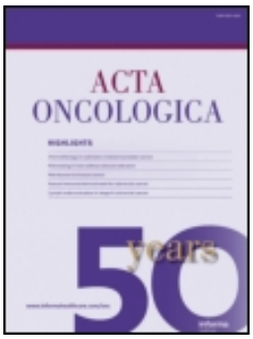

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ORIGINAL ARTICLE

Evaluating repetitive ^{18}F-fluoroazomycin-arabinoside (^{18}FAZA) PET in the setting of MRI guided adaptive radiotherapy in cervical cancer

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Abstract

Background. The aim of this pilot study was to assess tumour hypoxia in patients with cervical cancer before, during and after combined radio-chemotherapy and Magnetic Resonance Imaging (MRI) guided brachytherapy (BT) by use of the hypoxia Positron Emission Tomography (PET) tracer ^{18}F-fluoroazomycin-arabinoside (^{18}FAZA). *Material and methods.* Fifteen consecutive patients with locally advanced cervical cancer referred for definitive radiotherapy (RT) were included in an approved clinical protocol. Stage distribution was 3 IB1, 1 IB2, 10 IIB, 1 IIIB, tumour volume was 55 cm^3 (+/− 67, SD). Dynamic and static ^{18}FAZA -PET scans were performed before, during and after external beam therapy (EBRT) and image guided BT +/− concomitant cisplatin. Dose was prescribed to the individual High Risk Clinical Target Volume (HR CTV) taking into account the dose volume constraints for adjacent organs at risk. *Results.* Five patients had visually identifiable tumours on ^{18}FAZA -PET scans performed prior to radio-chemotherapy and four patients before brachytherapy. One of five ^{18}FAZA PET positive patients had incomplete remission three months after RT, one had regional recurrence. Four of ten ^{18}FAZA-PET negative patients developed distant metastases. The one patient with incomplete remission received 69 Gy (D90) in the HR CTV, whereas all other patients received mean 99 Gy (+/−12, SD). *Conclusion.* PET imaging with ^{18}FAZA is feasible in patients with cancer of the uterine cervix. However, its predictive and prognostic value remains to be clarified. This applies in particular for the additional value of ^{18}FAZA-PET compared to morphologic repetitive MRI within the setting of image guided high dose radiotherapy which may contribute to overcome hypoxia related radioresistance.

Radiation therapy (RT) is the primary modality for the treatment of locally advanced cervical cancer. There is much evidence that hypoxia represents an essential prognostic factor for several cancers, including cervical cancer [1,2].

Hypoxia can be visualised by Positron Emission Tomography (PET) via regional accumulation of hypoxia-specific PET-tracers. Several tracers have been developed for this purpose and fluoromisonidazole (^{18}FMISO) is the hypoxia tracer most extensively studied both in humans and animals [3,4]. However, its major disadvantages refer to its slow clearance kinetics and its high lipophilicity. ^{18}F-fluoroazomycin-arabinoside (^{18}FAZA) has recently been introduced as a hypoxia tracer in pre-clinical studies and showed superior biokinetics in comparison to ^{18}F-MISO in animals [5,6]. The safety and feasibility of ^{18}FAZA was evaluated recently in patients with advanced squamous cell carcinoma of the head and neck [7]. Recently, ^{18}FAZA PET-hypoxia imaging was shown to be able to generate accurate quantitative maps that reflect the underlying microscopic reality (hypoxic cell density) in a tumour model [8].

Currently the most advanced adaptive radiotherapy strategy in cervical cancer is based on anatomical imaging and is relying on the grey zones [9]. This concept has limitations with regard to identifying tumour subvolumes which could be radioresistant. Thus there may be place for introducing biological functional imaging in this setting.

The aim of the present pilot study was to assess feasibility of repetitive hypoxia imaging with ^{18}FAZA

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PET in patients with cervical cancer undergoing MRI guided adaptive radiotherapy. Furthermore, changes in ^{18}FAZA uptake were evaluated using information prior, during and after radiation therapy. Finally, ^{18}FAZA-PET information was correlated with clinical outcome.

Materials and methods

Patient-, hypoxic tumour imaging- and treatment characteristics

This pilot study included 15 consecutive patients (mean age 57, range 29–82 years) with biopsy proven carcinoma of the cervix referred to AKH for definite RT. Patients were ineligible if they had recurrent disease, a prior malignancy, or if they had received neoadjuvant chemotherapy. Written informed consent was obtained from each participant prior to study entry and the Research Ethics Board at the Medical University ofVienna approved the trial. Of the 15 patients, 11 had squamous cell carcinoma, two had adenocarcionoma and two had adenosquamous carcinoma.

All patients were treated with definitive radiotherapy, applying External Beam Radiation Therapy (EBRT) with 45–50.4 Gy in 25–28 fractions of 1.8 Gy with or without cisplatin (40 mg/m^2 of body surface per week for five weeks) plus 4 × 7 Gy Image Guided Adaptive Brachytherapy (IGABT). IGABT was performed by using a tandem-ring applicator (Nucletron, Veenendaal, The Netherlands). In patients with locally advanced disease, additional interstitial catheters were used. The 84–89 equivalent dose in 2 Gy per fraction (EQD2) was prescribed to the high-risk clinical target volume (HRCTV) [10]. Follow-up including clinical examination, and MRI assessment, was performed every three months for the first two years and twice annually thereafter. Repetitive MRI was performed before EBRT, once every week during EBRT, at each brachytherapy and three months after treatment (for details see Dimopoulos et al. [11,12]).

In addition to the routine pre-therapeutical staging (gynaecologic examination, MRI, CT, laparoscopic pelvic node staging) of cervical cancer and imaging for treatment planning (CT and MR), ^{18}18FAZA-PET scans were performed before, during (after 30–40 Gy EBRT) and three months after therapy. Six of 15 patients received a transurethral catheter before intravenous application of the tracer substance. The characteristics of the patients, histology, and tumour volume ^{18}FAZA–uptake (initial, before 1. BT), and stage are summarised in Table I.

^{18}FAZA-PET data acquisition and image reconstruction

^{18}FAZA imaging was performed in all patients on a dedicated full ring PET scanner (Advance, General

Table I. Patient and Treatment characteristics.

Patient No.	Age	Histology	FIGO	Pelvic lymph nodes	GTVin MRIat diagnosis*	FAZA uptakeat diagnosis	GTVin MRIat 1. BT*	FAZA uptake before 1. BT	HR CTV Vol.* in MRI	D90 for HR CTV[a]	D100 for HR CTV[a]	Outcome
1	38	SCC	IB2	Pos	103.3	positive	4.9	positive	37.8	91.4	73.7	CCR
2	74	AS	IIAB	Neg (CT)	69.2	positive	9.8	negative	35.4	91.1	71.7	CCR
3	66	SCC	IIAB	Neg	67	negative	1	negative	19.1	114.1	87.6	CCR
4	52	SCC	IIAB	Neg	17.9	negative	3.2	negative	25.8	109	72.6	CCR
5	79	AC	IIB	Pos (CT)	125	positive	66.1	positive	95	69.3	62.6	IR
6	40	AC	IIB	Pos	62.8	positive	7.4	positive	25.5	97.5	79.2	RR
7	77	SCC	IIB	Neg	55.1	positive	14.2	positive	28.5	102.7	66.1	CCR
8	51	SCC	IB1	Neg	1.6	negative	0.5	negative	18.8	113.5	86.2	CCR
9	29	SCC	IIAB	Pos	108	negative	4	negative	40.8	95.4	68.2	DM
10	39	SCC	IIIB	Neg	54.8	negative	6	negative	27.5	100.3	74.8	DM
11	41	SCC	IIB	Pos	62.5	negative	34.2	negative	93.4	81.9	58.1	DM
12	46	SCC	IIAB	Neg	41.1	negative	9.3	negative	42.4	94	75.6	CCR
13	82	SCC	IB1	Pos	11.7	negative	3.6	negative	17.8	110.5	78.4	DM
14	56	AS	IB1	Pos	4.9	negative	3.6	negative	23.7	109.6	81.4	CCR
15	80	SCC	IIB	Neg	38.1	negative	10.9	negative	48	103	72	CCR

CCR - continous complete remission; IR - incomplete remission; RR - regional recurrence; DM - distant metastasis; SCC – Sqamous Cell Carcinoma; AC – Adenocarcinoma; AS – Adenosquamous Carcinoma; GTV – Gross Target Volume.

*Volume in cm^3.

[a]Dose in Gy.

Electric Medical Systems, Milwaukee, WI) and approximately 370 MBq ^{18}FAZA were injected intravenously. ^{18}FAZA was prepared by the Austrian Research Centres - Seibersdorf according to the method described by Kumar et al. [13]. All images were acquired in a 3D-mode with a matrix of 128×128 and for attenuation correction transmission scans with a ^{68}Ge source were done. To assess the kinetics of ^{18}FAZA and to determine the optimal time point for image interpretation after tracer injection dynamic scans from the pelvic area were performed for the first hour after tracer administration. One hour and two hours post injection additional static images in three bed positions covering the abdomen and the pelvis were acquired (acquisition time five minutes/bed position). Time curves over the tumour area and a thigh muscle were generated from dynamic imaging. All PET images were reconstructed using an iterative algorithm (OSEM).

Image analysis

Qualitative analysis. ^{18}FAZA-PET images (coronal, sagittal and transaxial projections) were evaluated visually by two experienced nuclear medicine physicians. The uptake of ^{18}FAZA in the primary tumour was classified using a previously described four grading score [14]: Grade 0 corresponds to a tracer uptake in the tumour less than in the surrounding normal background tissues; Grade 1 shows no regions of focal uptake in the tumour area higher than that of surrounding tissue. Grade 2 corresponds to a focal uptake in tumour moderately higher than that of surrounding tissue and grade 3 is defined as a focal uptake in tumour markedly higher than of surrounding tissue.

Tumour tissues with a visual score of 2 or 3 were referred to as "visually positive" or "visually identifiable".

Quantitative analysis. For analysis of the static images irregular ROIs were placed manually around the tumour area for calculation of Standard Uptake Value (SUVmax). In addition SUV_{max} were calculated for cylindric ROIs drawn over the thigh muscles in five consecutive axial slices. Consecutive from the SUV values, tumour to muscle (T/M) ratios were determined. ^{18}FAZA-PET images data were analysed using the PMOD software Vers. 2.95 (PMOD Technologies Ltd., Zürich, Switzerland).

Results

Radiochemical quality of ^{18}FAZA was excellent in all studies and sterility and pyrogenicity was evaluated for each ^{18}FAZA dose. After the administration of ^{18}FAZA no clinical evident side effects like skin rush, itching, fever or other signs of an allergic reaction were observed.

FAZA kinetics and optimal scanning time

Both, the curves over the tumour area as well as the curves over the thigh muscle showed a plateau after one hour. There was no significant change in SUV values and tumour to muscle ratio for two hour images compared to results from one hour static images. Therefore for further analysis only values from static imaging one hour after tracer application were used. Static images from the abdomen and pelvis demonstrated high tracer concentration in the kidneys and the bladder. No significant tracer accumulation was observed in the gut up to two hours after tracer application.

Assessment of changes in ^{18}FAZA uptake at time of diagnosis, during and after radiation therapy

In qualitative visual analysis, five patients (patient no. 1, 2, 5, 6, 7) showed higher tracer uptake than background at diagnosis (defined as visual scores 2 and 3) on static ^{18}FAZA -PET images. During radiochemotherapy, four of these five patients (patient number 1, 5, 6, 7) displayed regions with increased tracer uptake than background. In the follow-up scan one patient (patient number 6) showed regions of focal uptake higher than that of background at the transposed right ovary where recurrent disease was confirmed histologically by surgery a few months later. The tracer uptake in the positive scans showed an inhomogeneous pattern. Figure 1 displays a case with markedly increased uptake of ^{18}FAZA in the tumour tissue before and during treatment. The semiquantitative analysis showed a tumour to muscle (T/M) SUVmax ratio range for positive scans from 1.2–3.6.

MRI, DVH-parameters, ^{18}FAZA -PET and clinical outcome

Mean follow-up time was 27 months for all patients, and 37 months for all patients alive.

The mean D90 and D100 for the HR CTV were 99 Gy (+/− 12 Gy, SD) and 73 Gy (+/− 8 Gy, SD). Eleven patients showed tumours ≥ 5 cm. The mean tumour volume at diagnosis was 55 cm^3 (+/− 37, SD), at brachytherapy 11.9 cm^3 (+/− 17, SD) (MRI). The mean tumour regression during EBRT was 74% (+/− 21, SD) based on repetitive morphologic MRI (Table I). There were two poor responders (number 5, 11) with significant residual tumour at the time of brachytherapy (66 cm^3, 34 cm^3), and tumour volume reduction less than 50%. Only one was ^{18}FAZA -PET positive (number 5).

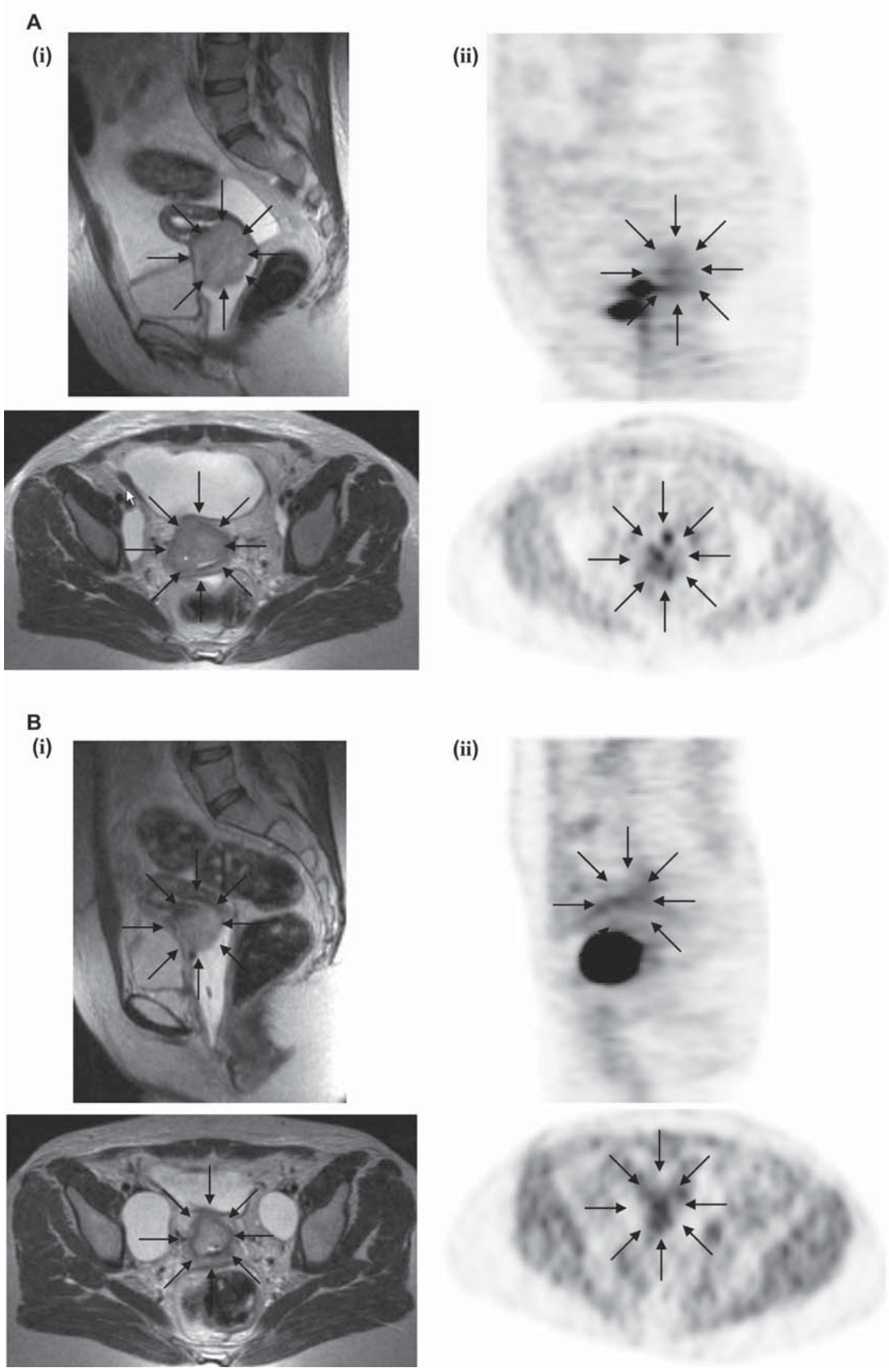

Figure 1. Sagittal and axial MRI (i) and sagittal and axial ^{18}FAZA PET (ii) imaging in a patient with cervical cancer FIGO stage IIb before therapy (A) and during RT (B) (patient number 6). Arrows indicate the tumor on the MRI (i) and the hypoxic areas within the tumor (ii).

The 5 ^{18}FAZA PET positive tumours were all large at diagnosis with 55 to 125 cm^3 whereas the 10 ^{18}FAZA PET negative tumours were 1.6 to 67 cm^3 (Table I).

Complete remission at three months was achieved in 14 of 15 patients. In total, one incomplete remission, one regional recurrence and four distant metastases were observed. At the time of analysis six patients had died – five due to tumour progression including the patients with incomplete remission and the regional recurrence. One patient died of complications caused by cirrhosis of the liver.

The detailed ^{18}FAZA -PET results, the morphologic imaging data, the radiation doses in the HR CTV and the clinical outcome are summarised in Tables I and II and in Figure 2.

There was no local recurrence, neither in the ^{18}FAZA -PET positive group nor in the ^{18}FAZA -PET negative group. None of the patients with distant metastasis showed markedly increased tracer uptake within the tumour region, neither at diagnosis nor at follow-up.

Due to poor response during EBRT and poor performance status at the time of brachytherapy, in patient number 5 only three fractions of BT were applied (total dose in HR CTV 69 Gy, D90). In this patient increased ^{18}FAZA uptake in the scans at diagnosis and during EBRT was documented and the only incomplete remission was observed. This patient died from a pulmonary embolism six months after treatment.

Table II. ^{18}FAZA -PET one hour after application in cervical cancer patients at the time of diagnosis obtained before (Scan I), during (Scan II) and after radiotherapy (Scan III).

	^{18}FAZA uptake				
Pts. no	Scan I	Scan II	Scan III	Outcome	
1	Positive	Positive	Negative	CCR	NED
2	Positive	Negative	Negative	CCR	NED
5	Positive	Positive	Negative	IR	DOOD
6	Positive	Positive	Negative*	RR	DOD
7	Positive	Positive	Negative	CCR	NED
3	Negative	Negative	Negative	CCR	NED
4	Negative	Negative	Negative	CCR	NED
8	Negative	Negative	Negative	CCR	DOOD
9	Negative	Negative	Negative	DM	DOD
10	Negative	Negative	Negative	DM	DOD
11	Negative	Negative	Negative	DM	DOD
12	Negative	Negative	Negative	CCR	NED
13	Negative	Negative	Negative	DM	AWD
14	Negative	Negative	Negative	CCR	NED
15	Negative	Negative	Negative	CCR	NED

CCR: continuous complete remission; IR: incomplete remission; RR: regional recurrence; DM: distant metastases; NED: no evidence of disease; DOD: dead of disease; DOOD: dead of other disease; AWD: Alive with disease.

*Primary tumor negative/ovarian metastasis positive.

Patient number 6 showed a 88% tumour volume regression on MRI after radiochemotherapy, with 7.4 cm^3 at the time of brachytherapy compared to 62.8 cm^3 at diagnosis. A D90 of 97 Gy for the HR CTV was applied and this patient achieved a complete remission and remained locally without tumour. However, a metastasis in the right ovary occurred, transposed by a surgical intervention to the right iliac fossa before treatment. This metastasis was detected on MRI after therapy and on the ^{18}FAZA Scan three months after treatment. After surgical removal of this ovary metastasis, a further recurrence occurred in the right iliac fossa, which could not be controlled.

The other three patients (number 1, 2, 7), who had visually positive ^{18}FAZA PET scans at diagnosis, became all ^{18}FAZA PET negative three months after treatment, number 2 already during radiochemotherapy. They received radiation doses of 91 Gy, 91 Gy and 102 Gy (D90) in the HR CTV and remain in continuous complete remission. The patient (^{18}FAZA -PET negative) with poor response according to morphologic imaging achieved continuous complete remission after 82 Gy D 90 in the HR CTV and died 18 months later from carcinosis of the peritoneum.

Discussion

Tumour hypoxia has been repeatedly demonstrated as a characteristic feature of many solid tumours, including cancer of the uterine cervix. A large body of evidence indicates that the presence of poor oxygenation within tumour tissue affects the progression of cancer in general, which makes hypoxia an overall adverse prognostic factor for patient outcome [1,2,15]. Furthermore hypoxia has a negative influence on response to radiotherapy [16–18]. Since patients with hypoxic tumours may benefit from hypoxia-adapted treatment regimes, identification of hypoxic tumour regions is assumed to be useful in the clinical setting.

Detection of hypoxia using the O_2-sensitive Eppendorf needle electrodes has been regarded as the "gold standard" for a long time [19,20]. Previous studies including our groups demonstrated hypoxic tumours in about half of cervix cancer patients estimated by intratumoral pO2 measuments [14–17]. However, owing to its invasiveness and technical as well as methodological limitations, this method has not become a clinical routine tool.

PET nowadays offers a non-invasive method to study hypoxia in patients by using hypoxia-selective radiopharmaceuticals. The hypoxia tracer ^{18}FAZA has been recently evaluated in patients with head and neck cancer [7]. No data are available on the application of ^{18}FAZA in other solid tumours. No information has been provided so far to our knowledge for patients with cervix cancer. Hence this study was performed

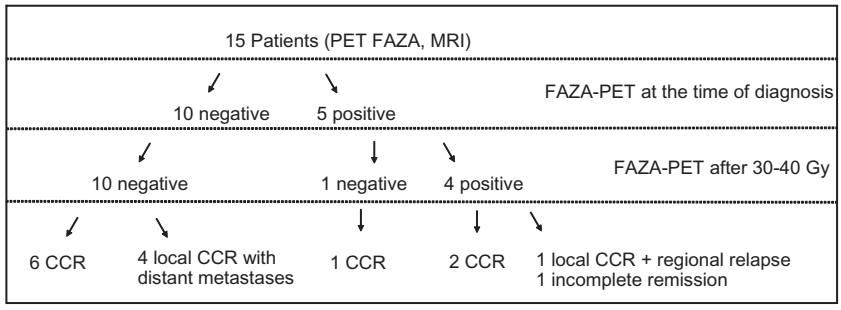

Figure 2. Clinical results from repetitive ^{18}FAZA PET within MRI guided adaptive radiotherapy in cervical cancer after a mean follow-up of 27 months for all patients.

to generate information regarding the feasibility and the prognostic value of ^{18}FAZA-PET imaging of tumour hypoxia in patients with cervix cancer within the frame of image guided adaptive radiotherapy.

Five of 15 patients had visible ^{18}FAZA uptake in the tumour at diagnosis. Four became ^{18}FAZA negative after complete radiotherapy with very high radiation doses in the HR CTV (D90 >91 Gy), one already towards the end of radiochemotherapy. These four patients stayed also in complete continuous local remission and three are alive without disease. One of these four patients died after a regional relapse which could be finally not controlled. One patient with visible ^{18}FAZA uptake had persistent local disease, however after limited radiation dose (69 Gy) and died from pulmonary embolism six months after the end of therapy.

This was a pilot study and the small number of patients allows only descriptive statistical analysis. Therefore the specific predictive and prognostic value of ^{18}FAZA could not be elaborated in detail. Although the increased ^{18}FAZA uptake in five patients was associated only with large tumours at diagnosis, the response rate in this group during radio-chemotherapy seemed not to be different from that of the ten patients with no increased ^{18}FAZA uptake at diagnosis. There was one poor responder each in both groups, whereas all other patients responded well according to morphologic imaging. Therefore, the additional predictive value of ^{18}FAZA PET compared to morphologic repetitive MRI remains questionable.

There was no local recurrence in this patient cohort with predominantly large tumours (11/15). Only one patient (^{18}FAZA positive) achieved an incomplete remission. The radiation dose applied in this patient (69 Gy) was significantly lower than those applied in all other patients (mean 99 Gy) and also in the other patient with poor response and complete remission (82 Gy). Such high radiation doses as typical for image guided brachytherapy for cervix cancer (Vienna), are well recognised to bear the capability to overcome hypoxia related radio-resistance and result in a low risk of local recurrence [21]. Several papers are now available on the dose levels that can be reached with IGABT confirming the Vienna results [22].

It can be assumed, that the fact that local recurrences were not observed in study is mainly due to this specific treatment method. It cannot be excluded that this may on the other hand mask an existing prognostic value for ^{18}FAZA. In other recent investigations using DCE MRI, a correlation between poor vascularisation and poor local and general outcome was shown [23,24], which is in line with results from invasive hypoxia measurement in the past [9–12]. All these studies have been performed without any individualised dose and volume adaptation.

All patients showing distant metastases by other imaging modalities belonged to the FAZA PET negative group (four of ten negative patients). Moreover the site of the metastases was not in the field of view of PET scanning for most of the patients.

As with many other clinical PET studies using hypoxia tracers, there are limitations that have to be taken into account when interpreting the results of this pilot study using ^{18}FAZA as hypoxia tracer in cervical carcinomas. Unlike the study conducted by Souvatzoglou et al. on ^{18}FAZA in head and neck cancer [7], co-registration of PET images with CT images was not performed and an integrated PET/CT scanner was not available for static PET acquisition. Hence, the correct localisation of tumour tissue on static images was difficult and further complicated by the anatomical preconditions. Because ^{18}FAZA is eliminated via the urinary system, very high tracer activity was observed in the ureters and bladder, which made the delineation of adjacent tumour tissue difficult. However, a visual correlation to MRI was performed to check plausibility (Figure 2). Another limitation of this study is the lack of a reference gold standard for the quantification and validation of tumour hypoxia (e.g. polarographic needle electrode measurements, immunohistochemical examination). This holds, however, also for other studies [25]. However, it has to be taken into account, that in invasive studies using needle electrode measurements, the rate of hypoxic patients was higher with >50% [14–17] compared

to our ^{18}FAZA PET findings with only 33%. Overall, the moderate number of patients in this study limits generalisation of the results.

Conclusion

PET imaging with ^{18}FAZA is feasible in patients with cancer of the uterine cervix. However, its predictive and prognostic value remains to be clarified. This applies in particular for the additional value of ^{18}FAZA PET compared to morphologic repetitive MRI within the setting of image guided high dose radiotherapy which may contribute to overcome hypoxia related radioresistance.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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