SCIENTIFIC RESEARCH

STUDY THE CHARACTERISTICS OF PET/CT IN STAGING CERVICAL CANCER CANCER AT HO CHI MINH CITY ONCOLOGY HOSPITAL, HCM CITY

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SUMMARY

Objectives: Identify the mean SULmax level of the tumor in cervical cancer and compare the SULmax level between different histological types. Identify the mean size and mean SULmax level of metastatic lymph nodes in cervical cancer. Determine the percentage of cervical cancer patients with stage change after PET/CT. Determine the rate of accidental distant metastases detected by PET/CT.

Research subjects: 37 patients with a diagnosis of cervical cancer underwent PET/CT scans at Ho Chi Minh City Oncology Hospital from January 2020 to November 2021, the purpose of PET/CT was to evaluate the stage of the disease before treatment.

Study design: Cross-sectional description

Results: The mean SULmax of the primary tumor in cervical cancer was 13.88. The mean SULmax of squamous cell carcinoma and adenocarcinoma is quite similar and much higher than that of small cell carcinoma. Squamous cell carcinoma type had the highest median SULmax. The mean size of metastatic lymph nodes in cervical cancer was 20.79 mm with a mean SULmax of 10.72. There were 48.6% of cervical cancer patients who changed their disease stage after PET/CT scan. In which, 35.1% of the patients increased stage and 13.5% of the patients decreased stage. The rate of newly discovered distant metastasis was 27%. The most common site of newly discovered distant metastasis was in the supraclavicular lymph nodes.

Conclusion: Cervical cancer had a high affinity for 18F-FDG and the mean of SULmax of primary tumors was often very high. Squamous cell carcinoma tumors had the highest SULmax uptake of all histopathological types. Lymph node metastases in cervical cancer also had high 18F-FDG uptake values. Nearly half of cervical cancer patients had stage changes after PET/CT scan, in which, most patients have increased the stage due to new distant metastases detected after PET/CT scan. The majority of patients increased stage due to newly discovered distant metastatic lesions after PET/CT in the group of patients with stages IIIC1r to IIIC2r. This showed that the changes in indications for PET/CT scans in cervical cancer currently applied at Ho Chi Minh City Oncology Hospital were very practical and effective.

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I. INTRODUCTION

Cervical cancer is a one of the most common cancers in women worldwide. In Vietnam, about 4132 new cases of cervical cancer are diagnosed every year and about 2223 deaths due to this disease per year (GLOBOCAN 2020). PET/CT has many roles in the diagnosis and treatment of cervical cancer, such as staging, treatment planning, response assessment, recurrence, metastasis, and prognosis.

In cervical cancer staging, PET/CT images show many advantages over other imaging methods in evaluating all three factors: tumor (T), lymph node (N) and distant metastasis (M). In tumor evaluation, SUVmax of primary tumor has prognostic value in risk of lymph node metastasis and disease-free survival [1]. In the evaluation of lymph node metastasis, thanks to its ability to evaluate both structural and metabolic aspects, PET has higher sensitivity and specificity than CT in the evaluation of regional lymph node metastasis [2] [3]. In the evaluation of distant metastases, PET improves the accuracy of the assessment of distant metastases significantly because of its ability to detect potential metastatic lesions such as lung, supraclavicular nodes, and other distant metastatic lesions [4].

In the world, PET/CT is indicated to evaluate pre-treated stage of cervical cancer patients, from early invasive stages (IB2 according to ESGO, or IB1 according to NCCN). However, in clinical practice, this will depend on the resources of each country and treatment facility. At Ho Chi Minh City Oncology Hospital, before September 2021, PET/CT was only indicated for diagnosing recurrence and distant metastases that cannot be diagnosed by any other imaging method. Therefore, the number of cervical cancer patients receiving PET/CT before treatment is very limited. After September 2021, PET/CT was additionally indicated for stage IIIC1r, IIIC2r cases, in order to clearly identify the metastatic lymph nodes for treatment planning, and at the same time explore the metastatic sites. As a result, the number of cervical cancer patients receiving PET/CT before treatment has increased significantly.

Specifically, from January 2020 to November 2022, at Ho Chi Minh City Oncology Hospital, we conducted PET/CT scans for 66 patients diagnosed with cervical cancer, listed in the table below according to the purpose of the PET/CT scan:

The percentage of common PET/CT scan indications

Indications	n	Percentage
Staging	37	56%
Assessment of response to treatment	05	7.6%
Evaluation of recurrence, metastasis	24	36.4%
Radiation therapy simulation	0	0%
Total	66	100%

After nearly two years of performing PET/CT in cervical cancer staging, we conducted this study to investigate the imaging features of PET/CT on primary tumor and metastatic lymph nodes as well as evaluating the effectiveness of PET/CT in staging the disease, thereby demonstrating the important role of this imaging method in cervical cancer staging before treatment.

STUDY OBJECTIVES

- Identify the average SULmax level of the tumor in cervical cancer and compare the SULmax level between different histopathological types.

- Identify the mean size and mean SUL level of metastatic lymph nodes in cervical cancer.

- Study the percentage of cervical cancer patients with disease stage change after PET/CT scan.

- Determine the rate of distant metastases incidentally detected by PET/CT.

II. OVERVIEW

In terms of imaging principle, PET uses different radiopharmaceuticals, depending on the organ to be investigated, to record functional images at the molecular level when these substances enter the cellular metabolism. However, images obtained from PET have low resolution due to the limited number of photons on the patient's surface, making it difficult to examine small lesions and distinguish anatomical structures. Therefore, the combination of PET with CT enhances the ability to investigate small lesions and provides a more precise anatomical location than PET alone. Among the radioactive tracer used in PET/CT,

^{18}F-fluoro-2-deoxyglucose (abbreviated as ^{18}F-FDG or FDG) is the most used. FDG is structurally similar to glucose, transported from the interstitial tissue across the cell membrane to the interior by the glucose transport protein (GLUT) channel. Once inside the cell, FDG is phosphorylated to FDG-6-phosphate and is stored in the cell because it cannot be further metabolized or stored in the form of glucose. Because cancer cells metabolize more glucose, and have more GLUT channels and hexokinase II enzymes, they will absorb more FDG and can be detected on PET/CT.

SUV (Standardized Uptake Value) is a semi-quantitative value that determines the degree of FDG concentration in a tumor or lesion. To determine the SUV of the tumor, we have to determine the region of interest on the 2D plane (ROI- region of interest) and the volume of interest in 3D space (VOI- volume of interest). SUV is the ratio of the concentration of FDG in the tumor and the radioactivity injected into the body divided by the body mass.

$$SUV\ \left(\frac{g}{ml}\right) = \frac{Radioactivity\ in\ tumors\ \left(\frac{kBq}{mL}\right)}{Injection\ dose\ (MBq)}\ x\ \ Body\ mass\ (g)$$

SUVmax is the highest SUV value in the ROI or VOI region.

▪ SUVmean is the average of all pixels in the ROI region or voxels in the VOI region.

▪ SUVmax is used more often than SUVmean because it is less dependent on PET/CT readers (who draw ROI or VOI).

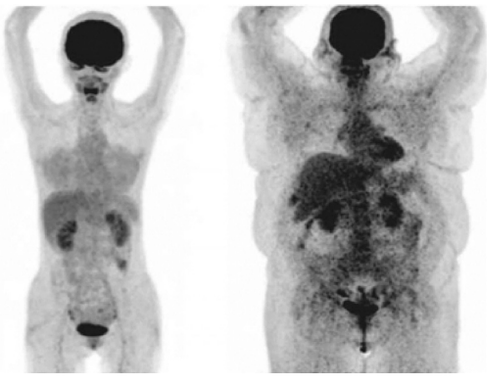

Figure 1. *MIP image of a thin patient and an obese patient. SUV measured at the liver and mediastinum of obese patients was much higher than that of lean patients with equal SUL levels*

We all see that SUV depends on body mass in which there are fat cells that do not absorb glucose, so normalizing SUV according to lean tissue mass or non-fat tissue will give a more accurate FDG uptake level (or Standardized Uptake Value normalized to Lean body mass – SUL, unit: g/ml). SUV values are more commonly expressed in obese patients than in patients with normal BMI levels [5] (Figure 1).

In staging cervical cancer, PET/CT shows many advantages over other imaging methods, including:

1) In terms of tumor assessment:

Many studies have shown that MRI is the best imaging method for evaluating primary tumors due to its ability to distinguish well the depth of tumor invasion [6], the accuracy of MRI in tumor assessment is 90- 100%, compared to CT only 60-70%.

Using PET/CT in tumor evaluation, increased uptake of FDG was observed in most tumors ≥ 7mm in size and was not usually absorbed in the necrotic components of the tumor or in the fluid, blood, or uterine lumen due to obstruction of the cervical canal. The increase in FDG uptake is proportional to the tumor proliferation rate, reflecting the malignancy of the tumor. Kidd and colleagues showed that the mean SUVmax of the primary tumor was 11.62 (range 2.5-50.39) in 240 cervical cancer patients with stage IB2-IVB [1]. Poorly differentiated tumors tend to have higher SUVs. Squamous cell carcinoma (SUVmax 11.92) has a significantly higher SUV profile than adenocarcinoma (SUVmax of 8.85) and adenocarcinoma (SUVmax of 8.05). A higher SUVmax is associated with a higher risk of lymph node metastasis. SUVmax of primary tumor also can predict the risk of disease survival after treatment, risk of recurrence and survival time. The higher the SUVmax of the primary tumor, the shorter the disease-free survival time [1]. In this study, due to the small number of patients and short follow-up time, we will only examine the mean SULmax value of tumors, as well as compare the mean SULmax level between different histological types.

2) In terms of lymph node assessment

In cervical cancer, lymph node metastasis is an independent prognostic factor. FIGO 2018 included lymph

node metastases into a separate staging subgroup (IIIC1, IIIC2). Neither MRI nor CT depicts microinvasion in lymph nodes with a short axis of less than 1 cm and is limited in distinguishing between hyperplastic and metastatic nodes. Therefore, both of these imaging methods are limited in the assessment of lymph node metastasis before treatment. In patients with advanced cervical cancer (≥ IB2), PET/CT is effective in evaluating lymph nodes, especially in locally advanced cases when CT is normal. Grigsby and colleagues in a retrospective study comparing CT and PET regional lymph node evaluations in 101 patients with cervical cancer. CT detected pelvic lymph nodes in 20% of cases and para-aortic lymph nodes in 7% of cases, whereas PET showed abnormally increased FDG uptake in pelvic lymph nodes in 67% of cases and identified para-aortic lymph nodes in 21% of cases and supraclavicular nodes in 8% of cases [2], the 2-year progression-free rate was 64% with negative results in both CT and PET, 18% with negative CT and positive PET, 14% with both positive CT and PET.

Lee and colleagues evaluated the accuracy of PET in detecting supraclavicular lymph node metastases in patients with cervical cancer. Of the 100 biopsied PET supraclavicular nodes, 86 had malignant cells [3]. With a threshold SUVmax of 3.0, PET has a sensitivity of 74.4%, a specificity of 78.6%, and an accuracy of 75%. For supraclavicular nodes with SUVmax > 3.0, PET has a positive predictive value of 95.5%. For lymph nodes with SUVmax ≤ 3.0, when using ultrasound to rule out false negative PET cases, PET has a negative predictive value of 100%. When combining ultrasound for SUVmax <3.0 cases, the accuracy increased to 92%.

Loft and colleagues also performed a prospective study on 120 patients diagnosed with stage ≥ IB cervical cancer who underwent PET/CT re-evaluation within 2 weeks [7]. Patients were divided into 2 groups: radical surgery group including lymphadenectomy and concurrent chemoradiotherapy. 27 patients underwent radical surgery, 4 of which PET/CT showed pelvic lymph nodes, 3 cases were positive correctly and 1 was falsely positive. In 22 cases, PET accurately assessed pelvic lymph nodes, 1 case was false negative. In evaluating pelvic lymph node metastases, PET/CT showed a sensitivity and a specificity of 75% and 96% respectively. For 92 non-operative patients, the sensitivity and specificity were 75% and 87% respectively. PET/CT has 100% and 99% sensitivity and specificity in evaluating para-aortic lymph nodes, and 100% and 92% in evaluating distant metastases. Loft and the group concluded that PET/CT should be used in patients newly diagnosed with FIGO stage IB or higher cervical cancer.

The above studies show that the benefit of PET/CT in the evaluation of lymph node metastasis is clear. In this study, since none of the patients had surgery after PET/CT, there was no gold standard for calculating the sensitivity and specificity of PET/CT, as well as finding the SUL threshold to differentiate benign lymph nodes. In the worst case, we will simply investigate the size and mean SUL characteristics of the metastatic nodes.

The most common SUL threshold for discriminating metastases is 2.5. In a study in squamous cell carcinoma of the head and neck, the threshold of 1.9 for nodes 10 mm, 2.5 for nodes 10-15 mm, and 3.0 for nodes 15 mm had a sensitivity of 79. % and a specificity of 99% [8]. In some other studies in lung cancer and esophageal cancer, the cut-off value of SUV in the assessment of mediastinal lymph nodes is 4.1-5.3, which will give an accuracy of up to 92% [9], [10]. There are very few studies on SUV threshold to distinguish metastatic lymph nodes in cervical cancer, with a threshold of 3.0, PET has a sensitivity of 74.4%, a specificity of 78.6%, and an accuracy of 75% [3]. Our criteria for determining metastatic lymph nodes were performed in this study, including lymph nodes with size ≥ 10mm and SULmax ≥ 2.5.

2) In terms of distant metastases assessment:

PET/CT improves initial staging by its ability to detect iliac, para-aortic, supraclavicular, and distant metastatic lesions. The group of Wong evaluated the accuracy of PET in distinguishing cervical cancer patients with local stage and distant metastasis, patients were staged by PET. After follow-up time, PET showed 100% in the possibility of discrimination.

In this study, we will investigate the rate of newly detected distant metastases, as well as the percentage of cervical cancer patients with stage change after PET/CT scan.

III. RESEARCH SUBJECTS AND METHODS

1) Research subjects: 37 patients with cervical cancer diagnosis received PET/CT scans at Ho Chi Minh City Oncology Hospital from January 2020 to November 2021 to identify the stage of cervical cancer before treatment.

- Selection criteria: Patients with the diagnosis of cervical cancer, have been staged through clinical examination and other imaging methods (such as: ultrasound, X-ray, MRI, CT scan, and so on…). The indication of PET/CT scans is to identify the disease stage.

- Exclusion criteria: Patients who had not had the confirmed diagnosis of cervical cancer or had not been staging or PET/CT scan is not indicated for staging.

2) Research method: Cross-sectional descriptive.

PET/CT scan procedure:

+ Prepare the patient:

The patient fasted for at least 4 hours before the injection and PET/CT scan.

Check blood glucose level before injecting 18F-FDG (blood glucose level should be less than 150 mg/dl or 8.0 mmol/l). Renal function is checked if a contrast agent is indicated.

Intravenous injection of 18F-FDG 0.15 - 0.20 mCi/Kg body weight (7 -12 mCi).

After injecting 18F-FDG, the patient drink plenty of fluids (at least 0.5 liter of water) before the scan. The patient rests in the monitoring room from 45 to 90 minutes before scanning and avoids walking, talking, and exercising

The patient urinated before entering the scanning room.

+ PET/CT imaging:

Scanning after injection of 18F-FDG from 45 to 90 minutes. Whole body scanning from the crown of the head to the upper third of the thigh will be performed. Additional areas of interest or dual time will be indicated as needed.

+ After PET/CT scan:

The patient is monitored in a private room. The doctor re-checks the acquired image to make sure that the requirements have been met. Instruct the patient to empty urine into the septic tank before leaving and to continue drinking plenty of water and urinating several times a day. Patients should limit contact with people around for 3 hours, and avoid contact within 24 hours with pregnant women and children.

- *Data collection*: After processing PET/CT images, the study team will collect data on size and SUL value of tumor lesions, lymph nodes, and metastatic lesions.

- *Data processing*: Using MS Excel 2019 and SPSS 26 software.

RESULTS

PET/CT imaging features of primary tumors in cervical cancer

Table 1. *Characteristics of primary tumors in cervical cancer*

n	29	7	1	37
Histopathology	**Squamous Cell Carcinoma**	**Adeno-carcinoma**	**Small cell neuroendocrine carcinoma**	
Average SULmax	14,00	14,45	6,65	13,88
Median SULmax	13,95	11,20	6,65	
Average tumor size (mm)	59.52	75.57	50	62.29

- The mean SULmax of the primary tumor is 13.88. The median SULmax of the primary tumor was 13.66. SULmax of the smallest primary tumor was 3.14 and the largest was 34.81.

- The average tumor size was 62.29 mm.

-Tumors of squamous cell carcinoma and adenocarcinoma had similar mean SULmax (from 14.00 to 14.45), but much higher than that of neuroendocrine small cell carcinoma (6.65).

- Squamous cell carcinoma had the largest median SULmax (13.95)

PET/CT imaging characteristics of metastatic lymph nodes in cervical cancer

Table 2. *Characteristics of metastatic lymph nodes in cervical cancer*

Lymph node location	Number of lymph nodes	Average size (mm)	Average SULmax
Pelvic lymph nodes	25	23.40	9,06
Para-aortic lymph node	17	19.12	10,94
Supraclavicular lymph nodes	6	14.67	9,92
Total	48	20.79	10,72

- The average size of the metastatic nodes was 20.79 mm (from 10 mm to 47 mm).

- The average SULmax value of metastatic nodes was 10.72 (from 3.10 to 36.74).

Percentage of cervical cancer patients with stage change after PET/CT scan

Table 3. *Stage of cervical cancer patients before and after PET/CT*

Stage	I	II	III	IV	Total
Stage before PET/CT scan	0	2	23	12	37
Stage after PET/CT scan	1	3	14	19	37
Change the stage after PET/CT scan	1 IVB→IB2	1 IIB→IIIC1r 2 IVB→IIB	1 IIIC1r→IIIC2r 1 IIIC1r→IVB 1 IIIC2r→IIIC1r 1 IIIC2r→IVA 9 IIIC2r→IVB	1 IVB→IIIC1r	18

- The number of patients with stage change was 18/37, with a rate of 48.6%.

- The rate of patients who increased the stage after PET/CT scan was 13/37 (35.1%.)

- The rate of patients who decreased the stage after PET/CT scan was 5/37 (13.5%) .

The rate of new distant metastases detected after PET/CT

The rate of newly discovered distant metastases was 27%, the most common newly detected distant metastasis sites were supraclavicular lymph nodes, lung, pleura, bone, and pancreas.

Table 4. *Newly detected distant metastasis sites after PET/CT*

Location of distant metastasis	n	Mean SUL of metastatic lesions
Supraclavicular lymph nodes	6	10,2
Lung-pleura	5	8,4
Bone	3	20,9
Pancreas	2	6,4

IV. DISCUSSION

Although the number of new cervical cancer patients diagnosed each year is high, the number of indications for PET/CT scans to assess the stage of the disease before treatment is still very limited. It is because the cost of PET/

CT is much more expensive than other imaging methods and health insurance only partially covers for the scan while most patients have middle-low income. Although worldwide, PET/CT is indicated for pre-treatment evaluation of cervical cancer patients from early invasive stages (from IB2 according to ESGO, from IB1 according to NCCN), clinical practice will depend on national resources and each treatment facility. At Ho Chi Minh City Oncology Hospital, before September 2021, PET/CT was only indicated to diagnose distant metastatic sites that cannot be detected by any other imaging method. Therefore, the number of cervical cancer patients having pre-treatment PET/CT scan was very rare. After September 2021, PET/CT has been indicated for cases at stages IIIC2r and IIIC1r or cases with suspected distant metastasis to identify the metastatic nodes for treatment planning, or to evaluate potential distant metastases. This led to an increase in the number of patients receiving pre-treatment PET/CT scans. Specifically, up to 18 out of 37 cases in the study were scanned from September to November 2021. In the future, we hope that the number of cervical cancer patients undergoing pre-treatment PET/CT will increase, creating favorable conditions for continuing to carry out further studies on PET/CT application in the diagnosis and treatment of cervical cancer.

In general, cervical cancer had a high affinity for 18F-FDG, with the mean SULmax of primary tumors up to 13.88, compared to 11.62 in Kidd's study [1]. This difference may due to the fact that in our study, most of the patients were in stages III and IV (35 out of 37 patients), with an average tumor size of 62.29 mm, while in the study of Kidd and colleagues, 240 patients were at stages from IB2-IVB. We found that the mean SULmax of squamous cell carcinoma and adenocarcinoma was quite similar and much higher than that of small cell endocrine carcinoma. However, due to the small sample size, if comparing the median of SULmax, squamous cell carcinoma had the highest median of SULmax (13.95), consistent with the results of other studies in the world. The SULmax values of the primary tumor obtained in this study will be the premise to carry out further studies to compare the relationship between SULmax and the risk of residual disease after treatment, the risk of recurrence and survival time.

In terms of metastatic lymph nodes in cervical cancer, we found that the metastatic lymph nodes had sizes from 10mm to 47mm with an average size of 20.79mm. The average SULmax level of the metastatic nodes was 10.72. Para-aortic nodes tend to absorb radiopharmaceuticals more strongly than lymph nodes in other sites, with a mean SULmax of 11.84. The supraclavicular nodes were usually smaller than the regional nodes, with an average size of 14.67 mm, but had a similar mean SULmax. The results of this study showed that not only the primary tumor but also the metastatic lymph nodes in cervical cancer had a high affinity for FDG, with the mean SULmax level being usually high (from 9 to 10). We can apply this conclusion to clinical practice in many situations where cervical cancer patients have enlarged or atypically lymph nodes in locations that are difficult to reach by fine needle aspiration or biopsy. After PET/CT scan, the lymph nodes with higher FDG uptake will have higher positive predictive value. In order to find out the specific SULmax threshold to distinguish metastatic lymph nodes in cervical cancer, we need to continue to do a prospective study with early stages patients with indications for surgery to have post-operative pathological results for comparison. We hope that further studies will be done in the near future.

The percentage of patients with changes in the stage after scanning was 48.6%, of which 35.1% of patients increased stage. Most cases of stage increase were due to newly discovered distant metastatic lesions (10 out of 13 patients) in the group of patients with stage IIIC1r, IIIC2r. 13.5% of patients reduced stage, in which 4 out of 5 cases due to exclusion of suspected pulmonary lesions as distant metastases, 1 case excluding para-aortic lymph node involvement as metastasis. Almost half of the patients changed the stage after PET/CT scan, much higher than in other studies in the world. This difference may be due to in our study, most patients were in stages IIIC1r and IIIC2r with the high possibility of latent distant metastases. This also showed that routine PET/CT before treatment should be performed for this group of patients.

The rate of newly discovered distant metastases was 27%, in which the most common sites were the supraclavicular lymph nodes, followed by lung and pleura, bone, and pancreas. The size of supraclavicular lymph nodes in 6 newly detected cases ranged from 15 to 23 mm, with SULmax levels ranging from 6.8 to 22.4. All patients were in stage IIIC2r and all did not have neck ultrasound before PET/CT

scan. In clinical practice is currently applied at Ho Chi Minh City Oncology Hospital, neck ultrasound is not included in routine tests to assess the stage of cervical cancer. The results of this study suggest to us the question of whether routine neck ultrasound should be performed in patients with stage IIIC2r. It is because if only neck ultrasound and fine needle aspiration can identify lymph node metastases, there will be no need for PET/CT scan, reducing the economic burden for patients and reducing pressure on medical staff.

V. CONCLUSION

- Cervical cancer had a high affinity for 18F-FDG, the mean SULmax of the primary tumor was often very high.

- Squamous cell carcinoma had the highest SULmax uptake among all histopathological types.

- Lymph node metastases in cervical cancer also had a high affinity for 18F-FDG.

- Nearly half of cervical cancer patients have changes in the stage after PET/CT scan, in which, most patients increased the stage due to newly discovered distant metastatic lesions in the group of patients with stages IIIC1r and IIIC2r. This shows that the changes in indications for PET/CT in cervical cancer currently applied at the Ho Chi Minh City Oncology Hospital are very practical and effective.

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