IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2015; 6(4): 377-381. doi: 10.7150/jca.10968

Research Paper

Tailoring Pelvic Lymphadenectomy for Patients with Stage IA2, IB1, and IIA1 Uterine Cervical Cancer

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Received: 2014.11.02; Accepted: 2014.12.21; Published: 2015.02.25

Abstract

Purpose: The purpose of this study was to assess the risk factors for pelvic lymph node metastasis (PLNM) in patients with early-stage uterine cervical cancer.

Methods: A total of 192 patients with early-stage uterine cervical cancer (FIGO stage IA2, IB1, and IIA1) receiving radical hysterectomy with pelvic lymphadenectomy were included in the statistical analysis.

Results: Thirty-six patients (18.8%) developed PLNM, and the incidences of PLNM in patients with stage IA2, stage IB2, and stage IIA1 were 0% (0/6), 13.9% (20/144), and 38.1% (16/42), respectively. The most common location of PLNM was the obturator lymph node. Univariate analysis showed that stage IIA1 ($p < 0.001$), tumor size greater than 3 cm ($p = 0.019$), deep-full thickness stromal invasion ($p < 0.001$), and lymphovascular invasion ($p = 0.001$) were associated with PLNM. Multivariate analysis showed that deep or full-thickness stromal invasion and lymphovascular invasion were significantly and independently associated with PLNM ($p < 0.05$ for both). The incidence of PLNM was 34.9% and 28.7% in patients with deep-full thickness stromal invasion and lymphovascular invasion, respectively, but that was only 5.7% and 9.2% in patients with superficial–middle stromal invasion and absence of lymphovascular invasion, respectively.

Conclusion: Patients with superficial–middle stromal invasion and without lymphovascular invasion may be avoided pelvic lymphadenectomy in stage IA2, IB1, IIA1 uterine cervical cancer.

Key words: Uterine cervical cancer, pelvic lymphadenectomy, lymph node metastasis, stromal invasion, lymphovascular invasion

Introduction

Cervical cancer is a common gynecologic malignancy in women from China and other developing countries (1, 2). Radical hysterectomy including pelvic lymph node dissection (PLND) is the criterion standard of treatment for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA2-IIA1 cervical cancer (3), and clinicians increasingly emphasize assessment the status of pelvic lymph nodes (4). The results of PLND can help to guide the adjuvant therapy of patients. However,

there are serious post-operative complications associated with lymphadenectomy, such as lymphedema in the lower extremities and pelvic lymph cysts with concomitant infection and these can develop into chronic conditions (5-7).

There is controversy regarding the effect of PLND on the prognosis of patients with early-stage cervical cancer (4, 8-10). The number of removed lymph nodes with PLND had no effect on the prognosis of patients with early-stage cervical cancer with negative pelvic lymph nodes (8). Thus, we speculate that PLND may be avoided in early cervical cancer patients with low risk of pelvic lymph node metastasis (PLNM), and may help to improve the quality-of-life of patients.

In the present study, we retrospectively reviewed the records of patients with stages IA2, IB1, and IIA1 cervical cancer who received radical hysterectomy and PLND. We examined the effect of post-operative clinicopathologic factors on the risk for PLNM to identify patients with low risk for whom PLND may be avoided.

Materials and methods

Patients

We performed a retrospective analysis of data from cervical cancer patients treated at the First Affiliated Hospital of Xiamen University between January 2010 and July 2014. Criteria for inclusion in the analysis were: *(i)* stage IA2, IB1, or IIA1 cervical cancer according to the FIGO staging system, and received radical hysterectomy and pelvic lymphadenectomy; *(ii)* negative surgical margins; *(iii)* no preoperative radiotherapy or chemotherapy. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Xiamen University. All patients provided written consent for storage of their information in the hospital database and for use of this information in our research.

Clinicopathological factors

We determined the association of the following clinicopathologic factors with pelvic lymph node metastasis: age, menopausal status, FIGO stage, histological subtype, histological grade, pathologic tumor size, depth of stromal invasion, and lymphovascular invasion.

Surgical procedures

The primary surgery consisted of initial pelvic lymphadenectomy followed by radical hysterectomy. A systematic pelvic lymphadenectomy consisted of removal of external, internal, inter-iliac, obturator, common iliac, and inguinal lymph nodes, at both sides. The cranial, caudal, ventral, dorsal, lateral and medial boundaries of the pelvic lymphadenectomy were 3 cm above the bifurcation of the internal and external iliac arteries, the level of deep iliac circumflex vein, the level of peritoneum, the level of the obturator nerve, the inside of the psoas major muscle and the lateral border of ureter, respectively, as described previously (11). Para-aortic lymphadenectomy was performed only in case of gross metastasis to the common iliac nodes or para-aortic nodes was suspected.

Examination of tumor and lymph nodes

All resected specimens were assessed by two gynecologic pathologists with a great deal of experience in gynecologic cancer. These pathologists reviewed microscopy slides to evaluate pathologic tumor size, histological subtype, histological grade, depth of cervical stromal invasion, lymphovascular invasion, and lymph node involvement, which were routinely and independently labeled by the surgeons. One section from each lymph node was analyzed by hematoxylin and eosin (H&E) staining. The examined lymph nodes included those that were embedded in the *en bloc* specimen and not labeled by surgeons, but were identified by the pathologists. The lymph node number was counted by low-power field microscopy. The number of involved lymph nodes and number of removed lymph nodes were determined.

Statistical analysis

All data were analyzed using the SPSS statistical software package (version 16.0; IBM Corporation, Armonk, NY, USA). The relationship between clinical and pathological factors and PLNM was examined by univariate analysis using the χ^2 and Fisher's exact probability tests. The independent effects of clinical and pathological factors on pelvic lymph node metastasis were then determined by multiple logistic regression analysis, in which factors that were statistically significant in univariate analysis were entered into multiple logistic regression analysis. A p-value < 0.05 was considered significant in all analyses.

Results

Clinicopathologic characteristics of patients

There were 856 patients treated for cervical cancer between January 2010 and July 2014, of who 192 met criteria for inclusion in the present study. Table 1 summarizes the clinicopatholgic characteristics of the 192 patients who had early-stage uterine cervical cancer with a median age of 49 years (range, 30-74 years). A total of 119 patients (62.0%) received laparotomy and 73 patients (38.0%) underwent laparoscopic surgery. One hundred and eighteen patients

(61.5%) were premenopausal and 74 patients (38.5%) were postmenopausal. Staging indicated that 6 patients (3.1%) had stage IA2 cancer, 144 patients (75.0%) had stage IB1 cancer, and 42 patients (21.9%) had stage IIA1 cancer. Analysis of histological type indicated that 82.2% patients (158/192) had squamous cell carcinoma, and 97.9% patients (188/192) had moderately to poorly differentiated cancer. Eighty-six patients (44.8%) had deep-full thickness stromal invasion, and 94 patients (49.0%) with lymphovascular invasion.

Table 1. Clinicopathological characteristics of patients with stage IA2/IB1/IIA1 cervical cancer (n = 192), who presented with (n = 36) and without (n = 156) pelvic lymph node metastases.

Characteristics	n	Without lymph node metastasis n (%)	With lymph node metastasis n (%)	p-value
Age, years				
<40	38	35 (22.4)	3 (8.3)	0.064
≥40	154	121 (77.6)	33 (91.7)	
Menopausal status				
Premenopausal	118	100 (64.1)	18 (50.0)	0.117
Postmenopausal	74	56 (35.9)	18 (50.0)	
FIGO stage				
IA2/IB1	150	130 (83.3)	20 (55.6)	< 0.001
IIA1	42	26 (16.7)	16 (44.4)	
Histological type				
Squamous	158	129 (82.7)	29 (80.6)	0.380
Adenocarcinoma	28	21 (13.5)	7 (19.4)	
Others	6	6 (3.8)	0 (0)	
Histological grade				
Well differentiated	4	4 (2.6)	0 (0)	0.236
Moderately differentiated	125	105 (67.3)	20 (55.6)	
Poorly differentiated	63	47 (30.1)	16 44.4)	
Tumor size (cm)				
≤2	84	73 (46.8)	11 (30.6)	0.094
>2	108	83 (53.2)	25 (69.4)	
Tumor size (cm)				
≤3	143	122 (78.2)	21 (58.3)	0.019
>3	49	34 (21.8)	15 (41.7)	
Depth of stromal invasion				
Superfical	85	80 (51.3)	5 (13.9)	<0.001
Middle	21	20 (12.8)	1 (2.8)	
Deep	47	35 (22.4)	12 (33.3)	
Full	39	21 (13.5)	18 (50.0)	
Lymphovascular invasion				
Negative	98	89 (57.1)	9 (25.0)	0.001
Positive	94	67 (42.9)	27 (75.0)	

Lymph node dissection

The patterns of lymph node metastasis are summarized in Table 2. The median number of dissected lymph nodes was 38 (range, 10-71). Thirty-six patients (18.8%) had pelvic lymph node metastasis with 48 positive lymph nodes. The incidences of patients with PLNM in stage IA2, stage IB1, and stage IIA1 were 0% (0/6), 13.9% (20/144), and 38.1% (16/42), respectively. The obturator lymph node was the most common location of lymph node metastasis (n = 28, 58.4%), followed by the external iliac lymph node (n = 6, 12.5%), internal iliac lymph node (n = 6, 12.5%), common iliac lymph node (n = 4, 8.3%), and parametrial lymph node (n = 4, 8.3%). There was no evidence of inguinal and para-aortic lymph node metastasis.

Univariate analysis of risk factors with PLNM

Table 1 shows the results of univariate analysis of the correlation between clinicopathologic factors and PLNM. Patients with stage IIA1 cancer ($p < 0.001$), tumor size greater than 3 cm ($p = 0.019$), deep to full thickness stromal invasion ($p < 0.001$), and lymphovascular invasion ($p = 0.001$) were significantly associated with PLNM. Age, menopausal status, histological subtype, and histological grade were not associated with PLNM ($p > 0.05$).

Multivariate analysis of risk factors with PLNM

Table 3 shows multivariate analysis of the clinicopathological factors associated with the PLNM in which factors that were statistically significant in univariate analysis. The results showed that deep-full thickness stromal invasion and lymphovascular invasion were significantly and independently associated with PLNM ($p < 0.05$ for both). FIGO stage and tumor size were not significantly associated with PLNM ($p > 0.05$ for both).

Table 2. Location of pelvic lymph node metastases in 36 patients (48 positive lymph nodes) with stage IA2/IB1/IIA1 cervical cancer.

Pelvic Lymph Node Location	Metastasis, n (%)
Common iliac	4 (8.3)
Internal iliac	6 (12.5)
External iliac	6 (12.5)
Obturator	28 (58.4)
Parametrial	4 (8.3)
Inguinal	0 (0)

Table 3. Multivariate analysis of the association of clinicopathological characteristics with pelvic lymph node status in patients with stage IA2/IB1/IIA1 cervical cancer.

Characteristics	HR	95% CI	p-value
FIGO Stage			
IA2-IB1	1		
IIA1	1.170	0.664-4.400	0.266
Tumor size (cm)			
≤3	1		
>3	1.556	0.646-3.746	0.324
Depth of cervical stromal invasion			
Superfical	1		
Middle	0.626	0.068-5.773	0.679
Deep	4.491	1.439-14.014	0.010
Full	10.719	3.480-33.016	<0.001
Lymphovascular invasion			
Negative	1		
Positive	2.936	1.218-7.079	0.016

The incidence of PLNM was 34.9% and 28.7% in patients with deep-full thickness stromal invasion and lymphovascular invasion, respectively, but that was only 5.7% and 9.2% in patients with superficial–middle stromal invasion and absence of lymphovascular invasion, respectively.

Discussion

In the present study, we retrospectively examined the clinical and pathological characteristics of 192 patients with stage IA2, IB1, and IIA1 cervical cancer who received radical hysterectomy and PLND, and assessed the relationship of PLNM with these factors. The results showed that deep-full thickness stromal invasion and lymphovascular invasion were significantly and independently associated with PLNM.

Previous studies reported that the incidence of PLNM in cervical cancer was 0-7% for patients with stage IA2 cancer, 7-40% for patients with stage IB1 cancer, and 21.8-38.6% for patients with stage IIA1 cancer (12-15). These previous results are similar to the present study. Thus, about 60% of patients without PLNM with early-stage cervical cancer, and that PLND may be safely avoided in such patients. A survey by the Japanese Gynecologic Oncology Group found that PLND was recommended in 86.7% of stage IA2 patients when fertility preservation was unnecessary, and in 66.3% of stage IA2 patients when fertility preservation was necessary; for patients with stage IB1 and IIA1 cancer, these percentages were 98.7% and 96.3%, respectively (16). Thus, it is important to identify factors associated with the risk of PLNM to reduce unnecessary pelvic lymphadenectomy.

Currently, the risk factors for PLNM are uncertain, but may include advanced FIGO stage, large tumor size, deep stromal invasion, involvement of the parametrium, and lymphovascular invasion (17). In the present study, patients were diagnosed with stage IA2, IB1, or IIA1 cervical cancer and received surgery, but did not receive neoadjuvant chemotherapy. Our multivariable logistic regression analysis showed that deep-full thickness stromal invasion and lymphovascular invasion significantly and independently increased the risk for PLNM, but FIGO stage, tumor size, histological subtype, and histological grade had no predictive value. Togami et al. (12) investigated patients with stage IA2-IIB cervical cancer and found that parametrial involvement and primary tumor size greater than 2 cm increased the risk of PLNM. However, they focused on preoperative clinical factors (including stage IIB cancer and parametrial involvement), but did not analyze the involvement of lymphovascular invasion and the extent of stromal invasion. Li et al. (11) also studied patients with cervical cancer and found that stage IIA and advanced histological grade increased the risk for PLNM; however, they also did not assess other factors, such as lymphovascular invasion and the extent of stromal invasion, and they did not use multivariate analysis.

Our results showed that the incidence of PLNM was 34.9% and 28.7% in patients with deep-full thickness stromal invasion and lymphovascular invasion, respectively, but that was only 5.7% and 9.2% in patients with superficial–middle stromal invasion and without lymphovascular invasion, respectively. Previous study showed that 30% of patients who had lymphovascular invasion and 1/3 of the stromal invasion developed recurrence when postoperative radiotherapy was not performed (18). Combined with present study, patients with deep-full thickness stromal invasion and lymphovascular invasion should be performed pelvic lymphadenectomy and subsequent radiotherapy/chemotherapy.

After extensive PLND in women with gynecologic cancer, about 34.5% of patients develop pelvic lymphocysts and 11.4% of patients develop lower extremity lymphedema, both of which significantly harm the quality-of-life (5). Previous studies indicated that the axillary lymph nodes may be avoided in some breast cancer patients when the status of axillary lymph nodes is determined by sentinel lymph node biopsy (SLNB) before surgery, and this may significantly reduce the incidence of upper extremity edema (19-21). In recent years, clinicians were increasingly using SLNB in the therapy of cervical cancer (22-26). A systematic review reported that the sensitivity of SLNB in early cervical cancer was 92% (95% CI: 84–98%) and the detection rate was 97% (95% CI: 95–98%) when the combined technique of technetium-99 radiotracer and blue dye was used (27). A recent prospective study of 35 cervical cancer patients (FIGO stage IA1-IIA1) showed that patients without sentinel lymph node metastasis who did not receive subsequent PLND experienced no recurrence of pelvic lymph node, and also had a lower incidence of lower extremity edema (8.7% vs. 42%, $p = 0.030$) (28). However, prospective studies with large sample sizes are required to confirm whether SLNB can be used to replace PLND for patients with early-stage uterine cervical cancer.

There were several limitations in our study. First, this was a single-center retrospective study and the sample size was small, so our patients should not be considered representative of the general population. In addition, the prediction of PLNM was mainly evaluated on the basis of postoperative clinicopathologic factors, and the intra-operative clinicopathological factors were not assessed. Thus, further study is needed to evaluate the intra-operative clinicopathological factors to confirm our findings.

Conclusion

In conclusion, stage IA2, IB1, and IIA1 cervical cancer patients with deep-full thickness stromal invasion and lymphovascular invasion were risk factors with PLNM. Patients with superficial–middle stromal invasion and without lymphovascular invasion maybe avoided pelvic lymphadenectomy and thereby reduce the incidence of postoperative complications. More studies are required to confirm our findings.

Abbreviations

PLNM: pelvic lymph node metastasis; PLND: pelvic lymph node dissection; H&E: hematoxylin and eosin; FIGO: The International Federation of Gynecology and Obstetrics.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 81402527), the Sci-Tech Office of Guangdong Province (No. 2013B021800157) and the Education Scientific Research Project of Young Teachers in Fujian Province (No. JB13131).

Competing Interests

The authors have declared that no competing interest exists.

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