2.0 Gy/fraction. Table 2 summarizes the dosimetric parameters of IMRT plans for 28 patients. Figures 1A and 1B show the isodose curves in cross section, sagittal section, and coronal section of one representative patient treated by IMRT and para-aortic field RT, which indicate 90% isodose curve including the PTV.

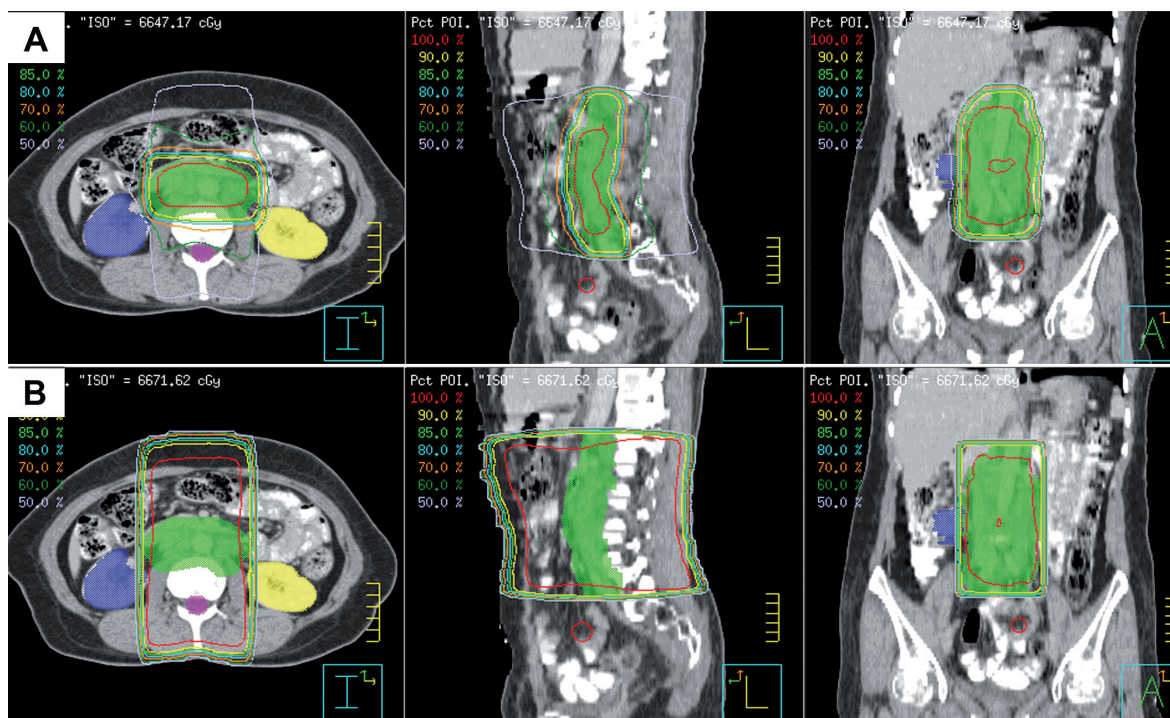
Figure 2 shows the dose-volume histogram of PTV and organs at risk of one representative patient treated by IMRT and para-aortic field RT. Dose-volume histogram results for organs at risk analysis are described in Table 3. IMRT provided better critical organs sparing than para-aortic field RT based on mean dose and provided significantly better values for other parameters for the spinal cord, kidney, and small intestine. IMRT also allowed better dose reduction in organs at risk.

### Tumor response and treatment outcome

As shown in Table 4, the rates for complete response and partial response were significantly higher in the IMRT group than in the para-aortic field RT group (complete response: 57.1% vs 28.1%,  $P = 0.023$ ; partial response: 32.1% vs 12.5%,  $P = 0.039$ ).

The mean survival was 25 months (range, 3 to 27 months). The actuarial 2- and 3-year overall survival rates were significantly higher in the IMRT group than in para-aortic field RT group (2-year: 58.8% vs 25.0%,  $P = 0.019$ ; 3-year: 36.4% vs 15.6%,  $P = 0.016$ ; Table 5). However, there was no sig-

Figure 1.



Isodose curves of a cross section, sagittal section, and coronal section of one representative patient for intensity-modulated radiation therapy (A) and one patient for para-aortic field radiotherapy (B).

TABLE 2. Outcome variables for intensity-modulated radiation therapy (IMRT) and para-aortic field radiotherapy (RT) patients\*

Outcome variables (mean± standard deviation)	Target volume			
	clinical		planning	
	IMRT	para-aortic field RT	IMRT	para-aortic field RT
Conformity	0.680±0.067	0.300±0.054	0.910±0.067	0.350±0.057
V100% (%)	99.0±0.6	95.0±4.2	98.0±2.1	95.0±4.8
Dose (Gy)	59.00±0.48	49.00±1.13	58.60±0.87	48.60±0.74

\*Abbreviations: V100% – percent volume receiving the prescribed dose; conformity –the volume of the PTV/the volume receiving the prescribed dose.

nificant difference in 1-year survival rate between the two groups (67.7% vs 51.3%,  $P = 0.201$ ). A plot of the survival curves is shown in Figure 3.

Acute and chronic radiation toxicities

Acute major toxic effects included myelosuppression, dermatitis, and enteritis. Grade 3/4 leukopenia occurred in 1 of 28 (3.6%) patients in the IMRT group and 6 of 32 (19%) patients in para-aortic field RT group. Two (6.3%) patients in the para-aortic field RT group experienced grade 3 skin re-

actions. One (3.6%) patient in the IMRT group and 6 (19%) in the para-aortic field RT group experienced grade 3/4 acute enteritis. Grade 3/4 late radiation enterocolitis occurred in 6 (19%) patients in the para-aortic field RT group after radiotherapy. No patient experienced radiation myelitis.

TABLE 3. Dose received by different organs at risk in intensity-modulated radiation therapy (IMRT) and para-aortic field radiotherapy patients

Organ at risk	IMRT (Gy)	Para-aortic field radiotherapy (Gy)	t-test	P
Spinal cord	26.1±9.8	46.3±30.8	3.327	0.001
Kidney	15.8±4.1	21.5±11.8	2.478	0.041
Small intestine	21.7±8.9	34.5±17.2	3.497	0.001

TABLE 4. Short-term treatment effects in intensity-modulated radiation therapy (IMRT) and para-aortic field radiotherapy (RT) patients\*

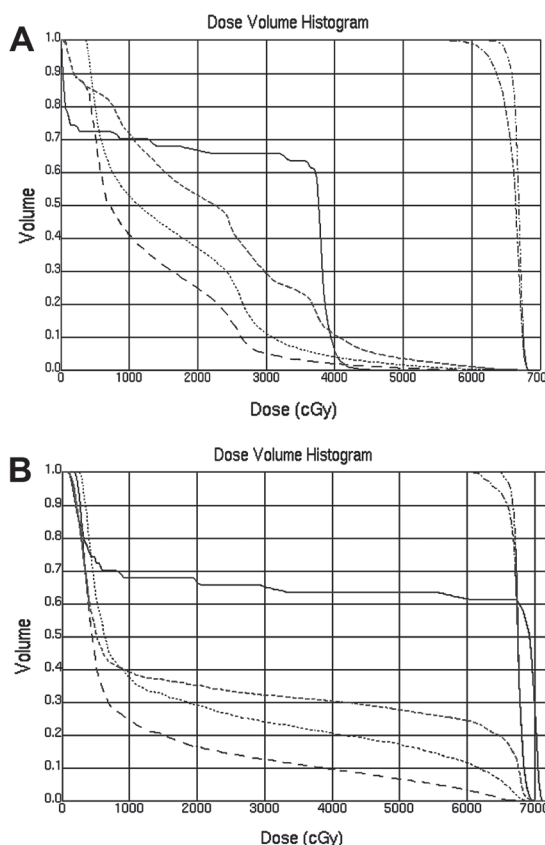
Response*	No. of patients who received (%)		$\chi^2$	P
	IMRT (n=28)	para-aortic field RT (n=32)		
Complete	16 (57.1)	9 (28.1)	5.173	0.023
Partial	9 (32.1)	4 (12.5)	3.395	0.039
Complete +partial	25(89.3)	13 (40.6)	15.227	0.001

\*Criteria for complete response and partial response are defined in the Methods.

TABLE 5. Overall survival rates in intensity-modulated radiation therapy (IMRT) and para-aortic field radiotherapy (RT) patients

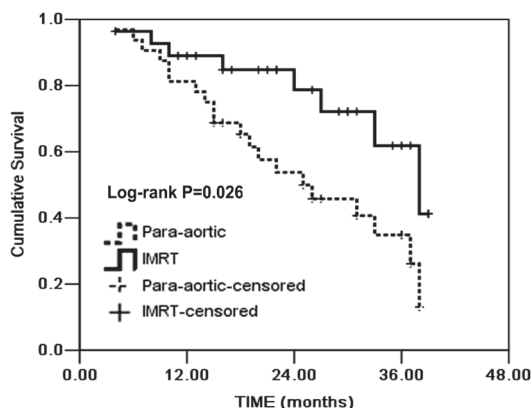
Overall survival	Percentage of patients who received (mean±standard deviation)		$\chi^2$	P
	IMRT	para-aortic field RT		
1-year	67.7±18.6	51.3±19.7	2.127	0.201
2-year	58.8±12.9	25.0±9.8	5.465	0.019
3-year	36.4±11.7	15.6±10.6	5.840	0.016

Figure 2.



Dose-volume histogram (DVH) of a representative patient for intensity-modulated radiation therapy (A) and para-aortic field radiotherapy (B): dash-double dot-dash – gross tumor volume; dash-dot-dash – planning target volume; dots – right kidney; em dashes – left kidney; solid line – spinal cord; en dashes – small intestine.

Figure 3.



Kaplan-Meier survival curve showing overall survival for patients with recurrent cervical cancer: broken line – intensity-modulated radiation therapy group; dotted line – para-aortic field radiotherapy group.

Fifty-eight of 60 patients (96.7%) completed radiotherapy without interruption in a median time of 42 days (range, 37-44). In 2 patients (3.3%), radiotherapy was interrupted for several days due to grade 3/4 skin or gastrointestinal tract toxicity; in these cases, radiotherapy was completed in 50 days.

The acute radiation toxicity of myelosuppression, dermatitis, and gastrointestinal tract was significantly lower in the IMRT group than in the para-aortic field RT group (3.6% vs 18.8%,  $P=0.005$ ; 0 vs 6.3%,  $P=0.037$ ; and 3.6% vs 18.8%,  $P=0.005$ ; respectively). Moreover, the chronic radiation toxicity of radiation enterocolitis was also lower in the IMRT group (0 vs 18.8%,  $P=0.001$ ).

## DISCUSSION

Our study showed that IMRT provided better clinical outcomes than para-aortic field radiotherapy in patients with PALN metastasis.

Although the use of higher radiation doses is associated with an improved likelihood of tumor eradication and enhanced pelvic control, it inevitably exposes organs at risk. In the last decade, many efforts, such as the rotation technique and the lateral-field radiation method, have been made to reduce the radiation dose and volume of organs at risk (13). However, protecting organs at risk remains a challenge. IMRT was found to be superior to conventional techniques because it spares critical organs

and provides adequate coverage of the target volumes (14,15). Paley et al (16) found that IMRT using 30-Gy external beam radiotherapy was superior to conventional therapy, especially when there was tumor regression and internal organ motion. Repeated IMRT planning can improve sparing of the intestine and rectum in patients with substantial tumor regression. This technique was associated with an acceptable acute toxicity without significant treatment protraction (17).

In 5 cervical cancer patients with PALN involvement who received IMRT, Ahmed et al (18) demonstrated the feasibility of increasing the dose delivered to grossly positive PALNs to 60 Gy with a 95.6% median GTV coverage. They found that PALN-IMRT caused less bone marrow exposure than AP/PA and 4-field box techniques: median exposure was 21.3%, 98%, and 49.7%, respectively. The doses received by the kidney and small intestine were also significantly lower. We found that, for the same PTV dose, IMRT made a better dose distribution and gave a significantly lower dose to organs at risk than para-aortic field RT.

In the present study, significant differences in digestive tract side effects and myelosuppression were found between the two groups, and the occurrence of proctitis and cystitis was lower in the IMRT group than in the para-aortic field RT group. IMRT provided a better dose distribution than para-aortic field RT for treatment of PALN metastasis of cervical cancer after conventional RT or surgery and it led to lower acute and chronic radiation toxicities.

The effectiveness of IMRT in our study correlated with target volume, dose, and dose uniformity. If radical dose is not sufficient and GTV does not receive effective coverage, the metastases will not be cured. If the dose is not uniform, parts of GTV will receive lower doses, while if the dose is too high, it will cause serious irradiation injury, even local necrosis. In the IMRT group in our study, the prescribed dose and the uniformity of target volume were adequate, with a median dose of 63.5 Gy delivered to the PTV and 90% of the isodose curve covering more than 99% of the CTV.

Our study showed encouraging short-term treatment effects and short-term survival benefits for patients with PALN metastasis of cervical cancer after conventional RT or surgery. The 2-year and 3-year survival rates were also significantly better in the IMRT group, as reported in other studies (19,20). However, the 1-year survival rates in the two groups were not significantly different.

Ten out of 60 our patients (17%) were lost to follow-up. There was no significant difference in age, previously determined pathologic type, grade, and previous treatment modality between patients lost to follow-up and those who completed the study. Previous studies reported an attrition range from 6.2% to 28.4% in different areas and disease stages (21-23).

Our results showed that IMRT provided better dose distribution than para-aortic field RT and encouraging short-term survival benefits in patients with PALN metastasis who had already been treated with conventional RT or surgery. However, to observe the long-term survival rates and chronic toxicities, longer follow-up and greater number of patients are needed.

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