Turkish Journal of Medical Sciences

Volume 44 | Number 5 Article 22

1-1-2014

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TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 844-852
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doi:10.3906/sag-1212-3

Does lymph node involvement affect the patterns of recurrence in stage IB cervical cancer?

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Received: 03.12.2012 • **Accepted:** 21.12.2013 • **Published Online:** 15.08.2014 • **Printed:** 12.09.2014

Background/aim: To investigate the variations in the recurrence patterns of stage IB cervical cancer according to lymph node involvement.

Materials and methods: We reviewed the medical records of 170 patients who had undergone type III radical hysterectomy and systematic lymphadenectomy from 1993 to 2007.

Results: Among the patients in the study group, 115 did not have lymph node metastases, whereas 55 did. A total of 27 patients developed recurrences. Twelve were in the lymph node-negative group, and 15 were in the lymph node-positive group. The recurrence rate was higher in lymph node-positive group (27.3% versus 10.4%, P = 0.011). The recurrence pattern was not affected by lymph node involvement. However, distant recurrence was more common in the lymph node-positive group (53.3% versus 25%, P = 0.137). Additionally, distant failure was observed only in the patients in the lymph node-negative group who received adjuvant radiotherapy. In this group, 3 patients who did not receive adjuvant radiotherapy developed recurrences only in the pelvic region.

Conclusion: The presence of lymph node involvement in stage IB cervical cancer does not affect the site of recurrence. However, distant recurrence was more frequent in the lymph node-positive group.

Key words: Cervical carcinoma, lymph node metastasis, recurrence

1. Introduction

Carcinoma of the cervix uteri is the second most common cancer and the third most common cause of cancer deaths in women worldwide (1,2). The definitive primary treatment for patients with early-stage disease consists of radiation therapy or radical hysterectomy with pelvic and/or paraaortic lymph node dissection (3). Knowledge about prognosis and recurrence is critical for the management of early-stage cervical cancer. Lymph node involvement is an important risk factor for recurrence in patients with early-stage cervical cancer. The recurrence rate in lymph node-negative patients was 10% and the 5-year survival rate ranged from 85%–90%. In contrast, the recurrence rate in lymph node-positive patients was 27% and the 5-year survival rate ranged from 20% to 74% depending on the number of nodes that were involved and the location and size of the metastases (4–6).

In this retrospective study, we analyzed the variations in the recurrence patterns of stage IB cervical cancer according to lymph node involvement. These data may improve the management of early-stage cervical cancer to reduce the risk of recurrence and predict the recurrence patterns of early-stage cervical cancer.

2. Materials and methods

The medical records of patients diagnosed with stage IB cervical cancer and who were treated with type III radical hysterectomy, bilateral salpingo-oophorectomy, or systemic pelvic and paraaortic lymphadenectomy from January 1993 to December 2007 were evaluated retrospectively. The complete pathological data of 170 patients were evaluated. Patients who received neoadjuvant chemotherapy were excluded because chemotherapy is known to improve surgical pathological results (7).

All of the patients were evaluated by rectovaginal examination under general anesthesia, computerized tomography of the upper abdomen and pelvic magnetic resonance imaging, or intravenous pyelography. Clinical

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staging was performed according to the International Federation of Gynecology and Obstetrics 1988 criteria. The tumor size that was defined in the study was the greatest tumor diameter as determined by rectovaginal examination under general anesthesia.

High-risk patients received postoperative radiotherapy. Up until 2001, the criterion for postoperative adjuvant radiotherapy was the presence of at least 1 of the major risk factors (positive lymph nodes, parametrial involvement, the presence of a tumor within the surgical margins, and a tumor size ≥4 cm) or 2 of the minor risk factors (lymphovascular space involvement [LVSI], stromal invasion of ≥½, a tumor size of 2–4 cm, and 3 or more lymph nodes with microscopic metastasis). After 2001, only patients who had positive lymph nodes and/or parametrial involvement and/or a tumor within the surgical margins received adjuvant radiotherapy. Radiotherapy was administered alone or in combination with chemotherapy (concurrent radiochemotherapy [CCRT]) as the initial treatment. Adjuvant radiotherapy had been the sole treatment for cervical cancer until the National Cancer Institute announced in 1999 that CCRT was accepted as a standard therapy. Radiotherapy was administered by the Department of Radiation Oncology. External radiotherapy was administered using the 4-field box technique with 6–18 MV photon beams at a total dose of 4500–5000 cGy with conventional daily fractionation. In patients with paraaortic lymph node metastasis, 45 Gy of paraaortic radiotherapy was added. In cases with surgical margins that were close to the vagina, 21 Gy of high-dose vaginal brachytherapy was applied in 3 fractions. Vaginal brachytherapy was applied 0.5 cm below the vaginal mucosa, and the upper 4 cm of the vagina was treated.

In the CCRT group, weekly cisplatin was given to the patients during radiotherapy. The calculated cisplatin dosage was infused in 1000 mL of normal saline solution over 1 h with 150 mL of 20% mannitol following premedication. Before chemotherapy was given, the following criteria were met: 1) adequate bone marrow function (leukocytes ≥3000/mL, neutrophils ≥1500/mL, platelets ≥100,000/mL, and hemoglobin ≥10 mg/dL); 2) adequate hepatic function (total bilirubin, AST, and ALT less than twice the normal levels); and 3) sufficient renal function (a glomerular filtration rate of ≥60 mL/min).

Patients were evaluated every 3 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter. Follow-up included rectovaginal examination, a Pap smear test, abdominal sonography, a complete blood count, and serum biochemistry.

The presence of a single region of recurrence was defined as an isolated recurrence. Disease-free survival (DFS) was defined as the time interval between the initiation of treatment and recurrence. Overall survival (OS) was defined as the time interval between the initiation of treatment and death.

Chi-squared and ANOVA table tests were used to analyze the differences between the mean values and the percentages. The statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., USA), and statistical significance was considered at $P < 0.05$.

3. Results

We identified 170 patients who were diagnosed with stage IB cervical cancer and who were treated with type III radical hysterectomy and bilateral pelvic and paraaortic lymphadenectomy. Lymph node involvement was determined in 55 patients. The remaining 115 patients of the study group did not have lymph node metastases.

The mean age of the study group was 53.4 years with a range of 34–80 years, and the mean tumor size was 28.5 mm with a range of 5–75 mm. Although tumor size was measured as 5 mm for 4 patients, these patients were accepted as having stage IB1 disease according to biopsy results. Lymph node status, patient characteristics, distribution of surgical and pathologic risk factors, and differences between the groups are shown in Table 1. Lymph node involvement was higher in stage IB2 cervical cancer and the tumor size was larger in the lymph node-positive group ($P = 0.003$ and $P = 0.002$, respectively). LVSI was more significant in patients with lymph node involvement ($P < 0.001$). Age, cell type, grade, depth of stromal invasion, presence of parametrial involvement, surgical margin positivity, ovarian metastasis, number of lymph nodes that were removed, and median follow-up time were similar among the 2 groups (Table 1). However, ovarian metastases were 4 times higher in the lymph node-positive group.

All of the patients with positive lymph nodes received adjuvant radiotherapy, whereas 50.4% of the patients with negative lymph nodes received this therapy ($P < 0.0001$). The groups were similar regarding the type of adjuvant radiotherapy (only radiotherapy or CCRT). CCRT was administered to 66% and 58% of the patients with positive lymph nodes and negative lymph nodes, respectively ($P = 0.410$). We could not obtain information about the type of adjuvant radiotherapy in 3 patients in the lymph node-negative group and in 5 patients in the lymph node-positive groups.

The lymph node status could not be used to predict distant failure when the recurrence site was adjusted by the lymph node status and the administration of adjuvant radiotherapy (Table 2). Distant failure was observed in 33.3% (3/9 patients with recurrence) of the patients with negative lymph nodes who received radiotherapy, whereas distant failure was observed in 53.3% (8/15 patients with recurrence) of the patients with positive lymph

Table 1. The distribution of characteristics and surgical pathological risk factors.

Parameter		Mean (range) / n (%)		P
		Lymph node-negative	Lymph node-positive	
Age		52.9 (34–76, median: 52)	54.3 (34–80, median: 52)	0.374
Tumor size (mm)		27.2 (5–45, median: 30)	31.2 (10–75, median: 30)	0.002
Stage	IB_1	109 (94.8)	44 (80)	0.003
	IB_2	6 (5.2)	11 (20)	
Cell type	Squamous	91 (79.1)	43 (78.2)	0.956
	Adenocarcinoma	17 (14.8)	9 (16.4)	
	Adenosquamous	7 (6.1)	3 (5.5)	
Grade	1	14 (12.2)	8 (14.5)	0.897
	2	87 (75.7)	41 (74.5)	
	3	14 (12.2)	6 (10.9)	
Bilateral salpingo-oophorectomy	No	23 (20)	6 (10.9)	0.140
	Yes	92 (80)	49 (89.1)	
Ovarian metastasis	Negative	91 (98.9)	47 (95.9)	0.200
	Positive	1 (1.1)	2 (4.1)	
Surgical margin invasion	Negative	107 (93)	49 (89.1)	0.380
	Positive	8 (7)	6 (10.9)	
Lymphovascular space invasion	Negative	63 (54.8)	9 (16.4)	<0.001
	Positive	52 (45.2)	46 (83.6)	
Stromal invasion	≤1/2	50 (43.5)	15 (27.3)	0.100
	>1/2	65 (56.5)	40 (72.7)	
Parametrial invasion	Negative	19 (86.1)	43 (78.2)	0.194
	Positive	16 (13.9)	12 (21.8)	
Adjuvant radiotherapy	No	57 (49.6)	-	<0.0001
	Yes	58 (50.4)	55 (100)	
Applied adjuvant radiotherapy	Only radiotherapy	23 (41.8)	17 (34)	0.410
	Concurrent radiochemotherapy	32 (58.2)	33 (66)	
Lymph node metastasis	Negative	115 (100)	-	-
	Positive	-	55 (100)	
Number of lymph nodes removed		51.9 (13–113, median: 47)	54.2 (16–102, median: 52)	0.520
Number of metastatic lymph nodes		-	3.8 (1–19, median: 2)	-
Site of metastatic lymph node	Isolated pelvic	-	47 (85.5)	-
	Isolated paraaortic	-	2 (3.6)	
	Pelvic + paraaortic	-	6 (10.9)	
Recurrence	Negative	103 (89.6)	40 (72.7)	0.011
	Positive	12 (10.4)	15 (27.3)	
Disease-free survival (months)		25.2 (4–66, median: 11)	18.8 (3–51, median: 14)	0.441
Site of recurrence	Isolated pelvic	9 (7.8)	7 (12.7)	-
	Isolated pulmonary	1 (0.99)	2 (3.6)	
	Pulmonary + upper abdomen	-	1 (1.8)	
	Pelvic + upper abdomen + pulmonary	-	2 (3.6)	
	Isolated bone	1 (0.9)	1 (1.8)	
	Bone + brain	1 (0.9)	-	
	Bone + pulmonary	-	1 (1.8)	
	Bone + supraclavicular lymph node	-	1 (1.8)	
Final situation	Alive	104 (90.4)	41 (74.5)	<0.001
	Dead	11 (9.6)	14 (25.5)	
Overall survival (months)		32.1 (1–83, median: 16)	26.4 (1–77, median: 19)	0.571
Median follow-up (months)		71.3 (1–182, median: 68)	60.8 (1–179, median: 53)	0.114

Table 2. Recurrence sites with regard to lymph node status and adjuvant radiotherapy.

Adjuvant radiotherapy	Recurrence site								Total
	Isolated pelvic	Isolated pulmonary	Upper abdomen + pulmonary	Pelvic + upper abdomen + pulmonary	Isolated bone	Bone + supraclavicular lymph node	Bone + pulmonary	Bone + brain	
LN (-) + RT (-)	3	0	0	0	0	0	0	0	3
LN (-) + RT (+)	6	1	0	0	1	0	0	1	9
LN (+) + RT (+)	7	2	1	2	1	1	1	0	15

LN: Lymph node. RT: Radiotherapy.

nodes. In the lymph node-negative group that did not receive adjuvant radiotherapy, there were 3 patients who developed recurrences and all 3 recurrences were in the pelvic region.

Recurrence and mortality were more common in patients with lymph node metastasis (27.3% versus 10.4%, P = 0.011 and 25.5% versus 9.6%, P < 0.001, respectively) (Table 1). Time intervals from surgery to recurrence and from surgery to death were approximately 6 months longer in the lymph node-negative group; however, this improvement was not statistically significant.

3.1. Development of recurrence

3.1.1. Lymph node-negative group

Tumor recurrence developed in 10.4% (n = 12) of the lymph node-negative patients after initial treatment, and the mean DFS rate was 25.2 months with a range of 4–66 months. Recurrence occurred as an isolated pelvic recurrence in 9 patients. In addition, isolated bone recurrences were observed in 2 patients and isolated pulmonary recurrence in 1 patient. One of the patients who developed bone metastases also had brain metastasis at the same time (Table 1). Death occurred in 11 cases of recurrence, and the mean OS time was 32.1 months with a range of 1–83 months. One of the patients who developed an isolated pelvic recurrence underwent CCRT and remained in remission during follow-up. Cell type of the tumor for this patient was squamous cell carcinoma and the tumor was LVSI positive and grade 1. The parametrium and surgical margins were free of disease (Tables 3 and 4).

3.1.2. Lymph node-positive group

In the lymph node-positive group, 85.5% of the patients had isolated pelvic metastasis, 3.6% had isolated paraaortic

Table 3. Recurrence site and stage, histological diagnosis, and grade.

Recurrence site	Stage		Cell type			Grade		
	IB1	IB2	Squamous	Adenosquamous	Adenocarcinoma	1	2	3
Lymph node-negative group								
Isolated pelvic	8	1	9	-	-	2	7	-
Isolated pulmonary	1	-	1	-	-	-	1	-
Isolated bone	1	-	1	-	-	-	-	1
Bone + brain	1	-	1	-	-	-	1	-
Lymph node-positive group								
Isolated pelvic	6	1	5	1	1	1	6	-
Isolated pulmonary	2	-	2	-	-	1	1	-
Upper abdomen + pulmonary	-	1	-	1	-	-	1	-
Pelvic + upper abdomen + pulmonary	1	1	2	-	-	1	-	1
Isolated bone	1	-	1	-	-	-	1	-
Bone + supraclavicular lymph node	1	0	1	-	-	-	1	-
Bone + pulmonary	1	0	1	-	-	-	1	-

Table 4. Recurrence site and surgical pathological factors.

Recurrence site	Parametrial invasion		Surgical margin invasion		Depth of stromal invasion		Lymphovascular space invasion		Ovarian metastases	
	-	+	-	+	≤1/2	>1/2	-	+	-	+
Lymph node-negative group										
Isolated pelvic	8	1	9	-	2	7	6	3	9	-
Isolated pulmonary	1	-	1	-	-	1	-	1	1	-
Isolated bone	1	-	1	-	-	1	-	1	1	-
Bone + brain	-	1	1	-	-	1	-	1	1	-
Lymph node-positive group										
Pelvic	5	2	6	1	2	5	-	7	6	1
Pulmonary	2	-	2	-	1	1	1	1	2	-
Upper abdomen + pulmonary	1	-	-	1	-	1	-	1	1	-
Pelvic + upper abdomen + pulmonary	1	1	1	1	-	1	-	2	2	-
Isolated bone	1	-	-	1	-	1	1	-	1	-
Bone + supraclavicular lymph node	1	-	1	-	-	1	-	1	1	-
Bone + pulmonary	1	-	1	-	-	1	-	1	1	-

metastases, and 10.9% had both pelvic and paraaortic lymph node metastases. The mean number of involved lymph nodes was 3.8 with a range of 1–19 nodes.

In this group, 27.4% (n = 15) of the patients developed tumor recurrences after initial treatment. The mean DFS rate was 18.8 months with a range of 3–51 months. Recurrence occurred as isolated pelvic disease in 7 patients, isolated pulmonary disease in 2 patients, simultaneous pulmonary and upper abdominal disease in 1 patient, and simultaneous pulmonary, upper abdominal, and pelvic disease together in 1 patient (Table 3). In 3 patients, recurrences were detected as bone metastases. Among the patients who developed bone metastases, 1 patient had a pulmonary recurrence and another patient had supraclavicular lymph node involvement (Tables 1–3).

Lymph node status was not associated with the presence of isolated pelvic recurrence or distant recurrence. However, the frequency of distant metastases was 53.3% (n = 8/15) in the lymph node-positive group and 25% (n = 3/12) in the lymph node-negative group, which was not statistically significant (P = 0.137). Pulmonary metastasis was detected in only 1 of the lymph node-negative patients who developed recurrences; however, 6 of the lymph node-positive patients had pulmonary metastases. Similarly, upper abdominal recurrences were observed in only the lymph node-positive patients. The bone metastases were similar in both groups (n = 2/12 versus 3/15).

3.2. Pelvic recurrence

All of the isolated pelvic recurrences in the lymph node-negative group were squamous cell cancer (Table 3). In contrast, 2 of 7 isolated pelvic recurrences in the lymph node-positive group were adenocarcinoma and adenosquamous carcinoma. Tumor recurrences manifested as a combination of pelvic, upper abdominal, and pulmonary metastases in 2 of the lymph node-positive patients. In these patients, the histological cell type was squamous cell carcinoma and 1 of the patients had a grade 3 tumor (Table 3). There were no grade 3 tumors in the patients with isolated pelvic recurrences in both groups. LVSI was positive in one-third of the lymph node-negative patients, whereas all of the lymph node-positive patients exhibited LVSI positivity (Table 4). LVSI was observed in the patients who had a pelvic recurrence together with upper abdominal and pulmonary metastases. Parametrial and surgical margin involvement were negative in most of the patients involved in the study (Table 4). The age, DFS, OS, number of lymph nodes that were removed, and tumor sizes were similar in both groups (P = 0.056, P = 0.352, P = 0.243, P = 0.195, P = 0.644, respectively) (Table 5). Only 1 of the patients in the lymph node-negative group who had an isolated pelvic recurrence survived. All of the patients in the lymph node-positive group who had an isolated pelvic recurrence died (Table 6).

3.3. Pulmonary recurrence

In the lymph node-negative group, only 1 patient had an isolated pulmonary recurrence of the squamous cell type. The initial cancer in this patient was grade 2 and positive for LVSI. In addition, depth of stromal invasion was greater than ½ (Tables 3 and 4). Recurrence was detected in the 66th month of follow-up, and the patient died in the 75th month of follow-up (Tables 5 and 6).

Table 5. Recurrence site and demographic properties.

Recurrence site		Age	Tumor size (mm)	Number of removed lymph nodes	Disease-free survival (months)	Overall survival (months)
Lymph node-negative group						
Isolated pelvic (n = 9)	Mean	55.1	32.8	50.3	24.9	37
	Maximum	76	40	72	65	83
	Minimum	45	20	30	4	12
	Median	52	30	52	12	21
Isolated pulmonary (n = 1)		72	30	34	66	75
Isolated bone (n = 1)		69	30	51	6	9
Bone + brain (n = 1)		51	40	71	6	9
Lymph node-positive group						
Isolated pelvic (n = 7)	Mean	45.7	30.3	54.3	14.9	21.9
	Maximum	52	52	79	36	40
	Minimum	34	10	27	3	9
	Median	48	30	48	14	19
Isolated pulmonary (n = 2)	Patient 1	50	30	59	15	20
	Patient 2	34	20	52	6	17
Upper abdomen + pulmonary (n = 1)		50	55	50	36	77
Pelvic + upper abdomen + pulmonary (n = 2)	Patient 1	73	40	44	51	58
	Patient 2	50	40	22	6	8
Isolated bone (n = 1)		52	40	56	10	#
Bone + supraclavicular lymph node (n = 1)		50	45	102	9	15
Bone + pulmonary (n = 1)		50	20	47	45	54

#: Alive without disease.

Table 6. Final situation after recurrence.

Recurrence site	Final situation	
	Alive	Dead
Lymph node-negative group		
Isolated pelvic	1#	8
Isolated pulmonary	-	1
Isolated bone	-	1
Bone + brain	-	1
Lymph node-positive group		
Isolated pelvic	-	7
Isolated pulmonary	-	2
Upper abdomen + pulmonary	-	1
Pelvic + upper abdomen + pulmonary	-	2
Isolated bone	1#	-
Bone + supraclavicular lymph node	-	1
Bone + pulmonary	-	1

#: Alive without disease.

Pulmonary recurrences were detected in 6 patients who had positive lymph nodes. Among 6 patients with pulmonary recurrences, 2 of them had isolated pulmonary recurrences; 2 had pulmonary, pelvic, and upper abdominal recurrences; 1 had pulmonary and upper abdominal recurrences; and 1 had pulmonary and bone recurrences. Five of these recurrences were squamous cell carcinoma, and the remaining recurrence was adenosquamous carcinoma (Table 3). None of the pelvic recurrences were in the form of ovarian metastasis among these patients. The mean DFS was 26.5 months with a range of 6–51 months. The mean OS was 39 months with a range of 8–77 months (Table 5). All of the patients with a pulmonary recurrence died (Table 6). Detailed data of the patients with pulmonary recurrences are featured in Tables 1, 3, and 5.

3.4. Bone recurrence

Bone recurrences were observed in 5 of the patients, and all of these recurrences were of the squamous cell type. Two patients with negative lymph nodes had bone metastases. One of these metastases was reported as isolated bone metastases, whereas the other metastasis was reported as bone and brain metastases. Both of the patients were given adjuvant radiotherapy after the surgery. The recurrences were detected in the 6th month of follow-up, and both of the patients died in the 9th month of follow-up (Table 5).

In the lymph node-positive group, 1 patient had isolated bone metastasis, another patient had bone and pulmonary metastases, and the remaining patient had bone and supraclavicular metastases. The DFS of the 3 patients in the lymph node-positive group were 10, 9, and 45 months, respectively. In this group, the patient with isolated bone metastasis survived; however, the other 2 patients died (Table 6). The OS was 15 and 54 months for these patients, respectively (Table 5).

3.5. Metastatic lymph node region and recurrence

Overall, 7 of 10 patients with isolated pelvic lymph node metastases developed a pelvic recurrence and 5 of these patients had an isolated pelvic recurrence. In 2 patients, bone metastases were also reported (Table 7). One of 2 patients with isolated paraaortic lymph node metastases had an isolated pelvic recurrence and the other patient had an isolated pulmonary recurrence. Two of 3 patients with pelvic and paraaortic lymph node metastases had distant metastases.

In total, 25 patients with a recurrence died. One of the patients who survived was in the lymph node-negative group and had an isolated pelvic recurrence. The other patient who survived was in the lymph node-positive group and had an isolated bone recurrence. In the first patient, recurrence was detected in the 42nd month of follow-up and the patient underwent CCRT. The treatment response was good, and the patient is still alive and without disease. In the other patient, recurrence was detected in the 10th month of follow-up and chemotherapy (cisplatin + 5-fluorouracil) was given. The treatment response was good, and the patient is still alive and without disease.

4. Discussion

To date, several reports have presented the prognostic factors for cervical cancer. The major prognostic factors that affect survival and recurrence are the stage, lymph node status, tumor volume, depth of cervical stromal invasion, lymphovascular space invasion, and, to a lesser extent, histological type and grade. Lymph node metastasis is one of the most important prognostic factors for cervical carcinoma. Lymph node metastasis is an important route by which cervical carcinoma can spread and relapse after surgical treatment.

The pelvic lymph node metastasis rate in patients with early-stage cervical cancer is 20%–25% (8,9). However, Benedetti et al. reported that the rate of metastasis to any lymphatic chain is approximately 36.2% (10). In this study, pelvic lymph node metastases were detected in 27.6% of the patients; pelvic and paraaortic lymph node metastases were detected in 32% of the patients.

Lymph node metastasis was an independent prognostic factor (11–17). However, in a univariate analysis of patients with positive lymph nodes, Rutledge et al. reported that 2-year DFS decreases from 89% to 63%, whereas a

Table 7. Recurrence localization of lymph node-positive patients with the effect of the positive lymph node area.

Metastatic lymph node area	Recurrence site							Total
	Isolated pelvic	Isolated pulmonary	Upper abdomen + pulmonary	Pelvic + upperabdomen + pulmonary	Isolated bone	Bone + supraclavicular lymph node	Bone + pulmonary	
Isolated pelvic	5	1	-	2	1	-	1	10
Isolated paraaortic	1	1	-	-	-	-	-	2
Pelvic + paraaortic	1	-	1	-	-	1	-	3

multivariate analysis did not demonstrate this prognostic effect (18). Metindir et al. reported that lymph node involvement does not affect the 5-year DFS rate (19). In this study, the prognostic factors for cervical cancer were not studied. However, when the data were evaluated in a univariate analysis, the determinative impact of the lymph node status on the survival rate was indicated. Following radical surgery, patients with early-stage cervical cancer have a recurrence rate of 10% and a mortality rate of 10% in the presence of negative lymph nodes. In the presence of lymph node metastasis, the recurrence rate is 27% and the mortality rate is 25%.

The prognostic role of nodal involvement in primary cervical cancer is maintained when recurrence is detected; however, lymph node status did not significantly correlate with the presence or absence of distant failure in our study. In the study group, 6 of 7 patients with pulmonary recurrences had lymph node metastases. In addition, an upper abdominal recurrence was detected only in the lymph node-positive group. Additionally, in the group with negative lymph nodes, distant failure was observed only in the patients who received adjuvant radiotherapy. These patients had a high risk of recurrence. In this group, pelvic recurrence was observed in only 5.2% of the patients who did not receive radiotherapy. This finding may indicate the need for new treatment modalities, which would include systemic chemotherapy, in patients who require adjuvant radiotherapy following radical hysterectomy. In the Cochrane Review, Rosa et al. recently reported that the addition of platinum-based chemotherapy to adjuvant radiotherapy may improve survival in women with early-stage cervical cancer and reduce the risk factors for recurrence (20). Another study by Hosaka et al. revealed that postoperative chemotherapy using paclitaxel/cisplatin may be more beneficial for survival than adjuvant radiotherapy and could reduce postoperative complications for cervical cancer patients who are treated with radical hysterectomy (21).

In this study, the disease recurred as bone metastases (isolated or included other regions) in 5 of 27 patients with recurrences. In all of these patients, the histological diagnosis was squamous cell carcinoma and all of these patients were given adjuvant radiotherapy after surgery. Interestingly, the disease recurred earlier and the OS was less than 1 year in 2 patients with negative lymph nodes who developed bone metastases. However, in the lymph node-positive group, 1 patient responded to salvage therapy and the survival was significantly higher in 2 patients (15 and 54 months). The frequency of bone metastases ranges from 0.8% to 1.9% in cervical cancer (22–24). The histological diagnosis is generally the squamous cell type (23). Radiotherapy alone or CCRT has no effect on the recurrence of disease in the form of bone metastases (25).

Demographically, the ages of the patients in the 2 groups were similar. Patients with an isolated pelvic recurrence with positive lymph nodes were 10 years younger than the patients with isolated pelvic recurrence with negative lymph nodes (45.7 years versus 55.1 years) (Table 5). However, this result was not statistically significant (P = 0.056). According to the DFS and OS, patients with negative lymph nodes improved by 6 months compared with those with positive lymph nodes. However, this 6-month improvement in the survival rate was not statistically significant; that may be due to the relatively small size of the study population. Improvement was significant in patients with an isolated pelvic recurrence, and patients with negative lymph nodes had a 10-month increase in the DFS and a 15-month increase in the OS. However, this difference between the lymph node-negative and lymph node-positive cases was also not statistically significant (P = 0.352, P = 0.243, respectively). In the lymph node-negative group, 1 of the isolated pulmonary recurrences was detected in the 66th month of follow-up. However, in the lymph node-positive group, 2 of the isolated pulmonary recurrences were detected sequentially in the 6th and 15th months of follow-up. Isolated pelvic and pulmonary recurrences were detected later in the lymph node-negative group; however, our patient group included a limited number of cases.

In our study, the mortality rate was 95.6% in the recurrence group. In each group, 1 patient survived. These 2 patients had an isolated recurrence and both patients responded to salvage therapy.

In this study, we found clinically significant differences that did not reach statistical significance. This may be due to the relatively small size of the study population. Another limitation of the study was that it was retrospective.

In conclusion, the probability of recurrence in cervical cancer increases in cases of lymph node metastasis. In addition, distant recurrences are more prominent in lymph node-positive patients. Among the lymph node-negative patients, three-fourths of all recurrences were central recurrences. In this group, distant failure was observed in the patients who received adjuvant radiotherapy. Consequently, systemic chemotherapy may be considered for the prevention of distant failure in patients who require adjuvant radiotherapy following radical hysterectomy. In this situation, a new treatment model should be considered.

Therefore, a prospective evaluation of surveillance programs is required to determine an evidence-based follow-up strategy for patients with cervical cancer. More prospective studies that are aimed at elucidating the recurrence patterns of cervical cancer can provide an evidence-based follow-up strategy for patients with cervical cancer.

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