research article

FDG PET-CT as an important diagnostic tool and prognostic marker in suspected recurrent cervical carcinoma after radiotherapy: comparison with MRI

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Background. Recurrent disease in post-irradiation patients with cervical cancer is often difficult to delineate on magnetic resonance imaging (MRI), because posttreatment changes can have a similar appearance, and further evaluation is often required. The aims of the study were to evaluate positron emission tomography/computed tomography with 18F-fluorodeoxyglucose (FDG PET-CT) diagnostic role in suspected recurrent cervical cancer after radiotherapy, compare it to MRI, and assess their prognostic impact in these patients.

Patients and methods. This cohort retrospective study included patients previously treated with radiotherapy for carcinoma of uterine cervix with suspected recurrence, who had undergone MRI of abdomen and pelvis, and were subsequently evaluated on FDG PET-CT, with minimum follow-up period of 12 months.

Results. In the total of 84 patients included in analysis, MRI *vs.* FDG PET-CT showed sensitivity, specificity and accuracy of 80.1%, 52.4% and 66.7%, *vs.* 97.6%, 61.9% and 79.8%, respectively. Patients with positive findings on MRI (Log Rank, $p = 0.003$) and PET-CT (Log Rank, $p < 0.001$) had shorter progression-free survival (PFS) than those with negative results. In univariate Cox regression models, MRI and FDG PET-CT results were found to be related to PFS ($p = 0.005$ and $p < 0.001$, respectively). However, multivariate analysis proved only FDG PET-CT to be independent prognostic factor, where patients with positive FDG PET-CT results had almost nine times higher risk of progression ($p < 0.001$).

Conclusion. FDG PET-CT represents useful diagnostic tool in suspected recurrent cervical cancer after radiotherapy, showing high sensitivity in its detection. In addition, it is an independent factor in predicting progression-free survival in these patients.

Key words: uterine cervical neoplasms; recurrence; PET-CT; MRI; progression-free survival; sensitivity and specificity

Introduction

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death in women.[1] In low-and middle-income countries, it is even more common, being the second most common cancer among women and the third most common in terms of mortality.[2]

Recurrent disease is defined as tumor re-appearance or development of metastatic disease more than six months after the end of treatment. The recurrence rates of International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA and IIB–IVA cervical cancer are 11% to 22% and 28% to 64%.[3] Treatment options in recurrent cervical cancer are limited. Patients with local

recurrence may be candidates for radical retreatment, with disease free survival rates reaching up to 40%.[4] However, more widespread disease can only be subjected to systemic chemotherapy with minimal chances of success or supportive care. Therefore, improved survival and outcomes require early detection of recurrence and precise localization of the disease spread.[5]

Magnetic resonance imaging (MRI) plays a significant role not only in guiding the primary treatment in women diagnosed with cervical cancer, but also in treatment response assessment and surveillance. However, recurrent disease in post-irradiation patients is often difficult to delineate, because posttreatment changes can have a similar appearance, and further evaluation is often required.[6]

Positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (FDG PET-CT) provides functional data about the glucose metabolism of the tumor, nodes, and metastases, in addition to morphological data from CT which are used for topographical localization and attenuation correction. One of the most important advantages of FDG PET-CT is its whole-body evaluation, *i.e.* the ability to detect disseminated disease along with locoregional status, compared to standard MRI. FDG PET-CT has an important role in cases of suspected recurrence where MRI or CT are equivocal, as suggested by the Royal College of Radiologists guidelines and in cases of local vaginal recurrence seen on CT or MRI as per the Cancer Care Ontario guidelines.[5] However, Updated National Comprehensive Cancer Network (NCCN) guidelines Version 1.2021, state FDG PET-CT as the preferred modality for surveillance imaging in stage II–IV disease and in suspected recurrence or metastasis.

The prognosis of cervical cancer is influenced by the disease stage, tumor grade and histological subtype, patient age, intratumoral oxygenation, tumor vascularity, DNA ploidy, and the presence of HPV infection.[7] Patients with higher FIGO stage, over 50 years old, with adenocarcinoma compared to those with epidermoid carcinoma, as well as with high, compared to low and intermediate-grade tumors, tend to have worse prognosis.[8,9] Pretreatment MRI and FDG PET-CT were also shown to have prognostic role in cervical cancer patients. Maximal standardized uptake value (SUVmax), lymph node status and volume-based FDG PET-CT parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as well as the mean apparent diffusion coefficient (ADC) on MRI have been shown to be of prognostic value in a number of studies.[10-15]

With increasing data available on imaging in various malignancies, there is no doubt that the information provided by FDG PET-CT is invaluable in guiding patient' management. However, data on FDG PET-CT imaging in gynecological malignancies are limited and more studies are needed to establish its utility especially in cancer of uterine cervix.[7] Therefore, the aims of this research were to evaluate diagnostic performances of FDG PET-CT in suspected recurrent cervical cancer after radiation therapy, and its prognostic impact in these patients, with comparison to MRI, clinical and histopathological factors.

Patients and methods

Study population

This retrospective cohort study included all consecutive patients previously treated with radiation for carcinoma of the uterine cervix (with or without surgery and chemotherapy), who underwent PET-CT examination for suspected recurrent disease from January 2014 until December 2019, and who fulfilled certain criteria. Indications for FDG PET-CT were: symptoms suspecting recurrence, new lesions on surveillance imaging studies, or abnormal results on physical or cytologic examination on routine surveillance. Inclusion criteria were: (1) histopathological confirmation of cervical cancer; (2) previous treatment by the standard therapeutic option which included radiation treatment, and was completed at least six months prior to PET-CT examination; (3) available data regarding initial disease stage and tumor histopathology; (4) MRI of the pelvis and abdomen within three months of FDG PET-CT examination; (5) follow-up for at least one year after FDG PET-CT. Exclusion criteria were previous histopathological confirmation of another malignant tumor, and unavailability of obtaining all necessary clinical and follow-up data. Data regarding initial disease stage and tumor histological type and grade were acquired from patients' medical documentation. Initial clinical staging was performed according to the FIGO 2009 classification system for cancer of uterine cervix. WHO criteria from 2004 were used in defining histopathological type, and tumor grade was determined according to the modified Broder's system or architectural and cytological criteria.[16,17] The study was approved by the Institutional Ethics Committee (approval No.

668/6) and written consent was obtained from all patients.

FDG PET-CT imaging

PET-CT examination was performed on hybrid PET-CT scanner Biograph True64 (Siemens Medical Solutions USA Inc, Malvern, PA, USA). Patients were given an average dose of 5.5 MBq/kg body weight ^{18}F-FDG intravenously, after starving period of at least 6 hours, and with blood glucose level below 11 mmol/l. After resting period (60–90 minutes following FDG administration), patients underwent low-dose CT (120 kV, 40 mAs, slice thickness 5 mm, pitch 1.5, rotation time 0.5 sec) without contrast, for topographic localization and attenuation correction. That was followed by PET acquisition (standard whole-body procedure) of region from the base of scull to the mid-thighs (3 minutes per bed, 6–7 beds per examinee) in three-dimensional mode. Obtained PET-CT data were interpreted on Syngo Multimodality Workplace VE31A (Syngo 2008B, Siemens, Medical systems, Erlangen, Germany). Any lesion with high ^{18}F-FDG uptake on PET-CT was defined as positive for recurrent disease if any abnormal ^{18}F-FDG uptake was observed after exclusion of benign and physiological lesions, with or without clearly visible corresponding CT malformation. Lesions were analyzed qualitatively and semi-quantitatively. For assessment of glucose metabolism level in active disease sites, SUVmax was used, that is singular voxel within volume of interest with maximal standard uptake value, calculated as follows: activity in tissue (count/pixel/s) multiplied by calibration factor and divided by dose applied (MBq/kg of body weight). Tumor lesions were defined by volume of interest (VOI) placed around every suspected focus of increased FDG uptake, with 50% threshold. The measurements of SUVmax were done on reconstructed images, after using ordered subsets expectation maximization as statistical reconstruction method, but no absolute cut-off value of SUVmax was used for

TABLE 1. Patients' characteristics

Characteristic	Value
Age *(years)*	
Mean ± sd	53 ± 11
Initial FIGO disease stage, *n (%)*	
IB	9 (11%)
IIA	2 (2%)
IIB	38 (45%)
III	26 (31%)
IV	9 (11%)
Tumor histological type, *n (%)*	
Squamous cell	70 (83%)
Adenocarcinoma	11 (14%)
Adenosquamous	2 (2%)
Small cell	1 (1%)
Tumor grade, *n (%)*	
Low grade	6 (7%)
Intermediate grade	50 (60%)
High grade	10 (12%)
Unknown	18 (21%)
Previous treatment, *n (%)*	
Surgery with (chemo)radiotherapy	11 (13%)
Radiotherapy only	10 (12%)
Radiotherapy with concurrent chemotherapy	49 (58%)
Primary (chemo)radiation with salvage hysterectomy	14 (17%)
MRI findings, *n (%)*	
Positive	54 (64%)
Negative	30 (36%)
PET-CT findings, *n (%)*	
Positive	57 (68%)
Negative	27 (32%)

MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography

TABLE 2. Diagnostic performance of MRI and PET-CT

	TP(n)	TN(n)	FP(n)	FN(n)	Sensitivity (%)	Specificity (%)	Accuracy (%)
MRI	34	22	20	8	80.1%	52.4%	66.7%
PET-CT	41	26	16	1	97.6%	61.9%	79.8%

FN = false negative; FP = false positive; MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography; TN = true negative; TP = true positive

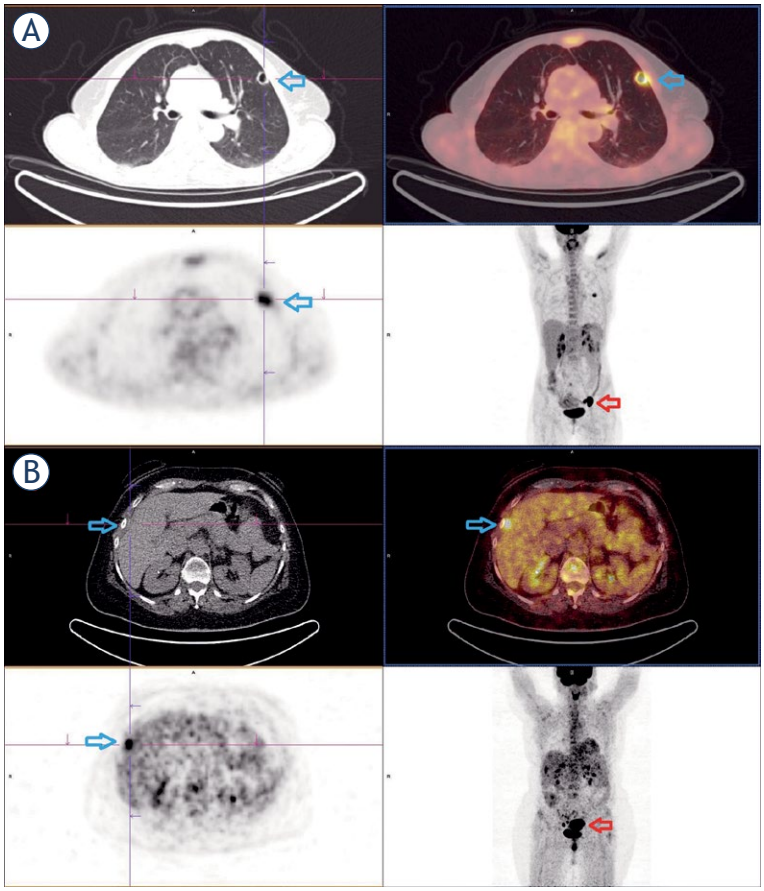

FIGURE 1. (A) A 51-year-old patient, with squamocellular carcinoma, presenting on FDG PET/CT with metastasis in left upper lung (blue arrow), and left iliac lymphadenopathy (red arrow). On MRI only left iliac disease was detected. **(B)** A 59-year-old patient, with adenocarcinoma, presenting on FDG PET/CT with active locoregional disease in pelvis (red arrow) also seen on MRI, and peritoneal deposit in front of the right liver lobe (blue arrow) which was missed by MRI.

the diagnosis. Images were interpreted separately by two nuclear medicine physicians, unaware of results of other imaging modalities. In cases of discrepancy, images were presented to multidisciplinary team and experts' opinion was adopted. Findings were classified as positive or negative for recurrent disease, and positive findings were further categorized as locoregional recurrence only, or distant spread of disease (with or without locoregional disease).

MR imaging

FDG PET-CT findings were compared to written reports of MR imaging. T1 weighted, T2 weighted, diffusion-weighted images (DWI), as well as contrast enhanced images of abdomen and pelvis were acquired in all patients. All findings were classified as positive or negative, based on standard evaluation criteria by visual characteristics.

Final diagnosis of recurrent disease, which was used as a gold standard in calculating diagnostic accuracy parameters for MRI and PET-CT, was made by either histopathological examination or clinical and imaging follow-up within the first six months after PET-CT.

Follow-up

Follow-up data were obtained from medical records, surveillance was done clinically, with imaging (CT and/or MRI and/or FDG PET-CT) performed once a year, with maximum follow-up period up to 5 years. Progression was defined as occurrence of cancer related death, new lesions seen on follow-up imaging, or progression in size and/or metabolic activity of existing lesions. Progression-free survival (PFS) was calculated from the day of FDG PET-CT examination until detected disease progression, or the end of follow-up period if no progression was detected. Median follow-up duration time was 18 months.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp, Armonk, NY, USA). Kaplan-Meier survival curves and Log Rank tests were used to analyze the survival data in patients with positive/negative MRI, positive/negative PET-CT findings, and with negative/only locoregional disease/distant disease present on FDG PET-CT. Univariate and multivariate Cox regression analyses were fitted to estimate the impact of patients' age, initial tumor stage (stages IB and IIA *vs.* stages IIB, III and IV), histological type (squamocellular *vs.* other), tumor grade (grades 1 and 2 *vs.* grade 3), MRI results (positive *vs.* negative) and FDG PET-CT results (positive *vs.* negative). Calculated p value < 0.05 was considered statistically significant. Sensitivity, specificity and accuracy for MRI and PET-CT were calculated on a patient-based level.

Results

A total of 84 patients were included in the analysis, with mean age 53 ± 11 years. The majority of patients were presented with locally advanced disease on initial diagnosis, where stage IIB or higher was diagnosed in 73 patients (87%), while the minority was diagnosed with early disease (*i.e.* stage IB or IIA). Most common histological tumor type

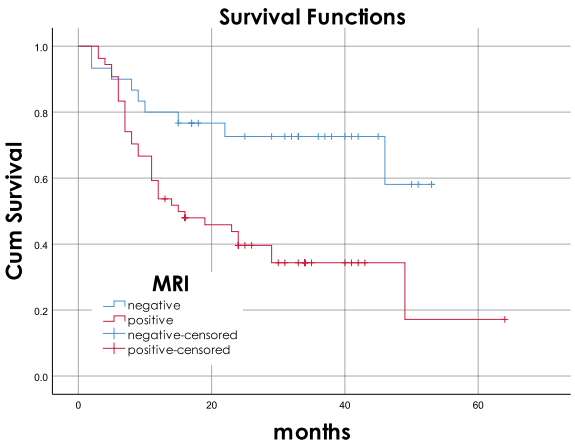

FIGURE 2. Kaplan-Meier survival curves showing progression free survival for patients with positive and negative magnetic resonance imaging; Log Rank, p = 0.003.

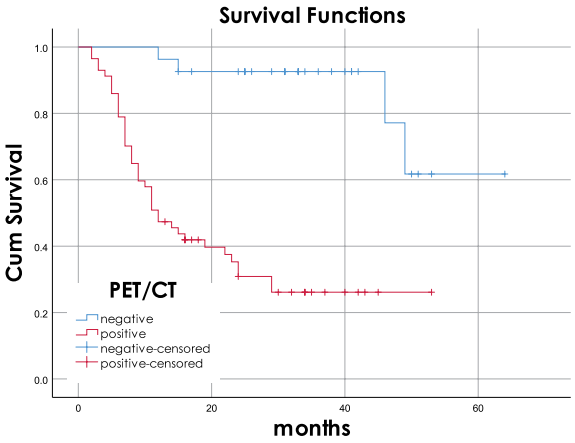

FIGURE 3. Kaplan-Meier survival curves showing progression free survival for patients with positive and negative fluorodeoxyglucose positron emission tomography/computed tomography; Log Rank, p < 0.001.

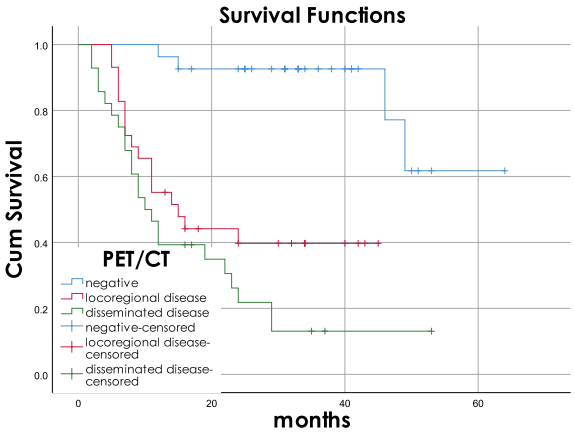

FIGURE 4. Kaplan-Meier survival curves showing progression free survival for patients with normal findings on fluorodeoxyglucose positron emission tomography/computed tomography, locoregional recurrence, and presence of disseminated disease (with or without locoregional disease); Log Rank, p < 0.001.

TABLE 3. Univariate Cox regression analysis of possible progression-free survival predictors in suspected recurrent cervical cancer (n = 84)

Predictor	HR (95% confidence interval)	p value
Age	1.013 (0.987–1.040)	0.336
Initial stage (IB/IIA vs. IIB/III/IV)	2.024 (0.753–5.962)	0.155
Histological type (squamocellular vs. other)	1.245 (0.597–2.598)	0.558
Histological grade (1/2 vs. 3)*	0.831 (0.448–1.905)	0.831
MRI (positive vs. negative)	2.873 (1.370–6.027)	0.005†
PET-CT (positive vs. negative)	9.491 (3.302–27.274)	< 0.001†

HR = hazard ratio; MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography; * = analysis was conducted on n = 66 patients with known tumor grade; † = statistical significance (p < 0.05)

TABLE 4. Multivariate Cox regression analysis of possible progression-free survival predictors in suspected recurrent cervical cancer (n = 84)

Predictor	HR (95% confidence interval)	p value
Age	0.995 (0.966–1.024)	0.727
Initial stage (IB/IIA vs. IIB/III/IV)	1.605 (0.520–4.957)	0.411
Histological type (squamocellular vs. other)	0.892 (0.419–1.898)	0.766
MRI (positive vs. negative)	1.959 (0.888–4.323)	0.096
PET-CT (positive vs. negative)	8.787 (2.877–26.834)	< 0.001*

HR = hazard ratio; MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography; *statistical significance (p < 0.05)

was squamocellular carcinoma, which was proven in 70 patients, and other types were adenocarcinoma in 11 patients, 2 adenosquamous cancers and one small cell carcinoma. Histological tumor grade was known in 66 patients, whereas in remaining 18 patients data regarding tumor grade were not available. All clinical, histopathological and imaging data are presented in Table 1.

Magnetic resonance imaging results were positive for recurrent tumor in 54 patients (64%), while 30 patients (36%) had normal MRI findings. Sensitivity of MRI in detecting recurrent disease was 80.1%, with 52.4% specificity. Positive predictive value of MRI was 63% and negative predictive value was 73.3%. Overall accuracy of MRI in suspected recurrent cervical cancer was 66.7%.

Twenty-seven patients (32%) had negative FDG PET-CT findings, with no recurrent disease. Out of the remaining 57 patients that were positive, 29 (35%) had only locoregional hypermetabolic lesions, six (7%) were diagnosed with distant metastasis, while 22 women (26%) had both locoregional

and distant spread of the disease (Figure 1). FDG PET-CT showed better diagnostic performance compared to MRI, with sensitivity 97.6%, specificity 61.9%, PPV 71.9%, NPV 96.3% and overall accuracy of 79.8% (Table 2).

Disease progression was detected in 44 patients during follow-up. In two patients, disease progression was confirmed by histopathology, 16 women had progressive disease on follow-up PET scan, and in remaining 26 women, progression was diagnosed based on clinical signs/examination and conventional imaging (CT/MRI). Patients with positive MRI had mean PFS time of 27.2 ± 3.6 months, whereas in those with normal findings, PFS was 40 ± 3.6 months ($p = 0.003$) (Figure 2). With regard to FDG PET-CT, PFS in patients with detected recurrence was 22.3 ± 2.6 months, and for those with negative PET scan results was 55.2 ± 3.7 months ($p < 0.001$) (Figure 3). In addition, patients with only locoregional disease on FDG PET-CT had longer PFS (24 ± 3.3 months) than women with distant metastases on PET scan (17.6 ± 3.1 months) ($p < 0.001$) (Figure 4). In univariate Cox regression models, MRI findings and FDG PET-CT results were found to be related to PFS ($p = 0.005$ and $p < 0.001$, respectively), whereas age, initial disease stage, histological type and tumor grade were not proven to be predictors of progression (Table 3). However, in multivariate analysis only FDG PET-CT remained statistically significant predictor of progression with HR 8.787 (95% CI = 2.877-26.834) (Table 4).

Discussion

This study evaluated diagnostic performances of FDG PET-CT and MRI in women with suspected recurrent carcinoma of uterine cervix previously treated with radiation therapy, and their impact as prognostic factors, together with age, disease stage, and histopathological tumor type and grade, in predicting progression free survival in these patients. The results suggest that FDG PET-CT is more sensitive and accurate in detection of recurrence and metastases of carcinoma of uterine cervix after radiation than MRI. Moreover, positive FDG PET-CT findings are associated with the disease progression.

MRI showed good sensitivity and low specificity. That is only partially in concordance with literature data, where the reported sensitivity and specificity of MRI in pelvic recurrence is higher, and varies between 82 and 100% and between 78 and 100%, respectively, in the systematic review and meta-analysis by Meads *et al*.[18] However, our sample included only patients previously treated with radiation, and it is known that capabilities of MRI could be subpar in these settings. With regard to FDG PET-CT, the same authors found pooled sensitivity of 94.8% and specificity of 86.9% by analyzing nine studies with mostly symptomatic patients, which is comparable with our study in terms of sensitivity, whereas we had lower specificity. However, the sensitivities and specificities of the detection of local and distant recurrence with FDG PET-CT in all researched papers ranged between 83 and 100% and between 50 and 100%, thus being in concordance with our results. In another meta-analysis, by Chu *et al*.[19], which included eight PET-CT papers, the pooled sensitivity and specificity were 94% and 84%, respectively. Overall low specificity in our research, of both MRI and FDG PET-CT, could be explained by high number of false positive findings, caused mostly by nonspecific inflammatory changes and in two cases by occurrence of another malignancy (renal cell carcinoma and low-grade malignant mesenchymal tumor).

To the best of our knowledge, this is the first study to directly compare FDG PET-CT with MRI on a patient level in suspected recurrent uterine cervix cancer, in terms of diagnostic accuracy. In our research, FDG PET-CT had better diagnostic performance than MRI in detecting recurrent disease, with regard to both sensitivity (97.6% *vs*. 80.1%) and specificity (61.9% *vs*. 52.4 %). Pallardy *et al*.[20] evaluated PET-CT in 40 patients with suspected recurrence, and compared it to CT or MRI, with a sensitivity of 94% for PET-CT compared to 42.5% for conventional imaging. Bjurberg *et al*.[21] also analysed PET-CT in 36 suspected recurrent patients, and comparison was done with conventional imaging (CT or MRI). They achieved 100% sensitivity and specificity for PET-CT, and 92% sensitivity and 78% specificity for CT/MRI. A prospective study of 40 patients with recurrent cervical carcinoma that underwent restaging on PET identified significant superiority of PET imaging compared to CT/MRI in detection of metastatic lesions (sensitivity 92% *vs*. 60%).[22] In another study, by Yen *et al*.[23] CT/MRI falsely downstaged 38.4% of the 125 patients and falsely upstaged 17.6%, with 85.4% of the falsely downstaged patients having extra-pelvic recurrence. In contrast, FDG PET falsely downstaged only 15.2% and falsely upstaged 16% of patients. The authors concluded that, for recurrent cervical cancer, the benefits of FDG PET exceeded those of

CT/MRI owing to the ability of FDG PET to identify extra-pelvic metastases and its higher sensitivity and specificity.

In our research, MRI and PET-CT findings in patients with suspected recurrence following radiotherapy were found to be linked with progression-free survival in both, Kaplan Meier analysis and univariate Cox analysis. However, only FDG PET-CT was proven to be an independent prognostic factor by multivariate analysis, and patients with positive PET scan have almost nine times more chance of disease progression. In addition, women with only locoregional disease tend to have better chances of disease-free survival than patients with distant metastasis detected on FDG PET-CT. Patient age, initial disease stage, histological type and grade did not have effect on PFS in our study cohort. With regard to PET-CT detection of recurrence and its impact in prognosis, it is important to mention that the disease evaluation is not only based on tumor visibility but also on tumor metabolic activity, and tumors with high metabolic activity generally have a poor prognosis. In the literature, there are mostly studies that evaluated FDG PET in therapy response assessment and its impact on prognosis, i.e., Grigsby *et al*.[24] showed in their research on 152 patients with mean time of 3 months between end of the standard treatment and PET scan, that patients with new, residual, or no disease demonstrate 5-years survival rates of 0%, 46%, and 92%, respectively. Schwarz *et al*.[25] reported that visual analysis of the PET data in therapy response assessment with three categories (complete metabolic response (CMR), partial metabolic response (PMR), and progressive disease (PD)) predicts survival. The 3-year PFS rate was 78% for CMR, 33% for PMR, and 0% for PD. Kim *et al*.[26] found in their systemic report and meta-analysis, based on 11 studies, that response results of a 18F-FDG PET after definitive radiotherapy with or without chemotherapy were significant prognostic factors in patients with uterine cervical cancer. With regard to patients with CMR after definitive chemoradiotherapy, TLG and MTV are predictive of both overall survival and PFS.[27] On the other hand, Chung *et al*.[28], conducted a research that included 276 patients evaluated on PET-CT for suspected recurrent disease. It was shown that the 5-year PFS and OS rates of patients with a negative PET-CT scan for recurrence were significantly better than those with a positive PET-CT (98.62% *vs*. 17.8 3%, $p < 0.0001$ for PFS, 99.31% *vs*. 85.38%, $p = 0.0015$ for OS), which agrees with our results, however there is some difference in study population, as we only included patients previously treated with radiotherapy.

There are some limitations of our study. It is mostly retrospective study design, which could lead to bias in the choice of patients. However, all patients fulfilled the inclusion criteria with suspicion of recurrence. Furthermore, not all of the progression was proven by histopathology. However, clinical follow-up justifies presence or absence of the disease progression. There is also an issue of heterogeneity in imaging follow-up of patients, which was done by different imaging modalities (CT, MRI, PET-CT), which could influence the time of detected disease progression since not all modalities have the same sensitivity.

Conclusions

Our results suggest that FDG PET-CT is an important tool in clinical practice in the detection of suspected recurrent cervical cancer in post-irradiation patients, with high sensitivity. In addition, it is proved to be an independent factor in predicting progression-free survival in these patients.

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