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ORIGINAL ARTICLE

Utility of ^{18}F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy: a parallel study of a prospective randomized trial

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Abstract

Purpose The aim of this prospective study was to assess the usefulness of ^{18}F-FDG PET/CT performed before and during treatment for predicting treatment failure in patients with advanced squamous cell carcinoma of the uterine cervix treated with concurrent chemoradiotherapy (CCRT).

Methods Patients with cervical squamous cell carcinoma, International Federation of Gynecology and Obstetrics stage III/IVA or positive pelvic or paraaortic lymph node (LN) metastasis without other distant metastasis on PET/CT entering a randomized trial of CCRT (AGOG 09-001) were eligible. PET/CT scans were performed at baseline, during week 3 of CCRT and 2−3 months after CCRT. PET/CT parameters were correlated with sites of failure and overall survival (OS). The resulting predictors developed from the study cohort were validated on

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two independent datasets using area under the curve values, sensitivities and specificities.

Results With a median follow-up of 54 months for survivors, 20 (36 %) of the 55 eligible patients were proven to have treatment failure. Sites of failure were local in five, regional in 11, and distant in 11. Four predictors for local failure, three for regional failure, and four for distant failures were identified. After validation with two independent cohorts of 31 and 105 patients, we consider the following as clinically useful predictors: pretreatment metabolic tumour volume (MTV) and during-treatment cervical tumour MTV for local failure; during-treatment SUVnode (maximum standardized uptake value of LNs) for regional and distant failure, and during-treatment MTV for distant failure. During-treatment SUVnode ($P = .001$) and cervical tumour MTVratio ($P = .004$) were independent significant predictors of OS by stepwise Cox regression.

Conclusion PET/CT imaging before and during treatment is useful for predicting failure sites and OS, making tailored therapeutic modifications feasible with potential outcome improvement during primary therapy.

Keywords ^{18}F-FDG PET/CT · Cervical cancer · Concurrent chemoradiotherapy · Treatment failure prediction

Introduction

Cervical cancer is the fourth most common cancer in women, with approximately 266,000 deaths worldwide in 2012 [1]. Concurrent chemoradiotherapy (CCRT) has become the mainstay of treatment for advanced cervical cancer. Unfortunately, about one-third of patients treated with CCRT will have persistent or recurrent disease following CCRT [2, 3]. PET/CT with ^{18}F-FDG is increasingly recognized for its potential clinical utility in patients with cervical cancer [4]. In a previous prospective study, the 3-year progression-free survival rates in patients with complete metabolic response, partial metabolic response and progressive disease on posttreatment ^{18}F-FDG PET/CT imaging were 78 %, 33 % and 0 %, respectively [5]. A pretreatment ^{18}F-FDG scan is useful in staging and prognostic evaluation in advanced cervical cancer [4, 6, 7]. Serial ^{18}F-FDG scans during treatment have shown a gradual decrease in cervical tumour maximum standardized uptake value (SUVmax) over time [8]. In this scenario, the monitoring of tumour response by ^{18}F-FDG imaging before and during treatment may be clinically useful for identifying patients at high risk of treatment failure.

A phase II clinical trial has shown that the addition of gemcitabine to standard CCRT may improve clinical outcomes in patients with advanced cervical cancer [9]. A phase III clinical trial has shown that the addition of gemcitabine to cisplatin CCRT significantly improves survival compared

with current standard of care [10]. Patients were treated with a combination of gemcitabine and cisplatin weekly for 6 weeks, with concurrent external-beam radiotherapy (XRT) then brachytherapy (BCT), followed by two adjuvant 21-day cycles of cisplatin plus gemcitabine, cisplatin and concurrent XRT, and BCT only without adjuvant therapy. Two years before the results of the study by Dueñas-González et al. [10] were known, a prospective, randomized phase III Asian Gynecologic Oncology Group trial (AGOG 09-001, ClinicalTrials.gov identifier NCT00842660) was designed to investigate whether the addition of gemcitabine to cisplatin in the CCRT phase (without adjuvant chemotherapy after CCRT) can improve survival in patients with advanced cervical squamous cell carcinoma [11]. Both treatment arms in the latter trial showed similar survival results. Moreover, a parallel imaging study with PET/CT imaging during treatment was devised to assess response to treatment in the AGOG 09-001 participants. Although accrual to the AGOG 09-001 trial was prematurely closed in March 2013 because of slow recruitment, overly optimistic assumption of benefit and an unexpectedly small difference in survival, the aim of examining the clinical usefulness of serial PET/CT scans in a parallel imaging study could be achieved, and the results are reported here.

Materials and methods

Patient eligibility

Inclusion criteria for the AGOG 09-001 trial included a diagnosis of primary squamous cell carcinoma of the uterine cervix and a clinical International Federation of Gynecology and Obstetrics (FIGO) stage III/IVA or clinical FIGO stage I/II with suspicious pelvic or paraaortic lymph node (LN) metastasis on MRI and verified on PET/CT imaging. The exclusion criteria were as follows: distant metastases at sites other than the paraaortic LNs; age less than 35 years or more than 70 years; inadequate bone marrow, pulmonary, liver or renal function; Eastern Collaborative Oncology Group performance status >1; or a history of chemotherapy or pelvic radiotherapy (RT). The patients randomized in the AGOG 09-001 trial were invited to participate in the parallel imaging study, which was approved by the local institutional review boards. All participants gave their written informed consent.

Concurrent chemoradiotherapy

The CCRT protocol has been previously described [11–14]. In general, patients were initially treated with XRT, delivered 5 days per week, one fraction per day and 1.8 Gy per fraction. Doses of large-field radiation to the whole pelvis were 45 Gy delivered using a conventional four-field box technique. Patients with parametrial extension or metastases to pelvic

LNs received nodal and parametrial boost doses (5.4 −12.6 Gy) using parallel-opposed anterior/posterior fields with a midline block of width 4 cm. In patients with lower vaginal tumour extension or with persistent bulky tumour after receiving a dose of 45 Gy, external beam doses to the lower pelvis were either increased to 50−54 Gy without a central block if followed by BCT or to 68−72 Gy when BCT was not used. Intracavitary high dose-rate ^{192}Ir BCT was delivered at 4.3 Gy per fraction for six fractions, two fractions per week. In the presence of metastases to common iliac or paraaortic LNs, the irradiation field was extended to include the abdominal paraaortic region up to the T12/L1 intervertebral space. Gross nodal lesions outside the parametrial boost field were treated to a total dose of 54 to 57.6 Gy. Intensity-modulated RT was optionally offered to patients who did not receive BCT or who were treated with paraaortic irradiation.

Chemotherapy consisted of weekly intravenous infusion of cisplatin (40 mg/m^2) either with or without gemcitabine (125 mg/m^2) administered during the course of RT up to six cycles (arm C vs. arm CG in the AGOG 09-001 trial). Reductions in dose or withholding of chemotherapy were considered upon development of haematological toxicity (granulocyte count <1,500/mL or platelet count <100,000/mL). Completion of six courses of chemotherapy was not mandatory in patients who had completed their RT course.

MR imaging

MR images were acquired using a 1.5-T (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) or a 3.0-T system (Trio Tim; Siemens Medical Systems) using phased-array body coils and parameters as previously reported [15]. In brief, we applied T1-weighted (repetition time, TR, echo time, TE, 626/11 ms; number of signal averages 2; matrix 256×320; field of view, FOV, 20 cm) and T2-weighted turbo spin-echo sequences (TR/TE 5,630/87 ms; number of signal averages 3; matrix, matrix 256 × 320; FOV 20 cm) to scan the pelvis in 5-mm axial and sagittal planes. The anatomical cervical tumour volume was determined by an experienced radiologist (G. Lin) as the sum of irregular tumour regions on transaxial T2-weighted MRI slices multiplied by the slice thickness.

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

In addition to the pretreatment PET/CT scan, PET/CT scans during and after treatment were arranged during week 3 of CCRT and between 2 and 3 months after completion of CCRT. Serial PET/CT scans in each patient were performed using the same PET/CT machine (Discovery ST16; GE Healthcare, Milwaukee, WI; or Biograph mCT; Siemens Healthcare, Erlangen, Germany) in the institution where CCRT was carried out. Each participating institution had to conform to the standardized PET/CT imaging protocol. Patients were required to fast for 6 h before examination. Imaging was started at 50 min after intravenous injection of ^{18}F-FDG (370 MBq ±10 %). A nonenhanced CT scan from the head to the thighs was initially acquired, followed by PET imaging. All images were acquired with the patient in the supine position. PET scans were corrected for attenuation using the CT data with an ordered subsets expectation maximization algorithm.

Image interpretation and parametric quantification

All PET/CT images were interpreted and analysed centrally. Parameters were quantified on a Syngo MI Workplace software platform (Siemens Healthcare, Forchheim, Germany). SUV was defined as the image-derived radioactivity concentration normalized to the whole-body concentration (injected dose divided by patient body weight). SUVmax was defined as the maximum SUV in the volume of interest (VOI). Metabolic tumour volume (MTV) is the volume of tumour cells with increased radioactivity uptake. VOIs for the primary tumour and positive LNs were drawn manually on the images displayed on the workstation with SUVmax recorded for each VOI. The MTVs of the cervical tumours were measured using a fixed boundary SUV of 3.0. SUVnode was defined as the maximum SUVmax of all positive LNs. The SUV and MTV ratios between the studies before and during treatment were defined as:

$$SUVratio = during - treatment\ SUVmax/pretreatment\ SUVmax \times 100\%$$

$$MTVratio = during - treatment\ MTV/pretreatment\ MTV \times 100\%$$

If there were multiple positive LNs, the highest SUVratio of all positive LNs was taken as the maximum LN SUVratio. All these imaging parameters were analysed as continuous variables.

Patient follow-up and classification of failure sites

The first patient follow-up was arranged for 2 months after CCRT completion. Posttreatment MRI was routinely arranged and PET/CT was performed in patients entering the parallel study. During follow-up, biopsies were arranged in patients with incomplete regression of tumour, suspicious progression, or positive findings on posttreatment MRI or PET/CT. Further follow-up was based on the protocol used in our previous studies [11–14]. The failure sites were categorized as local (cervix, bladder or rectum), regional (pelvic or paraaortic LN), and distant (other distant sites) based on the posttreatment imaging and biopsy

findings. The failure sites in a patient with treatment failure could be of one or more categories.

Independent patient cohorts for validation

Due to the limited number of patients in the study, we decided to validate the resultant predictors developed from the study in two independent cohorts. The first cohort came from a prospective study performed in Chang Gung Memorial Hospital (Linkou) with three PET/CT examinations during treatment (IRB 99-0834C) and the following inclusion criteria: (1) diagnosis of primary epithelial carcinoma of the uterine cervix without a history of other malignancy; (2) bulky primary tumour larger than 4 cm without distant metastases other than the paraaortic LNs; (3) age between 45 and 60 years; (4) scheduled for curative-intent CCRT. The second cohort consisted of patients with pretreatment PET/CT studies in Chang Gung Memorial Hospital (Linkou) from 2006 to 2014 collected retrospectively, with the following selection criteria: diagnosis of primary squamous cell carcinoma of the uterine cervix receiving CCRT without a history of other malignancy and clinical FIGO stage III/IVA or pelvic/paraaortic LN metastases on pretreatment PET/CT imaging without distant metastases outside the paraaortic LNs.

Statistical analysis

The associations between categorical variables and tumour relapse were examined using Fisher's exact test. The Mann-Whitney U test was used to compare differences in continuous variables between different treatment arms and the significance of the associations with treatment failure and different failure sites. Receiver operating characteristic (ROC) curve analysis of significant parameters was performed to calculate the area under the curve (AUC) values with sensitivities (proportion of failures correctly predicted) and specificities (proportion of non-failures correctly predicted) determined using Youden's index as the cut-off point. The predictive values of the predictors/cut-off points were determined using two cohorts independent of the study population. Overall survival (OS) was defined from the date of enrolment until the date of death or censored to the last date of follow-up. Univariate Cox regression analysis and stepwise multivariate Cox regression analysis using the forward Wald method for OS were performed. OS curves were generated using the Kaplan-Meier method and compared using the log-rank test between patients grouped according to significant OS predictors at the cut-off points acquired as above. Two-sided P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS statistical software version 19.0 (IBM Corp., Armonk, NY).

Results

Patient characteristics and failure patterns

Between March 2009 and March 2013, a total of 74 patients were enrolled for random assignment in the AGOG 09-001 trial. Six patients were excluded before protocol treatment, and in 13 patients a scan was not performed during treatment or was performed at the wrong time (protocol violation). A total of 55 patients completed this parallel study (Fig. 1). The general characteristics of the participants and the associations

Fig. 1 CONSORT diagram of the study. *Arm C* Treatment consisted of cisplatin combined with radiotherapy. *Arm CG* Treatment consisted of cisplatin plus gemcitabine combined with radiotherapy. *LTFU* Lost to follow-up
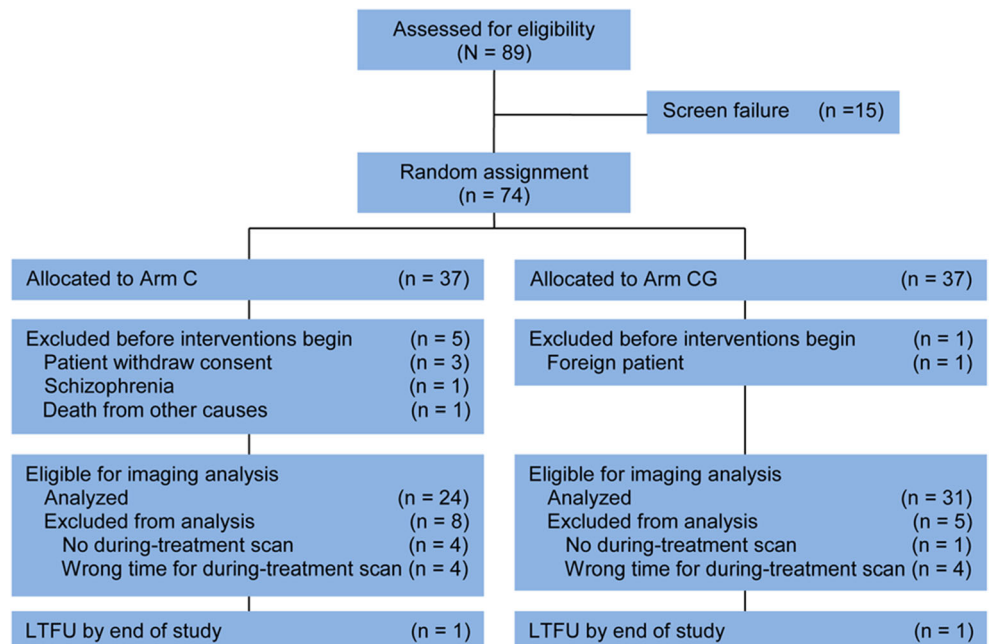
Table 1 Patient characteristics and associations with treatment failure

Characteristic	Patient group			P value
	Total ($n = 55$)	Without treatment failure ($n = 35$)	With treatment failure ($n = 20$)	
Age (years)				
≤56	29 (53)	19 (54)	10 (50)	.786
>56	26 (47)	16 (46)	10 (50)	
ECOG performance status				
0	40 (73)	24 (69)	16 (80)	.531
1	15 (22)	11 (31)	4 (20)	
FIGO stage				
I/II	32 (58)	20 (57)	12 (60)	.999
III	23 (42)	15 (43)	8 (40)	
Primary tumour grade				
Moderately differentiated	28 (51)	21 (60)	7 (35)	.097
Poorly differentiated	27 (49)	14 (40)	13 (65)	
Pelvic lymph node				
Negative	8 (15)	5 (14)	3 (15)	.999
Positive	47 (85)	30 (86)	17 (85)	
Paraaortic lymph node				
Negative	42 (76)	33 (94)	9 (45)	<.001
Positive	13 (34)	2 (6)	11 (55)	
Chemotherapy regimen of CCRT				
Cisplatin only	24 (44)	14 (40)	10 (50)	.575
Cisplatin and gemcitabine	31 (56)	21 (60)	10 (50)	

The values presented are number (%) of patients

with treatment failure are summarized in Table 1. Parameters from PET/CT and MRI between arm C and arm CG did not show significant differences and are presented in Table 2. With a median follow-up of 54 months and a minimum follow-up of 25 months in survivors, 20 of the 55 eligible patients (36 %) had treatment failure. Patients with positive paraaortic LNs had a significantly greater predisposition to treatment failure than those without (84.6 vs. 21.4 %, $P < .001$).

The failure sites are shown in Table 3. The numbers of patients with local, regional and distant failure are 5, 11 and 11, respectively.

Prediction of treatment failure

The parameter values obtained from PET/CT and MRI in patients without and with treatment failure are shown in Table 4. The following seven parameters were found to be significantly associated with treatment failure: pretreatment anatomical cervical tumour volume, pretreatment and during-treatment cervical tumour MTV, pretreatment and during-treatment SUVnode, cervical tumour MTVratio, and maximum LN SUVratio. The associations between imaging parameters and sites of failure are presented in Table 5. Pretreatment anatomical cervical tumour volume ($P < .001$), pretreatment MTV ($P = .001$), during-treatment MTV ($P < .001$), and

pretreatment SUVnode ($P = .043$) were significantly associated with local failure. Pretreatment SUVnode ($P = .023$), during-treatment SUVnode ($P = .001$), and maximum LN

Table 2 Parameters from PET/CT and MRI in the two treatment arms

Parameter	Arm C[a]	Arm CG[b]	P value
SUVmax of cervical tumour			
Pretreatment	14.5 ± 6.0	13.5 ± 4.4	.773
During treatment	8.7 ± 3.3	9.1 ± 3.3	.623
Pretreatment anatomical cervical tumour volume (mL)	50.6 ± 47.9	58.1 ± 49.8	.263
MTV of cervical tumour (mL)			
Pretreatment	80.8 ± 78.1	90.5 ± 84.8	.387
During treatment	37.1 ± 37.7	43.7 ± 78.1	.825
SUVnode			
Pretreatment	6.8 ± 5.8	6.4 ± 2.9	.410
During treatment	4.1 ± 3.6	4.1 ± 2.3	.468
SUVratio of cervical tumour (%)	63.0 ± 18.9	69.6 ± 23.1	.415
MTVratio of cervical tumour (%)	44.6 ± 20.8	42.5 ± 31.1	.425
Maximum LN SUVratio (%)	70.8 ± 25.7	71.7 ± 39.0	.680

The values presented are means ± SD

[a] Treatment consisted of cisplatin combined with radiotherapy

[b] Treatment consisted of cisplatin plus gemcitabine combined with radiotherapy

Table 3 Failure sites

Patient no.	Local	Regional	Distant
3		PLN, PALN	SCLN, lung
5			MLN
7		PALN	SCLN, MLN, bone
8		PALN	
9			Lung, kidney
10			Peritoneal
12	Pelvic seedings		Peritoneal
13		PLN	ILN, MLN
14		PLN, PALN	
17			ILN, SCLN
20			SCLN, lung
23		PALN	
25		PLN	
31	Cervix, uterus		Lung
32	Cervix		
33			SCLN
35		PLN	
39		PLN, PALN	
44	Cervix, uterus	PLN	
54	Cervix	PLN	

ILN inguinal lymph node, *MLN* mediastinal lymph node, *PALN* paraaortic lymph node, *PLN* pelvic lymph node, *SCLN* supraclavicular lymph node

SUVratio ($P = .002$) were significantly associated with regional failure. During-treatment MTV ($P = .011$), during-treatment SUVnode ($P = .018$), primary tumour MTVratio ($P = .014$),

Table 4 Associations between treatment failure and continuous parameters obtained from PET/CT and MRI

Parameter	Without treatment failure	With treatment failure	P value
SUVmax of cervical tumour			
Pretreatment	13.7 ± 4.5	14.3 ± 6.3	.820
During treatment	8.7 ± 3.3	9.3 ± 3.3	.582
Pretreatment anatomical cervical tumour volume (mL)	39.2 ± 23.8	82.1 ± 66.9	.010
MTV of cervical tumour (mL)			
Pretreatment	59.5 ± 33.5	133.0 ± 114.9	.029
During treatment	21.5 ± 18.0	74.6 ± 94.5	.001
SUVnode			
Pretreatment	5.1 ± 2.5	9.2 ± 5.4	.001
During treatment	2.9 ± 1.8	6.1 ± 3.3	<.001
SUVratio of cervical tumour (%)	65.3 ± 21.5	69.4 ± 21.7	.726
MTVratio of cervical tumour (%)	35.7 ± 20.8	56.8 ± 31.3	.010
Maximum LN SUVratio (%)	61.4 ± 28.5	88.9 ± 36.4	.001

The values presented are means ± SD

Table 5 Associations between imaging parameters and failure site

Parameter	Failure site		
	Local	Regional	Distant
SUVmax of cervical tumour			
Pretreatment	.725	.614	.674
During treatment	.349	.549	.983
Pretreatment anatomical cervical tumour volume	<.001	.950	.081
MTV of cervical tumour			
Pretreatment	.001	.900	.178
During treatment	<.001	.207	.011
SUVnode			
Pretreatment	.043	.023	.224
During treatment	.070	.001	.018
SUVratio of cervical tumour	.558	1.000	.265
MTVratio of cervical tumour	.101	.050	.014
Maximum LN SUVratio	.195	.002	.025

The values presented are *P* values

and maximum LN SUVratio ($P = .025$) were significantly associated with distant failure.

The AUCs, optimum cut-off values by ROC analysis and resultant sensitivities and specificities of significant parameters for predicting different failure sites are presented in Table 6. Anatomical volume and pretreatment and during-treatment cervical tumour MTV significantly predicted local failure with high AUCs (0.980, 0.964 and 0.976, respectively). Images in a patient with local failure are shown in Fig. 2. Pretreatment SUVnode predicted local and regional failure with lower AUCs. During-treatment SUVnode predicted regional and distant failure with AUCs of 0.840 and 0.756, respectively. Maximum LN SUVratio predicted regional and distant failure with AUCs of 0.811 and 0.743, respectively. During-treatment MTV (AUC 0.750) and cervical tumour MTVratio (AUC 0.742) also predicted distant failure. Images in an example patient with distant failure are shown in Fig. 3.

Validation using independent patient cohorts

The validation set 1 consisted of 31 patients with one PET/CT scan during treatment at the same time point as in the current study. Of the 31 patients, 12 (39 %) had treatment failure with a median follow-up of 73 months for survivors. The failure patterns were as follows: combined local and regional in two patients, regional only in two, combined regional and distant in three, and distant only in five. The validation set 2 consisted of 105 patients with only a pretreatment PET/CT scan . Of the 105 patients, 34 (32 %) had treatment failure with a median follow-up of 42 months for survivors. The failure patterns

Table 6 AUCs, optimum cut-off values, sensitivities and specificities of different imaging parameters for predicting failure site

| Parameter	Failure site	AUC	Cut-off	Sensitivity (%)	Specificity (%)
Pretreatment anatomical cervical tumour volume (mL)	Local	0.980	110	100	98.0
MTV (mL)					
Pretreatment	Local	0.964	149	100	94.0
During treatment	Local	0.976	82	100	96.0
	Distant	0.750	30.7	72.7	70.5
SUVnode					
Pretreatment	Local	0.808	6.7	100	65.1
	Regional	0.729	8.9	54.5	86.1
During treatment	Regional	0.840	3.9	90.9	72.2
	Distant	0.756	3.9	88.9	68.4
Maximum LN SUVratio	Regional	0.811	63.5 %	90.9	66.7
	Distant	0.743	70.4 %	77.8	73.7
MTVratio of cervical tumour	Distant	0.742	38.8 %	81.8	56.8
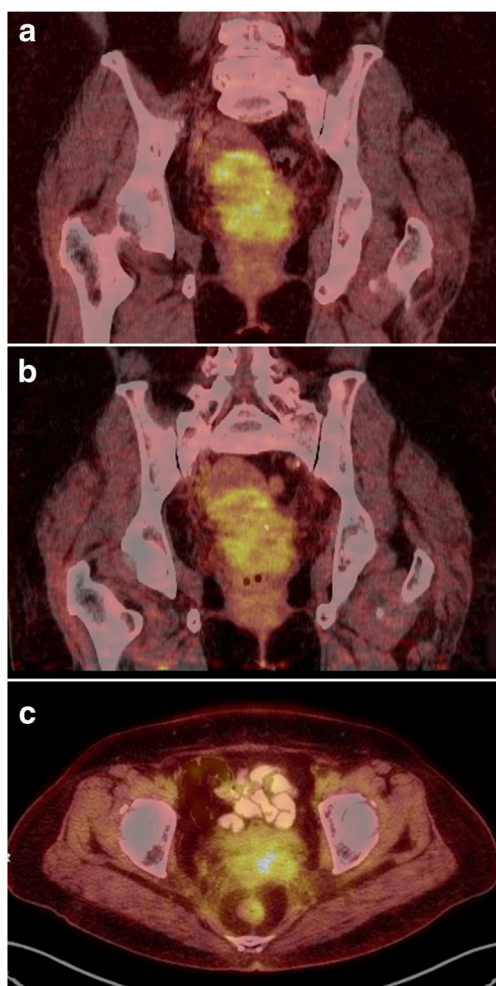
Fig. 2 A 60-year-old patient with FIGO stage IIIB cervical cancer and no definite lymph node metastases treated with chemoradiotherapy. The PET/CT image before treatment (**a**) shows a bulky primary tumour with SUVmax 10.2 and MTV 151 mL. The PET/CT image during treatment (**b**) shows a primary tumour with SUVmax 5.8 and MTV 93 mL. The PET/CT image after treatment (**c**) shows residual tumour activity in the uterine cervix. Biopsy findings confirmed the presence of local failure, and surgical salvage was then performed

were as follows: local only in four patients, combined local and regional in four, combined local, regional and distant in four, regional only in four, combined regional and distant in eight, and distant only in ten. The characteristics of the patients in the study cohort and validation sets showed no significant differences (Table 7).

The validation results including AUCs, sensitivities and specificities of predictive factors determined in the current study cohort for different failure sites are shown in Table 8. For local failure prediction, pretreatment and during-treatment MTV had higher AUCs and sensitivities/specificities. For regional failure prediction, during-treatment SUVnode had higher AUC and sensitivity/specificity. For distant failure prediction, during-treatment MTV and during-treatment SUVnode had moderate AUCs and better sensitivities/specificities.

Posttreatment follow-up and overall survival

Overall, of the 55 patients, 15 (27 %) died of disease with a median follow-up of 54 months (range 25 – 73 months). The univariate Cox regression analysis demonstrated that primary tumour grade, positive paraaortic LN, pretreatment anatomical cervical tumour volume, pretreatment and during-treatment MTV, pretreatment and during-treatment SUVnode, cervical tumour SUVratio and MTVratio, and maximum LN SUVratio were significant predictors of OS (Table 9). Stepwise multivariate Cox regression analysis demonstrated that during-treatment SUVnode ($P = .001$) and cervical tumour MTVratio ($P = .004$) were independent significant predictors of OS (Table 10). OS curves of patients grouped according to during-treatment SUVnode with a cut-off value of 3.9 and cervical tumour MTVratio with a cut-off value of 38.8 % are shown in Fig. 4.

Discussion

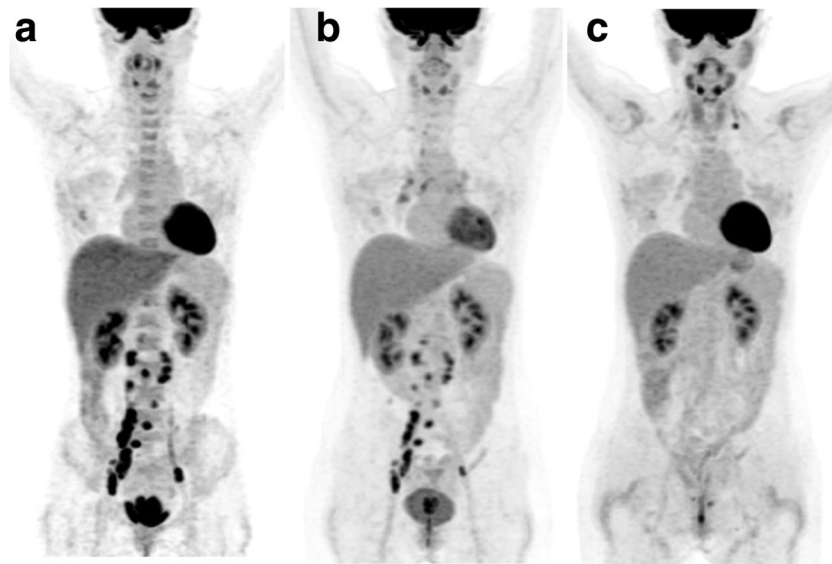The 5-year OS of cervical cancer patients with persistent or recurrent disease after primary treatment remains

Fig. 3 A 39-year-old patient with FIGO stage IIB cervical cancer treated with chemoradiotherapy. The PET image before treatment (**a**) shows multiple regional and paraaortic lymph node metastases (SUVnode 11.2). The PET image during treatment (**b**) shows residual lymph node metastases (SUVnode 8.6). The PET image after treatment (**c**) shows regression of regional and paraaortic lymph nodes, but also shows a new lesion in a left supraclavicular node. Aspiration of the supraclavicular lymph node confirmed the metastatic nature of the lesion, and salvage chemoradiotherapy was then performed

dismal (about 10 %) [3]. Curative-intent therapy is indicated only in a minority of patients with isolated relapse [16]. In this scenario, novel strategies for improving primary therapeutic outcome are eagerly sought. Compared with RT alone, primary CCRT has been shown to increase the 5-year OS from 60 % to 66 % [17]. If we can monitor early treatment response and predict failure sites during primary therapy, treatment modifications may be applied

early with the hope of improving outcome. Our main goal in the current study was to identify useful pretreatment and in-treatment PET parameters which allow timely modification of therapeutic planning. Although posttreatment PET parameters have been shown to predict survival, they do not allow early and meaningful therapeutic adjustments [5, 18]. Significant parameters predictive of local, regional and distant failure identified in the current

Table 7 Characteristics of the patients in the study cohort and the validation sets

Characteristic	Patient group			P value	
	Study cohort (n = 55)	Validation set 1 (n = 31)	Validation set 2 (n = 105)	Validation set 1 versus study cohort	Validation set 2 versus study cohort
Age (years)					
≤56	29 (53)	20 (65)	61 (58)	.289	.516
>56	26 (47)	11 (35)	44 (42)		
FIGO stage					
I/II	32 (58)	23 (74)	61 (58)	.138	.992
III/IV	23 (42)	8 (26)	44 (42)		
Grade of differentiation					
Well/moderate	28 (51)	12 (39)	46 (44)	.276	.392
Poor	27 (49)	19 (61)	59 (56)		
Pelvic lymph nodes					
Negative	8 (15)	8 (26)	6 (6)	.198	.078
Positive	47 (85)	23 (74)	99 (94)		
Paraaortic lymph nodes					
Negative	42 (76)	24 (77)	71 (68)	.911	.249
Positive	13 (34)	7 (23)	34 (32)		

The values presented are number (%) of patients

Table 8 AUCs, optimum cut-off values, sensitivities and specificities for predicting different failure sites in the validation datasets

Parameter	Failure pattern	Cut-off	Validation set 1 (n = 31)			Validation set 2 (n = 105)		
			AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)
Pretreatment anatomical cervical tumour volume (mL)	Local	110	0.966	0	100	0.761	25	96.1
MTV (mL)								
Pretreatment[a]	Local	149	0.999	100	96.6	0.807	41.7	96.8
During treatment[a]	Local	82	0.999	100	100			
During treatment[a]	Distant	30.7	0.707	75	69.6			
SUVnode								
Pretreatment	Local	6.7	0.636	0	68.2	0.656	55.6	64.4
Pretreatment	Regional	8.9	0.608	16.7	82.4	0.688	50	87.7
During treatment[a]	Regional	3.9	0.745	83.3	82.4			
During treatment[a]	Distant	3.9	0.696	66.7	76.5			
Maximum LN SUVratio	Regional	63.5 %	0.676	66.7	41.2			
Maximum LN SUVratio	Distant	70.4 %	0.471	50	52.9			
MTVratio of cervical tumour	Distant	38.8 %	0.712	75	43.5			

[a] Clinically useful predictors

study can be incorporated into our new clinical pathway for cervical cancer treatment.

The prognostic importance of primary tumour size and volume has long been recognized [19]. A prospective study in 52 cervical cancer patients with PET/CT and MRI scans before, during and after CCRT revealed significant decreases in tumour volume both on PET/CT and MRI during CCRT [20]. In our study cohort, pretreatment cervical tumour volume was

Table 9 Univariate Cox regression analysis for overall survival

Parameter	Hazard ratio	95 % confidence interval	P value
Age (>56 vs, ≤56 years)	0.92	0.34 to 2.55	.877
ECOG performance status (1 vs, 0)	0.88	0.24 to 3.20	.845
FIGO stage (III vs, I/II)	0.88	0.31 to 2.46	.803
Primary tumour grade (poorly vs, moderately differentiated)	3.21	1.02 to 10.07	.046
Pelvic LN (+ vs, −)	2.99	0.39 to 22.74	.291
Paraaortic LN (+ vs, −)	6.15	2.18 to 17.35	.001
CCRT chemotherapy regimen (cisplatin and gemcitabine vs, cisplatin)	0.92	0.34 to 2.55	.878
SUVmax of cervical tumour			
Pretreatment	1.03	0.93 to 1.13	.626
During treatment	1.13	0.98 to 1.30	.085
Anatomical cervical tumour volume on MRI			
Pretreatment	1.01	1.00 to 1.02	.004
MTV of cervical tumour			
Pretreatment	1.01	1.00 to 1.01	.010
During treatment	1.01	1.00 to 1.01	.014
SUVnode			
Pretreatment	1.13	1.05 to 1.22	.002
During treatment	1.32	1.16 to 1.50	<.001
SUVratio of cervical tumour	8.29	1.14 to 60.16	.037
MTVratio of cervical tumour	22.74	4.64 to 111.50	<.001
Maximum LN SUVratio	7.13	2.32 to 21.86	.001

Table 10 Multivariate Cox regression analysis for overall survival

Parameter	Full model		Stepwise	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Age (>56 vs. ≤56 years)	6.06	.219		
ECOG performance status (1 vs. 0)	3.38	.326		
FIGO stage (III vs. I/II)	23.66	.045		
Primary tumour grade (poorly vs, moderately differentiated)	1.14	.916		
Pelvic LN (+ vs. −)	−	−		
Paraaortic LN (+ vs. −)	106.19	.032		
CCRT chemotherapy regimen (cisplatin and gemcitabine vs, cisplatin)	3.45	.297		
SUVmax of cervical tumour				
Pretreatment	1.95	.271		
During treatment	0.34	.257		
Anatomical cervical tumour volume on MRI				
Pretreatment	1.08	.059		
MTV of cervical tumour				
Pretreatment	0.99	.721		
During treatment	0.96	.149		
SUVnode				
Pretreatment	0.58	.087		
During treatment	3.89	.016	1.27	.001
SUVratio of cervical tumour	909.65	.545		
MTVratio of cervical tumour	536.42	.098	11.27	.004
Maximum LN SUVratio	0.01	.068		

significantly associated with local failure both on MRI and PET/CT. Similar association was noted for during-treatment MTV. More intensive local therapy or post-CCRT surgery may be required in patients with larger cervical tumour volumes. Pretreatment SUVnode was associated with local and regional failure with moderate AUCs. During-treatment SUVnode was associated with regional and distant failure, and was the most significant predictor of OS. Maximum LN SUVratio was also associated with regional and distant failure with moderate AUCs. Higher during-treatment SUVnode or maximum LN SUVratio may reflect the presence of treatment-resistant tumour cells in LNs, ultimately leading to the requirement for increased regional RT doses, the addition of radiosensitizing drugs to platinum compounds, and/or adjuvant therapy. During-treatment cervical tumour MTV and MTVratio were associated with distant failure. Primary and regional tumours with limited response to therapy may show a more aggressive biological nature and higher propensity for haematogenous and distant lymphatic spread, ultimately leading to poor outcome.

Cervical cancer spreads mainly via the lymphatic system and sequentially from the primary tumour to the pelvic, paraaortic and supraclavicular LNs [21]. In the RTOG 0116 study, 26 patients with paraaortic or high common iliac LN metastasis received extended-field RT and BCT with cisplatin. Local failure occurred in 8 % and nodal failure occurred in 38 % [22]. Yoon et al. found that a complete metabolic nodal response after RT predicted better 3-year OS, whereas a complete metabolic response of the primary tumour did not [23]. Taken together, these findings highlight the paramount importance of LN control in patients with advanced cervical cancer. In our institution, the radiation dose to positive LNs is generally between 54 and 57.6 Gy. How to increase the effectiveness of LN control in patients with a high risk of regional and distant LN failure will be the topic of our new trials.

In this study, a fixed SUVmax of 3.0 was used to define the boundaries for the MTV of cervical tumours. We did not utilize a percentage tumour SUVmax threshold because this parameter decreases significantly during treatment, possibly leading to overestimation of during-treatment tumour volume [24]. Kidd et al. have suggested that pretreatment MTV and week-4 cervical tumour SUVmax are predictors of posttreatment PET response [25]. Oh et al. found that cervical tumour SUVratio after 4 weeks of CCRT was associated with progression-free survival [26]. Patient selection bias, different timing of during-treatment imaging and analysis of different parameters make the comparison of these and our studies complicated.
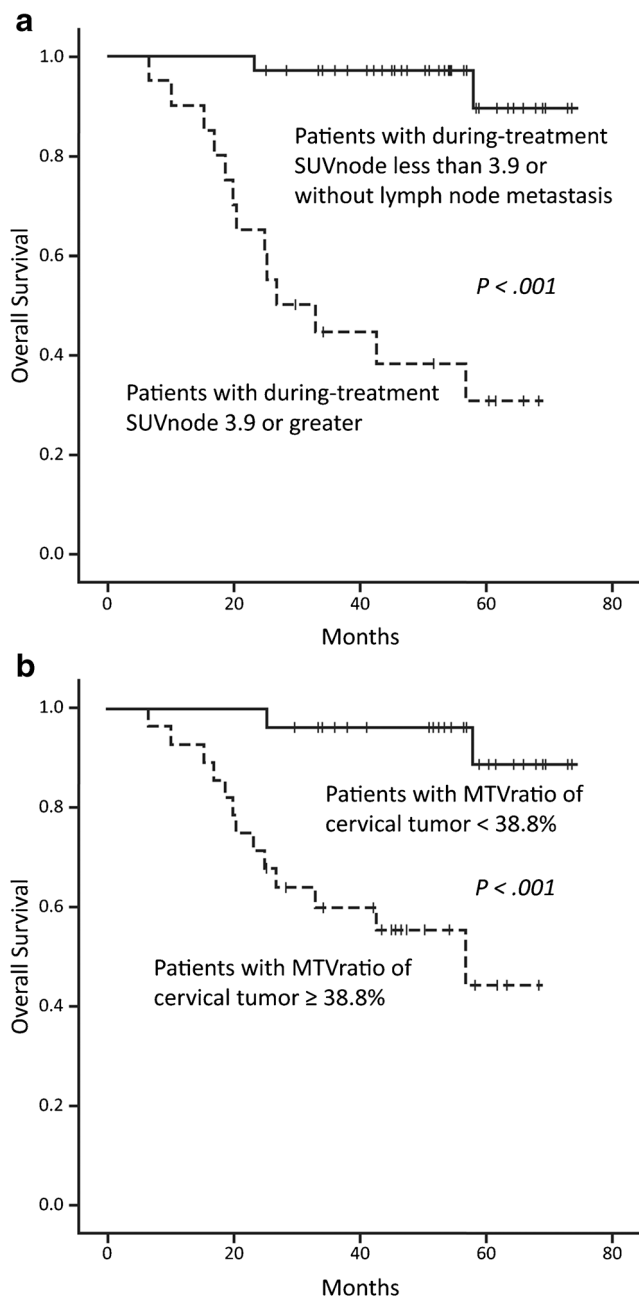
Fig. 4 Overall survival curves of patients grouped according to during-treatment SUVnode with a cut-off value of 3.9 (**a**) and cervical tumour MTVratio with a cut-off value of 38.8 % (**b**)

the values of the quantitative PET/CT parameters. Thirdly, the patients in the validation sets were analysed retrospectively and the treatment in these patients was less standardized, possibly reducing the resultant AUCs, sensitivities and specificities. Large-scale validation of our findings is needed.

Nonetheless, the current study was the first prospective trial to predict treatment failure in advanced cervical cancer by classification of failure sites into local, regional and distant categories, and identified the following clinically useful predictors: pretreatment and during-treatment MTV for local failure, during-treatment SUVnode for regional and distant failures, and during-treatment MTV for distant failure. During-treatment SUVnode and cervical tumour MTVratio were independent significant predictors of OS.

In conclusion, we found that pretreatment and during-treatment PET/CT imaging may be clinically useful for predicting failure sites and OS in patients with advanced cervical cancer. Based on the results of serial PET/CT scans, therapy may be tailored to the individual patient at week 3 during treatment, potentially leading to improved outcomes in patients with advanced cervical cancer.

There were several limitations of the current study. Firstly, the numbers of patients with failure at different sites were small, consequently reducing the reliability of the findings. Validation with independent patient cohorts was thus performed to reduce type I errors. Secondly, the timing of pretreatment and during-treatment PET/CT imaging relative to the start of treatment had a range of 1 week among the patients. The heavy clinical loading of the PET/CT facility and difficulties in patient scheduling prevented this period from being reduced further. This may have had some influence on

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