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ORIGINAL ARTICLE

PET/CT dilemma in para-aortic lymph node assessment in locally advanced cervical cancer?

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ABSTRACT

Objective: We aimed to discuss the relationship between the maximum standardized uptake value (SUVmax), which is the degree of involvement obtained in the radiopharmaceutical 18-Fluor-labeled glucose-utilized positron emission tomography-computed tomography (PET-CT), which is widely used in locally advanced cervical cancer, and para-aortic lymph node positivity as a result of histopathology in the light of the literature.

Material and Methods: The pre-operative PET-CT results of 66 patients who had been examined and treated for locally advanced (Stage IB3-IVA) cervical cancer between 2015 and 2020 were retrospectively examined and the relationship between the SUVmax values and para-aortic lymph node positivity in the histopathology results was evaluated. Patients with SUVmax 4≤ in PET-CT were accepted to have para-aortic lymph node involvement. In terms of para-aortic lymph involvement, a cross tabulation was created with PET-CT results and the final pathology, which is the gold standard, and the sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated.

Results: The mean age of 66 patients included in our study was 48.2±13.2 years. The majority of our patients were at stage 1B3 (36.4%), while eight were at stage 3C2P. While para-aortic evaluation was performed through the laparoscopic method in 36 (54.5%) patients, it was performed by laparotomy in the remaining 30 (45.5%) patients. When the complaints of the patients were assessed, it was seen that the highest rate was that of post-coital bleeding in 32 patients (48.5%) and pelvic pain was observed in two patients (3%). The mean body mass index (BMI) was 22.69±4.14 and the squamous type was the most common in 44 patients (66.7%) in terms of histopathological typing. When we evaluated the results of 66 patients, the prevalence rate was around 12% and when we compared the SUVmax uptake rates found in PET-CT, which we used as a new diagnostic test with the pathology results, which is our gold standard test, the sensitivity and specificity rates were 50% and 48%, respectively. The PPV, the NPV, and accuracy were calculated as 11.7%, 87.5%, and 48.8%, respectively.

Conclusion: Considering the high risk of para-aortic lymph node metastasis in locally advanced cervical cancer through assessment of the high SUVmax values in PET-CT, it is necessary to confirm the status of the para-aortic lymph node with minimally invasive surgery in the foreground by experienced surgeons.

Keywords: Cervical cancer, para-aortic lymph node metastasis, PET-CT, SUVmax value.

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INTRODUCTION

Cervical cancer is the fourth most common female cancer among gynecological cancers in terms of morbidity and mortality.[1] Cervical cancer has lower incidence and mortality rates compared to uterine corpus and ovarian cancer as well as many other organ cancers. However, cervical cancer still remains an important cause of increased morbidity and mortality in female cancers in countries that do not have access to screening and prevention programs. Human papilloma virus is the main cause of cervical neoplasia and can be detected as the main factor in 99.7% of cervical cancers.[2] While the most common histological types of cervical cancer are the squamous cell types with a rate of approximately 70%, 25% are adenocarcinomas, and 5% are other rare types.[3]

Cervical cancer has traditionally been clinically staged, but surgical and radiological evaluation is part of staging after 2018 to detect pelvic and para-aortic lymph node involvement.[4–7] Surgery and post-operative histopathological evaluation and radiological staging provide important information that may affect the treatment.[8] It may be better and more practical to assess locally advanced disease (i.e., tumor size, vaginal, and parametrial involvement), especially since it is an easier and more accessible method in low-income areas where cervical cancer continues to be the most common malignancy among women. Thus, morbidity and mortality related to surgery are avoided in patients who are not candidates for surgical treatment.[9] The tumor stage is determined during the primary diagnosis of cervical cancer and does not change even when prognostic factors that increase the risk of recurrence after treatment are determined. This is also true for other gynecological cancers. Correct pre-treatment staging of cervical cancer is critical as it determines both surgical and medical treatment and the prognosis.

Cervical cancer increases the mortality and morbidity by causing more distant metastatic lesions as well as pelvic or para-aortic lymph node involvement. Historically, surgery with lymphadenectomy was required to evaluate lymph node metastases in cervical cancer. However, today, lymph node dissection, imaging methods, or both are used to evaluate lymph node metastases. The presence of lymph node involvement is the most important factor determining the prognosis in cervical cancer and is associated with a worse prognosis. Determining the stage by diagnosing lymphatic and distant metastases and planning the treatment of the cases accordingly are the most important factors in the prognosis, and in particular, detection of local advanced stage and metastatic cancer by pre-operative imaging methods affect the decisions regarding radiotherapy. Thus, be it laparotomy or laparoscopic surgery, the associated mortality and morbidity are decreased.[10]

We evaluated our cases diagnosed with local advanced stage cervical cancer, who had undergone pre-operative fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) and operated and histopathologically examined for staging, through histopathological comparisons, which is accepted as gold standard, with PET-CT. We aimed to discuss the dilemma of the use of FDG PET-CT to detect para-aortic lymph node involvement in the light of the literature.

MATERIAL AND METHODS

Approval was obtained from the ethics committee of our hospital for 66 cases who had been examined and treated for locally advanced (stage IB3-IVA) cervical cancer between 2015 and 2020. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number KAEK-21 (date: 13.01.2021). Subsequently, the pre-operative FDG PET-CT maximum standardized uptake value (SUVmax) values and the histopathology results were evaluated retrospectively; the relationship between FDG PET-CT SUVmax reference value of 4 and above and below 4 with histopathological para-aortic lymph node positivity was evaluated. Sixty-six patients with a mass size of 4 cm and above, from Stage IB3 to IVA, where there is adjacent organ mucosa involvement according to The International Federation of Gynecology and Obstetrics (FIGO) 2018 staging, and who had undergone para-aortic lymph node dissection by either the laparoscopic technique or laparotomy, were included in our study. Two cases with early Stages IA and IB1, Stage IVB cases with distant metastasis and patients who did not continue their examination and treatment or who had not undergone histopathological sampling, were not included in the study.

The histopathological, demographic, and clinical characteristics of the cases were evaluated according to age, gravidity, parity, contraceptive use and methods, smoking status, first application complaints, BMI, and the cervical biopsy results.

While all patients were therapeutically given simultaneous cisplatin (40 mg/m^2), with extended-field radiotherapy to patients with positive para-aortic lymph node involvement, patients with lymph node negativity received pelvic radiotherapy.

After the treatment, in the first 2 years, the patients were followed-up every 3 months with cervical cytology and physical examination, pelvic examinations were carried out and the controls were continued every 6 months for the next 3 years. During the follow-up, pelvic examination, transvaginal or transabdominal ultrasonography, serum tumor markers evaluation, and radiological evaluations were performed in all cases.

For the descriptive statistics, the mean, standard deviation, median, min-max values, and frequencies were used considering whether there was a normal distribution or not. The categorical data were expressed in numbers and percentages (%). For the numerical data, Mann–Whitney U-test was used according to the normal distribution status. Patients with SUVmax ≤4 in PET-CT were accepted as having para-aortic lymph node involvement. The PET-CT results in terms of para-aortic lymph node involvement, and the final pathology results, which is the gold standard, were cross-tabulated and the sensitivity, specificity, PPV, and NPV were calculated. The Statistical Package for the Social Sciences 23 program was used to analyze the data. P values in all tests of lower than 0.05 were considered statistically significant.

RESULTS

The mean age of the 66 patients included in our study was 48.2±13.2 years. The gravity and parity evaluation of the patients showed that there was 1 case who had no pregnancy and no delivery, and all deliveries had been carried out through normal vaginal delivery. It was

determined that 36 patients (54.5%) did not use any contraceptive method and 54 patients were smokers and smoked at least 8 pack-years and 32 pack-years at most. When the presenting complaints of the patients were examined, it was seen that the highest rate was 32 patients (48.5%) with post-coital bleeding and two patients (3%) with pelvic pain. The mean BMI was 22.69±4.14 and the squamous type was the most common in 44 patients (66.7%) in terms of histopathological typing, followed by adeno-type in 18 patients (27.2%) (Table 1). Most of the patients were at Stage 1B3 (36.4%), and eight patients were at Stage 3C2P. While para-aortic evaluation was made using the laparoscopic method in 36 (54.5%) patients, it was made through laparotomy in the remaining 30 (45.5%) patients.

When we examined the number of para-aortic lymph nodes removed, the median for laparoscopy was found to be 7 (min: 0-max: 18) and 5 (min: 0-max: 13) for laparotomy. However, there was no statistically difference between the two groups (p:0.569).

When all of the SUVmax values in the FDG PET-CT of our 66 patients included in the study were evaluated, the mean value of 4 was accepted as reference, and in all calculations, a value of 4 and above was accepted as high risk for para-aortic lymph node positivity, while values below 4 were considered normal. When we evaluated the results of 66 patients, the prevalence rate was around 12.1% and when we compared the SUVmax uptake rates found in PET-CT, which we used as a new diagnostic test, with the pathology results, which is our gold standard test, the sensitivity and specificity rates were 50% and 48%, respectively. The PPVs and NPVs and the accuracy were calculated as 11.7%, 87.5%, and 48.8%, respectively. In addition, while our false positivity rate was 51%, our false negativity rate was calculated as 50% (Table 2).

Table 1: Clinical and demographic characteristic risk factors of the patients

	n	Mean/Median	SD/Min-Max/%
Age		48.2	±13.2
Gravidity		3	0–10
Parity		2	0–7
Contraception			
No	36		54.5
OC	20		30.3
IUD	10		15.2
Smoking			
Yes	54	16 (pack year)	8–32
No	12		
Complaint			
Post-coital bleeding	32		48.5
Vagial discharge	30		45.5
Menometroragy	2		3
Pelvic pain	2		3
BMI	33	22.69	±4.14
Histological type			
SCC	44		66.7
Adenocarcinom	18		27.2
Others	4		6.1
Stage			
1B3	24		36.4
2A2	8		12.1
2B	9		13.6
3A	1		1.5
3B	4		6.1
3C1P	10		15.2
3C2P	8		12.1
4A	2		3.0
Surgical type			
L/S	36		54.5
L/T	30		45.5
Number of para-aortic lymph nodes			
L/S		7 (0–18)	p=0.569
L/T		5 (0–13)	

SD: Standard deviation; OC: Oral contraseption; BMI: Body mass indeks; SCC: Skuamous cell cancer; IUD: Intra uterine device; L/S: Laparoscopy; L/T: Laparotomy.

DISCUSSION

In particular, patients with Stage IB3 and IVA disease are considered to be locally advanced stages, and it is necessary to clearly demonstrate lymph nodes and distant organ or system involvement to plan their treatment in detail with the least complication rates. In recent years, FDG PET-CT, which is a method based on the uptake and metabolic activity of the labeled glucose, FDG, by the lymph nodes, tumor cells, and metastatic foci, has emerged as a new method on the basis of CT scanning, which is one of the imaging methods to ensure less surgical complications.

The superiority of FDG PET over other imaging methods has been demonstrated in a meta-analysis of 72 studies including 5042 women, which reported the following sensitivities and specificities for detecting lymph node metastases: PET (sensitivity: 75% and specificity: 98%), magnetic resonance imaging (MRI) (sensitivity: 56% and specificity: 93%), and CT (sensitivity: 58% and specificity: 92%).[11] Compared to CT alone, PET-CT was found to be significantly sensitive in terms of diagnosis, treatment, and prognosis, especially in determining the width of radiotherapy areas and showing lymph node metastases, which is the most important risk factor affecting recurrence and disease-free survival.[12]

Although FDG PET-CT is the most accurate imaging examination for lymph node evaluation, it should be kept in mind that the rates of false-negative diagnosis are high.[12,13] As an example, in a study in 60 patients with Stage IB2 to IVA disease, 12% of those without positive para-aortic node findings on PET-CT were found

Table 2: Comparison of PET-CT and histopathological results

	Histopathological results		
PET-CT Results	**Positive**	**Negative**	**Total**
Positive (suvmax≥4)	4	30	34
Negative (suvmax<4)	4	28	32
Total	8	58	

Sensitivity: 50%; Specificity: 48%; Positive predictive value: 11.7%; Negative predictive value: 87.5%; Accuracy: 48.5%; False positive rate: 51%; False negative rate: 50%. PET-CT: Positron emission tomography-computed tomography.

to have histopathologically positive para-aortic nodes.[12] A higher rate of pathologically positive para-aortic disease was observed in a subgroup of patients with PET-CT findings with positive pelvic and negative para-aortic nodes (22%). In another PET-CT study and pathological analysis of para-aortic nodes, patients with PET-positive pelvic nodes were more likely to have surgically confirmed para-aortic lymph node metastases than patients with PET-negative pelvic nodes (24% vs. 3%).[14]

In 1950, after William Sweet and Gordon L. Brownell, Chief of Neurosurgery Service at Massachusetts General Hospital, had seen the need for some new imaging methods that were more sensitive for imaging brain tumors, the idea that annihilation radiation should be used for imaging, especially after positron emission, emerged.[11,15] Since biology and anatomy are combined with this technology, which required a long time to develop and use in the health field, the diagnostic accuracy rates have increased. Thus, especially with presurgical imaging methods, complications related to primary surgery have been reduced and adjuvant or neoadjuvant treatment methods and their effectiveness have been increased. Furthermore, it supports the need for additional treatment or surgery in cases with recurrence after treatment.[16]

All cases diagnosed with cervical cancer have been recommended lymph node evaluation by FIGO and the American Cancer Joint Committee, and lymph node condition was added to the latest FIGO 2018 cervical cancer staging, according to the radiological imaging or histopathological evaluation results.[17]

With the latest revision, lymph node involvement has been very important in the FIGO staging and the prognosis, and survival is lower in patients with lymph node metastasis. The 5-year survival at all stages in patients with pelvic and para-aortic lymph node metastases is between 19% and 60%.[18,19] Therefore, evaluation of lymph nodes, especially with imaging methods, is important in determining the prognosis of the disease and choosing the treatment in terms of the disease stage and related recurrence and disease-free survival.

In our study, we found that the sensitivity of FDG PET-CT to be 50% and this was compatible with the range of 30–93% reported in the literature, but the specificity, that is, the rate of finding para-aortic lymph node involvement negativity was 48%, and this rate was lower than the rates in the literature. The reason for this discrepancy can be considered as the retrospective design of our study and the non-targeted evaluation of the radiological findings of the patients, and these values were compared with histopathology results. We can say that if the SUVmax values of FDG PET-CTs had been obtained for the target of detecting para-aortic lymph node and the evaluation had been made accordingly, these values would be much higher and more compatible with the literature.

In the literature, PET-CT revealed lymph nodes larger than 10 mm better than both MRI and CT with a false negative rate of 4–15%. These conditions should be taken into consideration as false positivity is particularly present where there is a high incidence of tuberculosis, sarcoidosis, lymphoma, and HIV that cause lymphatic reactivity.[20]

Nowadays, with the advances in minimally invasive procedures, it may be more rational to surgically evaluate para-aortic lymph nodes. In addition, revealing the para-aortic lymph node status surgically by either laparoscopy or laparotomy has a better prognosis than radiological exclusion and has been accepted as the gold standard,[21] since it is clear that some patients will demonstrate a disruption in their actual staging and treatment due to the absence of radiological imaging and high false negativity. In the only randomized controlled UTERUS-11 study comparing surgical and radiological staging in advanced cervical cancer, 33% of the patients were shown to be at high stage as a result of laparoscopic staging. In the same study, both short-term and long-term survival was better in patients who had underwent laparoscopy, although it was not statistically significant. It was emphasized that performing laparoscopy on the patients in this study did not delay the chemoradiotherapy.[22]

Our study revealed that histopathological lymph node positivity was determined in 50% of the cases, who were found to be negative on FDG PET-CT. In other words, it turns out that our accuracy rate was around 50%, so that one out of two patients with positive para-aortic lymph nodes could not be detected and pre-operative evaluation should be performed precisely in the direction of imaging. However, we can confidently say that despite the low rate of detecting positive patients, our rate of detecting true negative patients was as high as 87.5%, and in this case, when we accept the SUVmax value of 4 and above in FDG PET-CT as a reference, our rates of finding true negatives are compatible with the literature and are high.

The limitations of our study comprise the fact that our study was conducted retrospectively and the targeted SUVmax values were not evaluated. Furthermore, the effect of SUVmax values on the treatment results, local control and survival was not investigated. However, histological confirmation of lymph node metastasis is the most important aspect of our study, and to avoid the complications of surgery and planning of extended-field radiotherapy, the evaluation of lymph node in locally advanced cervical cancer can be made according to its spread in imaging studies. In addition, in patients with lymph node involvement in FDG PET-CT, surgical lymph node dissection may have a decreasing effect on disease-free survival and overall survival, but this should be investigated.

CONCLUSION

In locally advanced cervical cancer, high SUVmax values and particularly, the high risk for para-aortic lymph node metastasis should be taken into consideration. However, the para-aortic lymph node status should be confirmed by experienced specialists in the foreground with minimally invasive surgery.

Statement

Ethics Committee Approval: The Akdeniz University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 13.01.2021, number: KAEK-21).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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