The impact of PET with ^{18}FDG in radiotherapy treatment planning and in the prediction in patients with cervix carcinoma – results of pilot study*

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Positron emission tomography (PET) is used to distinguish between benign and malign tumors, to diagnose relapse or post-therapeutic changes. Lately, PET is used to predict the treatment response. and also a complementary method to determine target volumes in radiotherapy. Daily using of PET in the oncology praxis can change treatment strategy and improve its outcome. Results of this pilot study show the role of PET with 18-F-fluorodeoxyglucose (^{18}FDG) for staging of cervical carcinoma and in the radiotherapeutic planning.

Between March 2005 and May 2007, 51 patients with cervical carcinoma were treated with combination of external beam radiotherapy and HDR brachytherapy, with or without concomitant cisplatin. The lymphatic nodes treatment field size was determined by PET/CT fusion. Treatment results were evaluated by PET 3 and 9 months after treatment.

The differences in the results of PET and CT were evaluated in this study. In 32 cases (62.75%) the results of PET and CT were identical, in 14 cases (27.45%) the nodal involvement was more extensive according to PET, in 5 cases (9.8%) the nodal involvement was more extensive according to CT. PET results 3 months after treatment were as follows: in 3 cases (5.88%) stable disease, in 35 cases (68.63 %) negative, in 4 cases (7.84%), progression of disease, in 3 cases (5.88 %) partial regression. There were no false positive results caused by inflammatory reaction persisting 3 months after radiotherapy, as was confirmed by repeating PET 9 months after treatment.

The results of this study confirmed the important role of PET in diagnosis and treatment of cervical carcinoma and in determination of target volumes in radiotherapy. PET was found to be a standard staging examination of cervical carcinoma in Masaryk Memorial Cancer Institute. The predictive value of PET has not yet been validated.

Key words: positron emission tomography, 18-F-fluorodeoxyglucose, radiotherapy, cervical carcinoma

Carcinoma of cervix uteri is one of the most frequent malignant diseases in women. In Czech Republic there are 21 new cases on 100 thousands people in year. The incidence increases from 25th year, with the maximum of occurrence between 45th and 49th year. The mortality is 6,9 cases on 100.000 people in Czech Republic, 5,8 in Europe and 4,3 in the world [1, 2].

There are many cases of advanced disease due to late control examination. Cervix cancer clinical stage I and IIa can be treated by surgery. Up clinical stage IIb radiotherapy is the primary treatment modality. Five years survival depends on clinical stage. Curative radiotherapy can be used separate or in combination with chemotherapy. Radiotherapy (RT) is combinated by external beam radiotherapy (EBRT) and brachytherapy (BRT) [2, 3, 4].

The extent of EBRT depends on involvement of lymph nodes. It is necessary to know exactly the involvement before starting of radiotherapy. Standard used diagnostic methods includes CT examination. In this method the involvement of lymph nodes could be detected if these nodes are increased. But there are cases when lymph nodes are involved without their size increasing. Positron emission tomography (PET) using 18-F-fluorodeoxyglucose can detect metastatic lymph node even of normal size. The impact of PET in diagnosis and staging malignant tumor were proved in several trials. In

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our study we wanted to know the impact of PET in staging and radiotherapy planning in cervix carcinoma. The second goal was to determine if it is possible to predict the treatment response. We would like to identify patients with higher risk of relapse and we want them offer more aggressive therapy [5, 6, 7, 8, 9, 10].

Patients and methods

Patients were included to our trial in order as they came to our hospital. All patients had diagnosis of primary cervical carcinoma. In our institute they underwent gynaecologic examination, CT and PET examination and lung scan.

The treatment strategy was done by the results of CT and PET examination. In cases when the involvement on PET was larger then on CT the radiation fields were increased to this area. Radiotherapy was applied on linear accelerator. All patients were irradiated on supine position. The pelvis was irradiated by technique box, paraaortal lymph nodes by opposing fields. We used standard regime of radiotherapy: 1.8 Gy/fraction; 5 fractions/week. The upper board of radiation field depends on lymph involvement: in case no lymph involvement the upper board was in $L_{4/5}$; with involved external illiac nodes the upper board was in $L_{3/4}$ and in case of positive common illiac nodes or paraaortic nodes the upper board was moved to $Th_{12/L1}$. Brachytherapy was applied on HDR source. We used uterovaginal application in 4–7 fractions.

Three months after finishing therapy the gynecologic examination, CT and PET examination were performed. We also followed up the treatment toxicity. Next 6 months later (9 months after therapy) new PET examination was used in some patients to cancel false positive results after RT due radiotherapy toxicity. Patients have been still under continuing follow up in gynecologic and radiotherapy examination.

Statistic works were done by Matlab and Kaplan-Meier methods by Department of Applied Mathematics Faculty of Science Masaryk University.

Results

We included 51 patients with diagnosis of primary cervix carcinoma. Median of age was 49.8 years (29.4–75.1). In 94% of cases it was present squamous cell carcinoma (48 patients). Three patients had other histology: one clear cell carcinoma and two had adenocarcinoma. In cases of squamous cell carcinoma the histological grade I was present in one patient (1.96%), grade II in 23 patients (45%) and grade III in 24 patients (47%). Clinical stages were as follows: IIb 22 patients (43%); IIIb 28 patients (54.9%) and IIIc in one patient (1.96%) (Table 1).

We compared CT and PET examination before treatment. In 32 cases (63%) the involvement on CT was similar that on PET. Fourteen patients had the involvement on PET larger than on CT. Five cases showed larger involvement on CT examination. Three of them had suspect positive lymph nodes and two showed the involvement of lymph nodes.

Using of PET in treatment planning had changed radiation fields in 9 patients (17.4%).

Most of patients were irradiated on pelvis with upper board in L4/5 (57%); two patients had upper board in L3/4 and two had in L2/3. Eighteen patients were irradiated on pelvis and paraaortal lymph nodes. 96% obtained dose 45 Gy in 25 fractions. One patient had dose 34.2 Gy and one 43.2 Gy. Boost on parametria were applied in 28 patients. Most of them obtained dose 6 Gy in 3 fractions. Every patient underwent brachytherapy. Twenty eight had dose 27.5 Gy (54.9%), 13 had 30 Gy. The rest of patients had doses between 25 and 30 Gy.

Gynecologic examination 3 months after finishing of therapy were negative in 86.3%. Seven patients had still the sign of vital tumor. Also CT and PET examination 3 months after therapy were done. CT was done in 44 patients. In 21 cases were the finding was negative of tumor. Nineteen patients had tumor regression and 4 had stationary finding. Two patients had new metastasis in lung.

PET examination showed: three stationary finding, 35 negative finding, four patients had tumor progression and three had tumor regression. Six patients did not undergo PET examination. Regression or negative finding on CT corresponds to negative PET finding. It can be concluded that PET shows the treatment response very early.

We wanted to know if SUV (Standardized Uptake Value), can predict treatment response. The value of SUV were 3–19.22 with median value 9.2. In six patients this value was lost. We predict that higher value of SUV can meen worse prognosis. Statistical tests did not prove our hypothesis.

One patient had lung, liver and bone metastasis diagnosed on CT examination. PET showed positive accumulation only in pelvis. Patient died early on tumor progression. In one case of progression the finding on PET and CT was similar. Two patients had lung metastasis on PET scan. One had suspect lung metastasis. Next follow up showed negative finding. Nine months after finishing therapy 38 new PET were done. There were not any false positive findings (Table 2).

From all 51 patients nine had tumor progression (17.64%). Forty two patients are alive without signs of tumors (82.35%). Eight patients died (15.68%). One of them died on heart atact. Characteristics of dead patients is in Table 3. Characteristic of patients with relapse is in Table 4.

Eight patients had tumor progression. The median time of progression was 10 months. In five cases there were lung metastases. Three patients had progression in lymph nodes, one had liver metastasis and two had progression in bones. The median follow up of all patients is 17 months (4–36 months). The median time of follow up of patients who died was 10 months.

Nine patients had changed treatment volume by the results of PET scan, one of them died on progression. The rest of them are alive without signs of tumor (15.7%).

Table 1. Patients'charakteristics

Numer of patiens	**51**			
Age (median)	**49,8 y** (29,4-75,1 y)			
Follow-up (median)	**17 m** (4-36 m)			
Histology				
squamous cell carcinoma	48 pts.	(94 %)		
adenocarcinoma	2 pts.	(3.92 %)		
clear cell carcinoma	1 pt.	1.96 %)		
grading	G1: 2 %		G2: 45 %	G3: 47 %
Clinical stages (FIGO)	**IIb:** 22 pts. (43.12 %)		**IIIb:** 28 pts. (54.88 %)	**III:** 1 pt. (1.96%)
External radiotherapy	**49 pts.** (96 %); 45 Gy (5x1,8 Gy/week)			
pelvis	29 pts.	(56.86 %)		
pelvis with upper board in L_{2-3}	2 pts.	(3.92 %)		
pelvis with upper board in L_{3-4}	2 pts.	(3.92 %)		
pelvis with upper board in Th_{12}	18 pts.	(35.3 %)		
Brachytherapy	**51 pts.**	(100 %):	5 fractions of HDR	
Chemotherapy	**39 pts.**	(76,47 %):	cDDP/weekly 35-40 mg/m^2	
Acute toxicity G 3-4	**7 pts.**	(14 %)		
Comparison CT and PET examination				
conformity on CT + PET	32 pts.	(62.75 %)		
larger result on PET	14 pts.	(27.45 %)		
larger result on CT	5 pts.	(9.8 %)		
Change of PTV on results of PET	**9 pts.**	(17.4 %)		
SUV (Standardized Uptake Value) Median:	9,2	(3-19.12)		

PTV – planning treatment volume

Table 2. Results of therapy (51 patients with cervical carcinoma)

Local kontrol	44 pts.	(86.27 %)	(gynecol. examination 3 months after therapy)
Residual tumor	7 pts.	(13.73 %)	(gynecol. examination 3 months after therapy)
CT examination 3 months after therapy	**44 pts.**		
without signs of tumor	21 pts.	(41.18 %)	
tumor regression	19 pts.	(37.25 %)	
stable disease	4 pts.	(7. 84 %)	
PET examination 3 months after therapy	**45 pts**.		
without signs of tumor	35 pts.	(68.63 %)	
tumor regression	3 pts.	(37.25 %)	
stable disease	3 pts.	(5.88 %)	
tumor progression	4 pts.	(7.84 %)	
PET examination 9 months after therapy	**38 pts.**		
tumor progression	8 pts.	(15.68 %)	
without signs of tumor	30 pts.	(58.8 %)	
Dissemination (median 10 m.)	**11 pts.**		
Disease free survival	**43 pts.**	(84.43 %)	
Died	**8 pts.**	(15.68 %)	
tumor progression	7 pts.	(13.72 %)	
another reason	1 pts.	(1.96 %)	

Discussion

The cervix carcinoma is one of the most frequent malignant disease in women. The most important prognostic factors are the tumor volume and involvement of lymph nodes. Early stages are treated by surgery, in advanced stage the primary treatment modality is radiotherapy. The accurate staging is very important for the choice of optimal treatment strategy. The tumor of cervix progresses from uterus to pelvic and paraaortal lymph nodes and next to other organs. The involvement of lymph nodes is prognostic factor which influences the local control and overall survival. The control of disease in regional lymph nodes can ensure the control of the disease moreover and can increase overall survival [2, 3, 4].

The ability of CT examination to identify the involvement of lymph nodes is limited. GOG trials showed that CT identifies only 34% of really positive paraaortal lymph nodes [11, 12].

PET investigation is a great help to diagnose malignant disease. The using of 18F-fluorodeoxyglucose can identify tumor cells, which cannot be diagnosed by other diagnostic methods. The value of PET scan in staging malignant disease

Table 3. Characteristics of dead patients

Patients' number	Clinical stage	Grade	SUV_{max}	PET vs. CT
1	3	2	5.3	1
2	3	2	x	1
3	3	3	x	2
4	3	3	x	1
5	2	2	5.6	1
6	3	x	8.8	1
7	3	2	6.2	1
8	3	3	17.4	2

SUV_{max} – Standardized Uptake Value,

Table 4. Characteristic of patients with relapse

Patients' number	Stade	Grade	SUV_{max}	PET vs. CT
1	3b	2	5.3	1
2	3b	2	x	1
3	3b	3	x	2
4	3b	3	x	1
5	3b	3	6.8	1
6	3b	x	8.8	1
7	3b	2	6.2	1
8	3b	3	17.4	2

SUV_{max} – Standardized Uptake Value,

was proved in several trials. It can be used also in diagnose of primum ignotum or relapse of the disease. Several studies wanted to find if there is a predictive value of PET in the treatment of malignant disease. Based on results of these studies it would be possible to increase effect of the treatment [13].

There were published several trials, which used PET in the staging and treatment of cervix carcinoma. The lack of these studies was that most of them are retrospective. Grigsby et al. [14, 15] included 101 patients with cervix carcinoma to his study. Patients underwent pretreatment PET and CT scans. The patients were treated by combination of radiotherapy and chemotherapy. All patients who had positive paraaortal lymph nodes on CT, had similar results on PET scans. Patients were divided into three groups. There were found significant statistical differences among groups. Two years free survival was following: 73% for CT and PET negative; 49% for CT negative and PET positive; 39% for CT and PET positive paraaortal lymph nodes. In conclusion based on this study it can be found that abnormal PET of paraaortal lymph nodes is the most important predictive factor of progression of this disease.

Singh et al. [16] used PET in patients with cervix carcinoma in clinical stage IIIb. Three years survival were in patients without lymph involvement 79%, patients with pelvis positive lymph nodes had survival 58% and paaraortal positive nodes showed survival 29%. GOG studies [12, 13] present that patients in clinical stage IIIb had in 30% involvement of paraaortic lymph nodes. Survival rate of these patients is 26-30%. Singh et al. [16] concluded that PET should be done in all patients with cervix carcinoma before treatment.

High sensitivity and specificity of PET scan was proved in the study of Rose et. al. [17] Patients underwent pretreatment PET scan. Then the operation with lymphadenectomy was done. The aim of this study was to investigate the correlation between PET scan and histology. Sensitivity was found 75%, specificity 92%, positive predictive value 75% and negative predictive value 92%.

PET can be also used in follow up of patients after therapy. Nakamoto et al. [18] included PET into diagnosis of tumor relapse. PET was done 3–7 months after therapy. Local relapses were in all cases positive on PET scan. False positive results were due to inflammation reactions after radiotherapy. Sensitivity was 100%, specificity 60%, positive predictive value 45%, negative predictive value 100%.

In our study the using of PET in pretreatment strategy was studied and nine patients (17.4%) had changed treatment volume by the results of PET scan. It could be said that these patients had be underdosed if we used only standard diagnostic methods.

The SUV value did not predict the treatment response. Several trial occupied this theory, but results are obscure. The trial of Kitagawa et al. [19] showed that pretreated values of SUV can predict viable tumors cells. Patients with lower values had better prognosis. In this study patients with tumor of head and neck were included. Similar results showed studies with rectal carcinomas. On other hand Ichiya et al. [20] published other results. Higher SUV values was in the group of patients, who were in complete remission. Patients with lower values had progression. Very interesting is study of Koike et al. [21] in which patient underwent two phases of PET scan three months after finishing therapy. PET was done 60 and 180 minutes after FDG application. Only retention index showed significant diference between patients with residual tumor or without sign of tumor.

In conclusion, the results of this study confirmed the important role of PET in diagnosis and treatment of cervical carcinoma and in determination of target volumes in radiotherapy. Interesting results which we obtained were that PET shows the effect of the therapy more quickly than CT examination. The fusion of these scans resulted even in some errors. Early new hybrid CT/PET apparatus will be instalated in our institute and it can remove these errors. However PET was found to be a standard staging examination of cervical carcinoma in Masaryk Memorial Cancer Institute. The predictive value of PET has not yet been validated.

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