The relationship between pre-treatment ^{18}F-FDG PET/CT metabolic data and treatment response in patients with cervix uteri cancer

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Keywords: Cervix uteri cancer - HPV - Heterogeneity factor - Radiotherapy - Recurrence

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Received:
15 December 2020
Accepted revised:
23 March 2021

Abstract

Objective: To determine the risk group of patients with locally advanced squamous cell carcinoma of the uterine cervix that will resist to treatment before concomitant chemoradiotherapy and who will develop metastasis via fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) metabolic data. **Subjects and Methods:** Fifty two patients with carcinoma of the uterine cervix who were treated in our clinic between 2015-2018 were evaluated. The presence of human papilloma virus (HPV) from the first paraffin blocks diagnosed in all patients has been tested with real time polymerase chain reaction (PCR). All patients received brachytherapy after concomittant chemotherapy with external radiotherapy. The first ^{18}F-FDGPET/CT and magnetic resonance images (MRI) images obtained for pretreatment staging and MRI after external radiotherapy were retrospectively reviewed. The patients who resisted concomittant chemoradiotherapy were tried and determined with pre-treatment ^{18}F-FDGPET/CT metabolic data. **Results:** The follow-up period of our patients with an average age of 53 years (42.5-60.75) was 53.5 months (42.5-60.75). Radiotherapy with a total median dose of 85 EqD2 (84-86) was delivered to all patients. The heterogeneity factor (HF) was found to be statistically significantly lower in patients in whom complete response was obtained after external radiotherapy in MRI (P=0.049). Any statistically significant difference was not found between groups of patients who did, and did not develop metastases as for primary tumor standardized uptake value (SUVmax, SUVmean), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) values. In patients without metastasis, heterogeneity factor (HF) was found to be statistically significantly lower than those who developed metastasis (P=0.026). **Conclusion:** It is possible to predict poor prognostic patients with the help of HF, although we could not predict the resistant patients to treatment of primary tumor.

Hell J Nucl Med 2021; 24(1): 18-24 *Epub ahead of print: 20 April 2021* *Published online: 30 April 2021*

Introduction

Cancer of the cervix uteri, which takes fourth place in the world after breast, colorectal and lung cancer, is the second most frequently seen cancer in countries with low socioeconomic income and it occupies third place among causes of mortality [1].

In more than 90% of the patients,cervix uteri cancer was found to develop years after HPV contamination. While the most frequently human papilloma virus (HPV) types 16 and HPV 18 (in 71% of patients) are detected, HPV types 31, 33, 45, 52 and 58 are responsible for the contamination in the remaining 10% of these patients [2]. Different mutations have been identified in squamous and adenocarcinoma cancer of the cervix uteri. Human papilloma virus 16 and EGFR mutation are detected more frequently in squamous cell carcinoma of the uterine cervix while KRAS mutation, and HPV 18 indicating a worse prognosis develop in adenocarcinomas seen with an incidence rate of 25 percent [3-5].

Staging is an important prognostic factor in carcinoma of the uterine cervix. Magnetic resonance imaging is safely used for staging cervical tumors larger than 1cm for a therapeutic decision to apply surgery or concomitant chemoradiotherapy can be made with more than 90% reliability [6]. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) included lymphatic involvement in the staging process, the importance of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) increased further in staging. Fluorine-18-FDGPET/CT is superior to computed tomography and MRI in the determination of lymph node involvement, local recurrence and metastasis in carcinoma of the uterine cervix [7, 8].The NCCN treatment guideline recommends imaging with ^{18}F-FDGPET/CT in the pre-treatment evaluation of the patients beginning from Stage 1B3 [9]. In our previous study, we eva-

luated the relationship between HPV contamination and radioresistance [10]. In this study, the aim is to be able to identify the small group of our locally advanced patients who did not respond to concomitant chemoradiotherapy by using metabolic parameters in the ^{18}F-FDG PET/CT images before treatment.

Subject and Methods

Fifty two patients treated in our clinic between the years 2015 and 2018 were evaluated retrospectively after obtaining ethics committee approval. Patients with stage IB2-IIIC2, according to FIGO 2018 criteria, carcinoma of the cervix uteri, who could not be operated were included in the study.

Patients with squamous carcinoma of the cervix uteri were included in the retrospective study after obtaining their informed consent. In their first biopsy paraffin blocks prepared for diagnostic purposes, the presence of HPV DNA was first investigated by polymerase chain reaction (PCR). The tests were conducted in Acibadem Labmed Laboratories with the financial support of Turkish Society for Radiation Oncology (APDP-TROD-2019-2).

The characteristics of the patients are summarized in Table 1.

After all patients were diagnosed based on their biopsy results, radiological staging with ^{18}F-FDG PET/CT, and MRI was performed. Curative chemoradiotherapy was planned with concurrent administration of weekly doses of 40mg/m^2 cisplatin. Intensity-modulated externalradiotherapy (IMRT) was applied with daily doses of 1.8-2Gy, for five days a week reaching a total dose of 45-50Gy. An additional dose of 6-10Gy was delivered to the areas with pathological lymph node involvement in ^{18}F-FDG PET/CT.

At the end of the external radiotherapy, an additional dose of 10-14Gy was administered to those whose parametrial involvement continued during the interim evaluation before brachytherapy. Maintenance chemotherapy was given to those with a progressive disease. Before brachytherapy, all patients had pelvic MRI for planning and early evaluation of the treatment response. The doses and volume to be delivered were decided by considering the residual volume and examination findings in axial and sagittal sections at T2-weighted MRI. The new tumor volume after external radiotherapy was calculated by the formula considering tumor volume detected in MRI based on the following formula: Width x Length x Height /2.

When applying brachytherapy, the tumor volume and organs at risk of all patients were contoured as defined by The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC ESTRO) [11] and a computer-based three-dimensional conformal after loading system was used in treatment with Ir192 (Nucletron-Electa). The treatment was completed with tandem ring or ovoid applicator, once or twice a week for 4-5 sessions. Treatment lasted for mean 8 weeks (7-20). The treatment dose was determined based on tumor volume, and total dose was calculated as EqD2.

Control examinations were performed at 3-month intervals after the treatment was completed. In the third month after the treatment, the metabolic response was evaluated by ^{18}F-FDG PET/CT, and 6 months later by clinical examination and vaginal smear. In subsequent controls, MR evaluation was performed every six months.

Table 1. *Patients characterists.*

		All groups	
		n	%
Stage	2B	28	53.85
	3C1	16	30.77
	3C2	8	15.38
HPV	Negative	22	42.31
	Positive	30	57.69
Early Response	Complete	38	73.08
	Rest	14	26.92
^{18}F-FDG PET/CT	Complete	48	92.23
	Progressive	1	1.09
	Partial	3	5.70
Smear at 6 months	Not-contaminated	28	93.33
	HCIL	2	6.67
Local Control	Local control achieved	48	92.31
	Local control failed	4	7.69
Metastasis	Metastasis (-)	47	90.38
	Metastasis (+)	5	9.62

^{18}F-FDG PET/CT imaging protocol

The ^{18}F-FDGPET/CT images evaluated in our study were obtained before the treatment for the staging of the patients, in the clinics where they were referred to or in our hospital. In this way, in our daily practice we wanted to determine that the data obtained in the literature are reproducible with the shots made by the referred hospitals. So, the probability of the data obtained in this way to be biased will also decrease. However, the calculation of metabolic tumor parameters in the first ^{18}F-FDG PET/CT of all patients were reassessed by our hospital nuclear medicine specialist.

In patients who underwent PET/CT in our clinic before treatment, whole-body PET scans were performed using LSO-based full ring PET scanner (Siemens Biograph 6, Chicago, IL, USA Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany).

^{18}F-FDG PET/CT analysis

Images were visually interpreted by experienced nuclear medicine specialist. The increased ^{18}F-FDG uptake at the cervix were identified as representing primary tumorif the accumulation of ^{18}F-FDG was increased relative to comparable normal surrounding tissues. Maximum standardized uptake value (SUVmax), SUVmean, and metabolic tumor volume (MTV) (cm^3) of the primary cervix tumor were estimated automatically from the volumes of interest (VOI) identified by the work station. The margin of the target lesion inside the VOI was automatically produced and voxels greater than a threshold of 41% of SUVmax in the VOI were defined to measure MTV and SUVmean.

Total lesion glycolysis (TLG) was calculated by multiplying MTV with SUVmean [12]. Heterogeneity factor (HF) which shows the variable cells in tumor was quantified by dividing the SUVmax with the SUVmean of the primary tumor. A lymph node was considered PET-positive and accepted as metastatic if its ^{18}F-FDG uptake was greater than blood pool activity or uptake of the surrounding background tissues.

Evaluation of the treatment response

To evaluate the treatment response, ^{18}F-FDG PET/CT was repeated three months after finishing concomitant chemoradiotherapy. The criteria used to evaluate treatment response in ^{18}F-FDG PET/CT imaging after treatment are as follows: Complete metabolic response was defined as absence of abnormal ^{18}F-FDG uptake noted on the pre-treatment ^{18}F-FDG PET/CT study, partial metabolic response was defined as any persistent abnormal ^{18}F-FDG uptake at these sites greater than normal surrounding tissues and progressive disease (PD) was defined as any new sites of abnormal ^{18}F-FDG uptake that were not present on the pretreatment ^{18}F-FDG PET/CT study [13]. The diagnosis of local recurrence was made by biopsy,clinical examination and radiological evaluation after the clinical and metabolic complete response was obtained.

Statistical evaluation

In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. Descriptive statistical methods (mean, standard deviation, median, interquartil range) were used in the evaluation of data, and the distribution of variables was analyzed using Shapiro-Wilk normality test. Independent t test was used in the comparison of binary groups of variables demonstrating normal distribution, while Mann-Whitney U test was employed in the comparison of binary groups of withoutnormaldistribution. Also, qualitative data were compared using chi-square test. The results were evaluated at the significance level of $P<0.05$.

Results

Patient characteristics

The follow-up period of our patients with an average age of 53 years (42.5-60.75) was 53.5 months (42.5-60.75) (Table 1). The presence of HPV was investigated from the first biopsy paraffin blocks using PCR method.

Treatment doses

Radiotherapy with a total median dose of 85 Eq D2 (84-86) was delivered to all patients. Any statistically significant difference was not observed as for primary tumor SUVmax ($P=0.35$), SUVmean ($P=0.415$) and MTV values among the patients who could and could not get an early response prior to brachytherapy with external concomitant chemoradiotherapy. However, the HF was found to be statistically significantly lower in patients in whom complete response was obtained after external radiotherapy ($P=0.049$).

Assessment of response to treatment

However, with ^{18}F-FDGPET/CT obtained 3 months after the completion of external and intracavitary treatment, it was determined that 48 of 52 patients responded to treatment, but 4 patients were resistant to treatment and did not get a complete response of primary tumor (7.69%). Maintenance chemotherapy was applied to patients who could not get local control. No statistically significant difference was observed between groups with and without local control as for primary tumor SUVmax, SUVmean, MTV, TLG and HF values (Table 2).

In patients without metastasis, HF was found to be statistically significantly lower than those who developed metastasis ($P=0.026$). However any statistically significant difference was not found between groups of patients who did, and did not develop metastases as for primary tumor SUVmax, SUVmean, MTV and TLG values (Table 3).

The effect of HPV on ^{18}F-FDG PET/CT

Contamination with HPV was detected in 30 (57.6%) patients. Human papilloma virus positivity was present in 1 of 4 (7.69%) patients who failed to achieve local control. Any statistically significant difference was not observed between HPV (-) and HPV (+) groups in terms of primary tumor SUVmax, SUVmean, MTV, TLG, HF values (Table 4).

Three of 4 patients whose primary tumor resisted to treatment were HPV negative. However, 22 patients who developed cervical cancer unrelated to HPV were evaluated according to achievement of local control, any statistically significant difference was not found regarding ^{18}F-FDG PET/CT

Table 2. *Metabolic data according to local control.*

		Local control was achieved n:48	Local control was not achieved n:4	P
Primary tumor SUVmax	**Mean±SD**	18,78±9,96	20,36±8,77	
	Median (IQR)	18.1 (11.66-23.41)	20.89 (11.67-28.51)	0,514‡
Primary tumor SUVmean	**Mean±SD**	10.43±4.87	10.55±4.12	
	Median (IQR)	10.49 (6.86-12.54)	10.21 (6.83-14.62)	0.731‡
MTV	**Mean±SD**	40.12±46.24	42.2±11.5	
	Median (IQR)	29.27 (14.46-49.97)	39.75 (33.05-53.79)	0.336‡
TLG	**Mean±SD**	479.31±576.01	441.25±173.64	
	Median (IQR)	267.74 (103.4-617.51)	473.72 (264.45-585.58)	0.514‡
Heterogenity factor	**Mean±SD**	1.66±0.11	1.77±0.13	
	Median (IQR)	1.68 (1.6-1.74)	1.77 (1.64-1.89)	0.122†

†Independent t test ‡Mann -Whitney U test

Table 3. *Metabolic data relative to development of metastases.*

Metastasis		**Metastases (-) n:47**	**Metastases (+) n:5**	**P**
Primary tumor SUVmax	**Mean±SD**	19.1±10.05	17.04±7.7	
	Median (IQR)	18.64 (12.15-24.35)	16.47 (10.78-23.59)	0,740‡
Primary tumor SUVmean	**Mean±SD**	10.57±4.94	9.17±2.95	
	Median (IQR)	10.55 (6.86-12.7)	7.73 (6.7-12.36)	0,733‡
MTV	**Mean±SD**	40.93±46.5	34.11±17.54	
	Median (IQR)	29.76 (14.86-50.31)	32.64 (20.22-48.74)	0,889‡
TLG	**Mean±SD**	495.4±578.63	297.55±166.87	
	Median (IQR)	344.02 (102.16-626.74)	224.24 (158.05-473.72)	0.792‡
Heterogenity factor	**Mean±SD**	1.66±0.11	1.77±0.13	
	Median (IQR)	1.68 (1.6-1.74)	1.77 (1.68-1.87)	0.026†

†Independent t test ‡Mann -Whitney U test

Table 4. Metabolic data according to HPV status of the patients.

		HPV (-) n:22	HPV (+) n:30	P
Primary tumor SUVmax	**Mean±SD**	15.98±7.28	21.05±10.94	
	Median (IQR)	15.9 (10.06-22.59)	19.87 (12.84-26.58)	0.103‡
Primary tumor SUVmean	**Mean±SD**	9.11±4.04	11.42±5.11	
	Median (IQR)	9.09 (5.67-11.96)	10.74 (7.04-13.13)	0.134‡
MTV	**Mean±SD**	32.16±22.89	46.23±54.9	
	Median (IQR)	30.71 (13.31-44.28)	30.85 (15.5-62.36)	0.437‡
TLG	**Mean±SD**	333.98±288.02	580.81±674.01	
	Median (IQR)	284.13 (98.54-497.89)	354.25 (128.97-832.81)	0.229‡
Heterogenity factor	**Mean±SD**	1.66±0.12	1.67±0.09	
	Median (IQR)	1.67 (1.61-1.72)	1.69 (1.6-1.74)	0.566†

†Independent t test ‡Mann- Whitney U test

metabolic data.

Discussion

In the treatment of early stage cervix cancer surgery is performed in the first step. When diagnosed at an advanced stage, the patient should be treated with chemoradiotherapy but recurrence develops in 30% of patients within two years [14]. However, according to the results obtained from the first two EMBRACE studies, it was reported that the treatment of a small group of patients was not successful even if high dose radiotherapy was administered [15].

Since in our previous study, metastasis developed within a short time in patients who were resistant to therapy, we aimed to detect these patients with pre-treatment ^{18}F-FDG PET/CT metabolic data. However, our study data with the help of HF detected patients with the same histological group and poor prognosis. Although we predict poor prognostic patients with the help of HF, we could not identify patients whose primary tumor resisted to concomittant chemoradiotherapy. Some authors support, but others refute the predictive capacity of published ^{18}F-FDG PET/CT parameters.

In series of 93 patients with locally advanced carcinoma of the uterine cervix Chong et al. (2017) evaluated pre-treatment ^{18}F-FDG PET/CT data, and showed relatively shorter recurrence-free survival in patients with high HF, and reported that the HF may be an auxiliary parameter such as nodal SUVmax in determining patients whose disease will recur [16].

In all studies on locally advanced disease (including non-squamous cancers with a poor clinical course) [17-20] patients who developed recurrence were previously identified with ^{18}F-FDG PET/CT metabolic data. However, in these studies, no assessment was made regarding primary tumor control.

In a study by Hong (2019), all of the ^{18}F-FDG PET/CT of the patient group consisting of 129 patients with only squamous cell carcinoma of the uterine cervix were evaluated together with HPV data, as in our study, at the same center. Three risk groups were identified, including the presence of nodal SUVmax and HPV. In the study, nodal SUVmax, nodal MTV, and HF were found to be predictive in determining recurrence. In the group of patients with a worst case prognosis, HPV-positivity was detected in patients with high nodal SUVmax [21].

Grigysby et al. (2008) also showed that tumor heterogeneity is an important factor for a less favourable prognosis and high primary tumor SUVmax at diagnosis was predictive of subsequent biopsy-proven local recurrence [22].

In our study, HF was statistically lower in patients who had early response in MRI before brachytherapy than those who did not get early response to external radiotherapy (P= 0,049). A complete response was not achieved in some of the patients who have residuel tumor in the cervix after external treatment in MRI. In this non-early responded group, there was no statistical difference in terms of HF in patients with or without complete response of primary tumor to treatment (P=0,122) (Table 2).

In our previous study, we found that metastasis developed over a short period of time in patients who resisted to treatment in the primary tumor. Heterogeneity factor was found to be lower in patients who did not develop metastasis compared to patients who developed (P=0.026). This sug-

gests that the heterogeneous tumor has the potential to metastasis (Table 3).

Also, there was not a statistically significant difference between HPV positive and negative groups in terms of heterogeneity or other ^{18}F-FDG PET/CT parameters (Table 4). As with head and neck cancers, the presence of HPV can facilitate the effect of radiotherapy. But, as in the Hong's study (2016) [20], we observed that a small number of HPV 16-positive patient did not have a full response to treatment and metastases developed.

In a succesful study which were designed to predict on local control, Chen et al. (2018) used the gray level run-emphasis (GRE) tissue index based on tumor heterogeneity. Using this index, they were able to predict local recurrence and survival in patients with a poor prognosis. In the study, the prognosis of patients with squamous cell cervical cancer was better than those with non-squamous types. In addition, pelvic residual disease, recurrence, and shorter survival times were detected in patients with low index according to the index they had used.They demonstrated that response to radiotherapy changed even though they had the same histology [23].

Since the 3-dimensional brachytherapy unit has been actively working in our center since 2015, limited number of patients, and our shorter follow-up time decreased the strength of our study. Nevertheless, since a similar treatment dose could be applied to the patients and all patients diagnosed with squamous cell carcinoma of the uterine cervix, our study had a homogeneous design and demonstrated that there may be different treatment responses in types of carcinoma of the uterine cervix with similar histology. Standard ^{18}F-FDG PET/CT parameters have not been created yet to predict patients for whom primary tumor control cannot be achieved. Tissue culture study in which different forms of brachytherapy fractionation would be applied for previously determined resistant group had been planned. So we have not obtained the data that will form the basis of the next study that we have planned to do. In order to create tailor-made treatment modalities or radiotherapy dosing regimens, reliable and reproducible parameters which take tumoral tissue differences in the same histology are needed.

In conclusion, the patient group with recurrence could be predicted with the HF by the help of ^{18}F-FDG PET/CT metabolic parameters but the subgroup of patients whose primary tumor resistant to treatment could not be determined. In terms of HF there was no statistical difference between early responder and non response groups to external radiotherapy and among HPV groups. Based on the results we have, knowing the heterogeneity factor in advance may be useful for patient selection for systemic treatment options to be developed. However, new criteria that can predict the treatment-resistant group are still needed to develop studies to increase local control.

Ethıcal consent

The local ethics committee of our hospital approved this retrospective study, and informed consent was obtained from all individual participants included in the study.

Acknowledgement

We would like to thank Rana Konyalıoğlu, statistics.
Doç.Dr. Savaş Karyağar and Dr.Osman Güven, Nuclear Medicine,data collection.
Prof. Dr. Esra Kaytan Sağlam, Istanbul University Institute of Oncology Radiaton Oncology,study evaluation.

Funding

The PCR tests of HPV DNA were conducted in Acibadem Labmed Laboratories with the financial support of Turkish Society for Radiation Oncology (APDP-TROD-2019-2).

The authors declare that they have no conflicts of interest.

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