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Original Article

Risk factors of para-aortic lymph node metastasis in stages IB, IIA and IIB cervical carcinoma

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Abstract: Objective: The purpose of the present study was to investigate the incidence and risk factors of para-aortic lymph node metastasis in stages IB, IIA and IIB cervical carcinoma and provide the basis for para-aortic lymph node dissection. Method: Four hundred and twenty-three patients with stages IB, IIA and IIB cervical cancer who had undergone radical hysterectomy, pelvic lymphadenectomy, and para-aortic lymph node dissection were investigated for risk factors of para-aortic lymph node metastasis using univariate and multiple analyses. The efficacy of imaging and intraoperative exploration for diagnosing para-aortic lymph nodes metastasis was evaluated compared with histological results. Results: The incidence of para-aortic lymph node metastases was 2.2% and 7.7% in stages IB1 and IIA1, and stages IB2, IIA2 and IIB, respectively. Clinical stages, parametrial invasion, upper canal invasion, pelvic lymph node metastasis, and common iliac lymph node metastasis were related to para-aortic lymph nodes metastasis analyzed by univariate analyses ($P<0.05$). Multiple analyses revealed that upper canal invasion correlated significantly with para-aortic lymph nodes metastasis (OR=2.662, 95% CI: 1.047-6.769). No statistical difference was found between patients with a negative pelvic lymph node and a single positive pelvic lymph node, but multiple ($n \geq 2$) positive pelvic lymph nodes significantly increased the risk of para-aortic lymph node metastasis (OR=31.492, 95% CI: 8.895~111.496). The sensitivity, specificity, positive predictive value, and negative predictive value of imaging and intraoperative exploration for diagnosis of PALN metastases were 36% and 68%, 98.7% and 73.6%, 64.3% and 13.9%, 96.1% and 97.3%, respectively. Conclusions: Upper canal invasion, multiple PLN metastases, and common iliac lymph node metastasis may be the significant risk factors of PALN metastasis. Because of the low incidence of PALN metastasis, routine para-aortic lymph node dissection may be unnecessary in the absence of any risk factors or of suspicious positive lymph node in images taken of stages IB, IIA and IIB cervical carcinoma.

Keywords: Cervical carcinoma, para-aortic, lymph node, metastases, dissection, risk factors

Introduction

The status of the para-aortic lymph node (PALN) is one of the most important factors for prognosis and guiding treatment in cervical carcinoma [1-5]. Previous studies revealed that the three-year post-surgical survival rate was 94% for patients with negative nodes compared to 64% for patients with positive pelvic lymph nodes (PLN). But the rate declined to only 35% when PALN was involved [1]. Individuated therapy of combined lymph node dissection and extended field radiation may improve patients' prognosis. Leblanc reported patients who received a successful resection of a positive lymph node, followed by extended field radiation showed an overall 5-year survival rate of 58.3% [6]. Thus, assessment of PALN status is essential in determining individuated therapy and prognosis evaluation [1-5]. However, imaging tests have demonstrated a low sensitivity to PALN metastasis. The sensitivity of computer tomography (CT), magnetic resonance imaging (MRI) and Color Doppler sonography is 19%, 30.3% and 34% respectively. Although PET-CT has a higher sensitivity of 57.6%, it also produces a false negative rate of 8.4%-12% [5, 7-10]. PALN status should therefore be confirmed by surgical pathology according to PALN dissection, which may also provide a therapeutic impact for patients with node metastases [2, 5, 6, 11, 12]. However, routine PALN dissection in combination with radical hysterectomy and bilateral pel-

Table 1. Clinicopathological characteristics and PALN metastasis of patients (univariate analysis)

Variables	Number	PALNm (%)	P	χ^2
Age (year)			0.32	0.98
<45	116	9 (7.76%)		
≥45	307	16 (5.21%)		
BMI			0.71	0.14
≤25	350	20 (5.71%)		
>25	73	5 (6.85%)		
Tumor size			0.482	0.49
<4 cm	128	6 (4.69%)		
≥4 cm	295	19 (6.44%)		
Clinical stage			0.045	0.98
IB1, IIA1	136	3 (2.21%)		
IB2, IIA2 and IIB	287	22 (7.67%)		
Histological types			0.8	0.45
Squamous	283	16 (5.65%)		
Adeno	50	4 (8.00%)		
Others	90	5 (5.56%)		
Histology differentiation			0.634	0.91
G1	14	0		
G2	83	5 (6.02%)		
G3	326	20 (6.13%)		
LVSI			0.131	2.29
-	294	14 (4.76%)		
+	129	11 (8.53%)		
Cervical stromal invasion			0.098	2.74
<1/2	100	2 (2.00%)		
≥1/2	323	23 (7.12%)		
Parametrial invasion			0.006	7.58
-	262	9 (3.44%)		
+	161	16 (9.94%)		
Upper canal invasion			0.001	10.48
-	292	10 (3.42%)		
+	131	15 (11.45%)		
PLN			<0.001	47.06
-	309	3 (0.97%)		
+	114	22 (19.30%)		
CILN			<0.001	64.80
-	221	5 (2.26%)		
+	19	9 (47.37%)		

PALNm: Para-aortic lymph node metastasis, G: Grade, PLN: Pelvic lymph node, CILD: Common iliac lymph node, LVSI: Lymph vascular space invasion, BMI: Body mass index.

vic lymphadenectomy for cervical cancer remains debatable, because a large number of patients may not experience any benefit [13]. Thus, risk factors of PALN metastasis could be indications of the need to perform PALN dissection. Some risk factors have been identified in previous studies, such as tumor size, histological types, lymph vascular space invasion (LVSI), cervical stromal invasion, clinical stages, parametrial invasion, PLN metastasis, or common iliac lymph node metastasis, but those results are still debated [14-21]. Furthermore, most of those reports were based on small series research. Otherwise, a large number of patients with PALN metastasis were found to have upper canal invasions (upper one-half of canal), although this relationship has not been reported.

Our study sought to determine the risk factors of para-aortic node metastases based on 423 consecutive cases in stages IB, IIA and IIB cervical carcinoma diagnosed at the affiliated Cancer Hospital at Guangxi Medical University, and to evaluate the diagnostic value of imaging and grossly enlarged PALN by intraoperative exploration.

Patients and methods

From January 2007 to July 2014, 423 patients with (FIGO 2009) stages from IB1 to IIB cervical cancer who underwent radical hysterectomy, pelvic lymphadenectomy and para-aortic lymph node dissection by either laparoscopy or laparotomy were studied at Affiliated Cancer Hospital of Guangxi Medical University. The patients' characteristics are shown in **Table 1**. Median age was 49 years, ranging from 22 to 71, and median body mass index (BMI) was 22.2 Kg/m^2 with a range between 17.79~37.22 Kg/m^2. The histological types were identified as squamous carcinoma (n=283), adenocarcinoma (n=50), and other types (n=90). The other types included adenosquamous carcinoma, clear cell carcinoma, carcinosarcoma and neuroendocrine small cell carcinoma. MRI, ultrasonography and CT tests were administered in 9, 23 and 391 patients preoperative, respectively. Neoadjuvant chemothera-

Table 2. Multiple analyses for risk factors of PALN metastasis

Variable	Number	PALNm (%)	B	OR	95% CI
Upper canal invasion					
-	292	10 (3.4%)			
+	131	15 (11.5%)	0.979	2.662	1.047-6.769
Number of PLN metastasis					
0	309	3 (1%)			
1	45	2 (4.4%)	1.624	5.072	0.810-31.741
≥2	69	20 (28.9%)	3.450	31.492	8.895-111.496
Clinical stage					
IB1, IIA1	136	3 (2.2%)			
IB2, IIA2, IIB	287	22 (7.7%)	0.522	1.685	0.371-7.652
Parametrial invasion					
-	262	9 (3.4%)			
+	161	16 (9.9%)	0.492	1.636	0.552-4.845

PLN: Pelvic lymph node, PALNm: Para-aortic lymph node metastasis, OR: Odds ratio, CI: Confidence interval, B: Beta value.

Table 3. Grossly enlarged PLAN and confirmation of PALN status

Grossly enlarged PLAN	PALN status		Total
	Negative	Positive	
No	293	8 (2.66%)	301
Yes	105	17 (13.93%)	122
Total	398	25	423

PALN: Para-aortic lymph node metastasis.

py (NACT) was administered before surgery in order to shrink the original tumor and improve the feasibility of surgery, as well as decrease the rate of potential surgical complications [22, 23]. One hundred and eighty-five patients received NACT based on platinum agent preoperative, while the other 238 cases underwent surgery directly. Grossly enlarged PALNs were intraoperatively explored by visualization and palpation. Pelvic lymphadenectomy was performed as described by Benedetti [24]. The midpoint of the common iliac artery served to divide the pelvic lymph nodes from the aortic lymph nodes. The common iliac lymph nodes (CILD) were isolated from PLN in 240 patients. The lymph nodes anterior and lateral to the aorta and inferior vena cava and also those between the aorta and the inferior vena cava were removed. The superior boundary of the PALN dissection was defined by the inferior mesenteric artery (IMA) in 413 cases. PALN dissections were performed as high as the renal vein in 10 patients, since grossly enlarged nodes superior to IMA were found intraoperatively. All specimens were examined by histological tests, which revealed the histological type and differentiation as well as lymph vascular space invasion (LVSI), deep stromal invasion (outer one-half), upper canal invasion (upper one-half), parametrial invasion, and lymph node metastasis. This study was approved by the Medical Ethics Committee of the Affiliated Cancer Hospital of Guangxi Medical University. Written informed consent was obtained from all patients.

Either the Chi-squared test or Fisher's Exact test was used to determine the independent variable. Binary regression analysis was used to evaluate the significant predictors of PALN metastasis. The level of statistical significance was set at P≤0.05. The diagnostic performances of sensitivity and specificity were calculated by receiver operating characteristics (ROC) curves. Statistical analyses were performed using the SPSS version 16.0 software.

Results

The median number of PLN, CILN and PALN came to 15 (range, 3-45), 4 (range, 1-17) and 5 (range, 1-31), respectively. The incidence of PLN metastasis, CILN metastasis and PALN metastasis was 26.7% (n=113), 7.9% (n=19) and 5.9% (n=25), respectively. The incidence of PALN metastasis according to FIGO stage was 2.2% in stages IB1 and IIA1, while it was 7.7% in stages IB2, IIA2 and IIB. Twenty-two patients had PALN metastasis in the presence of PLN metastasis. Three patients (0.7%) without PLN metastasis were found with PALN metastasis.

Table 4. Parameters of several tests in diagnosis of PALN metastases

Variable	Sensitivity	Specificity	NPV	PPV	Cut off value	Youden's index
Imaging test	36%	98.7%	96.1%	64.3%	0.5	0.26
CT test	42.8%	98.6%	96.8%	54.3%	0.5	0.21
Intraoperative exploration	68%	73.6%	97.3%	13.9%	0.5	0.13

PALN: Para-aortic lymph node metastasis, CT: Computer tomography, NPV: Negative predictive value, PPV: Positive predictive value.

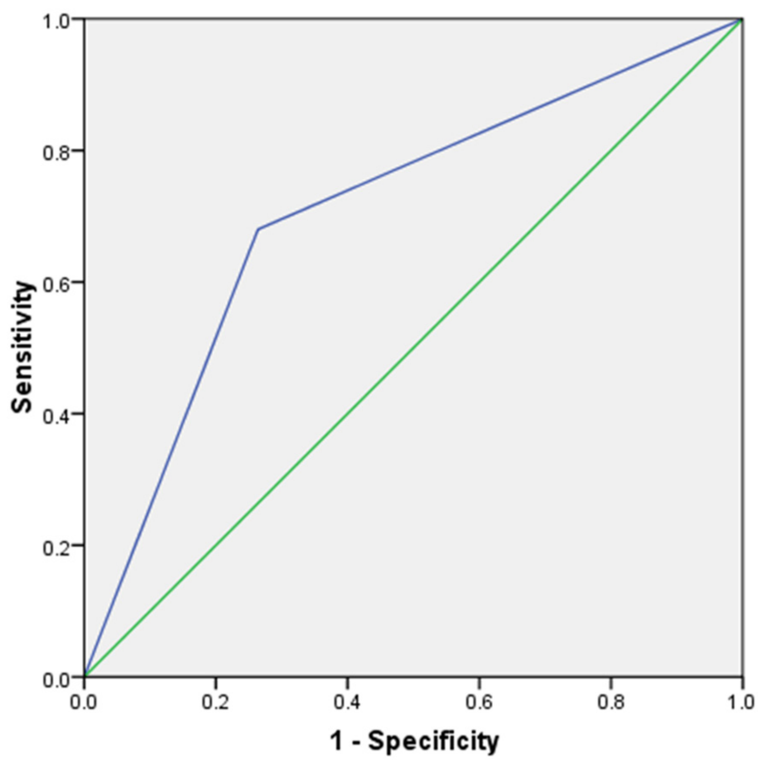

Figure 1. ROC Curve of intra-operative exploration.

Three in ten cases were found with metastasis to PALN superior to IMA (PALNsup). Of three, two had metastasis of PALN inferior to IMA (PALNinf), while the other one were found with negative PALNinf.

There was no statistically significant difference in the incidence of PALN metastasis among ages, histological types, histology differentiation, LVSI and cervical stromal invasion. Parametrial invasion, clinical stages, upper canal invasion, PLN metastasis, and common iliac lymph node metastasis were shown to relate to PALN metastasis by univariate analyses (**Table 1**).

Multiple analyses revealed that upper canal invasion correlated significantly with para-aortic lymph node metastasis (P=0.040, OR= 2.662, 95% CI: 1.047-6.769). The rate of PALN metastasis was not significantly different between patients with negative PLN and single positive PLN, but it was significantly higher in patients with multiple (n≥2) positive PLN (OR=31.492, 95% CI: 8.895~111.496) (**Table 2**).

One hundred and twenty-two cases had grossly enlarged PALN, of which 17 (13.9%) showed confirmed PALN metastasis. Eight of 293 cases (2.66%) without grossly enlarged PALN were found to be PALN positive. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of enlarged PALN for metastases were 68.0%, 73.6%, 13.9% and 97.3%, respectively (**Tables 3** and **4**; **Figure 1**).

Forthteen patients were found with suspicious PALN metastasis by imaging, of which 9 were confirmed by histology. MRI and ultrasonography failed to detect 1 and 3 positive PALN cases, respectively. The sensitivity, specificity, PPV, and NPV of imaging in diagnosis of PALN metastases were 36%, 98.7%, 64.3% and 96.1%, respectively, while they were 42.8%, 98.6%, 64.3% and 96.8% for CT tests (**Tables 4**-**6**; **Figures 2**-**6**).

Discussion

Lymph node metastasis is the most prevalent pathway for the spread of cervical carcinoma. Pelvic lymph nodes (PLN) are the first step to those metastases. PALN metastases are usually secondary to PLN invasion. The incidence

Table 5. Imaging test results and confirmation of PALN status

Imaging (CT, MRI, and ultrasonography)	PALN status by histology		Total
	Negative	Positive	
No	393	16	409
Yes	5	9	14
Total	398	25	423

PALN: Para-aortic lymph node metastasis, CT: Computer tomography, MRI: Magnetic resonance imaging.

Table 6. CT test results and confirmation of PALN status

CT	PALN status by histology		Total
	Negative	Positive	
No	365	12	377
Yes	5	9	14
Total	370	21	391

PALN: Para-aortic lymph node metastasis, CT: Computer tomography.

of PALN metastasis has varied widely in previous researches, ranging from 1% to 8% in stage I, and from 7.2% to 25% in stage II [6, 25-27]. Those results may be affected by limited series and bias of clinical stages. In our study, the incidence of PALN metastasis was 5.9% (2.2% in stage IB1 and IIA1, 7.7% in stage IB2, IIA2 and IIB, respectively). Skip metastases to the PALN are rare, and their incidence ranges between 0.7% and 3% [14, 28]. The possible route of spread may be through the posterior cervical trunk, which drains into the sacral nodes, the common iliac nodes, and the PALN [14], or though the ovarian vessel to PALN when a tumor has invaded the uterine corpus or ovary [16]. Our study found skip metastasis in three of 423 patients (0.71%), which is in accord with previous reports [14, 28].

Some studies have revealed that all of the metastases to PALNsup were secondary to the PALNinf involvement [16, 29]. Those results suggest that PALNsup dissection should be omitted in the absence of malignant findings in the PALNinf in frozen section [16, 29]. But one case was found of a PALNsup metastasis without PALNinf involvement in our study. So the boundary of PALN dissection in cases of PALNinf involvement may need to be reconsidered.

Some studies found that tumor size was related to PALN metastasis. Patients with a small tumor size have a low rate of PALN metastasis. Huang reported PALN metastasis was not found in patients with a tumor size of less than 2 cm [14]. Patsner described 125 stage IB patients with tumors of 3 cm or less; only 2 (1.5%) had PALN metastasis [25]. Michel reported that incidence of PALN metastasis was only 2.9% (4/136) in patients with tumor size of less than 2 cm [15]. However, tumor size did not appear to be related to PALN metastasis in the current study. The bias of cases may be one of the reasons. Patients with tumor size of less than 2 cm were in a low ratio (2.6%). Furthermore, since visualization is the main method to measure tumor size, deviation can not be avoided. Otherwise, it is difficult to measure the size of an endogenous tumor via visualization. An MRI test combined with visualization may be a more precise to survey method. Nevertheless, results of imaging are not included in FIGO stage.

The relationship between clinical stage and PALN metastasis remains debatable. Michel and Huang reported that the clinical stage was associated with PALN metastasis by univariate analyses [14, 15]. However, Sakuragi's study revealed that the clinical stage was not related to PALN metastasis [16]. In the present study, the clinical stage was related to PALN metastasis using univariate analyses, but it was not an independent risk factor as analyzed by multiple analyses. Some reasons should be considered for this controversy: firstly, since FIGO stage was diagnosed based on manual gynecological examination, results may vary from individual doctors. Secondly, tumor size and parametrial invasion were included in the clinical stage. It may not be inappropriate to analyze the clinical stage as a single factor.

Previous studies indicated that LVSI was strongly associated with PLN metastasis [12]. Sakuragi's research revealed LVSI was related to PALN metastasis using univariate analyses, but it was not an independent risk factor found by multiple analyses [16]. Our result indicated that LVSI was not a risk factor of PALN metastasis. However, Memarzadeh et al reported that parametrial LVSI was related to both PLN and PALN metastasis [21], which implied the site of LVSI may be a significant factor for lymphatic spread.

The relationship between deep cervical stromal invasion and PALN metastasis remains contro-

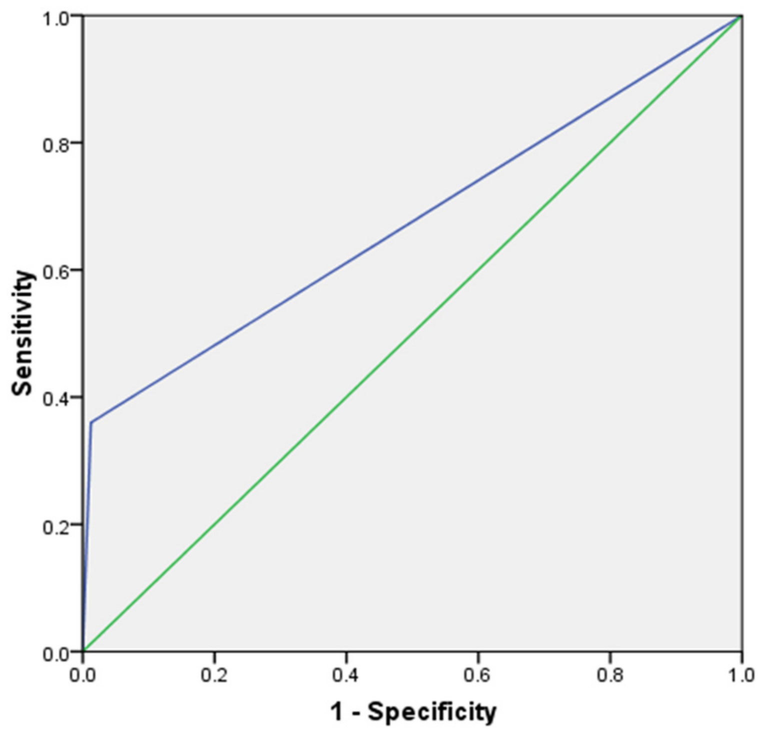

Figure 2. ROC Curve of imaging text.

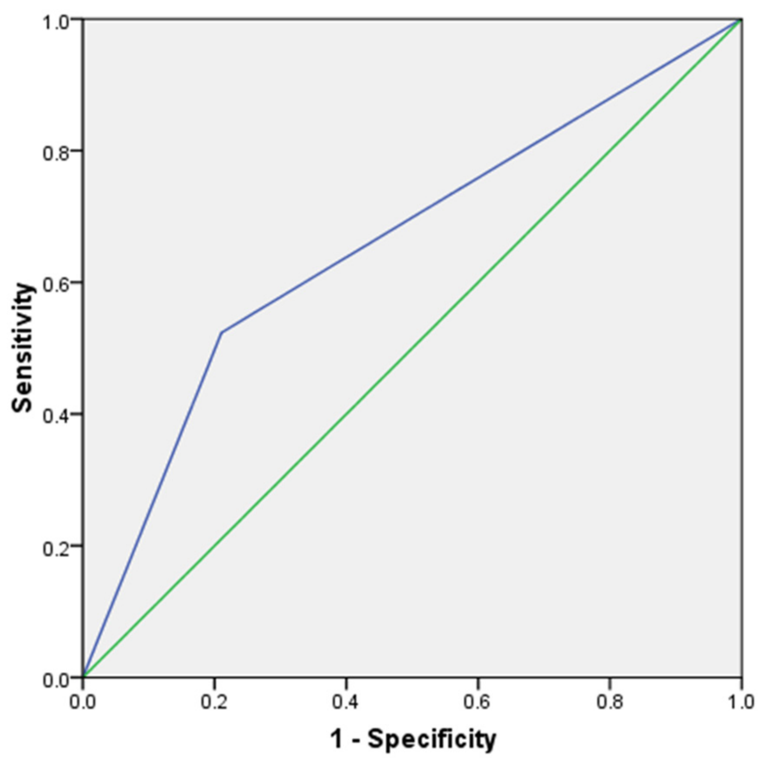

Figure 3. ROC Curve of CT test. CT: Computer tomography.

versial. Sakuragi found deep cervical stromal invasion was related to PALN metastasis analyzed by univariate analyses, but was not an independent risk factor using multiple analyses [16]. Huang's study revealed that deep stromal invasion was not associated with PALN metastasis [14]. Our result is consistent with Huang's study. Controversy may be attributed to the varied definition of deep stromal invasion. Invasion to the outer third of cervical stromal was defined as deep stromal invasion in some studies [12, 30], while the outer half of cervical stromal was considered by other authors [14].

Upper canal invasion, which was mainly found in patients with endogenous tumors or large tumor size, was rarely condidered in previous studies. In the present study, upper canal invasion was showed to be an essential risk factor for PALN metastasis analyzed by multiple analyses. The reason needs to be determined in a further study.

Pelvic lymph node (PLN) involvement was a known risk factor of PALN metastasis [14, 16]. In the present study, multiple PLN metastases was an independent risk factor, which parallels with Sakuragi's study [16].

Imaging tests were the main methods to detect PALN metastasis preoperative. Previous studies revealed that the sensitivity of sonography, CT and MRI ranged from 19% to 34% [6, 10]. Our results showed the imaging (including sonography, CT and MRI) sensitivity was 36%, similar to previous reports. However, higher specificity was found in the present study (98.7%). Therefore, PALN dissection should be employed when suspicious PALN involvement has been

Figure 4. CT test for a patient with cervical caner in stage IB2. The red arrow is pointing to a para-aortic lymph node.

Figure 5. CT test for a patient with cervical caner in stage IB2. The red arrow is pointing to a para-aortic lymph node.

detected by imaging because of its low false negativity.

Grossly enlarged lymph nodes are more likely to contain metastasis than normally appearing nodes [31]. Some authors have suggested that PALN dissection should be omitted in the absence of enlarged PALN for early stage cervical cancer [32, 33]. However, the PPV of grossly enlarged lymph nodes is low to 13.9% in our study. Therefore, sizes of enlarged lymph nodes need to be defined in a future study. In addition, lymph node texture and margin should be taken into account.

Conclusions

Upper canal invasion, multiple PLN metastases and common iliac lymph node metastasis were

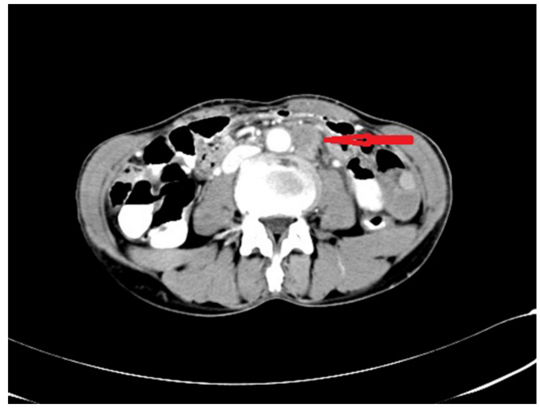

Figure 6. CT test for a patient with cervical caner in stage IIB. The red arrow is pointing to a para-aortic lymph node.

shown to be the significant risk factors of PALN metastasis in the present study. These results may provide useful information to select patients for performing PALN dissection in clinical practice, which extensive procedure was omitted for a large number of patients with stages IB, IIA and IIB cervical carcinoma. Nevertheless, those factors were diagnosed based on frozen section intro-operation, which may fail to detect micro metastasis [34]. We expect a new risk model combining pathology and imaging, which should be a more effective predictor of PALN metastases.

Disclosure of conflict of interest

None.

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