



Original Research Article

A comparison of two imaging modalities for detecting lymphatic nodal spread in radiochemotherapy of locally advanced cervical cancer



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ABSTRACT

Background and purpose: In uterine cervical cancer tumour spread reaching the para-aortic lymph nodes is the most significant independent pre-treatment predictor of progression-free survival. When introducing [¹⁸F] fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) in our clinic for patients with advanced cervical cancer planned for definitive radiochemotherapy, the purpose of this study was to quantify to what extent the added information lead to changes in radiotherapy planning.

Material and methods: We included 25 consecutive patients with cervical cancer stages IB2 – IIIB planned for definitive radiochemotherapy between November 2010 and May 2012. The patients were examined both with magnetic resonance imaging (MRI) and FDG-PET/CT before treatment and after four weeks of treatment.

Results: In 11/24 (46%) of the patients the FDG-PET/CT before treatment provided additional diagnostic information leading to changes in treatment planning compared to information from MRI. Seven of these eleven patients (64%) were alive and without evidence of disease at four-year follow-up. The MRI detected pelvic tumour spread not seen on the FDG-PET/CT in 2/24 patients. The disease-free four-year survival was 59%.

Conclusions: Additional diagnostic information from FDG-PET/CT changed treatment strategy in almost half of the patients and may have increased chances of survival in this limited group of patients with locally advanced uterine cervical cancer. We recommend both modalities for nodal detection.

1. Introduction

Tumour spread reaching the para-aortic lymph nodes from the primary site in the uterine cervix is the most significant independent pre-treatment predictor of progression-free survival and overall survival [1,2]. Already at early stage disease there is a high risk of nodal involvement. The globally used staging system according to the International Federation of Gynaecology and Obstetrics (FIGO) is based on clinical examination and does not take nodal spread into consideration, underestimating tumour spread in up to 67% of the patients with stage II to IV disease [3,4].

Compared with computed tomography (CT), magnetic resonance imaging (MRI) is superior in estimating tumour size and in detecting local tumour growth and has good potential to show overgrowth to corpus uteri, parametria, urinary bladder, colon or pelvic walls [5–7].

However, MRI and CT have comparable moderate accuracy in detecting lymph node metastases with sensitivity of approximately 55% and specificity of approximately 90% [8]. Both methods are limited by their inability to detect small volume metastatic involvement in normal-sized lymph nodes, and to determine whether enlarged nodes represent metastases or reactive hyperplasia. Current results show that the combination of [¹⁸F]fluorodeoxyglucose-positron emission tomography and CT (FDG-PET/CT) is the most sensitive diagnostic method to detect lymph node metastases in cervical cancer, with sensitivity of 75–82% and specificity of 95–99% according to three meta-analyses [8–10]. Both functional and anatomical information are obtained at the same time.

Differences between information from MRI and FDG-PET/CT are reported to lead to changed treatments in a significant number of cervical cancer patients planned for radiotherapy [12–14]. When

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introducing FDG-PET/CT in our clinic for patients with advanced cervical cancer planned for definitive radiochemotherapy, the aim was for all involved specialists in gynaecological oncology, radiology, and functional imaging to gain knowledge on how to interpret images and communicate findings to optimize treatment. The purpose of this study was, therefore, to quantify to what extent nodal spread detected by MRI and FDG-PET/CT lead to changes in radiotherapy planning in our clinical setting. We also evaluated primary tumour size and FDG maximum standard uptake, at diagnosis and after four weeks of treatment, and related this to survival.

2. Material and methods

2.1. Patients

In a prospective study we investigated all 25 consecutive patients with uterine cervical cancer stages IB2 – IIIB who were planned for definitive radiochemotherapy. According to national and regional guidelines, surgery was no option for any of these patients nor were lymph node staging. Only one patient during the study period was excluded and treated differently due to massive nodal spread on MRI. The patients came from the Western Region of Sweden and were treated between November 2010 and May 2012 at a centralized tertiary centre for gynaecological oncology covering one sixth of the population. Written informed consent was given from the patients included in the study. The study was performed in accordance with the Declaration of Helsinki, and approved by the regional ethical review board.

The patients were examined both with MRI and FDG-PET/CT before treatment and after four weeks of radiochemotherapy corresponding to 38–40 Gy using a uniform protocol to describe the primary tumour, loco-regional and distant tumour spread. The referring clinic performed the MRI as soon as possible after their initial examination of the patient and at the staging procedure (examination under anaesthesia) the treatment plan was determined. If the patient were to receive chemoradiation the PET/CT was scheduled 1–2 weeks before start of treatment. The results of MRI were judged independently by specialists in Radiology (H.L., F.H.) and FDG-PET/CT by specialists in Nuclear Medicine (A.M., R.R.N.). The final imaging reports for MRI and FDG-PET/CT were written in consensus between H.L. + F.H., and A.M. + R.R.N., respectively. A detailed report of the tumour spread was then transferred to the radiation oncologist who contoured the target volumes and relevant risk organs in the CT-based dose-planning system. PET/CT images were fused with the planning CT scan while MRI images were contoured side by side with the planning CT. Margins between GTV, CTV, and PTV were specified according to international guidelines [15,16]. MRI and clinical examination under anaesthesia provided the base for treatment planning, but in case FDG-PET/CT showed signs of additional tumour spread this was included in the prescribed radiation volume and pathologic lymph nodes were boosted. Patients with nodal spread to the high common iliac nodes were treated with extended radiation fields covering the lumbar para-aortic region.

All patients were treated at the same institution. Treatment consisted of external beam radiation therapy (EBRT) delivered as intensity modulated radiation therapy or volumetric modulated arc therapy, combined with brachytherapy (BT) when applicable. The standard EBRT dose at the time was 2-Gy-fractions to 46 Gy followed by a boost of 1.5 Gy twice daily to a total dose of 55 or 67 Gy (corresponding to an equieffective dose delivered in 2 Gy-fractions with an $\alpha/\beta = 10$ Gy for tumour effects: EQD_{2,10} = 54.1 Gy or 64.9 Gy, respectively) to the primary tumour, depending on if BT was given or not. A nodal boost of 60 Gy was delivered to affected lymph nodes outside the primary tumour volume. BT was given as high-dose rate (HDR) and consisted of 3 fractions at 4.0 Gy (EQD_{2,10} = 4.7 Gy) per fraction given during the last weeks of external treatment. At the time of the study we did not have access to MRI and CT-based treatment planning for BT. Concurrent chemotherapy with cisplatin (40 mg/m²) once a week, maximum 6

cycles, was given if not contraindicated. We aimed at keeping the haemoglobin levels ≥ 120 g/l during the treatment period. Adjuvant chemotherapy was not given as a rule. Follow-up by MRI and clinical evaluation was performed three months after completion of treatment. Hereafter, clinical examination was performed every three months for the first two years, and then every six months; routine MRI was not performed during this period.

2.2. MRI

MRI was performed with 1.5 Tesla scanners in seven different centres in the Western Region of Sweden, 12/24 patients at Sahlgrenska University Hospital (Intera; Philips Medical Systems, Best, The Netherlands), with pelvic phased-array coils for optimal signal reception. The MRI protocol for the initial examination was as used in clinical routine in accordance with the European Society of Urogenital Radiology (ESUR) MRI-guidelines for staging of uterine cervical cancer [11]. Pelvic multislice T2-weighted turbo spin-echo (TSE) acquisitions were obtained in transaxial (repetition time/echo time 3700–4500/120 msec, flip angle 90°, field of view 230 mm, slice thickness 4 mm, gap 1 mm, matrix 352 × 352), sagittal, and coronal planes. For T1 signal intensity and perfusion, pelvic fat-saturated, T1-weighted, high-resolution isotropic volume (THRIVE) gradient-echo sequences (repetition time/echo time 3.6/1.8 msec, flip angle 10°, field of view 370 mm, slice thickness 4 mm, overcontiguous slices by 2 mm, matrix 256 × 256) were performed in the transaxial plane before and 0.5, 1, 2, 3, 4, and 5 min after rapid intravenous injection of a gadolinium-based contrast agent (gadopentetate dimeglumine, 469 mg/ml; Schering, Berlin, Germany) at a dose of 0.2 mmol/kg of body weight. In addition, the upper pelvis and abdomen were scanned after administration of contrast agent without phased-array coils and with a slice thickness of 8 mm, performing fat-suppressed T1-weighted gradient echo and T2-weighted sequences. The patient was fasting for at least four hours before scanning. No diuretics or laxatives were used. Before entering the MR-camera approximately 10 ml sterile sonographic gel was self-injected into the vagina. The MRI control of tumour size after four weeks of treatment was performed with a similar protocol, but not including the upper abdomen and without contrast agent.

The size of the primary tumour was measured in mm in the orthogonal directions, (length (l), width (w) and height (h)), before treatment start and after four weeks of treatment. Three different measures were compared for estimating tumour size; the largest trans-axial diameter (1D), the area based on the largest trans-axial diameter and its perpendicular diameter assuming an elliptic shape (2D), and volume (V) estimation according to the formula $V = l \cdot w \cdot h \cdot 0.5$ (3D). Tumour invasion in the corpus uteri, vagina, parametria, urinary bladder, and intestines was recorded, and also the presence of dilated ureters or hydronephrosis. Enlarged lymph nodes, defined as trans-axial short axis ≥ 8 mm in the parametria, short axis ≥ 10 mm in the groins and along the iliac vessels and aorta, were reported.

2.3. FDG-PET/CT

Patients fasted for six hours prior to intravenous injection of 4 MBq/kg ¹⁸F-FDG (with a maximum of 400 MBq). Blood glucose levels were checked before injection, levels < 10 mmol/L were accepted. One hour after injection a PET-scan was performed from head to proximal thighs, combined with a low-dose CT using a Biograph TruePoint 64 PET/CT scanner (Siemens medical Solutions, Knoxville, TN, USA), slice thickness 5 mm. All patients were scanned using the same scanner. An extra scan of the cervix area was performed after emptying of the urinary bladder. The CT scans were performed without administration of contrast agent.

Maximum standard uptake value (SUV_{max}) adjusted for patient weight before and after emptying of the urinary bladder was calculated for the cervix. FDG uptake in nodal areas of the parametria, groins,

para-iliacs and para-aortics was reported as well as asymmetrical up-take. FDG uptake in pre-sacral and other more uncommon nodal areas and in other organs was also reported.

2.4. Statistical analyses

Continuous variables were presented with mean and standard deviations as well as with median and range. Differences between two measurements were given as absolute and as relative values, with the pre-treatment value as reference. Patients with disease-free survival were compared to patients with loco-regional relapse/progressive disease. Comparisons between groups related to differences in SUV-max and in tumour metrics (diameter, area, and volume) were calculated with Mann-Whitney *U* test. A two-sided *P*-value less than 0.05 was considered statistically significant. All calculations were performed in MATLAB R2015b (The MathWorks Inc., Natick, MA, USA).

3. Results

3.1. Patients

Of the 25 consecutive patients diagnosed with locally advanced cervical cancer and treated with definitive radiochemotherapy, the majority had stage IIB (n = 10) or stage IIIB (n = 11; [Supplementary Table 1](#)). Median age was 58 years (range 32–77 years). Squamous cell carcinoma accounted for 21/25 tumours. Cisplatin was given concomitantly to all except one patient, the number of cycles varied due to toxicity. Median overall treatment time (OTT) of radiotherapy was 44 days (range: 39–53 days). The MRI preceded the FDG-PET/CT with a median of 14 days (range: (– 27, 40 days); one patient having her PET/CT scan after treatment start). One patient had a pacemaker that excluded her from MRI-scanning, leaving 24 patients for comparison.

3.2. MRI versus FDG-PET/CT

The initial FDG-PET/CT examination showed areas of nodal tumour spread that were not seen on MRI in 11/24 (46%; [Table 1](#)) of the patients. This resulted in extension of nodal treatment volumes in 8/11 patients who had para-aortic fields added. Two of eleven patients had extended treatment volume and/or increased dose where MRI indicated nodal metastases, e.g. round shape of lymph node or necrosis even if they were PET-negative.

3.3. Outcome at four-year follow-up

All patients were followed for at least four years and the disease-free survival was 13/22 (59%; [Table 1](#)). Another two patients were alive with no evidence of disease, one after resection of pelvic wall recurrence, one after pelvic exenteration due to local recurrence, a third patient was alive but had local progress, rendering a disease-specific survival of 73%. Four patients had died from local recurrence or progressive disease. Two patients died from initial supraclavicular/mediastinal and pulmonary tumour spread, respectively. Two patients died due to vascular disease and one patient due to pancreatic cancer, all three were without evidence of cervical cancer recurrence.

Of the eleven patients who had their treatment changed due to additional information from pre-treatment FDG-PET/CT, seven (64%) were alive and without evidence of disease at four-year follow-up. Both patients where the MRI examinations showed pelvic tumour involvement that was not detectable on FDG-PET/CT had received extended treatment volumes and were alive and without evidence of disease at four-year follow-up.

3.4. SUVmax

The SUVmax before treatment did not differ between patients with disease-free survival and patients with loco-regional relapse/progressive disease at four-year follow-up (*P* = 0.94) neither did the

Table 1

Lymphatic nodal spread visualized on FDG-PET/CT and MRI at diagnosis, changes in treatment, and outcome at 4-year follow up.

Patient (no)	Tumour stage (FIGO)	Tumour spread PET/CT	Tumour spread MRI	Change in EBRT planning	Outcome at 4-year follow up*
1	IB2	-	-	-	1
2	IIA	PA lymphnodes	-	Extended field PA	1
3	IIA2	Pelvic lymphnodes	Pelvis lymphnodes larger	Extended pelvic field	1
4	IIA2	-	-	-	3=Dead due to locoregional relapse after 5 months
5	IIB	-	-	-	1
6	IIB	-	-	-	1
7	IIB	-	-	-	2=Alive (local relapse x 2, hysterectomy, progress)
8	IIB	-	-	-	2=Alive NED (local relapse x 2, hysterectomy, pelvic exenteration)
9	IIB	-	Lymphnodes external iliaca dx	Extended pelvic field	1
10	IIB	PA lymphnodes	-	Extended field PA	1
11	IIB	Pelvic + PA lymphnodes	-	Extended field PA	1
12	IIB	Pelvic lymphnodes bilaterally	Lymphnodes external iliaca dx	Extended field PA	1
13	IIB	Pelvic lymphnodes	-	-	2=Alive NED (locoregional relapse after 1,5 years, rectum amputation)
14	IIB	Pelvic + PA + FSC lymphnodes	Pelvic lymphnodes	Extended field PA	4=Dead due to distant failure (FSC, mediastinum)
15	IIIB	Pelvic + PA lymphnodes	Pelvic lymphnodes	Extended field PA + chemo post RT	1
16	IIIB	Pelvic lymphnodes bilaterally	-	Extended pelvic field, boost volume	1
17	IIIB	Pelvic lymphnodes bilaterally	Lymphnodes external iliaca sin	Extended pelvic field, boost volume	1
18	IIIB	-	-	-	5=Dead after 3,5 years due to vascular disease, NED
19	IIIB	-	-	-	1
20	IIIB	Pelvic + SI lymphnodes	Iliacal lymphnodes	Boost volume pelvic field	5=Dead after 1,5 years due to vascular disease, NED
21	IIIB	PA lymphnodes	-	Extended field PA	5=Dead due to pancreatic cancer
22	IIIB	Pelvic + PA lymphnodes	Pelvic lymphnodes	Extended field PA	3=Dead due to progressive disease
23	IIIB	Pelvic lymphnodes bilaterally	(no MRI due to pacemaker)	-	3=Dead due to progressive disease
24	IIIB	Lung	-	-	4=Dead due to distant failure (lung)
25	IIIB	-	-	-	3=Dead due to progressive disease+myoma

NED = No evidence of (cervical cancer) disease.

SI = sacroiliacal

PA = paraaortal

FSC = fossa supraclavicular

* 1=Disease-free 4-year survival (n=13)

2=Loco-regional relapse - surgery - Alive (n=3)

3=Loco-regional relapse, progressive disease - Dead (n=4)

4=Distant spread at diagnosis - Dead (n=2)

5=Dead from other causes (n=3)

Table 2Differences in SUVmax for primary tumour after 4 weeks of radio- chemotherapy and outcome at 4-year follow-up in 17 patients with two measurements.[§]

Disease-free 4-year survival				Loco-regional relapse/progressive disease			
n = 11 [*]				n = 6 [#]			
Patient no	Before RT	After 4 weeks RT	Difference SUVmax	Patient no	Before RT	After 4 weeks RT	Difference SUVmax
3	11.3	3.0	8.3	7	24.8	12.2	12.6
5	7.2	3.6	3.6	8	12.6	7.3	5.3
6	31.5	6.1	25.4	13	19.6	6.1	13.5
9	21.6	12	9.6	22	12.7	8.6	4.1
10	17.2	9.1	8.1	23	15.5	8.3	7.2
11	11.4	11.8	0.4	25	16.4	6.6	9.8
12	16.6	2.5	14.1				
15	30.2	10.6	19.6				
16	32.0	11.5	20.5				
17	28.6	3.3	25.3				
19	14.7	6.0	8.7				
Mean 13.1 ± 8.5				Mean 8.8 ± 3.9			
Median 9.6 (0.4–25.4)				Median 8.5 (4.1–13.5)			
Mann-Whitney U test: P = 0.40							

* Two patients with progression-free survival did not have a second PET/CT (patients no 1 and 2).

One patient with locoregional relapse did not have a second PET/CT (patient no 4).

§ Two patients died due to distant treatment failure (mediastinal-supraclavicular or pulmonary disease; patients no 14 and 24) and three patients died from other causes (vascular disease or pancreatic cancer; patients no 18, 20 and 21).

differences in SUVmax before treatment and after four weeks of radiochemotherapy (Table 2).

3.5. Tumour size

There was no statistically significant difference in the relative reduction of the primary cervical tumour for the patients with disease-free survival at four-year follow-up compared to the patients with loco-regional relapse/progressive disease (Supplementary Table 2).

4. Discussion

In this prospective study, we report our experience of introducing FDG-PET/CT in a clinical setting for patients with advanced cervical cancer planned for definitive radiochemotherapy.

Twentyfour patients with stages IB2 – IIIB were scanned both with MRI and FDG-PET/CT before treatment and after four weeks of treatment, at 38–40 Gy. The addition of pre-treatment FDG-PET/CT to MRI detected undiagnosed nodal tumour involvement in 46% (11/24) of the patients resulting in change of treatment strategy with extended para-aortic fields or pelvic volumes and boosting of pathological lymph nodes.

In a systematic literature review, Salem et al. looked at 724 cervical cancer patients in studies addressing the effectiveness of PET/ PET-CT in EBRT planning [12]. The use of pretreatment PET/ PET-CT resulted in extension of radiation fields in 11–19% of patients to include all metabolically active nodes, including para-aortic and supraclavicular nodes. Tsai et al. reported a prospective, randomized clinical trial of cervical cancer stage I-IVA having MRI findings of positive pelvic, but negative para-aortic lymph nodes [13]. In the group of 66 patients treated with EBRT who received pretreatment FDG-PET, the result led to modification of radiation fields for 7 patients (11%). In a retrospective study by Akkas et al., 38 patients with stage IIB-IVA treated with a combination of EBRT and BT underwent both PET/CT and MRI in the pretreatment evaluation. PET/CT detected hypermetabolic para-aortic ± pelvic lymph nodes, not seen on MRI, in 13 patients (34%), leading to modifications in the radiation field [14]. Our results are in line with these data and, in addition, are based on an unselected consecutively recruited clinical cohort.

FDG uptake in the primary tumour before and during radiochemotherapy has been associated with treatment response. Kidd and

colleagues found a higher pretreatment SUVmax for the primary tumour associated with an increased risk of lymph node metastasis in 287 cervical cancer patients with FIGO stage IA1-IVB [19]. Xue et al. also found pretreatment FDG uptake within primary cervical tumour predictive of disease-free survival in 96 consecutive patients with FIGO stage IB1-IVB, treated with radiochemotherapy [20]. However, Akkas et al. looked at 58 patients with cervical cancer stage IIB-IVA and found no difference in pretreatment SUVmax between patients with persistent disease and those with no evidence of disease at a mean follow up of 22 months [21]. In line with Akkas et al. the pretreatment SUVmax in our study did not differ between the two groups at four-year follow-up.

Change in SUVmax during radiochemotherapy has been used to measure the effectiveness of treatment. Kidd et al. compared FDG-PET at the 2-week time point with the 4-week time point during radiochemotherapy in 25 patients with average pretreatment SUVmax 17.8 [22]. In their study the average SUVmax had decreased by 57% by week four and was significantly associated with post-treatment PET response, suggesting that an early prediction of treatment response is best made after four weeks of radiochemotherapy. In our group of 25 patients only 17 patients could be evaluated at four-year follow-up, eleven with disease-free survival and six with locoregional relapse/progressive disease. Numerically there was a larger difference in SUVmax after four weeks of treatment among the patients with disease-free survival although this difference was not statistically significant (Table 2).

MRI is a reliable imaging modality for assessment of local tumour extension. The tumour volume regression rate during radiochemotherapy has been shown to be predictive of local control and disease-free survival. Nam et al. reported from a study of 81 patients comparing radiotherapy alone with radiochemotherapy in which the tumour area was defined in each slice and the volume was calculated for each of the MRIs by a summation of all slices [17]. They found the mid-therapy tumour regression rate to be a predictor of local control rate in both patient groups, a 5-year local control rate of 100% with rapid response (more than 75% reduction at 36–45 Gy) compared with 72% for slower regression. Mayr et al. reported in a study of 66 patients that the mid-therapy MRI examination during radiochemotherapy (at 45–50 Gy), also using 3D region of interest (ROI) volumetry, best predicted outcome, especially for the intermediate-sized tumours [18]. The 5-year local control rate was 84% in patients who responded rapidly (less than 20% residual volume after 45–50 Gy) compared with 22% in

slow responders. There was no statistically significant difference in our data for the investigated tumour size metrics.

The number of patients in our study was limited, which may have affected the presented effect size. However, our results concerning modification of radiation fields are in line with previous data. When comparing FDG-PET/CT with MRI the limitation of each method matters. Diffusion-weighted MRI (DWI) is recommended in the ESUR guidelines and may, in addition to the other MRI sequences, improve the detectability of lymph nodes. At the time of this study this technique was not available for pelvic MRI at our institution. We did not measure tumour volume with the 3D ROI volumetry method. This technique is probably more accurate since it is independent of irregular tumour shapes. However, 3D ROI volumetry is time consuming and rarely used in clinical routine.

The majority of patients were treated with EBRT alone. Not having access to MRI and CT-based treatment planning system for BT in combination with large tumours or stenosis of the cervical canal limited our use of BT at the time of this study and might have influenced the outcome data regarding central failure or central recurrence. Since the time of the study we have developed new standards of care, and the treatment is in accordance with the image-guided intensity-modulated External beam radiochemotherapy and MRI-based adaptive BRACHYtherapy in locally advanced Cervical cancer (EMBRACE) guidelines.

In conclusion, when comparing MRI and FDG-PET/CT for detecting nodal spread in advanced cervical cancer in our daily routine work on 25 consecutive patients, eleven patients (46%) received altered treatment due to the pre-treatment FDG-PET/CT examination. Of these seven patients were alive and without evidence of disease at four-year follow-up. Our main focus was to detect lymphatic nodal spread that could be included in the treatment volume. Based on our findings, we recommend both modalities for nodal detection.

Declaration/conflict of interest

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2018.11.002>.

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