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Original article

(^{18}F)-FDG PET/CT parameters to predict survival and recurrence in patients with locally advanced cervical cancer treated with chemoradiotherapy

Nouveaux paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué

N. Scher[a,*], J. Castelli[a,b,c], A. Depeursinge[d,e], J. Bourhis[a], J.O. Prior[f], F.G. Herrera[a,1], M. Ozsahin[a,1]

[a] *Department of Radiation Oncology, Lausanne University Hospital, 46, rue du Bugnon, 1011 Lausanne, Switzerland*
[b] *Inserm, U1099, campus de Beaulieu, 35000 Rennes, France*
[c] *LTSI, université de Rennes 1, campus de Beaulieu, 35000 Rennes, France*
[d] *École polytechnique fédérale de Lausanne, 1015 Lausanne, Switzerland*
[e] *University of Applied Sciences Western Switzerland, 3960 Sierre, Switzerland*
[f] *Nuclear Medicine and Molecular Imaging Department, Lausanne University Hospital, 46, rue du Bugnon, 1011 Lausanne, Switzerland*

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ABSTRACT

Purpose. – To identify predictive (^{18}F)-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT)-based parameters for locoregional control, disease-free survival and overall survival, by testing different thresholds of metabolic tumor volume and total lesion glycolysis in patients with locally-advanced cervical cancer.

Patients and methods. – Thirty-seven patients treated with standard chemoirradiation underwent a pre-treatment (^{18}F)-FDG-PET/CT. Using different thresholds of maximum standardized uptake value, the following PET parameters were computed: maximum standardized uptake value, mean standardized uptake value, metabolic tumor volume and total lesion glycolysis for primary tumor and lymph nodes and a new parameter combining the metabolic tumor volume and the distance between lymph nodes and the primary tumor, namely metabolic node distance. Correlation between PET and clinical parameters with clinical outcome (overall survival, disease-free survival, and locoregional control) was assessed using univariate and multivariate analyses (Cox model).

Results. – In univariate analyses, PET/CT parameters associated with overall survival and disease-free survival were: metabolic tumor volume and total lesion glycolysis of the primary tumor, total lesion glycolysis of lymph nodes and metabolic node distance. The most predictive threshold segmentation for metabolic tumor volume and total lesion glycolysis was 48% of maximum standardized uptake value for the primary tumor and 30% for the lymph nodes. In multivariate Cox analysis, the total lesion glycolysis of primary tumor 48% and metabolic node distance were the two independent risk factors for overall survival ($P < 0.01$), disease-free survival ($P < 0.01$) and locoregional control ($P = 0.046$).

Conclusion. – Total lesion glycolysis of primary tumor and distance between the invaded positive lymph node and the primary tumor seem to have the highest predictive value when compared to classical clinical

* Corresponding author.
E-mail address: nathaniel.scher@gmail.com (N. Scher).
[1] Equally contributed to this article.

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prognostic parameters and may be useful to identify high risk groups at time of diagnosis and to tailor the therapeutic approach in locally-advanced cervical cancer.

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TEP au (^{18}F)-FDG
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Pronostic

RÉSUMÉ

Objectif de l'étude. – Les objectifs de ce travail étaient d'identifier, pour des cancers du col utérin localement évolués pris en charge par chimioradiothérapie, les paramètres quantitatifs de tomographie par émission de positons prédictifs du contrôle locorégional, de la survie sans récidive et de la survie globale.
Patientes et méthode. – Trente-sept patientes, avec un suivi médian de 52 mois, ont été incluses dans cette étude rétrospective. En plus de la standard *uptake value* maximale (SUVmax), les paramètres de tomographie par émission de positons (TEP) de volume (volume métabolique tumoral et indice de glycolyse lésionnelle globale) ont été calculés en utilisant différentes valeurs de seuillage en valeur absolue (de 0 à 20) ou relative (de 0 à 100 % de la SUVMax). Un nouveau paramètre de distance tumorale métabolique combinant le volume métabolique tumoral ganglionnaire avec la distance entre la tumeur primitive et chaque ganglion atteint a également été défini. L'ensemble des paramètres cliniques et de TEP a été analysé et une corrélation avec la survie globale, la survie sans récidive et le contrôle local a été recherchée. Un modèle pronostique de survie globale a été défini. Une validation interne a été réalisée par validation croisée.
Résultats. – En analyse multifactorielle l'indice de glycolyse lésionnelle globale de la tumeur et la distance tumorale métabolique étaient les deux facteurs pronostiques indépendants prédisant la survie globale ($p < 0{,}01$), la survie sans rédicive ($p < 0{,}01$) et le contrôle locorégionale ($p = 0{,}046$). Après validation croisée, les c-index étaient pour la survie globale, la survie sans récidive et le contrôle locorégional respectivement de 0,63, 0,68 et 0,66. Un score prédictif a été calculé, permettant d'identifier deux groupes à risque. Les probabilités de survie globale, de survie sans récidive et de contrôle locorégionale à 3 ans étaient de 88 %, 78 % et 84 % pour le groupe à bas risque contre 45 %, 33 % et 38 % pour le groupe à haut risque ($p < 0{,}01$).
Conclusions. – L'indice de glycolyse lésionnelle globale tumorale et la distance entre la tumeur primitive et chaque ganglion atteint, sont des paramètres pronostiques de la survie après chimioradiothérapie pour des cancers du col utérin. Ces paramètres pourraient permettre une identification précoce des patientes atteintes de cancer de pronostic défavorable, candidat potentiel à une intensification thérapeutique. Une validation externe prospective sera nécessaire pour confirmer ces résultats.

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1. Introduction

Cervical cancer is the fourth most common cancer among women in the world and a leading cause of cancer mortality [1]. Since the publication in 1999 of randomized trials using platinum-based chemotherapy in patients with locally advanced cervical cancer and the clinical recommendations announced by the National Cancer Institute, concurrent radiotherapy and cisplatin-based chemotherapy became the standard management with a significant improvement in survival rates compared with radiotherapy alone [2,3]. Nevertheless, increasingly more radio- and chemoresistant tumors still recur. New research strategies have focused on the development of tumor predictive biomarkers to identify patients most at risk of recurrent disease. In this setting, (^{18}F)-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) might help to identify more aggressive tumors.

More recently, other trials suggested that there might be a benefit for sequential chemotherapy after standard concomitant chemoradiotherapy and this therapeutic approach is now being tested in randomized trials [4]. The gains in survival observed with chemoradiotherapy have come at a substantial price because both acute and late morbidities increased with combined modality treatment. It is thus expected that intensifying the platinum-based chemotherapy regimen would increase side effects and reduce the patient's quality of life. Even with the significant reductions in the risk of cervical cancer death observed with chemoradiotherapy, the absolute gains are small for patients with early tumors, many of whom could have been cured with radiotherapy alone and recurrence rates are still high for patients with very large or advanced tumors for whom adjuvant chemotherapy might be of benefit. It is therefore important to establish accurate predictors of therapeutic response, particularly if adjuvant chemotherapy after primary chemoradiotherapy should become the new treatment paradigm. In locally advanced cervical cancer, FDG-PET/CT has become important in the initial evaluation of disease extent, especially for nodal staging [5,6]. Moreover, pretreatment FDG-PET/CT of cervical tumors predicts disease-free survival and overall survival [7]. Most of the reported studies used a visual analysis and maximum standardized uptake value [8,9]. More recently, quantitative parameters, metabolic tumor volume and total lesion glycolysis have been correlated with clinical outcome [10]. Nonetheless, these quantitative parameters require tumor segmentation. One of the most common methods consists of using a threshold, defined either by an absolute value of standardized uptake or a relative value of maximum standardized uptake. However, there are no consistent data for using a specific threshold to compute the metabolic tumor volume [11,12].

The International Federation of Gynecology and Obstetrics (FIGO) has defined the most widely accepted staging system for carcinoma of the cervix. Although the survival and pelvic disease control rates of patients with cervical cancer correlate with FIGO stage, the prognosis is also influenced by a number of tumor characteristics that are not included in the staging system. Lymph node metastasis is one such important prognostic factor.

Table 1
Retrospective analysis of (^{18}F)-FDG-PET/CT metabolic parameters to identify high-risk groups at time of diagnosis and to tailor the therapeutic approach in locally advanced cervical cancer: patient and tumor characteristics (n = 37).
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : caractéristiques cliniques des 37 patientes et des tumeurs.

	n (%)
FIGO stage groups	
IB1, IIA1, IB2	11 (30%)
IIA2, IIB	19 (51%)
IIIA, IIIb, IVA	7 (19%)
FIGO stage	
IB1	2 (5.4%)
IB2	4 (10.8%)
IIA1	5 (16.2%)
IIA2	4 (10.8%)
IIB	15 (40.5%)
IIIA	2 (5.4%)
IIIB	3 (8.1%)
IVA	2 (5.4%)
Histology	
Squamous-cell carcinoma	33 (87%)
Adenocarcinoma	4 (13%)
Grade	
1	7 (19%)
2	23 (62%)
3	7 (19%)
Lymph node status	
Positive lymph nodes	22 (59.5%)
Negative lymph nodes	15 (40.5%)
Lymphovascular space invasion	
Positive	25 (67.5%)
Negative	12 (32.5%)

In the context of locally-advanced cervical cancer treated with chemoradiotherapy, the aims of this study were:

- to identify the best predictive PET-based parameters of locoregional control, disease-free survival and overall survival, testing different thresholds to compute metabolic tumor volume and total lesion glycolysis;
- to compare the predictive value of this PET parameters with other classical parameters.

2. Materials and methods

2.1. Patients and tumor

Thirty-seven consecutive patients treated at the Lausanne University Hospital with concomitant cisplatin and radiotherapy for a locally advanced cervical cancer between January 2007 and December 2015 were included in this retrospective analysis. Inclusion criteria were:

- pathological diagnosis of cervical carcinoma, stage IB1-IVA according to the FIGO 2009 definition;
- complete staging comprising clinical staging, magnetic resonance imaging (MRI);
- FDG-PET/CT;
- a minimum follow-up period of 6 months.

Patients with stage IB1 and IIA1 cervical carcinoma were considered for inclusion if they had positive lymph nodes. Exclusion criteria were:

- history of previous chemotherapy or radiotherapy;
- metastatic disease.

Patient and tumor characteristics are presented in Table 1.

2.2. Treatment

All patients were treated following international guidelines [13–15]. Chemotherapy consisted of weekly cisplatin (40 mg/m^2) delivered concurrently with radiotherapy. Neither induction nor adjuvant chemotherapy was administered. Before starting radiotherapy treatment, patients underwent a pelvic planning CT-scan with intravenous contrast medium. Consortium guidelines were used to contour the pelvic and nodal clinical target volume and the planning target volume (PTV) [14,15]. Treatment plans were performed using the tomotherapy treatment planning system (Accuray Inc, Sunnyvale, CA). Pelvic radiation dose was between 45 and 50.4 Gy in 1.8 Gy daily fractions, in 25–28 fractions. In patients with positive pelvic or para-aortic nodes, extended-field radiotherapy was used to a dose of 45 Gy with a simultaneous-integrated boost to the positive nodes of 60 Gy in 2.4 Gy per fraction in 25 fractions. Daily image guidance before each fraction was implemented using the MV fan-beam CT of helical tomotherapy. Patients received three to four fractions of MRI-guided high-dose-rate intracavitary brachytherapy every 4 days. The prescribed dose was 7 Gy to the high-risk clinical target volume. Brachytherapy was administered after the end of external beam radiotherapy.

2.3. Clinical and imaging follow-ups

Clinical follow-up exams of the patients were performed weekly during chemoradiotherapy and after the completion of therapy as follows: every 3 months until 24 months, every 6 months during years 2–5 and annually thereafter. All patients had a (^{18}F)-FDG-PET/CT evaluation at three months following chemoradiotherapy to assess tumor response. Subsequently, follow-up imaging studies consisted of MRI/CT and/or (^{18}F)-FDG-PET/CT when clinically indicated.

2.4. (^{18}F)-FDG-PET/CT acquisition parameters

All patients fasted for at least 6 h before the PET study. The (^{18}F)-FDG-PET/CT was performed 60 min after administration of 3.5 MBq/kg (^{18}F)-FDG (Discovery 690FX TOF; GE Healthcare, Milwaukee, WI) and images (from the head to proximal thigh) were reconstructed using time-of-flight and point-spread function information. The SUV was calculated by correcting for the injected dose of (^{18}F)-FDG and patient's body weight. An increase in FDG uptake above a standardized uptake value of 2.5 g/mL was used to define malignancy based on previous publications [16–18].

2.5. (^{18}F)-FDG-PET-CT image analysis

For each patient, gross tumor volume (GTV T) and nodal GTV (GTV N) were manually delineated on each PET/CT by the same radiation oncologist (N.S.). Maximum standardized uptake value was first computed from GTV T as the maximum standardized uptake value in the delineated volume. Metabolic volume was computed using two different segmentation methods:

- an absolute threshold of standardized uptake value from 2.5–8 g/mL (0.5 g/mL steps);
- absolute threshold of maximum standardized uptake value from 30–70% (2% steps).

Six metabolic intensity parameters were calculated:

- mean standardized uptake value;
- standardized uptake value variance;
- skewness;

- kurtosis, metabolic tumor volume;
- total lesion glycolysis.

The first four parameters were calculated from the standardized uptake value histogram intensity. Metabolic tumor volume was defined as the volume of the group of voxels having a standardized uptake value greater than the chosen threshold. Total lesion glycolysis was defined as the mean standardized uptake value multiplied by metabolic tumor volume. Each parameter was calculated using the two segmentation methods at each threshold for both GTV T and GTV N [19]. The distance between the centre of the primary tumor and the centre of each lymph node was calculated and was weighted by the metabolic tumor volume (with an absolute threshold of 2.5) of GTV-N. This parameter was defined as metabolic nodes distance.

2.6. Statistical considerations

Survival curves were computed using the Kaplan–Meier method. Time to any event was measured from the day of diagnosis. The events were death (all causes) for overall survival and death (all causes) or relapse for disease-free survival. For locoregional control, the event consisted of local and/or regional relapse. Follow-up period was calculated using a reverse Kaplan–Meier estimation [20].

The association of the pretreatment parameters with locoregional control, disease-free survival and overall survival was first assessed using univariate Cox analyses. Harrel's c-index were used to compare different models (c-index $\approx$ 0.5 considered not predictive, c-index $\approx$ 1 considered predictive [21]. The c-index was used to determine the optimal standardized uptake value threshold giving the most predictive value for each of the PET parameters.

Factors with significance of P-value < 0.1 and with highest c-index after univariate analyses were included in a multivariate Cox regression model using backward elimination. Variables were removed from the model if $P > 0.1$. A cross validation with 5 folds was then performed to estimate the model's stability and accuracy. This method consisted to create two cohorts from the initial population. The first cohort (corresponding to four fifth of the whole population) is used to develop the model, while the second cohort (one fifth of the whole population) as validation. This process was repeated 100 times to estimate the confidence interval of the hazard ratio of each parameters of the model.

All analyses were performed using the R software 3.2.4 (R Development CoreTeam; http://www.r-project.org).

3. Results

Patients' pathological and treatment characteristics are detailed in Table 1. Median age was 51 years (range: 26–83 years) and median tumor size was 4.5 cm (range: 1.8–8 cm).

3.1. Disease outcome

Median follow-up period was 52 months (range: 7–128 months). Three-year overall survival, disease-free survival and locoregional control rates were 71.2% (95% confidence interval [CI]: 56–86%), 64.1% (95% CI: 48–80%) and 69.4% (95% CI: 53–84%), respectively. Eleven patients (29.7%) had died and 14 patients (37.8%) had a locoregional recurrence.

3.2. Univariate analyses

Results from univariate analyses for classical prognostic parameters are shown in Table 2. Regarding the classical prognostic factors, tumor size and tumor volume (GTV T) were significantly correlated with overall survival, disease-free survival, and locoregional control. FIGO staging was correlated with overall survival ($P = 0.04$) but not with disease-free survival ($P = 0.24$) and locoregional control ($P = 0.13$).

Regarding PET parameters, metabolic node distance was the only parameter significantly correlated with overall survival ($P < 0.01$), disease-free survival ($P < 0.01$), and locoregional control ($P = 0.03$). Metabolic tumor volume and total lesion glycolysis were correlated with overall survival and disease-free survival, but not with locoregional control (Table 3). The best predictive value for total lesion glycolysis for primary tumor and lymph nodes was reached using a relative threshold of 48% of maximum standardized uptake value (overall survival; c-index: 0.66; $P = 0.02$) and 30% of maximum standardized uptake value (c-index: 0.67; $P = 0.01$), respectively.

In multivariate analysis, total lesion glycolysis for primary tumor and metabolic node distance were the two independent risk factors for overall survival ($P < 0.01$), disease-free survival ($P < 0.01$) and locoregional control ($P = 0.046$) (Table 4). The c-indexes for the model were 0.75, 0.72 and 0.73 for overall survival, disease-free survival, and locoregional control; respectively. After cross validation, the model remained significant, with adjusted c-indexes of 0.63, 0.66 and 0.66 for overall survival, disease-free survival and locoregional control respectively.

3.3. Prognostic score and optimal cut-off value

A prognostic score was calculated, based on the β-parameter from the multivariate Cox model. Based on these two independent risk factors, a prognostic score was calculated (1.004 $\times$ total lesion glycolysis of primary tumor + 1.01 $\times$ metabolic node distance). A normalization was applied to obtain a score ranging from 0 to 5. The estimated cut-off point by Hothorn and Lausen method was 0.97 (Supplementary Fig. E1). Based on this cut-off value, two risk groups were identified. Three-year overall survival, disease-free survival, and locoregional control were 88% (95% CI: 67.4–100%), 78.7% (95% CI: 63.6–97.3%), and 83.6% (95% CI: 70.1–99.7%) for low-risk group vs 45.5% (95% CI: 23.8–86.8%), 33.3% (95% CI: 15–74.2%) and 38.1% (95% CI: 17.9–81.1%) for high-risk group ($P < 0.01$); respectively (Figs. 1 and 2).

4. Discussion

This study evaluated the predictive value of metabolic parameters computed from pretreatment PET images in patients with locally advanced cervical cancer undergoing chemoradiotherapy. Total lesion glycolysis of the primary tumor computed with a relative threshold of 48% combined with a new parameter (metabolic node distance) was the best predictor for overall survival, disease-free survival, and locoregional control; allowing to identify two groups at risk. Metabolic node distance corresponding to the distance between the primary tumor and each lymph node, weighted by metabolic tumor volume of the lymph nodes. Current staging guidelines concentrate on the fact that regional lymph nodes are invaded or not. The metabolic node distance parameter goes a step further, and allows to quantify the lymphatic spread and the metastatic volume.

Prognostic value of quantitative metabolic parameters such as metabolic tumor volume or total lesion glycolysis has been investigated at time of diagnosis with controversial results [11,12]. Our previous study showed that cervical carcinoma with high metabolic tumor volume and total lesion glycolysis has a higher risk of recurrence and lower risk of survival [22], like in other studies [23,24].

However, contradictory results have also been reported. Indeed, few studies have shown that the volume-based metabolic markers

Table 2
Retrospective analysis of (^{18}F)-FDG-PET/CT metabolic parameters to identify high risk groups at time of diagnosis and to tailor the therapeutic approach in locally-advanced cervical cancer: univariate analyses of clinical parameters ($n = 37$).
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : analyse unifactorielle des paramètres cliniques (n = 37).

Parameters	Overall survival			Disease-free survival			Locoregional control		
	HR [CI 95%]	c-index	*P*	HR [CI 95%]	c-index	*P*	HR [CI 95%]	c-index	*P*
Age	0.98 [0.94; 1.03]	0.49	0.9	0.99 [0.95; 1.03]	0.49	0.9	0.99 [0.95; 1.03]	0.52	0.82
FIGO staging	1.7 [0.6; 5.03]	0.61	**0.04**	1.25 [0.53; 2.96]	0.61	**0.04**	1.51 [0.58; 3.95]	0.57	0.13
Body mass index	0.98 [0.87; 1.1]	0.52	0.90	1.01 [0.91; 1.1]	0.57	0.58	0.99 [0.88; 1.11]	0.54	0.76
T classification	2.4 [0.85; 6.77]	0.62	**0.03**	1.4 [0.63; 3.14]	0.62	**0.03**	1.70 [0.72; 4]	0.59	0.11
N classification	1.17 [0.34; 4.04]	0.51	0.99	1.37 [0.45; 4.08]	0.52	0.72	1.3 [0.38; 4.47]	0.52	0.85
Tumor size	1.6 [1; 2.56]	0.65	**0.04**	1.54 [1; 2.36]	0.65	**0.04**	1.56 [0.99; 2.45]	0.68	**0.04**
Gross tumor volume (primary tumor)	1.01 [1.01; 1.02]	0.6	**0.01**	1.01 [1.01; 1.02]	0.60	**0.01**	1.01 [1.01; 1.02]	0.61	**0.05**
Histology (adenocarcinoma squamous-cell carcinoma)	0.82 [0.45; 1.9]	0.55	0.32	0.86 [0.5; 2.11]	0.61	0.41	0.79 [0.5; 1.7]	0.55	0.42
Lymph nodes (positive, negative)	1.18 [0.34; 4.04]	0.50	0.99	1.37 [0.46; 4.08]	0.52	0.72	1.3 [0.38; 4.47]	0.52	0.85
Grade	0.77 [0.32; 1.9]	0.57	0.50	0.93 [0.4; 2.13]	0.52	0.77	0.76 [0.3; 1.88]	0.56	0.48
Lymphovascular invasion (positive, negative)	0.78 [0.23; 1.89]	0.53	0.78	0.92 [0.4; 2.13]	0.5	0.99	0.76 [0.3; 1.87]	0.53	0.66

Bold: significant difference. HR: hazard ratio; CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics.

Table 3
Retrospective analysis of (^{18}F)-FDG-PET/CT metabolic parameters to identify high-risk groups at time of diagnosis and to tailor the therapeutic approach in locally advanced cervical cancer. Results of univariate analysis.
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : résultats de l'analyse unifactorielle.

Parameters	Overall survival			Disease-free survival			Locoregional control		
	HR [CI 95%]	c-index	*P*	HR [CI 95%]	c-index	*P*	HR [CI 95%]	c-index	*P*
Metabolic nodes distance	1.05 [1.00; 1.09]	0.79	**<0.001**	1.01 [1.00; 1.02]	0.79	**<0.001**	1.01 [1.00; 1.02]	0.73	**0.03**
Maximum distance between node and primary tumor	1.02 [0.98; 1.06]	0.65	0.047	1.02 [0.99; 1.05	0.65	**0.047**	1.02 [0.98; 1.06]	0.64	0.21
SUV max	1.03 [0.95; 1.12]	0.55	0.46	1.03 [0.96; 1.11]	0.58	0.49	0.70 [0.2; 2.4]	0.58	0.38
MTV N									
Absolute threshold (SUV = 4)	1.12 [1.04; 1.19]	0.67	**0.01**	1.06 [1.01; 1.12]	0.66	0.09	1.06 [1.01; 1.11]	0.69	0.06
Relative threshold (SUV = 35%)	1.12 [1.04; 1.21]	0.67	**<0.01**	1.07 [1.00; 1.13]	0.62	**0.1**	1.07 [1.01; 1.14]	0.67	0.08
MTV T									
Absolute threshold (SUV = 7.5)	1.01 [1.00; 1.02]	0.63	**<0.01**	1.01 [1.00; 1.01]	0.64	**<0.01**	1.01 [1.00; 1.01]	0.64	0.07
Relative threshold (SUV = 48%)	1.06 [1.01; 1.1]	0.63	**0.02**	1.04 [1.01; 1.06]	0.65	**<0.01**	1.02 [0.99; 1.04]	0.65	0.19
TLG N									
Absolute threshold (SUV = 4.5)	1.01 [1.00; 1.02]	0.83	**0.04**	1.005 [1.00; 1.01]	0.83	**0.04**	1.005 [1.00; 1.01]	0.79	0.23
Relative threshold (SUV = 30%)	1.01 [1.00; 1.02]	0.67	**0.01**	1.005 [1.00; 1.01]	0.67	0.06	1.006 [1.00; 1.01]	0.67	0.34
TLG T									
Absolute threshold (SUV = 4)	1.001 [1.00; 1.03]	0.64	**0.01**	1.001 [1.00; 1.01]	0.66	**<0.01**	1.001 [1.000; 1.002]	0.65	0.08
Relative threshold (SUV = 48%)	1.004 [1.00; 1.01]	0.66	**0.02**	1.002 [1.00; 1.01]	0.66	**<0.01**	1.001 [0.99; 1.01]	0.66	0.21
SUV mean T									
Absolute threshold (SUV = 7)	1.09 [0.87; 1.36]	0.56	0.51	1.12 [0.90; 1.38]	0.58	0.52	1.12 [0.88; 1.40]	0.57	0.49
Relative threshold (SUV = 70%)	1.04 [0.94; 1.16]	0.56	0.41	1.04 [0.94; 1.14]	0.58	0.36	1.05 [0.95; 1.18]	0.66	0.21
SUV mean N									
Absolute threshold (SUV = 4.5)	1.16 [0.99; 1.37]	0.83	**0.04**	1.09 [0.97; 1.23]	0.81	0.07	1.18 [1.01; 1.39	0.81	0.07
Relative threshold (SUV = 42%)	1.12 [0.99; 1.26]	0.81	0.21	1.09 [0.97; 1.23]	0.5	0.43	1.11 [0.98; 1.25]	0.5	0.43

Bold text indicates a statistically significant difference with a *P*-value less than 0.05. SUV: standardized uptake value; max: maximum; SUV mean T: mean SUV within the tumor; SUV mean N: mean SUV within the invaded nodes; MTV: metabolic tumor volume; MTV N: MTV within the invaded nodes; MTV T: MTV within the tumor; TLG: total lesion glycolysis; TLG N: TLG within the invaded nodes; TLG T: TLG within the tumor.

Table 4
Retrospective analysis of (^{18}F)-FDG-PET/CT metabolic parameters to identify high risk groups at time of diagnosis and to tailor the therapeutic approach in locally-advanced cervical cancer: results of multivariate analysis ($n = 37$).
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : résultats de l'analyse multifactorielle (n = 37).

Parameters	Overall survival			Disease-free survival			Locoregional control		
	P	Hazard ratio	95% confidence interval CV	*P*	Hazard ratio	95% confidence interval CV	*P*	Hazard ratio	95% confidence interval CV
Total lesion glycolysis of the primary tumor computed with a relative threshold of 48%	< 0.01	1.004	1.004; 1.004	< 0.01	1.003	1.002; 1.003	0.066	1.001	1.001; 1.002
Metabolic nodes distance	< 0.01	1.01	1.01; 1.01	0.01	1.005	1.005; 1.006	0.01	1.005	1.005; 1.006

on pretreatment PET are not associated with overall survival [25]. An important issue using PET/CT for prediction is the identification of the optimal threshold of the metabolic activity to predict the overall survival, disease-free survival and locoregional control. The choice of an optimal threshold value of standardized uptake value to quantify the metabolic tumor volume and total lesion glycolysis is controversial: a threshold of 55%, 50%, 40% of maximum standardized uptake value, or a threshold of standardized uptake value above 2.5 [10,25–28]. We used different thresholds for tumor segmentation. The most predictive value of maximum standardized

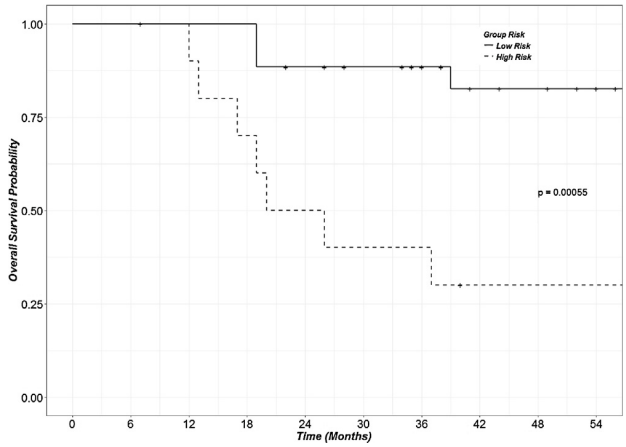

Fig. 1. Kaplan–Meier curves of overall survival according to the predictive score group (optimal cut-off defined by the Hothorn & Lausen method: high risk: score > 0.97, low risk: score < 0.97) among 37 patients with cervical cancer treated with chemoradiotherapy. This prognostic score is based on two metabolic parameters: total lesion glycolysis of the primary tumor computed with a relative threshold of 48% and metabolic nodes distance identified as two independent risk factors.
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : courbes Kaplan–Meier de survie globale de 37 patientes.

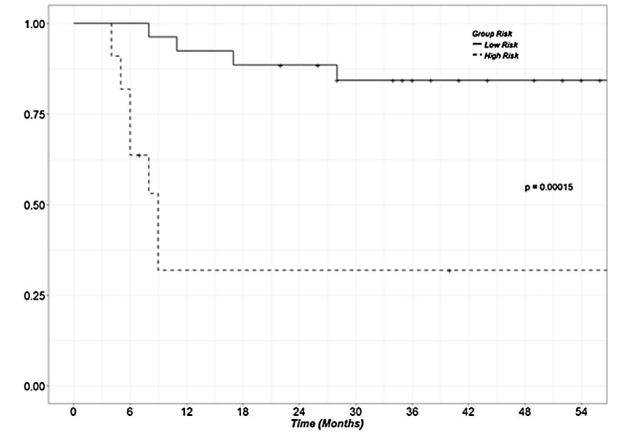

Fig. 2. Kaplan–Meier curves of locoregional control according to the predictive score group (optimal cut-off defined by the Hothorn & Lausen method: High risk: score > 0.97, low risk: score < 0.97) among 37 patients with cervical cancer treated with chemoradiotherapy. This prognostic score is based on two metabolic parameters: total lesion glycolysis of the primary tumor computed with a relative threshold of 48% and metabolic nodes distance identified as two independent risk factors.
Étude rétrospective des paramètres métaboliques de TEP au (^{18}F)-FDG pour prédire les récidives et la survie après chimioradiothérapie pour cancer du col utérin localement évolué : courbes Kaplan–Meier du contrôle locorégional chez 37 patientes.

uptake value for the segmentation was 48%. However, thresholds between 30% and 46% of maximum standardized uptake value were also correlated with clinical outcome, with a lower predictive value.

Historical factors connoting a poor prognosis for cervical cancer include lymph-node involvement, in particular. To our knowledge and concerning cervical cancer, no study evaluated the prognostic impact of the status of lymph nodes taking into account their metabolic activities and their distance from the primary tumor measured using an objective and continuous parameter. To better evaluate the prognosis of a patient with involved nodes, we created a new metabolic parameter, which combines the metabolic activities of involved nodes and the distance between the primary tumor and each of these nodes, the metabolic node distance. The predictive value of lymphatic dissemination was showed by Kidd and al., who developed a PET-based prognostic nomogram using the location of the highest PET lymph-node level; i.e., none, pelvic, para-aortic, or subclavicular [29]. However, they did not take into account the metabolic lymph-node activity and number of involved nodes. In our study, we used the concept of distance between invaded nodes and the primary tumor and incorporated the metabolic activity as markers of disease outcome.

This PET-based score identified risk groups for cervical cancer recurrence. Being able to select patients with high risk of recurrence before treatment may allow to modify local therapy. Using this new metabolic parameters, a variety of approaches to intensify the concurrent chemotherapy component of chemo radiation could be possible: more aggressive chemotherapy regimen or the addition of cytotoxic agents like the bevacizumab if the metabolic node distance is high for example. Moreover, we could imagine to intensify radiotherapy component of chemoradiation delivering high dose on high metabolic tumor volume: radiotherapy boost in MTV T 50% for example.

One third of patients with locally advanced cervical cancer will have disease recurrence, usually within 2 years of completing treatment [30]. The most important predictors of disease recurrence include clinical stage, lymph node status at diagnosis, tumor histology and early tumor response after treatment [31,32]. After chemoradiotherapy as definitive treatment of locally advanced cervical cancer there is sufficient evidence to support the use of (^{18}F)-FDG-PET/CT for the assessment of treatment response [33]. The presence of FDG activity (either persistent or new) can predict survival outcome. In accordance with our series, a study in which FDG-PET/CT was performed 3 months after completion of treatment showed that a metabolic response was predictive of long-term survival, with a 3-year survival rate of 78% in patients with a complete metabolic response, 33% in patients with a partial metabolic response and 0% in those with progressive disease. Multivariate analysis in that study showed that post-treatment response and lymph node status at diagnosis were the only accurate predictors of disease-free survival [32]. Standard surveillance programs have proposed the use of routine physical examinations and patient's symptoms education to facilitate early disease recurrence. However, by fully exploiting the diagnostic information derived from pre- and post-treatment FDG-PET/CT, patients with adverse metabolic prognostic factors could potentially benefit from either adjuvant systemic therapy or salvage curative therapy in the case of disease recurrence and raises the question whether dose escalation strategies are more likely to provide a therapeutic gain [34].

These prognostic factors that we propose in this study match well with historic prognostic factors for cervical cancer and go a step further by evaluating the best threshold for tumor segmentation.

This study has several limitations including its retrospective design and a relatively small sample size of 37 patients. Despite this, it provides a proof-of-concept to support the clinical value of volumetric functional assessment. Validation in a prospective and a larger cohort of patients is warranted. Evaluating the nodal disease by assessing nodes' distance weighted by their metabolic activity is a promising project and needs to be validated in a multi-institutional study.

5. Conclusion

Total lesion glycolysis of the primary tumor, and the distance between lymph node and the primary tumor, weighted by the metabolic tumor volume of lymph nodes, were significantly correlated with locoregional control, disease-free survival, and overall survival. These parameters seem to have a higher predictive value than the classical prognostics parameters and may be useful to

identify high-risk groups at time of diagnosis and to tailor the therapeutic approach in this type of cancer.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://www.sciencedirect.com and https://doi.org/10.1016/j.canrad.2017.10.003.

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