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ORIGINAL RESEARCH

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Preoperative imaging with positron emission tomography and computed tomography (^{18}F-FDG PET/CT) or contrast-enhanced computed tomography (CECT) scan in operable cervical cancer: a prospective study

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Abstract

We evaluated the accuracy of preoperative PET/CT and CECT for lymph node staging in cervical cancer, which is relevant in the context of recently revised staging. Patients with International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IB1–IB2 cervical cancer underwent preoperative ^{18}F-FDG PET/CT and CECT abdomen and pelvis. Lymph nodes in various anatomical stations (paraaortic, various right and left pelvic regions) were scored separately as involved or not involved on both imaging modalities and compared with histopathology. The sensitivity and specificity of PET/CT and CECT were estimated for each lymph node station, and all lymph node stations combined, per patient. The study population comprised 57 patients (stage IB1 37, IB2 19) with median age of 45 (32–64) years, 39 (68.7%) with squamous carcinoma, median tumor size of 3.1 (0.5–9.0) cm, mean (range) lymph node harvest of 23.5 (8–46), and 13 (22.8%) patients with histopathologically positive lymph node(s). The sensitivity and specificity of PET/CT for various pelvic lymph node stations were 22.2–100% and 96.3–100%, respectively, and of CECT were 22.2–100% and 96.2–100%, respectively. At patient level, for all lymph node stations combined, the sensitivity and specificity of PET/CT and CECT were 53.9% (95% confidence interval (CI), 26.8%–80.9%) and 90.5% (95% CI, 81.6%–99.4%), and 69.2% (95% CI, 44.1%–94.3%) and 95.0% (95% CI, 88.3%–100%), respectively. Primary tumor maximum standardized uptake value (SUVmax) was the only independent prognostic factor for overall survival. The sensitivity of PET/CT and CECT for lymph node staging in operable cervical cancer is modest, and these modalities can miss lymph node involvement, but they have high specificity and, when indicative of lymph node involvement, may be clinically useful in triaging patients for primary chemoradiation therapy.

Keywords

Early cervical cancer; Imaging; PET/CT; CECT

1. Introduction

Cervical cancer is the fourth most common cancer in women globally [1]. Radical surgery is the preferred treatment for early-stage disease, while concurrent chemoradiation (CTRT) is the standard of care for advanced-stage disease. Metastasis to pelvic and/or paraaortic lymph nodes is the most important prognostic factor for survival and has been assigned stage IIIC in the revised International Federation of Gynecology and Obstetrics (FIGO) 2018 staging classification [2]. Detection of lymph node metastasis in the surgical specimen after radical surgery is an indication for adjuvant concurrent chemoradiation[3] and exposes the patient to triple-modality treatment, which can cause toxicity without survival advantage over definitive concurrent chemoradiation. Therefore, preoperative knowledge of lymph node status in patients with clinically operable cervical cancer can help to triage patients for optimum treatment and help avoid surgery in patients with lymph node metastasis.

The sensitivity of contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) for the identification of involved lymph nodes in patients with early-stage cervical cancer has been reported to be variable and ranges from 31–58% and 37–71%, respectively [4]. Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET) is a functional imaging modality based on the increased glucose metabolism in cancer cells and has the potential to detect smaller lymph node metastasis which may be missed by CECT or MRI. Fused PET/CT improves

anatomical localization of functional abnormalities detected by PET scan and is preferred over PET alone.

Several studies have shown the superiority of PET/CT over CECT or MRI for the identification of metastatic pelvic and paraaortic nodes in patients with advanced-stage cervical cancer [5–8]. However, similar accuracy of PET/CT has not been found in early-stage disease [9–16], and its role and advantage over CECT or MRI in these patients remains to be proven. Therefore, we undertook this prospective study to evaluate the diagnostic performance and utility of PET/CT and CECT for the detection of pelvic and paraaortic lymph node metastasis in patients with clinically operable cervical cancer, comparing both modalities to pathology evaluation of surgically removed lymph nodes.

2. Materials and methods

The primary objective of the study was to evaluate the sensitivity, specificity, and predictive values of ^{18}F-FDG PET/CT and CECT for detection of pelvic and paraaortic lymph nodes in patients with early-stage cervical cancer, using histopathological evaluation of surgically removed nodes from various anatomical locations as the gold standard. The secondary objective was to study various prognostic factors for overall survival in these patients.

2.1 Study Population

This prospective, observational study was initiated after obtaining approval from the institutional ethics committee. Fifty-seven patients with operable cervical cancer (FIGO (2008) stage IA–IB2) who were planned for radical surgery at our centre were recruited into the study after obtaining written informed consent. Patients with contraindications to ^{18}F-FDG PET/CT or CECT or those with a history of second primary malignancy were excluded from the study.

2.2 Imaging protocol

A whole body ^{18}F-FDG PET/CT and CECT of the abdomen and pelvis was performed within two weeks of the scheduled date of surgery. ^{18}F-FDG PET/CT was performed on a GE Discovery STE^{18}F-FDG PET/CT scanner (GE Healthcare, Waukesha, WI, USA). After 6–8 hours of fasting, patients were given an intravenous injection of ^{18}F-FDG (5 MBq/kg body weight) and were encouraged to rest. Within 45–60 minutes of ^{18}F-FDG injection, sequential imaging CT followed by PET was performed from the base of the skull to mid-thigh. Images were read in PET, CT and fusion modes. CT scan acquisition parameters included display field of view (DFOV) 70 cm, kV 120, and mA 80–200 (auto mA). The slice thickness was 3.75 mm interval with 3.75 mm pitch. The filtered back projection was used for reconstruction with matrix 512 × 12 and the CT-based attenuation correction (CTAC) algorithm was used for attenuation correction. PET scan was acquired at 2 minute/bed position in 3D mode with iterative reconstruction, using matrix 128 × 128, subset 21, iteration 2, Z-filter and standard attenuation correction with CTAC, and scatter and random correction based on stored correction matrix. A maximum standardized uptake value (SUV) of more than 2.5 g/mL based on body weight was considered as positive in the present study.

CECT scan of the abdomen and pelvis was performed after administration of oral and intravenous contrast. Pelvic and retroperitoneal nodes were considered involved if the size was greater than or equal to 1 cm in the short axis. Nodes smaller than 1 cm in size were considered involved if they showed irregular margins and the presence of necrosis. ^{18}F-FDG PET/CT and CECT examinations were done sequentially, and two specialist consultants independently reported the results. Lymph nodes were reported in seven anatomical groups in both scans according to their locations in relation to major blood vessels: right and left internal iliac/obturator, right and left external iliac, right and left common iliac and low paraaortic. Lymph nodes parallel or ventral to the external iliac artery were labelled as external iliac while those dorsal to the external iliac artery or in relation to the internal or obturator artery were classified as the internal iliac/obturator.

2.3 Surgical Technique

All patients underwent open surgery. Bilateral common iliac, external iliac, and internal iliac-obturator lymph nodes dissection were done irrespective of imaging and intra-operative findings. Low paraaortic lymph node dissection was done if either preoperative pelvic and/or paraaortic lymph node involvement was found on imaging (CECT and/or PET-CT) or there were intra-operative enlarged pelvic and/or paraaortic lymph nodes or intra-operative frozen section showed lymph node involvement. Dissected lymph nodes were labelled as per their anatomical location and sent separately for histopathological examination. The final histopathology report on paraffin-embedded tissue was considered the gold standard for calculating the diagnostic accuracy of preoperative scans.

2.4 Histopathological evaluation

At the grossing table, the entire tissue was removed from its container and dimensions were measured. A careful search for lymph nodes was done by palpation and dissection. All nodes that could be palpated were put in cassettes. The number of nodes from each anatomical location was mentioned and all were examined in their entirety unless grossly involved by tumor. Lymph nodes up to 5 mm were put directly in cassettes. The histopathology reporting of lymph nodes included total number, the number involved by tumor, size of metastasis, presence of peri-nodal extension, and presence of any other pathology *(e.g.*, granuloma). These details were reported separately for each nodal station. Ultra-staging and immunohistochemistry were not performed.

2.5 Adjuvant Treatment and follow-up

Adjuvant concurrent chemoradiation was administered to patients with any one of the following three findings: positive lymph nodes, disease in parametrium, or positive surgical margin(s). The radiation field was extended to cover the paraaortic region in patients with paraaortic lymph node involvement. Adjuvant pelvic radiation was given to patients with any two of the following three findings: deep stromal invasion, tumor size of more than 4 cm, or lymph vascular space invasion. After

completion of treatment patients were followed up once every 3 months for the first two years, once every 6 months for the next three years, and annually after 5 years.

2.6 Statistical Analysis

The sensitivity, specificity, and accuracy (with their respective 95% confidence intervals) of ^{18}F-FDG PET/CT and CECT in the diagnosis of paraaortic and pelvic lymph node metastases were calculated as per pre-defined anatomical stations as well as on per patient basis. A true-positive (TP) scan report was defined as any lymph node in that anatomical station positive for metastasis on imaging and confirmed by histology. A false-positive (FP) report was defined as imaging suggestive of any lymph node involvement in an anatomical location but no lymph node within that station positive on histology. A true-negative (TN) report was defined as an imaging result not suggestive of any involved lymph node within an anatomical station confirmed by pathology evaluation, while a false-negative (FN) report was imaging not suggestive of any involved lymph node within an anatomical station but pathology evaluation showing positive node within that location. The sensitivity, specificity, false positive and false negative rates of ^{18}F-FDG PET/CT and CECT were also calculated on a per patient basis. At the patient level, true positive and true negative cases were defined as all lymph node stations being concordant between imaging and pathology, while any discordance was classified as a false positive or false negative, as appropriate.

Overall survival (OS), defined as the time interval between study enrolment and death due to any cause, was estimated using the Kaplan-Meier method, and patients who were alive at the time of analysis were censored. The effect of the following prognostic factors on OS was evaluated by univariable analysis and comparison between categories was performed using the log-rank test: age, FIGO (2008) stage, lymph vascular space invasion (LVSI), lymph node metastasis, histological subtype, and SUVmax. The Cox proportional hazards model was used to perform a multivariable analysis of these prognostic factors. We also evaluated any association between tumor characteristics and SUVmax by comparing the mean SUVmax between categories using the unpaired '*t*' test. All analyses were performed using SPSS Statistics for Windows version 20.0 (SPSS inc., Chicago, IL, USA).

A sample size of 57 produces a one-sided 95% lower-limit confidence interval of 10% when the target overall sensitivity of PET-CT is 85.0%.

3. Results

A total of 57 patients with early-stage -cervical cancer planned for surgery were included in the study from April 2007 to March 2010. ^{18}F-FDG PET/CT and CECT could not be done in 2 and 4 patients, respectively. Table 1 shows the baseline characteristics of patients. The median age of patients was 45 years, the median primary tumor size was 3.1 cm, and more than two-thirds of tumors were of squamous histology. The mean standard uptake value maximum (SUVmax) of the primary tumor was 9.7 (range: 0–26). All included patients were taken up for surgery, including protocol-defined lymphadenectomy, but radical hysterectomy was abandoned in 7 (12.28%) patients due to detection of positive lymph nodes on frozen section examination. Low paraaortic lymph nodal dissection was performed in 44 (77.2%) patients. A total of 1340 lymph nodes were submitted for histopathological evaluation with a mean of 23.5 (range: 8–46) lymph nodes per patient. Lymph node metastases were identified in 13 of 57 (22.8%) patients and in 25 of 386 (6.8%) lymph node stations studied. Granulomatous involvement was not seen on pathological evaluation in any lymph node. Of the 57 patients in our cohort, 7 (12.3%) patients underwent definitive chemoradiation because their surgery was abandoned, 6 (10.5%) patients received postoperative adjuvant chemoradiation, and 12 (21.1%) patients received postoperative adjuvant radiotherapy.

3.1 Diagnostic performance of ^{18}F-FDG PET/CT and CECT: Lymph node region-specific analysis

Table 2 shows lymph node region-specific diagnostic performance of ^{18}F-FDG PET/CT and CECT. Three patients had low para-aortic lymph node metastases on pathology, of whom none was picked up by either modality resulting in 0% sensitivity for this region. For pelvic lymph node stations (common iliac, external iliac, internal iliac), the ranges of sensitivity and specificity of ^{18}F-FDG PET/CT were 22.2% to 100% and 96.4% to 100%, respectively, while the sensitivity and specificity of CECT were 22.2% to 100% and 95.5% to 100%, respectively. The diagnostic performance of both imaging modalities by lymph node region with right and left sides combined is shown in **Supplementary Table 1**.

3.2 Diagnostic performance of ^{18}F-FDG PET/CT and CECT: Patient level analysis.

Table 3 shows the per-patient analysis. Overall, ^{18}F-FDG PET/CT and CECT showed discordance with pathology evaluation of lymph nodes in 12 and 7 patients, respectively. The sensitivity, specificity, false negative and false positive rates for ^{18}F-FDG PET/CT were 53.9%, 90.5%, 14.6% and 7.3%, respectively, while the corresponding values for CECT were 69.2%, 95.0%, 9.4% and 3.8%, respectively.

3.3 Survival analysis

At a median follow-up of 81.2 months in surviving patients, the 5-year overall survival was 85.0% (95% confidence interval (CI) 74.6%–95.4%) (Fig. 1). On univariable and multivariable analyses, SUV max of the primary tumor was the only significant factor affecting overall survival while age, primary tumor size, depth of stromal invasion, LVSI, lymph node metastasis, and histologic subtype were not found to be significant (Table 4).

3.4 Association between SUVmax and clinical/pathological parameters

We evaluated the association of SUVmax of the primary tumor with clinical and pathological variables as shown in Table 5. The mean SUVmax was significantly higher in patients with

TABLE 1. Baseline Characteristics.

		Number (%)
Age		
Median (range)		45 years (32–64)
Stage		
IB1		38 (66.7%)
IB2		19 (33.3%)
Tumor size		
Median (range)		3.1 cm (0.5–9)
Histology		
	Squamous cell carcinoma	39 (68.4%)
	Adenocarcinoma carcinoma	13 (22.8%)
	Adeno-squamous carcinoma	03 (5.3%)
	Others	02 (3.6%)
Mean lymph node number/patient (range)		23.5 (8–46)
Histological lymph node status		
	Pelvic Positive	10 (17.5%)
	Pelvic & Paraaortic Positive	2 (3.5%)
	Paraaortic Positive	1 (1.8%)
	Negative	44 (77.2%)
Depth of stromal invasion (N = 50)		
	Up to half	17 (34%)
	More than half	33 (66%)
Lympho-vascular space invasion (N = 50)		
	No	33 (66%)
	Yes	17 (34%)
Maximum standardized uptake value (SUVmax), primary tumor		
Mean (range)		9.7 (0–26)

lympho-vascular invasion, deep stromal invasion, and lymph node metastasis.

4. Discussion

This prospective, observational study of ^{18}F-FDG PET/CT and CECT for preoperative detection of lymph node metastases in patients with FIGO (2009) stages IB1 to IB2 cervical cancer, who were treated with radical surgery, suggests that both modalities provide useful information for preoperative therapeutic decision making in this setting. The modest patient-level sensitivity of both modalities for detection of lymph node metastases, combined with their low false positive rates, has the potential to appropriately triage many patients to surgery or concurrent chemoradiation (CTRT). To illustrate, a little under one-fourth (22.8%) of our patients with FIGO stage IB1-IB2 disease had pathologically proven lymph node metastases, of whom CECT correctly picked up 69.23% (15.8% of all patients). These patients could be confidently offered CTRT instead of surgery, given the 3.8% false positive rate with this modality. The results of a recent randomized trial, wherein a substantial minority of patients with FIGO 2009 stage IB2 disease had to receive postoperative adjuvant radiotherapy or CTRT in a cohort of patients not staged by either ^{18}F-FDG PET/CT or CECT [17], further attest to the utility of preoperative staging with either modality. The low false positive rates in our study with both modalities should allay apprehensions that a high incidence of infections such as tuberculosis in developing countries could interfere with the interpretation of results. However, low paraaortic lymph node involvement was missed by both modalities in all three patients in whom it was present. The probable explanation for this low sensitivity for paraaortic lymph node metastasis is that in early-stage cervical cancer paraaortic lymph node involvement is often of small volume and can be missed by imaging. High false negative results with PET/CT and CE-CT in paraaortic lymph node metastasis may result in potential under-treatment in these patients.

Our results also suggest that ^{18}F-FDG PET/CT does not have superior clinical utility compared to conventional CECT scan in choosing the most suitable treatment in patients with potentially operable early cervical cancer. Although there was an overlap between ^{18}F-FDG PET/CT and CECT with respect to the 95% confidence intervals of their sensitivities and false

TABLE 2. Metastatic Lymph Node Detection on CECT and ^{18}F-FDG PET/CT: Region-Specific Analysis.

	Contrast-enhanced computed tomography (CECT) scan*			Fluorodeoxyglucose F-18 positron emission tomography and computed tomography (^{18}F-FDG PET/CT)*		
Lymph node Group	Sensitivity TP/(TP + FN)† (95% confidence interval (CI))	Specificity TN/(TN + FP)† (95% CI)	Accuracy (TP + TN)/(TP + TN + FN + FP)† (95% CI)	Sensitivity TP/(TP + FN)† (95% CI)	Specificity TN/(TN + FP)† (95% CI)	Accuracy (TP + TN)/(TP + TN + FN + FP)† (95% CI)
Paraaortic lymph node	0/3 0% (95% CI 0–70.8%)	35/36 97.3% (95% CI 85.8–99.9%)	36/40 90% (95% CI 76.3–97.2%)	0/3 0% (95% CI 0–70.8%)	39/39 100% (95% CI 91.0–100%)	39/42 92.9% (95% CI 80.5–98.5%)
Right common iliac lymph node	2/3 66.7% (95% CI 9.4–99.2%)	50/50 100% (95% CI 92.9 –100%)	52/53 98.1% (95% CI 89.9–99.95%)	3/3 100% (95% CI 29.2–100%)	51/52 98.1% (95% CI 89.7– 99.95%)	54/55 98.2% (95% CI 90.3–99.95%)
Left common iliac lymph node	1/1 100% (95% CI 2.5–100%)	52/52 100% (95% CI 93.2–100%)	53/53 100% (95% CI 93.3–100%)	1/1 100% (95% CI 2.5–100%)	52/54 96.3% (95% CI 87.3–99.6%)	53/55 96.4% (95% CI 87.5%–99.6%)
Right external iliac lymph node	0/0 Not estimable	51/53 96.2% (95% CI 87.0–99.5%)	51/53 96.2% (95% CI 87.0–99.5%)	0/0 Not estimable	55/55 100% (95% CI 93.5–100%)	55/55 100% (95% CI 93.5–100%)
Left external iliac lymph node	2/4 50% (95% CI 6.8–93.2%)	48/49 97.96% (95% CI 89.2–99.95%)	50/53 94.3% (95% CI 84.3–98.8%)	1/4 25% (95% CI 0.6–80.6%)	50/51 98.0% (95% CI 89.6–99.95%)	51/55 92.7% (95% CI 82.4–97.98%)
Right internal iliac lymph node	2/9 22.2% (95% CI 2.8–60.0%)	42/44 95.5% (95% CI 84.5–99.4%)	43/52 82.7% (95% CI 69.7–91.8%)	2/9 22.2% (95% CI 2.8–60.0%)	44/45 97.8% (95% CI 88.2–99.9%)	47/55 85.5% (95% CI 73.3–93.5%)
Left internal iliac lymph node	2/5 40.0% (95% CI 5.3–85.3%)	45/47 95.7% (95% CI 85.546–99.5%)	47/52 90.4% (95% CI 78.97–96.8%)	2/5 40% (95% CI 5.27–85.3%)	49/49 100% (95% CI 92.8–100%)	51/54 94.4% (95% CI 84.6–98.8%)

***** *^{18}F-FDG PET/CT and CECT could not be done in 2 and 4 patients, respectively.*

† *TP = true positive, FN = false negative, TN = true negative, FP = false positive.*

TABLE 3. Metastatic Lymph Node Detection by CECT and ^{18}F-FDG PET/CT: Patient level analysis.

	Fluorodeoxyglucose F-18 positron emission tomography and computed tomography (^{18}F-FDG PET/CT)	Contrast-enhanced computed tomography (CECT)
Sensitivity	7/13 (53.9%, 95% confidence interval (CI) 26.8%–80.9%)	9/13 (69.2%, 95% CI 44.1%–94.3%)
Specificity	38/42 (90.5%, 95% CI 81.6%–99.4%)	38/40 (95.0%, 95% CI 88.3%–100%)
Positive predictive value (PPV)	7/11 (63.6%, 95% CI 35.2–92.1%)	9/11 (81.8%, 95% CI 59.0–100%)
False negative	8/55 (14.6%, 95% CI 5.2%–23.9%)	5/53 (9.4%, 95% CI 1.6%–17.3%)
False positive	4/55 (7.3%, 95% CI 0.4%–14.1%)	2/53 (3.8%, 95% CI 0%–8.9%)
Negative predictive value (NPV)	38/44 (86.4%, 95% CI 76.2–96.5%)	38/42 (90.5%, 95% CI 81.6–99.4%)

TABLE 4. Univariable and multivariable analysis of prognostic factors for overall survival.

Factor	Univariable 5-year overall survival (OS), (*p* value)	Multivariable hazard ratio (HR), 95% confidence interval (CI), *p* value
Age (continuous variable, every unit increase)	-	HR 1.04 (95% CI 0.93–1.16) $p = 0.48$
Stage IB2 (N = 38) *vs.* IB1 (N = 19)	80.0% *vs.* 86.9% ($p = 0.42$)	HR 1.79 (95% CI 0.07–45.89)
Histopathology non-squmous (N = 18) *vs.* squamous (N = 39)	72.9% *vs.* 91.1% ($p = 0.15$)	HR 2.53 (95% CI 0.30–21.60) $p = 0.40$
SUVmax >9.7 (N = 27) *vs.* ≤9.7 (N = 28)	72.8% *vs.* 95.0% ($p = 0.031$)	HR 1.19 (95% CI 1.00–1.42) $p = 0.05$
Lymph node involved (N = 13) *vs.* Not involved (N = 44)	72.2% *vs.* 88.5% ($p = 0.16$)	HR 1.33 (95% CI 0.06–28.80) $p = 0.86$
Depth of stromal invasion >half (N = 33) *vs.* ≤ half (N = 17)	85.4% *vs.* 84.4% ($p = 0.97$)	HR 0.77 (95% CI 0.09–6.51) $p = 0.81$
Lympho-vascular space invasion present (N = 17) *vs.* absent (N = 33)	87.1% *vs.* 84.0% ($p = 0.88$)	HR 0.46 (95% CI 0.06–3.85) $p = 0.47$

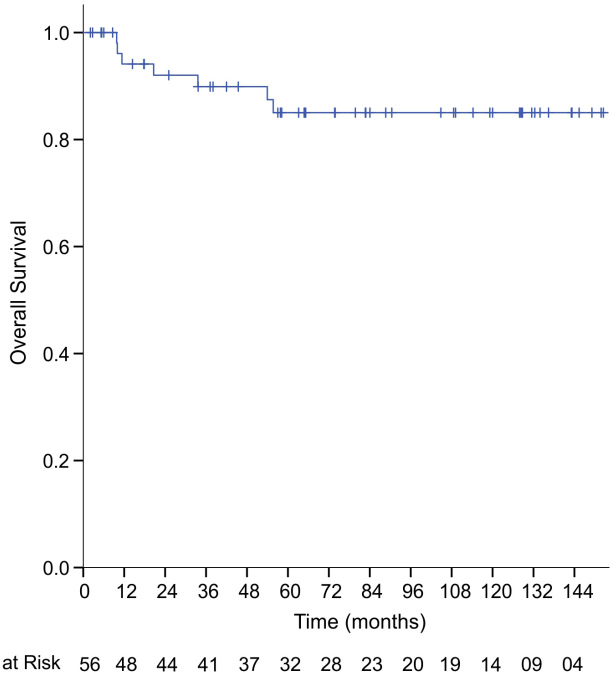

FIGURE 1. Overall Survival in Study Population.

positive rates, possibly because of limited sample size, the sensitivity was numerically higher and the false positive rate lower with CECT imaging. The relatively low sensitivity of PET/CT in this and other studies in early-stage disease could be because of missed small volume metastatic disease due to limited spatial resolution of PET, which includes only CT for attenuation correction [9–16]. It is likely that detection of lymph node metastasis based on only one parameter *i.e.*, SUV, may be sub-optimal and incorporation of multiple PET-CT parameters and tumor characteristics could improve accuracy. Recent advances in PET scanning, such as time-of-flight technology and the development of newer tracers and solid-state detectors, will also probably improve its accuracy.

The results of our study should be considered in the context of previous studies on the utility of PET/CT evaluation of lymph nodes in clinically early-stage cervical cancer. Signorelli and colleagues [13] evaluated 159 women with cervical cancer stages IB1 and IIA and found that PET/CT had low sensitivity for lymph node involvement and did not change the treatment plan. Driscoll *et al.* [14] found PET/CT of limited value in patients with early-stage (stages IA–IB1) cervical cancer with negative lymph nodes on MRI scan. Jung *et al.* [15] evaluated 114 clinically stage IA1–IIB cervical cancer

TABLE 5. Association of SUVmaxand other prognostic factors.

Factor	Mean SUVmax (standard deviation)	*p* value
Stage		
IB1(N = 37) *vs.* IB2 (N = 18)	8.78 (6.86) *vs.* 11.61 (7.58)	$p = 0.17$ (IB1 *vs.* IB2)
Depth of stromal invasion		
≤half (N = 15) *vs.* >half (N = 33)	5.71 (6.99) *vs.* 12.52 (6.07)	$p = 0.001$
Lympho-vascular space invasion		
Absent N = 32 *vs.* Present N = 17	8.32 (7.12) *vs.* 13.66 (5.92)	$p = 0.011$
Lymph node		
Not involved N = 42 *vs.* Involved N = 13	8.68 (7.57) *vs.* 13.02 (4.42)	$p = 0.015$
Histopathology		
Squamous (N = 37) *vs.* non-squmous (N = 15)	8.49 (7.12) *vs.* 12.21 (6.75)	$p = 0.07$

patients who were treated with radical surgery, and underwent preoperative CT, MRI and PET/CT scans. The results of this study showed that all three modalities have low-moderate sensitivity and PPV and moderate to high specificity and NPV for lymph node metastasis. However, most of these studies have not used lymph node station-wise pathological evaluation as the gold standard for characterization of imaging accuracy, as was done in our study.

Our study is especially relevant in the context of 2018 revised FIGO staging for cervical cancer wherein pelvic and/or retroperitoneal lymph node involvement by either radiological or pathological evaluation has been classified as stage IIIC. Given the potentially different sensitivities of different imaging modalities for lymph node involvement, specifying the imaging modality in staging information should be considered so that diverse datasets can be compared. It should also be noted that stage migration of almost 10–20% of patients from previous stage IB to new stage IIIC based on radiological imaging will apparently improve the outcomes of both these stages according to the principles of the Will Rogers phenomenon [18]. This should be considered when comparing stage-wise results between different eras and clinical settings.

An interesting finding in our study is the association of higher SUVmax in the primary tumor with clinical and biological features of aggressive disease, and reduced overall survival. This metabolic parameter is unavailable in conventional CECT scans and provides complementary information. Our SUV results are concordant with several other studies, which have also shown that this parameter in the primary tumor is an adverse prognostic factor and is associated with lymph node involvement and other features of biologically aggressive malignancy [19–22]. Given the higher spatial resolution of CECT or MRI and the metabolic information available with PET, the best imaging in clinically early-stage patients may be a combination of PET/CT and CECT or MRI.

The strengths of this study are its prospective nature and meticulous pathology evaluation of each anatomical lymph node group individually, as the gold standard for anchoring the imaging results. The major limitations are its relatively small sample size, and lack of ultra-staging and immunohistochemistry on lymph nodes. Thus, there is a possibility that micro-metastases were missed, although their prognostic and therapeutic significance is currently unclear.

5. Conclusions

Imaging with either PET/CT or CECT in patients with operable early-stage cervical cancer provided therapeutically useful information regarding lymph node staging, but PET/CT was not superior to CECT in this application, with the latter having numerically higher sensitivity. These findings have implications in low-resource settings where the cost and availability of PET/CT may limit its clinical utility. PET/CT is more expensive for patients and healthcare systems in these settings and the availability of radioisotope is limited in many locations.

SUVmax of the primary tumor on PET/CT was significantly associated with several features of biological aggressiveness and worse overall survival. Therefore, a combination of PET/CT and CECT may be the optimal imaging strategy in early-stage cervical cancer patients to triage patients for surgery versus concomitant chemoradiation. The use of primary tumor SUV is a potential biomarker to segregate patients with differing prognosis.

AUTHOR CONTRIBUTIONS

AM and SG designed the research study. AM, SG, KD, SC, VR, NP, and UM performed the research. AM and SG analyzed the data. AM and SG wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethics Committee (No.378/2007) and written informed consent was obtained from all participants prior to inclusion in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1554354648623529984/attachment/Supplementary%20material.docx.

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