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FDG-PET/CT identifies predictors of survival in patients with locally advanced cervical carcinoma and para-aortic lymph node involvement to increase treatment

Short running title: FDG-PET/CT and cervical cancer

Hélène Leray[1], Erwan Gabiache[2], Frédéric Courbon[2], Isabelle Brenot-Rossi[3], Hélène Colineaux[4], Benoît Lepage[4], Eric Lambaudie[5], Alejandra Martinez[1], Marie Voglimacci[1], Ariane Weyl[1], Marion Deslandres[6], Anne Ducassou[7], Stéphanie Motton[1], Charlotte Vaysse[1], Elodie Chantalat[1*]

Affiliations

[1] Department of Surgical Oncology, IUCT-Oncopole, Toulouse, France

[2] Department of Nuclear Medicine, IUCT-Oncopole, Toulouse, France

[3] Department of Nuclear Medicine, Institut Paoli-Calmettes, Marseille, France

[4] Department of Epidemiology, University Hospital Centre Rangueil, Toulouse, France

[5] Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France

[6] Department of Medical Oncology, IUCT-Oncopole, France

[7] Department of Radiation Oncology, IUCT-Oncopole, France

Corresponding Author:

Chantalat Elodie

Department of Surgical Oncology, IUCT-Oncopole, 1 avenue Irène Joliot-Curie, 31059 Toulouse Cedex 9, France

Cell phone: +33 5.61.32.37.51; Fax: +33 5.61.32.37.98

Mail: echantalat@yahoo.fr or chantalat.elodie@iuct-oncopole.fr

First Author:

Leray Hélène

Department of Surgical Oncology, IUCT-Oncopole, 1 avenue Irène Joliot-Curie, 31059 Toulouse Cedex 9, France

Cell phone: +33 5.31.15.53.40; Fax: +33 5.61.32.37.98; Mail: ln.leray@wanadoo.fr

ABSTRACT

Introduction: To use positron emission tomography coupled with computed tomography (^{18}FDG-PET/CT) to identify a high-risk subgroup requiring therapeutic intensification among patients with locally advanced cervical cancer (LACC) and para-aortic lymph node (PALN) involvement.

Methods: In this retrospective multicentric study, patients with LACC and PALN involvement concurrently treated with chemoradiotherapy and extended-field radiotherapy (EFR) between 2006 and 2016 were included. A senior nuclear medicine specialist in PET for gynaecologic oncology reviewed all ^{18}FDG-PET/CT scans. Metabolic parameters including maximum standardised uptake value (SUVmax), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were determined for the primary tumour, pelvic lymph nodes and PALN. Associations between these parameters and overall survival (OS) were assessed with Cox's proportional hazards model.

Results: Sixty-eight patients were enrolled in the study. Three-year OS was 55.5% (95% CI [40.8-68.0]). When adjusted for age, stage and histology, pelvic lymph node TLG, PALN TLG and PALN SUVmax were significantly associated with OS ($p<0.005$).

Conclusion: FDG-PET/CT was able to identify predictors of survival in the homogeneous subgroup of patients with LACC and PALN involvement, thus allowing therapeutic intensification to be proposed.

Keywords:

^{18}FDG-PET/CT, locally advanced cervical cancer, para-aortic lymph node involvement, SUVmax, Total lesion glycolysis

INTRODUCTION

The diagnosis of PALN involvement in patients with LACC is essential for risk stratification. Together with tumour volume, FIGO (International Federation of Gynaecology and Obstetrics) stage, depth of stromal cervix invasion, lympho-vascular space invasion, locoregional extension, response to chemoradiotherapy and nodal status, PALN involvement is inversely associated with survival (*1-4*). Since the Green meta-analysis, the treatment of LACC has consisted of pelvic radiotherapy (RT) with concurrent low-dose platinum-based chemotherapy, followed by uterovaginal brachytherapy (BT) (*5-10*), as recommended in the Guidelines of the European Society for Medical Oncology (ESMO), the National Cancer Institute (NCI), and the American Society of Clinical Oncology (ASCO) in 2016. Extended-field radiotherapy (EFR) is therefore performed in patients whose disease has spread to the PALN. Despite EFR, patients with PALN involvement have a substantially shorter median survival period (33 months), with 40% of patients developing distant metastases (*4,11,12*). The use of systemic adjuvant or neoadjuvant therapies, in combination with chemoradiotherapy, may be beneficial for improving the prognosis of these patients. However, many of these treatments are still being trialled, as improvements in survival are often associated with increases in toxicity (*13-15*). It is therefore crucial to identify factors which predict response to treatment in order to improve the survival of patients exhibiting the most unfavourable prognostic features. Not surprisingly, the consensus from the Gynaecologic Cancer Intergroup (GCIG) concludes that there is a real need for new trials directed at these high-risk cervical cancer patients (*12*).

Positron emission tomography coupled with computed tomography (^{18}FDG-PET/CT) is recommended as part of an extension to the LACC assessment and for detecting lymph node metastases in the para-aortic (PA) region (*11,16*). . Several authors have also evaluated the prognostic value of ^{18}FDG-PET/CT metrics. Of these, the maximum standardised uptake value (SUVmax) has been the most widely studied (*17*). However, the populations investigated in these types of studies were mostly heterogeneous and patients with PALN involvement were underrepresented.

The objective of this study was to assess the link between metabolic ^{18}FDG-PET/CT parameters and overall survival (OS) in patients with LACC specifically having PALN involvement.

MATERIALS AND METHODS

Patients and treatment

Patients with LACC (FIGO stage IB2-IVA) and positive PALN, treated at the Claudius Regaud Cancer Centre, at the University Hospital of Toulouse and at the Paoli-Calmettes Cancer Centre, Marseille, France, between January 2006 and November 2016, were selected for this study. All patients had cervical cancer confirmed by biopsy and underwent a physical examination, an initial pelvic MRI and a ^{18}FDG-PET/CT scan. Cervical cancers were retrospectively classified with the 2009 FIGO staging system. The diagnosis of PALN spread was based on the initial ^{18}FDG-PET/CT scan and/or on the histopathological examination of harvested PALNs as part of lymphadenectomy staging. Micro-metastatic PALN involvement was defined as a PA nodal metastasis of 0.2 to 2 mm (*18*).

Patients were treated with pelvic and PA external RT in 25 fractions of 1.8 Gray (Gy) for a total dose of 45 Gy for 5 weeks with concomitant platinum-based chemotherapy (cisplatin at a dose of 40 mg/m2 per week or carboplatin (AUC2) in cases where cisplatin was poorly tolerated). Gynaecologic examination and MRI 1.5 Tesla with gadolinium were performed during the first week after completion of the 45 Gy RT. Treatment varied depending on the type of response detected by Magnetic Resonance Imaging (MRI). Pre-therapeutic tumour size was defined as the largest tumour dimension measured on pre-therapeutic MRI. Tumour size post-therapy was the largest tumour size measured after 45 Gy RT. Response was considered as good when the maximum diameter of the tumour decreased by more than 50% at the 45 Gy MRI evaluation. When the decrease was >50%, further treatment consisted in an additional pulse dose rate intracavitary BT for an equivalent total dose of 80-90Gy. Before 2008, additional boosts up to 65 Gy in total were sometimes given at the end of BT in external RT in cases of macroscopic pelvic and/or PALN and/or parametrial involvement. When intensity-modulated radiation therapy (IMRT) became available, a simultaneous integrated boost was given on metastatic pelvic and PALN involvement at doses of 57.5 Gy in 25 fractions. In cases where the tumour reduction rate was < 50%, completion treatment was left at the discretion of the treating physician and included either BT alone or completion surgery to resect any residual tumour with clearly defined margins. This surgery was mostly performed 6 weeks after a preoperative BT for an equivalent total dose of 60Gy. For patients recruited at the Paoli Calmette Institute, systematic completion surgery was performed 6 weeks after preoperative BT, regardless of whether the response was complete or not.

We included 4 patients with distal metastatic disease identified at the initial diagnosis and subsequently treated with neo-adjuvant chemotherapy and who had good tumour responses to allow evaluation of a complete curative treatment regimen which included extended PA irradiation fields.

Follow-up included a clinical examination every 4 months for 2 years and every 6 months for the following 3 years. Imaging (MRI, CT, PET/CT) complementary to the clinical examination was performed as part of the follow-up. Relapse was defined as the emergence of a tumour locus following a complete response to treatment based on end-of-treatment reassessment imaging examinations (MRI and/or PET/CT). Progression was defined as an increase in the number or size of tumour foci under treatment, or after treatment in the event of a partial response, based on the evaluation of imaging according to the PERCIST criteria (or RECIST criteria when PET-CT was not available).

Exclusion criteria were the following: rare histologic subtypes, a lack of available ^{18}FDG-PET/CT images for centralised analysis by the two independent investigators, the absence of PALN involvement, peritoneal carcinosis, patients whose treatment was not given with curative intent and a lack of EFR for PALN involvement.

The study was approved by the local institutional review board from both institutions and the patients all gave written informed consent for their data to be used.

FDG-PET/CT parameters and interpretation

All patients had pre-treatment ^{18}FDG-PET/CT scans. The PET data were reconstructed using an iterative fully 3D algorithm with CT images for attenuation correction and anatomical identification and localisation of radiotracer uptake.

^{18}FDG-PET/CT imaging based on a standardised protocol was performed as part of the initial work-up prior to administration of any treatment. ^{18}FDG-PET/CT whole-body images were obtained using a full-ring PET/CT scanner. All patients fasted for at least 6 hours before the injection. Blood glucose levels were checked prior to the ^{18}FDG administration; injected dose and time between injection and acquisition were recorded. Patients underwent full body scans after a 60 min +/- 6 min resting period. The total scan duration varied depending on the PET-CT camera used, the ^{18}FDG injected dose, and the patient's bed number and protocols were adapted to each system's count rate. Owing to bladder refilling, complementary pelvic acquisitions were sometimes performed after intravenous administration of furosemide (20 mg).

The PET/CT scanners used for this study were the following: Siemens Biograph 6, General Electric Discovery IQ, General Electric DST4, and Philips Gemini TF16. A senior nuclear medicine specialist in PET for gynaecologic oncology reviewed all ^{18}FDG-PET/CT scans. All patient metabolic parameters were reviewed by another independent senior nuclear medicine specialist using a double-blind approach, in order to ensure the homogeneous measurement of metabolic variables throughout the study. Segmentation of tumour volumes for cervical tumours as well as pelvic and PA lymph nodes was performed using General Electric software AWServer 3.0, with an automatic threshold set at 40% of SUVmax, in accordance with the EANM (European Association of Nuclear Medicine) guidelines (*19*). This automatic contouring was manually corrected if necessary, taking CT and MRI data into account.

Metabolic parameters included SUVmax (maximal standardised uptake value), SUVmean (mean standardised uptake value), MTV (metabolic tumour volume) and TLG (total lesion glycolysis) measurements of the primary cervical tumour, pelvic and PA lymph nodes, with data from the most active site used in the subsequent analyses. Size of the primary cervical tumour was determined from the CT image along two axes of the transverse plane. The SUVmax is defined as the maximum uptake value of tracer within a tumour lesion. The TLG expresses the whole glycolysis of a lesion. The TLG is obtained by the product of MTV and SUVmean.

Statistical analysis

We evaluated any potential associations between OS and putative prognostic factors with Cox's proportional hazards model. To meet conditions for applying the model and at the same time maintain sufficient power for the analysis, quantitative variables were dichotomised at the median, with the exception of the PALN SUVmax for which the threshold of 3.3 proposed by Yen et al (*20*). was used. We evaluated all potential associations between individual metabolic parameters and survival by bivariate analysis, and subsequently, using models adjusted for specific clinical factors (i.e. age, histologic subtype and FIGO stage). P-values <0.05 were considered significant. We present results for parameters whose p-values were <0.20 in adjusted models. A dose effect was also explored graphically using a Cox survival curve derived from terciles of each variable. Statistical analyses were performed using STATA release 14.2 (StataCorp LP, College Station, TX, USA).

RESULTS

Sixty-eight patients were included in the study. Patients' characteristics are summarised in Table 1. Forty-two patients (66.7%) had pre-therapeutic surgical PA staging by laparoscopy. Four patients (9.5%) had micrometastatic PALN involvement.

Eleven of the 68 patients did not receive any BT: 2 for vaginism, 1 for neutropenia, 1 for progression during the course of treatment and 7 for non-compliance with the procedure.

Prior to chemoradiotherapy treatment, median cervical tumour size was 57.5 mm (range 26-127). Sixty-two patients presented abnormal pelvic lymph nodes and the median number of positive pelvic lymph nodes was 4 (range 1-12). Fifty-two patients presented abnormal PALN and the median number of positive PALN was 1 (range 1-8). Metabolic parameters prior to ^{18}FDG-PET/CT treatment are presented in Table 2.

After a median follow-up of 24.3 months [95% CI: 3.5-138.7 months], 31 patients (45.6%) had succumbed to their disease. Sixteen patients (23.5%) had progressed and 21 patients (39.6%) relapsed. Patients who progressed or relapsed developed metastases in 62.5% and 90.5% of cases, respectively. OS was 39.7% [95% CI: 56.5-79.7] after 2 years and 55.5% [95% CI: 40.8-68.0] after 3 years. Median OS was 43.9 months (Fig. 1).

In terms of patient characteristics, stage IIIB or IV tumour was associated with a significantly poorer outcome (HR = 4.08; p = 0.021), (Table 3). Among the ^{18}FDG-PET/CT pre-treatment parameters (Table 4), adjusted for patient age, stage and histology, pelvic lymph node TLG, PALN TLG and PALN SUVmax were significantly associated with survival (p<0.005). Patients with a higher cervical tumour or higher pelvic lymph node SUVmax also tended to have a higher mortality rate, at the limit of significance (p = 0.076 and p = 0.077 respectively). Graphically (Fig. 2), we observed a dose effect for pelvic and PA lymph node SUVmax and pelvic and PA lymph node TLG.

DISCUSSION

Despite current chemoradiotherapy management with EFR, the prognosis of LACC patients with PALN involvement remains very poor (*2,12,21,22*). Overall, results from our series are consistent with data reported in the literature. OS was 39.7% [95% CI: 56.5-79.7] after 2 years and 55.5% [95% CI: 40.8-68.0] after 3 years. Sixteen patients in our study (23.5%) progressed and 21 patients (39.6%) relapsed. Patients who progressed or relapsed developed metastases in 62.5% and 90.5% of cases, respectively. The rate of metastatic relapse raises questions about the presence of occult metastases at the initial diagnosis. Systemic therapies in addition to standard chemoradiotherapy may prove beneficial in these patients. The phase III INTERLACE (NCT01566240) and

OUTBACK (NCT01414608) trials are currently underway to evaluate these approaches by analysing the potential benefits of carboplatin and paclitaxel chemotherapy for neo-adjuvant or adjuvant applications, respectively. Regrettably, the presence of lymph node involvement above the common iliac artery is an exclusion criterion for these trials. Moreover, the significant side-effects of these treatments compel research teams to select subgroups of patients at high risk of relapse using novel prognostic factors.

In addition to its benefits in LACC staging, ^{18}FDG-PET/CT could therefore also provide useful prognostic data in these high-risk patient groups. To our knowledge, our current study is not only the first but also the largest to evaluate the predictive power of ^{18}FDG-PET/CT in an LACC patient population with PALN involvement. It shows that in patients matched for age, stage and histology, pelvic lymph node TLG (HR = 3.72; $p = 0.05$), PALN TLG (HR = 3.11; $p = 0.039$) and PALN SUVmax (HR = 4.80; $p = 0.011$) are independently associated with OS. TLG is the product of metabolic tumour volume (MTV) and the mean uptake value of the tumour lesion (SUVmean) and is related to the size and metabolism of the lesion. It also reflects the activity of the entire lesion volume, unlike SUVmax which is a maximum value retained from the voxel which fixes most metabolites. In addition, it is directly dependent on the extent of tumour volume included at the site.

Pelvic lymph node SUVmax was associated with OS in univariate analysis (HR = 2.27; $p = 0.043$). The prognostic significance of lymph node SUVmax in cervical cancer was highlighted by Kidd et al. in a prospective study of 83 patients (FIGO IB1 to IIIB). They demonstrated that a high pelvic lymph node SUVmax was associated with persistence of the disease after treatment ($p = 0.0025$), with relapse ($p = 0.0035$) and a worse OS ($p = 0.0378$) (*23*). For PALN SUVmax, a study published by Yen et al. involving 70 patients (FIGO stages I to IV), of whom 20 had PALN involvement, identified PALN SUVmax values above a 3.3 threshold to be significantly related to poor OS (*20*). The same threshold used in our study revealed a significant association between PALN SUVmax and OS in univariate analysis (HR = 4.67; $p = 0.05$) and also after adjusting for age, FIGO stage and histological subtype (HR = 4.8; $p = 0.011$).

In a retrospective study of 56 patients (FIGO IIB to IIIB stages), Chong et al. found that node SUVmax, node MTV and node TLG were correlated with relapse-free survival in univariate analysis, but only node SUVmax was shown to predict relapse-free survival in multivariate analysis (*24*). Unlike our study, where the highest node MTV and TLG metabolic values were those of the pelvic or PA lymph nodes, the values of node MTV and TLG were defined by Chong et al. as the sum of the MTV and TLG values of each hypermetabolic node. In any case, data

reported in the literature should be interpreted conservatively in light of the great variability due not only to the characteristics of cohorts but also to the different measurement criteria used.

SUVmax primary cervical tumour is the most commonly used metabolic parameter in current routine practice and its prognostic benefit in the management of cervical cancers has been extensively described in the literature (*17,25-28*). The prognostic value of primary cervical tumour MTV and TLG has been also investigated in several studies (*29-33*). In our study, none of the metabolic parameters of primary cervical tumours appeared to be correlated with OS. So, unlike in previous studies, our study population is highly specific since it consists exclusively of LACC with PALN involvement, which are well known for their dismal outcome. The other studies examined very heterogeneous groups of patients with regard to the stage of the primary disease, so they covered a much broader spectrum with very different prognoses.

^{18}FDG-PET/CT is also a useful test for evaluating metabolic tumour responses at the end of treatment. Several studies have shown that the metabolic response determined by ^{18}FDG-PET/CT and performed on average 3 months after the end of RT is predictive of survival (*33-36*). However, the analysis of the metabolic response by ^{18}FDG-PET/CT is very much operator-dependent, due to the application of visual scales and criteria that are sometimes complex to use routinely (PERCIST criteria (*37*)), as well as the prerequisite for specific anatomical understanding of pelvic oncology imaging practices. The measurement of TLG in a residual cervical tumour using post-therapeutic ^{18}FDG-PET/CT could provide functional information in addition to the morphological information provided by the re-evaluation of MRI images. In addition, by determining thresholds of ^{18}FDG-PET/CT reassessment of metabolic parameters, the evaluation of tumour responsiveness could be standardised. Specifically, the analysis of tumour responses with TLG could be developed with an artificial intelligence approach using automatic segmentation and software learning, i.e. deep learning. As such, it could constitute a useful aid in interpreting results, and even play an important role in centres not staffed with nuclear medicine, gynaecology or oncology specialists.

Our study has some limitations. it is retrospective and small, which can be justified by the choice of the patient subgroup. it includes patients from two cancer control centres, which introduces a degree of heterogeneity in the therapeutic management. Nevertheless, 93% of patients were treated with a complete chemoradiotherapy schedule and all received an EFR to the PA area. Despite the established recommendations, this heterogeneity of management has been previously highlighted in the literature in this subgroup of patients (*38*). The ^{18}FDG-PET/CT data in our study are based on the technical specifications of several different PET-CT camera manufacturers, who in some

cases use very different image acquisition and reconstruction methods. To limit this heterogeneity, we opted to eliminate data from machines that were too old, and not to use the most recent image reconstruction algorithms, which are known to modify significantly the way SUVmax is calculated (QClear, General Electric®). In addition, the centralised review of all ^{18}FDG-PET/CT examinations by a nuclear medicine specialist ensured a more accurate comparison of ^{18}FDG-PET/CT metabolic parameters.

CONCLUSION

FDG-PET/CT helped to identify predictors of survival in the homogeneous subgroup of patients with LACC and PALN involvement. Further studies are necessary to validate the prognostic impact of PALN SUVmax and PA and pelvic lymph node TLG as new metabolic parameters in this high-risk subgroup and especially to allow the therapeutic intensification to be adapted.

Statement:

The authors declare they have no conflict of interest or any financial disclosure

Keys points:

QUESTION: Can FDG-PET/CT help identify predictors of survival in patients with LACC and PALN involvement to increase treatment?

PERTINENT FINDINGS: A senior nuclear medicine specialist in PET for gynaecologic oncology reviewed all ^{18}FDG-PET/CT scans. 68 patients were enrolled in the retrospective multicentre study. Pelvic lymph node TLG, PALN TLG and PALN SUVmax were significantly associated with OS ($p<0.005$).

IMPLICATIONS FOR PATIENT CARE:

FDG-PET/CT was able to identify predictors of survival in the subgroup of patients with LACC and PALN involvement, thus allowing therapeutic intensification to be proposed.

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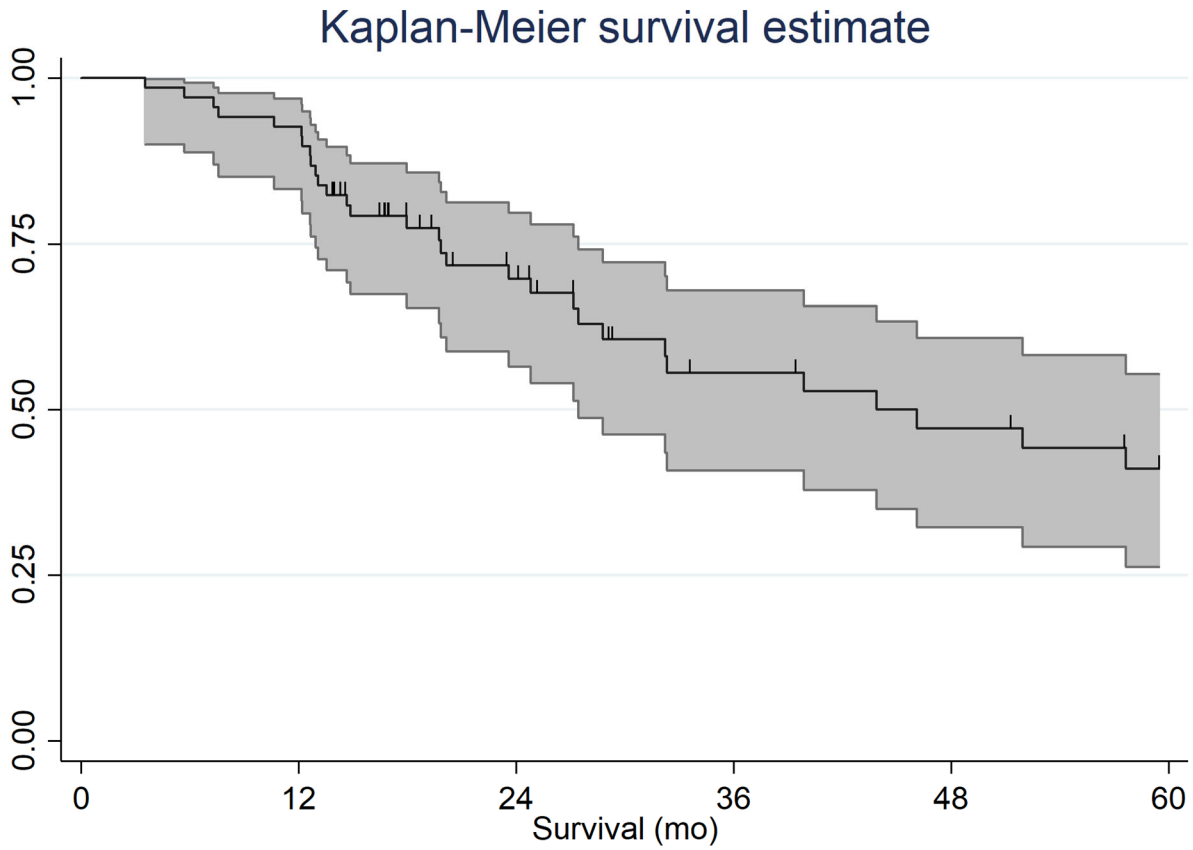

Figure 1 Kaplan-Meier plots of overall survival

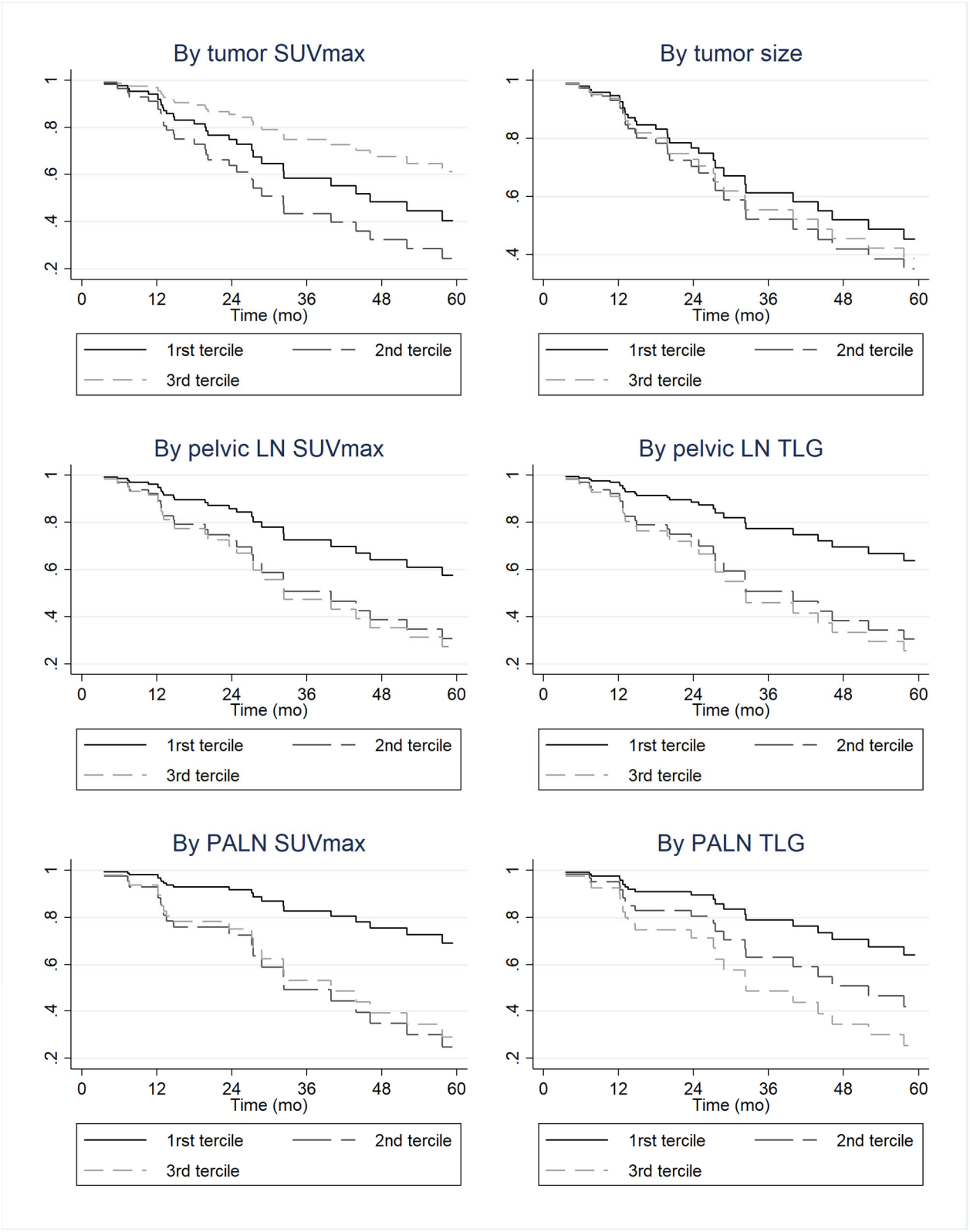

Figure 2 Cox analysis survival curves by terciles of metabolic parameters

Characteristics	n / median	% / min-max
Age (years)	54.4	27.4-80.7
Enrolling centre		
Toulouse centres	44	64.7
Marseille centre	24	35.3
Histologic subtype		
Squamous cell carcinoma	59	86.8
Adenocarcinoma	9	13.2
FIGO stage		
IB1, IB2, IIA	13	19.1
IIB, IIIA	43	63.2
IIIB, IVA, IVB	12	17.7

Table 1 Patient characteristics

Metabolic parameters	median	min-max
Cervical tumour SUVmax (N=68)	14.9	6-38.2
Cervical tumour MTV (N=68)	54.4	3.8-519
Cervical tumour TLG (N=68)	369.3	36.6-3475.6
Pelvic lymph node SUVmax (N=62)	7.8	1.8-21.2
Pelvic lymph node MTV (N=62)	2.8	0.2-41
Pelvic lymph node TLG (N=62)	12.5	0.4-300.7
PA lymph node SUVmax (N=52)	3.7	1.5-24.3
PA lymph node MTV (N=52)	0.9	0.2-15.4
PA lymph node TLG (N=52)	2.2	0.3-115

Table 2 Metabolic parameters prior to treatment

	n	HR	95%CI	*p-value*
Age (quartiles, in years)				
[27.4-46.3]	17	*ref*		
[46.7-54.0]	17	1.71	0.68-4.30	*0.256*
[57.8-59.1]	17	0.72	0.27-1.93	*0.511*
[60.0-80.7]	17	0.67	0.33-1.99	*0.466*
Histologic subtype				
Squamous cell carcinoma	59	*ref*		
Adenocarcinoma	9	2.24	0.96-5.21	*0.061*
FIGO stage				
IB1, IB2, IIA	13	*ref*		
IIB, IIIA	43	1.56	0.53-4.63	*0.420*
IIIB, IVA, IVB	12	4.08	1.23-13.5	*0.021*

Table 3 Overall survival according to age, histologic subtype and FIGO stage (Cox models)

		Unadjusted models			Adjusted models†		
	n	**HR**	**95%CI**	***p-value***	**HR**	**95%CI**	***p-value***
Cervical tumour SUVmax (median)							
[6.0; 14.8]	34	*ref*			*ref*		
[15.0; 38.2]	34	1.61	0.79-3.29	*0.192*	1.60	0.74-3.47	*0.233*
Cervical tumour size (median)							
[26; 57]	34	*ref*			*ref*		
[58; 127]	34	2.49	1.20-5.17	*0.014*	2.24	0.92-5.43	*0.076*
Pelvic lymph node SUVmax (median)							
[1.8; 7.5]	31	*ref*			*ref*		
[8.11; 21.2]	31	2.27	1.03-5.03	*0.043*	2.27	0.82-5.62	*0.077**
Pelvic lymph node TLG (median)							
[0.4; 12.5]	32	*ref*			*ref*		
[13.0; 300.7]	30	2.93	1.19-6.67	*0.010*	3.72	1.48-9.35	*0.005**
PA lymph node SUVmax (Threshold)							
[1.5; 3.3]	23	*ref*			*ref*		
[3.3; 24.3]	28	4.67	1.57-13.87	*0.005*	4.80	1.44-16.05	*0.011**
PA lymph node TLG (median)							
[0.3; 2.2]	27	*ref*			*ref*		
[2.4; 115.0]	25	3.00	1.22-7.39	*0.017*	3.11	1.06-9.19	*0.039**

Table 4 Overall survival according to metabolic parameters (Cox models)