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ORIGINAL ARTICLE

Chemoradiotherapy for locally advanced cervix cancer without aortic lymph node involvement: can we consider metabolic parameters of pretherapeutic FDG-PET/CT for treatment tailoring?

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Abstract

Purpose Aim of the study was to assess impact of pretherapeutic FDG-PET/CT metabolic parameters on response to chemoradiotherapy (CRT) and survival in locally advanced cervical cancer (LACC) patients without paraaortic lymph node involvement.

Methods LACC patients treated with CRT without macrometastatic involvement after paraaortic surgical staging were included. All patients had received at least 45 Gy radiotherapy and five cycles of platinum-based chemotherapy. High-risk histologies were excluded. Two senior nuclear physician experts in gynaecologic oncology reviewed all PET/CT exams, and extracted tumor SUVmax, MTV, and TLG (standardized uptake value, metabolic tumor volume, and total lesion glycolysis respectively). Response to CRT was assessed with a pelvic MRI done after 45 Gy. Medical charts were reviewed for clinical, pathology, and survival data.

Results Ninety-three patients were included in the study. The overall survival (OS) rates at 2 and 5 years were 83.0% [95%CI: 72.5–89.8] and 71.2% [57.5–81.2] respectively. The RFS rates at 2 and 5 years were 72.5% [61.5–80.9] and 64.4% [52.3–74.2] respectively. Higher cervical SUVmax and TLG were significantly associated with poor response to CRT. In multivariate analysis, cervical SUVmax was the main predictive factor for OS.

Conclusion Cervical tumor SUVmax was demonstrated to be a non-invasive prognostic biomarker for response to treatment and survival in LACC patients without paraaortic involvement. SUVmax and other PET/CT metabolic parameters require further prospective investigation to help tailoring of local treatment.

Keywords Cervix cancer · SUV · Prognosis · Chemoradiotherapy · FDG-PET/CT

Introduction

Worldwide, cervical cancer is one of the most common malignant diseases [1]. Although cervical cancer is often curable if detected early, more than one third of patients present locally advanced disease (LACC) at diagnosis [2]. Guidelines from the European Society for Medical Oncology (ESMO), NCI, and the American Society of Clinical Oncology (ASCO) in 2016 recommended the use of pelvic RT plus concurrent low-dose platinum based chemotherapy, followed by uterovaginal brachytherapy (BT) for LACC [3, 4]. When paraaortic nodes are involved, the radiation field is extended from the pelvis to include the aortic region [3, 5].

Overall survival (OS) of patients treated for LACC remains poor, with approximately 5-year survival rate of 65% whatever paraaortic lymph node invasion. Five-year local and distant control rates are around 70%, with a majority of distant relapse [2].

Consensus from the GCIG (Gynecologic Cancer Intergroup) concludes that most needed new trials should be directed to high-risk cervical cancer patients [6]. Of several prognostic factors such as stage, tumor volume, depth of

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cervical stromal invasion, LVSI, locoregional extension, response to chemoradiotherapy (CRT), or nodal status, paraaortic lymph node (PALN) involvement is the most important one. Indeed, of PALN-positive patients, 40% will develop distant metastasis [6], and several studies have shown low 5-year survival rates, around 30%, for these patients [7–9]. In PALN-negative patients, response to CRT remains one of the most important factors associated to local recurrence and OS [10]. However, factors associated to prediction of local response are poorly known.

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is a reference imaging exam in pre-treatment evaluation of LACC [3, 4] to assess disease extent, lymph node involvement, and distant sites for metastatic disease. A meta-analysis of 72 studies including 5042 LACC patients showed higher specificity and sensitivity of FDG-PET/CT, for detection of PALN involvement, when compared to MRI and CT scan (respectively 98, 92, and 93% for specificity, and 75, 56, and 58% for sensitivity) [11]. Several authors have suggested that the apparent low sensitivity of the FDG-PET/CT does not make it a relevant alternative to surgical LN staging when no uptake is visualized in the PA area [5, 12], and paraaortic lymphadenectomy is still performed in most French centers in this case [8].

FDG-PET/CT also provides functional information with prognostic value by tumor SUVmax (maximum standardized uptake value), MTV (metabolic tumor volume) and TLG (total lesion glycolisis) values. Other functional parameters such as pattern of tumor fixation and parameters of tumor heterogeneity and texture have recently been considered as predictive of tumor response [13]. Kidd et al. showed that pre-treatment tumor SUVmax, when categorized into three groups [14, 15], was correlated with lymph node involvement, residual tumor after CRT, local recurrence, and 5-year OS. However, other studies have failed to demonstrate the impact of high pre-treatment cervical SUVmax as a predictive factor of treatment response and survival [16, 17]. Recent data also highlight prognostic importance of volumetric parameters [18].

Most series have included patients with early and advanced stage, with different nodal status and different treatment strategies.

Aim of the study was to assess impact of metabolic parameters obtained from pre-therapeutic cervical tumor FDG-PET/CT on response to CRT and survival in LACC patients without aortic lymph node involvement.

Material and methods

Patients and treatment

From January 2006 through March 2015, patients with LACC (FIGO stage IB2-IVA) and negative aortic pretherapeutic FDG-PET/CT uptake treated at the Institut Claudius Regaud Cancer Center, Toulouse and at the Universitary Hospital of Toulouse, France, were included. Patients with preoperative fistula were excluded from the study protocol. Preoperative work-up included in all cases physical examination, cervical biopsy, pelvic MRI, FDG-PET/CT, and laparoscopic paraaortic lymph node retroperitoneal staging. During surgical staging, pelvic lymph nodes were removed if grossly positive. Patients underwent pelvic external beam radiotherapy combined with chemotherapy. Radiotherapy was administered to the whole pelvic region in 25 fractions of 1.8 Gray (Gy) for a total dose of 45 Gy for 5 weeks. Concomitant chemotherapy with cisplatin 40 mg/m2 was administered weekly during RT for five courses. Gynecologic examination and MRI 1.5 Tesla with Gadolinium were performed during the first week after the completion of 45 Gy. Treatment varied depending on the type of response at MRI evaluation. Pretherapeutic tumor size was defined as the largest tumor dimension measured on pretherapeutic MRI. Tumor size post-therapy was the largest tumor size measured after 45 Gy radiotherapy. Response was considered as good when the maximum diameter of the tumor decreased more than 50% at 45 Gy MRI evaluation. The treatment was then completed with an additional 35 Gy pulse dose rate intracavitary BT. Additional boosts (up to 85 Gy in total) were given at the end of brachytherapy in cases of pelvic lymph node and/or on parametrial involvement. When intensity-modulated radiation therapy (IMRT) was available, simultaneous integrated boost was performed on metastatic pelvic lymph nodes, at doses of 57.5 Gy in 25 fractions. In cases of tumor reduction rate inferior to 50%, completion treatment was left to the discretion of the attending radiotherapist. Either 35 Gy BT, or completion surgery with an objective of achieving resection of the residual tumor with clear margins, was offered 6 weeks after 15 Gy of preoperative brachytherapy. Follow-up included clinical examination of patients every 4 months for 2 years, and every 6 months for the 3 following years.

Exclusion criteria were: rare histologic subtypes, non-available images of FDG-PET/CT for double central reading, para-aortic macrometastatic involvement found at surgical staging, distant metastasis, peritoneal carcinomatosis, and incomplete CRT defined as non-platinum-based chemotherapy regimen, less than five cycles of platin-based chemotherapy, and/or less than 45 Gy of external radiotherapy.

Medical data extracted from computerised medical records included demographic, clinical, imaging, surgical staging, treatment, and follow-up data, as well as recurrence and survival status at the end of the study.

The study was approved by the institutional review board.

FDG-PET/CT modalities and interpretation

Before receiving any treatment, FDG-PET/CT was performed within initial work-up following a standardized protocol. FDG-PET/CT whole-body images were obtained using a full-ring PET/CT scanner. All patients fasted for at least 4 h before scanning. Blood glucose levels were checked before FDG injection; injected dose and time between injection and acquisition were noted. If necessary regarding bladder repletion, complementary pelvic acquisitions could be done after administration of furosemide (20 mg). PET/CT used for imaging were: Siemens Biograph 6, General Electric Discovery IQ, General Electric DST4, and Philips Gemini TF16. The administered FDG activity and scan duration for each bed position were adjusted to count rate of each system.

The PET data were reconstructed using an iterative, fully 3D algorithm, with CT images for attenuation correction. A senior nuclear physician expert in gynaecologic cancer interpreted all FDG-PET/CT images in standard clinical fashion, when the exam was done. All patients included had a double-blinded reading of metabolic parameters performed by another senior nuclear physician, realised at the moment of the study, in order to ensure homogeneous measurement of metabolic values. Segmentation of tumor volumes for cervix tumor and pelvic lymph nodes was done using General Electric software AWserver 3.0, with an automatic thresholding at 40% of SUVmax, following EANM (European Association of Nuclear Medicine) guidelines [19]. This automatic contouring was manually corrected if necessary, according to CT and MRI data.

Metabolic parameters studied were: SUVmax, MTV, TLG for primitive cervical tumor and for pelvic lymph nodes when positive. Size of pelvic lymph nodes was measured on CT imaging. Correlation between metabolic parameters and classic prognosis factors (age, FIGO stage, tumor size, histologic subtype) was studied.

Statistical analysis

Continuous variables were presented as median with range (min–max), and qualitative variables were summarized by frequencies and percentages. Correlations between continuous variables were assessed using the Spearman coefficient.

Comparisons between groups were performed using the Kruskal–Wallis test for continuous data. All survival data were estimated by the Kaplan–Meier method with 95% confidence intervals (95% CI). Relapse-free survival (RFS) was defined as the time from initiation of chemoradiotherapy to relapse or death. Patients alive and relapse-free at the date of last follow-up were censored. Overall survival (OS) was defined as the time from initiation of chemoradiotherapy to death. Patients alive at the date of last follow-up were censored. Univariate analysis was performed using the log-rank test for qualitative variables and the Cox proportional hazard model for continuous variables. Multivariate analysis was assessed using the Cox proportional hazard model including significant variables at 5% level in univariate analysis. The Cox proportional hazard model was used to estimate hazard ratios (HR) and 95% confidence intervals. Tumoral SUVmax was tested as a continuous variable, and dichotomized, also using the cut-off value of 13.3 published by Kidd et al. [10]. *P* values < 0.05 were considered statistically significant, and all tests were two-sided. Statistical analysis was conducted using Stata® 13 software.

Results

Ninety-three patients were included in the study (Table 1). The median age was 48 years at diagnosis (range 27–77 years), and the median BMI was 23.3 (range 15.4–44.9). Median tumor size was 4 cm (range 2–10 cm) at pretherapeutic MRI. One patient was HIV-positive. All patients had pretherapeutic surgical node stadging, and median number of paraaortic lymph nodes removed was 17 (range 6–46). After CRT, 50 patients (53.8%) had 35 Gy completion brachytherapy, whereas 25 patients (26.9%) had preoperative 15 Gy brachytherapy followed by completion surgery. Fifteen patients (19.3%) had completion surgery after CRT without any brachytherapy, due to technical problems such as uterine perforation or impossible uterine catheterization. Three patients (3.2%) had neither surgery nor brachytherapy: two presented rapid pelvic progression despite CRT, with

Table 1 Clinical characteristics of the study population

	N	%
OMS performance status		
0	85	91.4
≥ 1	8	8.6
Histologic subtype		
Squamous cell carcinoma	78	83.9
Adenocarcinoma	12	12.9
Adenosquamous	3	3.2
Clinic FIGO stage		
IB2	19	20.4
IIA	9	9.7
IIB	57	61.3
IIIB	7	7.5
IVA	1	1.1
Surgicopathologic lymph node status		
N0	79	84.9
Pelvic N+	11	11.8
Paraaortic micrometastatic N + (< 5 mm)	3	3.2

catheterization of uterus impossible. Furthermore, due to poor general condition, surgical treatment was rejected following pluridisciplinary discussion, and systemic chemotherapy was offered to these patients. The third patient was planned to have a completion exclusive brachytherapy but refused this treatment for personal reasons, and finally died due to locoregional and metastatic progression 1 year later.

Median cervical tumor SUVmax, MTV, and TLG for the whole group were 14.4 (range 2.1–34.4), 34.6 cc (range 0.8–162), and 235 (range 1.2–2495) respectively.

Cervical metabolic parameters (SUVmax, MTV, and TLG) were correlated with tumor size, as a continuous variable, and dichotomized using the median value of 4 cm ($p < 0.01$). There was no correlation with age, histologic subtype, and FIGO stage.

Thirty-three patients presented abnormal pelvic lymph nodes on FDG-PET-CT. Among them, lymph node SUVmax and MTV were 4.6 (range 1.7–16.4) and 2.3 cc (range 0.3–35.5) respectively. Tumor and pelvic lymph node SUVmax were not significantly correlated ($r = 0.18$, $p = 0.328$). Pelvic lymph node size and pelvic lymph node SUV and MTV were not significantly associated.

Good response to CRT measured by 45 Gy MRI was significantly associated with lower cervical SUVmax and TLG values (Table 2).

Survival data and prognosis factors

After a median follow-up of 40.5 months [95% CI: 33.4–49.6 months], 20 patients (21.5%) were dead of disease. Twenty-eight patients (30.1%) had recurred, 13 of whom had local recurrence.

The OS rates at 2 and 5 years were 83.0% [95% CI: 72.5–89.8] and 71.2% [57.5–81.2] respectively. The RFS rates at 2 and 5 years were 72.5% [61.5–80.9] and 64.4% [52.3–74.2] respectively. Figure 1 shows Kaplan–Meier overall and recurrence-free survival estimated curves.

In univariate analysis, FIGO stage and cervical tumor SUVmax as a continuous variable were significantly associated with RFS and OS (Table 3). Using cut-off value, patients with tumoral SUVmax > 13.3 tended to have worse outcome (Fig. 2), but the difference was not statistically significant ($p = 0.17$ for OS and $p = 0.07$ for RFS). For the 33 patients with pelvic lymph node uptake, there was no significant association between lymph node metabolic parameters and oncologic outcome.

In multivariate analysis, cervical tumor SUVmax adjusted for FIGO stage remained statistically associated with OS (HR = 1.07; 95%C I [1.01; 1.13]; $p = 0.029$), but not associated with RFS (HR = 1.05; IC 95% [1.00; 1.10]; $p = 0.070$).

Discussion

Tumor risk assessment is of utmost importance in the treatment of high-risk cervical cancer patients, to tailor treatment. There is growing evidence that FDG-PET/CT metabolic values are prognosis biomarkers in LACC treated with CRT [14–16, 20, 21]. According to a meta-analysis published in 2016, patients with high tumoral or lymph node SUVmax would be «at higher risk of adverse events or death» [22]. However, studies included different populations of cervical cancer patients.

SUVmax of primary tumor has been correlated to other clinical bad prognostic factors such as tumor size, depth of tumor invasion, LVSI, poorly differentiated pathology, and lymph node involvement [23, 24]. In our series, clinical tumor size was the only pretherapeutic prognostic factor associated with cervical SUVmax.

Tumor response assessment was performed by post-radiotherapy MRI. Wang et al. [25] studied serial MRI during and after CRT to compare the sensitivity and specificity of the tumor regression metrics, and to identify optimal time to perform MRI to identify high-risk patients. Outcome prediction of combined pretherapeutic and 4-week-CRT MRI volume regression ratios was demonstrated to be highly accurate in predicting local failure and death, and was the evaluation method used in these series. However, post-radiotherapy changes in the cervical tumor may limit MRI interpretation. Indeed, post-treatment evaluation evaluation could be improved by dynamic MRI and PET/MRI [26, 27].

Table 2 Cervical metabolic parameters: comparison of bad responders versus good responders to CRT ($n = 79$)

	Bad response ($n = 25$)	Good response ($n = 54$)	*P* value
SUVmax Median (range)	15.8 (4.3–32.5)	13.8 (3.5–34.4)	$p = 0.0299$
MTV (cc) Median (range)	52.5 (0.8–162)	33.7 (6.5–148)	$p = 0.0564$
TLG Median (range)	432.7 (3.3–2495)	227 (16.1–2204)	$p = 0.0175$

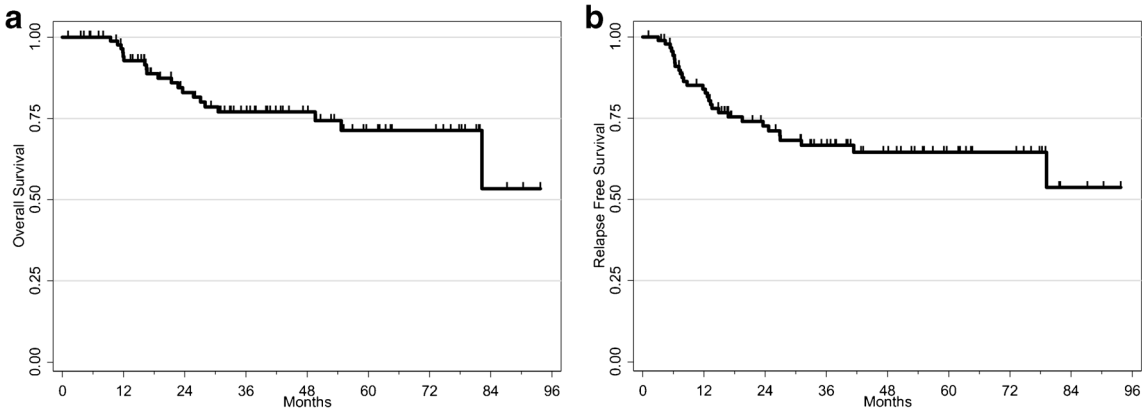

Fig. 1 Survival curves were estimated by Kaplan–Meier for all patients included in the study. **a** Kaplan–Meier estimates of overall survival for all patients included in the study. **b** Kaplan–Meier estimates of recurrence free survival for all patients included in the study

Pretreatment cervical metabolic value to tailor CRT

Few studies have determined the predictive value of PET/CT metabolic parameters on treatment response. Most of them evaluated residual tumor 12 weeks after CRT [28–30]. Kidd et al. showed that pretherapeutic cervix SUVmax was predictive of residual tumor after CRT [14], and that heterogeneity of FDG uptake in cervix tumor was associated with therapeutic response [13]. In another retrospective study including 21 LACC patients treated with CRT, Ueno et al. found that pretherapeutic cervix SUVmax and TLG were better biomarkers than ADC for predicting response to CRT [31]. In our study, we also found significantly higher SUVmax and TLG values in patients with poor response to CRT. MTV was also increased in patients with residual tumor after CRT ($p = 0.0564$). Even if these results require validation in larger prospective studies, pretreatment high metabolic parameters could be used in clinical practice to tailor treatment by optimising local treatment.

Table 3 Univariate analysis for OS and RFS

	OS		RFS	
Qualitative variables (Log-rank test)	% 2-years [95% CI]	*P* value	% 2-years [95% CI]	*P* value
OMS performance status:				
0	83.3% [72.4–90.2]	0.834	73.0% [61.6–81.6]	0.879
≥ 1	80.0% [20.4–96.9]		71.4% [25.8–91.9]	
Histologic subtype:				
Squamous	81.6% [69.8–89.2]	0.209	69.2% [56.9–78.6]	0.062
Other	91.7% [53.9–98.8]		92.3% [56.6–98.9]	
Clinic FIGO stage:				
1B2-IIA	95.0% [69.5–99.3]	0.011	95.7% [72.9–99.4]	0.002
IIB-IVA	76.9% [62.8–86.3]		61.1% [46.9–72.5]	
Cervical SUVmax:				
≤ 13.3	93.9% [77.5–98.4]	0.169	88.7% [72.5–95.6]	0.075
> 13.3	75.8% [60.3–85.8]		61.5% [46.3–73.6]	
Pelvic lymph node status (PET):				
No	83.4% [69.3–91.4]	0.973	69.7% [55.2–80.3]	0.670
Yes	82.6% [62.9–92.4]		77.3% [57.9–88.5]	
Continuous variables (Cox model)	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Age at diagnosis	0.99 [0.95–1.03]	0.550	0.99 [0.96–1.03]	0.689
Cervical SUVmax	1.08 [1.02–1.15]	0.005	1.06 [1.01–1.11]	0.014
Cervical MTV (/10)	1.10 [1.00–1.22]	0.054	1.08 [0.99–1.18]	0.069
Cervical TLG (/100)	1.05 [0.98–1.12]	0.160	1.04 [0.98–1.10]	0.171

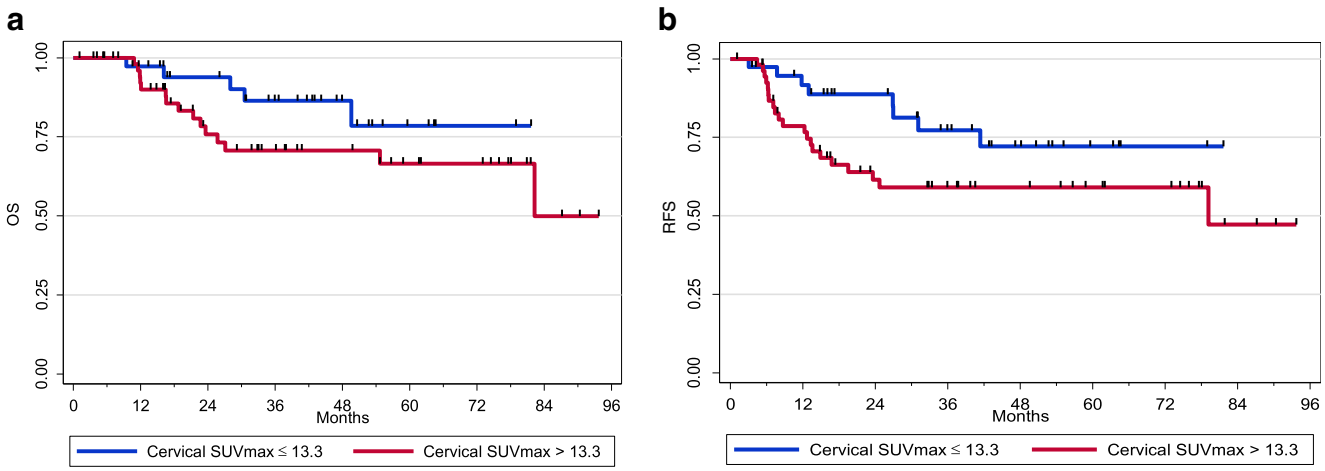

Fig. 2 Survival curves according to cervical SUVmax, using cut-off value of 13.3 published by Kidd et al. [14]. **a** OS ($p = 0.17$), **b** RFS ($p = 0.07$)

Predictive value of cervix metabolic parameters for relapse-free and overall survival

SUVmax and survival

In LACC, SUVmax has been correlated to RFS and OS in several publications (Table 4). Kidd et al. published the largest study [14], including 237 patients, and showed that 5-year OS was 95% for SUVmax < 5.2, 70% for SUVmax between 5.2 and 13.3, and 44% for SUVmax > 13.3 [14]. They also found that cervical SUVmax was significantly associated with risk of pelvic recurrence in the subgroup of 175 patients treated with CRT [14].

Onal et al. also showed that a cervix SUVmax value > 15.6 was associated with poor RFS and OS outcomes [38]. However, this study presented some limitations, as PALN status was not the same for all patients. Furthermore, only 83% of included patients had received more than four cycles of chemotherapy [38].

Many other retrospective studies have failed to show a significant association between cervix SUVmax and overall survival [32, 39–41], probably due to lack of power. Recently, Cima et al. showed that RFS was significantly associated with FIGO stage, PALN status, and cervical tumor SUVmax in a retrospective study including 92 LACC patients treated with CRT, and that the only prognostic factor associated with decreased OS was high SUVmax in the primary tumor [42].

The threshold SUVmax value at 13.3 published by Kidd et al. did not show significant differences in our series, suggesting differences in imaging equipment. Standardized uptake value is a metric that quantifies FDG uptake for each voxel in the picture, of which the repeatability has been debated over a period of several years [43]. However, currently, SUV is considered as the most reliable metric for quantifying FDG uptake in oncologic PET [44]. Furthermore, in our series, technical conditions of FDG-PET/CT were homogenous according to our standard protocol, and a double interpretation by an expert nuclear physician in gynaecologic malignancies was performed. All patients included in the study had tumors of at least 2 cm, allowing reliable calculation of SUV values. Finally, contrary to previous published studies, we found a significant prognostic role of SUVmax as a continuous variable.

Role of other metabolic parameters: MTV, TLG

A few studies have evaluated the prognostic role of pretherapeutic cervical tumor MTV [16, 17, 32, 33]. Leseur et al., using a threshold value of 55% of SUVmax value to determine cervix MTV [16], found a significant prognostic association between MTV and outcome. Using a classic 40% threshold value of SUV, we found a non-significant trend for association between MTV and OS (Table 3), probably due to lack of power.

In early cervical cancer, TLG was significantly correlated with pelvic nodal status [34]; and Burger et al. found that TLG was associated with overall survival in patients treated for recurrent pelvic gynaecologic cancer [35]. Yoo et al. showed that TLG was an independent prognosis factor for RFS, with a threshold value at 7600 [32]. In this series, we found a significant association between TLG and response to CRT measured by 45 Gy MRI. TLG was not correlated to decreased survival. Similar results have been found in other studies, showing no relationship between TLG and survival [36, 37].

High-order parameters and radiomics features

Several authors have studied second and higher order parameters, such as heterogeneity or texture, and shape features. Kidd et al. showed that cervical intratumoral FDG metabolic heterogeneity could predict risk of lymph node

Table 4 Main studies published concerning interest of pretherapeutic cervix tumor metabolic parameters in LACC patients

Authors (year, country)	Design	*N*	FIGO stage	PALN+ patients	Treatment	Cervix tumor metabolic parameters associated with:	
						RFS	OS
Kidd (2007, USA) [8]	R	287	IA2-IVB	35 (12%)	Surgery OR CRT OR Palliative	SUVmax < 5.5 vs 5.5 to 13.3 vs > 13.3 ($p < .0001$)	
Xue (2006, USA) [24]	R	96	IB1-IVB	Unknown	RT ± CT	SUVmax[a]	–
Pan (2012, China) [27]	R	82	IA-IVB	19 (23%)	Surgery ± RT OR RT + BT OR Palliative	–	SUVmax[a]
Yoo (2012, Korea) [25]	R	73	IB1-IVB	11 (15%)	Surgery ± RT OR RT ± CT OR Palliative	TLG ≥ 7600 vs < 7600 ($p = 0.005$)	–
Akkas (2013, Turkey) [32]	R	58	IB-IVB	21 (36%)	CRT OR CT	–	–
Onal (2013, Turkey) [23]	R	149	IB2-IVA	15 (10%)	CRT	SUVmax ≥ 15.6 vs < 15.6 ($p < 0.001$)	
Chong (2015, Korea) [31]	R	56	IIB-IIIB	13 (23%)	CRT	–	
Liu (2016, Taiwan) [33]	P	55	III-IVA	13 (34%)	CRT	–	
Hong (2016, Korea) [34]	R	56	IIB-IVA	12 (21%)	CRT	TLG ≥ 215.02 vs < 215.02 ($p = 0.03$)	–
Hong (2016, Korea) [35]	R	56	IIB-IVA	12 (21%)	CRT	MTV > 59.01 vs ≤ 59.01 ($p = 0.012$)	–
Leseur (2016, France) [10]	P	53	IB2-IVA	13 (24%)	CRT	$MTV_{55\%}$ > 9.8 cc vs ≤ 9.8 cc ($p = 7.10^{-5}$)	($p = 0.008$)
						$TLG_{32\%}$ > 30.4 vs ≤ 30.4 ($p = 0.003$)	–
Guler (2017, Turkey) [36]	R	129	IB2-IVA	22 (17%)	CRT	–	
Liang (2018, China) [37]	R	67	IB-IVA	Unknown	Surgery OR CRT OR CT	Total TLG > 373 vs ≤ 373 ($p = 0.029$)	
Cima (2018, Switzerland) [28]	R	92	IIB-IVA	17 (18%)	CRT	SUVmax > 7 vs ≤ 7 ($p = 0.01$)	
Our study (2018, France)	R	93	IB2-IVA	0 (0%)	CRT	–	SUVmax (continuous) ($p = 0.029$)

n number of patients, *P* prospective, *R* retrospective, *PALN+* paraaortic lymph node positive, *CRT* chemoradiotherapy, *CT* chemotherapy

[a] only significant in univariate analysis

involvement at diagnosis, response to therapy, and risk of pelvic recurrence [13].

In a retrospective study including 102 patients treated with CRT for LACC, Lucia et al. found that radiomics features extracted from DWI-MRI and FDG-PET/CT were more powerful than usual clinical parameters in predicting locoregional control [45]. Many high-order parameters can be calculated, and several texture analyses have been developed [46–48], but none of them is used in daily practice. Among these promising but complex approaches, further studies may identify which and how new parameters can be developed.

Main limitations of this series were its retrospective character, and different treatment completion approaches with surgical procedure after CRT in some patients. Main strengths of our study were: first, we present a remarkably homogeneous series, due to restrictive selection criteria. All patients underwent surgical staging of PALNs, and were excluded from the study in case of macroscopic involvement. PALN involvement defines a subgroup of patients with significantly decreased disease-free and overall survival rate, and could act as a confounding factor. Outcome prediction of metabolic values on cervical tumor is more accurate in lymph node negative patients. Finally, the central review of all PET/CT by an expert nuclear physician in gynaecologic oncology, done at the time of the study, ensures reliability of presented values and strengthens our findings.

Conclusion

In this series, quantitative value of pretherapeutic cervical SUVmax was associated with residual cervical tumor after CRT, and survival outcome. SUVmax as a non-invasive prognostic biomarker requires further prospective investigation to help tailoring of local treatment.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors of this article have no relevant relationships that could be perceived as a real or apparent conflict of interest.

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