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Role of positron emission tomography in pretreatment lymph node staging of uterine cervical cancer: A prospective surgicopathologic correlation study

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Abstract

We evaluated the accuracy of FDG-PET in diagnosing metastatic para-aortic and pelvic lymph nodes in patients with cervical cancer by comparing this noninvasive imaging technique with surgicopathologic results. We performed FDG-PET in 54 patients with cervical cancer at FIGO stages IB–IVA who were about to undergo lymphadenectomy. For region-specific comparisons, we divided the nodes into eight regions (four on each side: para-aortic, common iliac, external iliac, and internal iliac/obturator). Histological examination revealed metastases in 15 (28%) of the patients, with region-specific analysis identifying 37 (8.6%) metastases in 432 regions. The region-specific findings of FDG-PET exhibited a sensitivity of 38% and a positive predictive value (PPV) of 56%. The sensitivity increased to 52% and 65% when we restricted the pathologic criterion for metastases to tumour-invasion diameters of >5 and >10 mm, respectively. These results indicate that FDG-PET exhibited low sensitivity and PPV (especially for microscopic metastases) and hence cannot replace surgical staging, although it might still be useful for detecting metastases in patients with clinical conditions that make surgical staging inappropriate.

Keywords: Cervical cancer; Positron emission tomography; FDG-PET; Lymph node staging; Surgical staging

1. Introduction

Cervical cancer is the second most frequently diagnosed cancer in women worldwide, and is the only major gynecologic malignancy that is clinically staged according to recommendations of the International Federation of Obstetrics and Gynecology (FIGO) [1]. Such clinical staging of cervical cancers is accurate in approximately only 60% of cases when compared with surgical staging [2]. Major errors are related to undiagnosed lymph node (LN) metastases, which are not included in the current FIGO classification [2,3]. Inaccurate assessment of LN involvement, which is the most important independent prognostic factor, leads to suboptimal treatment choices [4,5].

Lymphangiography, computed tomography (CT), and magnetic resonance imaging (MRI), have all been used in the radiological assessment of para-aortic and pelvic LNs in cervical cancer [7]. A meta-analysis of such studies concluded that all three methods exhibit only moderate sensitivity and specificity for the detection of metastases [7].

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More recently, positron emission tomography (PET) employing the glucose analog [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) has been shown to be more sensitive than CT or MRI in the detection of LN metastases in cervical carcinomas [8–10]. Only limited data are available on the correlation of FDG-PET findings with histologic evaluations of para-aortic and pelvic LNs, although most previous studies have reported promising results in the pretreatment LN staging of cervical cancer [8–10].

Surgical staging remains the most accurate procedure for evaluating LN metastases in deciding the most appropriate treatment modality. Conventional lymphadenectomy using a transperitoneal or extraperitoneal approach was used in the 1970s and 1980s to diagnose LN involvement, but the procedure was not widely accepted because of the associated morbidity and delay in the initiation of curative treatment [4,11,12]. Several recent trials have shown that laparoscopic para-aortic and pelvic lymphadenectomy is safe and effective for pretreatment surgical staging, causing no postoperative morbidity or delay in the initiation of curative treatment [13,14]. This procedure has become progressively more popular, especially for patients with locally advanced cervical cancers and a high probability of LN metastases.

Whilst minimally invasive approaches cannot equal noninvasive ones, we should choose noninvasive ones – such as FDG-PET – if their accuracy is comparable to that of surgical staging.

The aim of this prospective clinical trial was to evaluate the accuracy of FDG-PET relative to surgical staging in the detection of metastatic LNs in patients with cervical cancer and to assess the possibility of replacing the surgical procedure with FDG-PET.

2. Patients and methods

2.1. Study subjects

The inclusion criteria were as follows: the presence of untreated, histologically confirmed invasive cervical cancer of FIGO stages IB–IVA determined by a conventional workup that included an MRI scan; age 18–65 years; no contraindications to the surgical procedure; no evidence of distant metastases; an Eastern Cooperative Oncology Group performance status of 0 or 1; and provision of informed consent to participate in the trial. Those with small-cell carcinoma with no evidence of extrapelvic disease were included.

Patients were classified into two groups according to FIGO staging. The first group consisted of patients with stage IB1 or IIA disease (tumour size $\leqslant$4 cm) who were to receive conventional lymphadenectomy combined with radical hysterectomy via laparotomy. The second group consisted of patients with stage IB2 or $\geqslant$IIB who were to receive chemoradiation preceded by laparoscopic para-aortic and pelvic lymphadenectomy. The Institutional Review Board of National Cancer Center approved the trial.

2.2. Conventional staging work-up

After histological confirmation of invasive cervical cancer, the FIGO stage was determined by bimanual pelvic examination, cystoscopy, and sigmoidoscopy. Except where it had been performed previously at another hospital ($n = 3$), an MRI scan of the pelvis and abdomen was performed using a 1.5-T whole-body scanner (General Electric Medical System, Milwaukee, WI, USA) with both pelvic and body coils. We considered an LN to be metastatic when its maximum transverse diameter was >1 cm [15].

2.3. Classification of LN regions

We divided the para-aortic and pelvic LNs into eight regions according to anatomic landmarks (four on each side: para-aortic, common iliac, external iliac, and internal iliac/obturator) (Fig. 1).

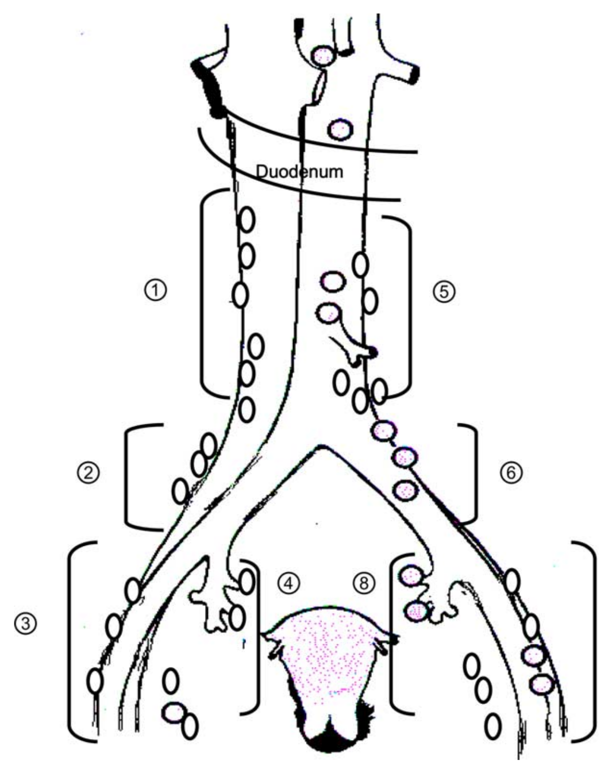

Fig. 1. Classification of para-aortic and pelvic lymph nodes regions: (1) right para-aortic; (2) right common iliac; (3) right external iliac; (4) right internal iliac and obturator; (5) left para-aortic; (6) left common iliac; (7) left external iliac, and (8) left internal iliac and obturator LNs.

2.4. FDG-PET

We used a dedicated whole-body PET scanner (Advance, GE Medical Systems, Milwaukee, WI, USA) with a radial spatial resolution of 5.2 mm (full width, half maximum), a tangential spatial resolution of 4.8 mm (full width, half maximum), and a 15.3 cm axial field of view. All patients were instructed to fast for at least 8 h prior to the injection of the FDG. Image acquisition for the whole-body scan started at a mean of 60 min after intravenous administration of 370–555 MBq (10–15 mCi) of FDG. The emission scan progressed from the proximal femur to the neck at 5 min per frame. We performed post-injection transmission scans at 3 min per frame. We collected data in a 128×128 matrix and performed segmented attenuation correction on the post-injection transmission image. We reconstructed the corrected post-injection transmission image using an iterative ordered-subsets expectation–maximization algorithm. If indicated, we obtained additional pelvic scans after the patient voided. Two specialists in nuclear medicine with 5 and 7 years of PET experiences (K.W.K. and S.-K.K., respectively) evaluated the images qualitatively for regions of focally increased glucose metabolism and quantitatively by determining standard uptake values (SUVs) [16]. We characterized malignancy as an increase in glucose uptake relative to the surrounding tissue and an SUV of more than 2.5.

2.5. Histopathologic evaluation

We used histopathological evaluation of the LNs as the diagnostic standard. Thin sections were cut, stained with hematoxylin and eosin, and examined microscopically by a pathologist. Every LN was sliced at 2 mm intervals perpendicular to the longest diameter to minimize the chance of missing micrometastases. We recorded the total number of LNs harvested in each region and the largest diameter of each node. Tumour invasions with the largest diameter were found to occur in metastatic foci.

2.6. Statistical analysis

We compared the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) between FDG-PET and surgicopathology using SPSS software (version 11.0).

3. Results

3.1. Clinical characteristics of the subjects

Between May 2002 and August 2003, 58 patients with newly diagnosed invasive cervical cancer were enrolled in this trial. Four patients were excluded from the study following FDG-PET scanning for the following reasons: a biopsy-confirmed supra-clavicular LN metastasis ($n = 1$), a major medical problem (paroxysmal nocturnal hematuria, $n = 1$), and an aborted laparoscopic lymphadenectomy due to severe intra-abdominal adhesions ($n = 2$). Table 1 lists the clinical characteristics of the remaining 54 patients, who ranged in age from 22 to 65 years (mean = 46 years). FDG uptake was evident for all primary tumours except for those in two patients who had previously received diagnostic conization of the cervix.

Table 2 lists the rate of LN metastases according to clinical stage, and Table 3 lists the rate determined by surgicopathology. The two approaches did not differ significantly in the mean number of LNs harvested per patient, although significantly more para-aortic LNs were obtained by laparoscopy than by laparotomy. Metastasis was most common in the internal iliac and obturator LNs (Table 4).

3.2. Data analysis

Table 5 lists the sensitivity, specificity, PPV, and NPV for para-aortic and pelvic LNs. In the region-specific

Table 1
Clinical characteristics of the 54 patients in the study

Characteristic	Number of patients (%)
Histologic type	
Squamous cell carcinoma	43 (80)
Adenocarcinoma	8 (15)
Small cell carcinoma	3 (5.6)
FIGO stage	
IB1	19 (35)
IB2	5 (9.3)
IIA	5 (9.3)
IIB	23 (43)
IIIB	2 (3.7)
Method of surgical staging	
Laparotomy	24 (44)
Laparoscopy	30 (56)

FIGO, International Federation of Gynecology and Obstetrics.

Table 2
Positive rate for LN metastases according to clinical stage of the 54 patients

Cervical cancer stage (n)	% Pelvic LN (n)	% Para-aortic LN (n)	% Total
Early (29)	14 (4)	0	14
IB1 (19)	11 (2)	0	11
IB2 (5)	20 (1)	0	20
IIA (5)	20 (1)	0	20
Locally advanced (25)	44 (11)	8 (2)	44
IIB (23)	39 (9)	4 (1)	39
IIIB (2)	100 (2)	50 (1)	100
Total (54)	28 (15)	3.7 (2)	28

Table 3
Surgicopathologic characteristics of LNs

Characteristic	Value
Total no. of LNs harvested	1926
Para-aortic	429
Pelvic	1507
No. of metastatic LNs (%)	67 (3.5)
Para-aortic	5 (1.2)
Pelvic	62 (4.1)
Mean no. of LNs harvested per patient (range)	35.7 (16–68)
Via laparotomy (24 patients)	33.5 (16–68)
Para-aortic	6.6 (0–20)[a]
Pelvic	27.3 (12–51)
Via laparoscopy (30 patients)	37.4 (24–52)
Para-aortic	9.0 (3–19)[a]
Pelvic	28.4 (16–46)
No. (%) of regions with metastatic LNs on eight-region analysis ($n = 432$)	37 (8.6)
Para-aortic ($n = 108$)	3 (2.8)
Pelvic ($n = 324$)	34 (10.5)
No. (%) of metastatic regions ($n = 37$) with maximum lesion diameters	
⩽5 mm	12 (32)
6–10 mm	5 (14)
>10 mm	20 (54)

LN, lymph node.
[a] Statistically significant difference ($P = 0.045$).

Table 4
Regional distribution of metastatic LNs ($n = 432$)

LN region	No. of metastatic regions (%)
Right para-aortic	2 (0.5)
Right common iliac	4 (0.9)
Right external iliac	4 (0.9)
Right internal and obturator	8 (1.9)
Left para-aortic	1 (0.2)
Left common iliac	3 (0.7)
Left external iliac	6 (1.4)
Left internal iliac and obturator	9 (2.1)
Total	37 (8.6)

LN, lymph node.

analysis, the overall sensitivity of FDG-PET in the detection of LN metastases (37.8%) increased considerably when the criterion for metastasis was restricted to tumour-invasion diameters of >5 mm (52.0%) and >10 mm (65.0%). Because the predictive value of the diagnostic method might depend on the frequency or incidence of the events (*i.e.* positive metastases), we assessed the efficacy of FDG-PET in detecting LN metastases only in patients with locally advanced cervical cancers (FIGO stage IIB–IVA). We found that the sensitivity for all LN metastases and for those >10 mm was somewhat larger than that for all stages in the region-specific analysis (Table 5).

4. Discussion

To our knowledge this is the first prospective, region-specific, surgicopathologic analysis covering all the stages and all the LN regions related to the management and prognosis of cervical cancer. Although other types of studies have indicated the potential utility of FDG-PET in evaluating LN metastases, our results showed FDG-PET to be of limited value – perhaps because, unlike other studies, our study correlated the FDG-PET findings with surgicopathology data [8,9,17,18]. Rose and colleagues reported that FDG-PET scanning

Table 5
Accuracy of FDG-PET for detecting metastatic LNs on region-specific analysis[a]

Measure of accuracy	For all patients ($n = 54$)%	For patients with stage IIB–IVA ($n = 25$)%
All pathology-confirmed LN metastases		
Sensitivity	38	43
Specificity	97	95
PPV	56	57
NPV	94	91
For metastasis diameter >5 mm[b]		
Sensitivity	52	52
Specificity	97	94
PPV	52	52
NPV	97	94
For metastasis diameter >10 mm[b]		
Sensitivity	65	69
Specificity	97	95
PPV	54	52
NPV	98	97

LN, lymph node; PPV, positive predictive value; NPV, negative predictive value.
[a] Region-specific analysis using eight matched regions of LNs in each patient (four on each side: para-aortic, common iliac, external iliac, and internal iliac/obturator). $n = 432$.
[b] Maximum diameter of histologic tumour invasion in an LN.

exhibited a sensitivity of 75% and a PPV of 75% for para-aortic metastases in locally advanced cancer, and other investigators have reported sensitivities of 70–91% and PPVs of 86–100% for pelvic nodal status in early stage of disease [9,18].

Several factors could explain the discrepancies between our study and previous ones. First, we examined transverse slices at 2 mm intervals, whereas LNs are conventionally examined in only one or two longitudinal sections. Thus, we may have detected metastases that conventional techniques missed. Belhocine and colleagues [18] reported that FDG-PET imaging missed 8 (80%) out of 10 pelvic nodal metastases that were <10 mm in diameter, whereas FDG-PET detected only 1 (6%) of 17 such metastases in our study. Second, the range and the completeness of surgical staging differed between studies. Previous studies did not perform systematic surgical staging for all cases. For example, para-aortic LN dissection was not performed in many cases of early stage cervical cancer [9], and sometimes only para-aortic lymphadenectomy was performed in advanced-stage cases. This may have resulted in fewer false negative and false-positive results in the present study. Additionally, relative few LNs obtained from lymphadenectomies performed in other studies (*e.g.* 11 in [18]), whereas previous studies suggest that at least 20 LNs are required for pelvic nodal staging [19,20]. Third, in contrast to other studies, we analysed our data by region, although this probably had little effect on the sensitivity given that our data were only slightly improved when the LNs were regrouped into three regions (para-aortic, right pelvic, and left pelvic) (data not shown). Thus, it is likely that the limitation of FDG-PET scanning are attributable to its poor sensitivity rather than to poor anatomic resolution.

The PPV of FDG-PET was also disappointing, in contrast with previous reports of good results. We thought that the predictive value might depend on the frequency or incidence of metastases as well as on the sensitivity and specificity of the test itself, but when we restricted the analysis to advanced-stage cases, the results were still unsatisfactory. A high false-positive rate might reflect the presence of reactive hyperplasia in LNs, and we did indeed find this in all our false-positive LNs. In summary, FDG-PET exhibits low sensitivity and PPV in the detection of metastatic LNs in cervical cancer, especially when micrometastases are involved.

For reference, we evaluated the accuracy MRI in evaluating LN status in the same patients. In the region-specific analysis, overall sensitivity for the MRI-based detection of LN metastases was 32.0%, and the sensitivity increased to 42.9% and 54.5% when we restricted the criterion for metastases to a tumour-invasion diameter of >5 and >10 mm, respectively. Thus, the ability of MRI to detect LN metastases was slightly worse than that of FDG-PET and substantially worse than that reported in previous studies [6,15]. The possible explanations are the same as those for FDG-PET.

According to Stehman and colleagues [21], who performed a multivariate analysis of prognostic factors that included patient age, tumour stage, tumour size, and LN status, positive LNs – especially para-aortic nodes – were the most significant predictor of recurrence or death, overwhelming all other risk factors. Clinical staging of cervical carcinoma based on imaging methods such as CT or MRI has been suboptimal in detecting metastases to LNs. Several studies have found that a subset of patients with early clinical stage and nodal metastasis exhibit reduced 5-year survival rates (of 45–55%) [22,23]. It might be better to treat patients with early clinical stages and nodal metastases with chemoradiation rather than surgery, but accurate information on the presence of metastases would be needed before making that decision. In the present study, 4 out of 29 patients who had received a radical hysterectomy exhibited nodal metastases. A pretreatment diagnosis could have avoided the use of surgery, allowing the patients to be treated in another way. Laparoscopic lymphadenectomy and confirmation of nodal status by frozen biopsy before hysterectomy would be the ideal for selecting those patients who are suitable for alternative treatments to chemoradiotherapy.

For locally advanced cervical cancer, conventional whole-pelvic external irradiation plus brachytherapy might control tumours still confined to the pelvis but not those that have spread. Nodal metastases, especially those in the para-aortic LN, are associated with the worst prognosis in patients treated with primary radiation [21]. Prophylactic extended-field radiotherapy has been used in locally advanced cervical cancer, but no conclusive improvement in survival rate is associated with the increased morbidity [24,25]. Ideally, extended-field radiotherapy should be given only to those with documented para-aortic LN metastases [26]. Although pretreatment staging by conventional laparotomy may be associated with an unacceptable rate of surgical morbidity, long-term radiation morbidity, and delay of definitive treatment, several groups using laparoscopic surgical technique have performed retroperitoneal lymphadenectomy with minimal morbidity and no delay in definitive treatment [13,14].

Even if accurate information for irradiation planning could be acquired, a survival benefit of pretreatment surgical staging for locally advanced cervical carcinoma remains unproven. Many retrospective studies suggest that pretreatment staging could provide a survival benefit via the debulking of macroscopically positive LNs [27,28]. However, in the only published prospective randomized trial, Lai and colleagues [29], reported that patients subjected to surgical staging had significantly worse progression-free survival rates than those who did not receive a pretreatment lymphadenectomy. Nevertheless, several factors pointed out by those authors should be considered. First, more adenocarcinomas, adenosquamous carcinomas, stage IIIB disease and patients with grossly abnormal pelvic LNs (as detected by imaging) were included in the surgical staging group. Second, the time to the start of radiotherapy in the cases subjected to surgical staging was significantly longer (median, 20 days; range 10–46) than in the other cases. With a laparoscopic technique, treatment of all patients in our trial could be started within a week (median 5 days). Delaying radiotherapy after surgical staging might be deleterious for advanced-stage patients. Third, the average number of LNs from surgical staging was much lower (pelvic LNs, 11.6; para-aortic LNs, 6.0) than in our study (pelvic LNs, 29.1; para-aortic LNs, 8.9). For "complete staging", Vidaurreta and colleagues [14] recommend that physicians examine an acceptable number of pelvic LNs, identify intraperitoneal disease, and determine the status of the vesicocervical and rectovaginal septums and parametrial involvement. Some investigators suggest that the minimum number of pelvic LNs needed for reliable staging is 20 [19,20]. Therefore, the surgical staging in the study of Lai and colleagues might have been insufficient for accurate planning of the irradiation field.

The FDG-PET results were unsatisfactory in the present study, but they were slightly better than the MRI results, suggesting that FDG-PET could be helpful in the evaluation of patients with major medical problems and at a high risk for nodal metastases. Integrated PET and CT scanning has been recently applied to LN staging in lung cancer, and the encouraging initial results have been superior to those of PET scanning alone [30].

We are now planning another prospective trial designed to evaluate the diagnostic accuracy of integrated PET-CT for nodal staging.

Conflict of interest statement

None declared.

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