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ORIGINAL RESEARCH

Increased bone marrow SUVmax on 18F-FDG PET is associated with higher pelvic treatment failure in patients with cervical cancer treated by chemoradiotherapy and brachytherapy

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ABSTRACT

The aim of this study was to evaluate if bone marrow (BM) SUVmax measured on pre-treatment 18F-FDG PET/CT predicts the clinical outcome of locally advanced cervical cancer (LACC). We recruited retrospectively patients with LACC who underwent staging 18F-FDG PET/CT and had baseline blood tests, then treated by chemoradiation therapy (CRT), followed by image-guided adaptive brachytherapy (IGABT). BM SUVmax was calculated and correlated to inflammatory blood markers. Tumor size and pelvic lymph node involvement were evaluated on baseline MRI. Prognostic value of SUV uptake and blood markers regarding overall survival (OS), pelvic and extra-pelvic recurrence-free survival (PRFS and EPRFS respectively) was assessed using Cox models with adjusted p-values. 116 patients with FIGO stage Ib-IVa cervical cancer, treated between 2005 and 2014, were analyzed. The median follow-up was 75.5 months. BM SUVmax was significantly correlated to tumor SUVmax. In multivariate analysis, PRFS was significantly poorer in patients with high BM SUVmax (>2.8) and neutrophilia (p < .05). Tumor size (>5 vs ≤5 cm) could predict PRFS, EPRFS and OS (p < .05). In our cohort, FIGO stage (I-II vs III-IV), pelvic lymph node involvement and tumor SUVmax (>12 vs ≤12) were not prognostic for OS or pelvic and extra-pelvic relapses. Patients with LACC and high BM SUVmax on 18F-FDG PET have worse PFRS following CRT plus IGABT. These results can be potentially explained by the pro-inflammatory role of the tumor microenvironment and G-CSF expressed by tumor cells. These data support the role of PET as a potential indicator of disease aggressiveness beyond tumor staging.

Introduction

Recent studies suggest that imaging biomarkers may provide clinically relevant prognostic information in locally advanced cervical cancer (LACC) before chemoradiotherapy and brachytherapy. Most of those prognostic factors are derived from inherent characteristics of the tumor including tumor size, FIGO stage and lymph node involvement. [1–3] Additionally, various tumor metabolic parameters derived from 18F-FDG PET, including maximum standardized uptake value (SUVmax), [4] metabolic tumor volume (MTV), [5] total lesion glycolysis (TLG) [6] and more recently, radiomic features, [7] have been shown to be accurate and sensitive prognostic biomarkers. Some treatment features, such as the volume of the high-risk clinical target volume (HR-CTV) or the dose received by 90% of the HR-CTV, [8] have also demonstrated potential in predicting local control.

Parametric FDG-PET imaging could also be useful for non-invasive quantification of Bone Marrow (BM) glucose metabolism. BM hematopoietic tissues tend to be dominated by granulocyte progenitors/precursors and are mainly stimulated by hematopoietic growth factors. BM hypermetabolism is correlated with leukocytes and neutrophils in the sacral and lumbar regions, both of which are suggested to be associated with poorer outcome. [9,10] Some patients with advanced stage cervical cancer, before any treatment including hematopoietic growth factors, present with a metabolic state on FDG PET similar to that observed in patients treated with colony stimulating factors. Granulocyte and granulocyte-macrophage colony stimulating factors (G–CSF and GM–CSF) are widely used to prevent post-chemotherapy neutropenia and lead to a substantial rise in bone marrow FDG uptake. [11–13] G-CSF and GM-CSF enhance proliferation and differentiation of granulocyte precursors in the BM, but also contribute to function of mature neutrophils. In cervical cancer patients treated with definitive radiotherapy, tumor-related leukocytosis (TRL) was associated with higher treatment failure level and higher serum

G-CSF concentrations [14] and was potentially involved in cancer cell resistance to ionizing radiation. [15,16] The purpose of this study was to evaluate if bone marrow (BM) SUVmax measured at baseline on 18F-FDG PET predicts the overall survival (OS), pelvic and extra-pelvic recurrence free survivals (PRFS and EPRFS, respectively) in patients undergoing chemoradiation therapy plus image-guided adaptive brachytherapy (IGABT) for LACC.

Results

Patient characteristics

Characteristics of the patients are shown in Table 1. Median age was 47 years and the majority had squamous cell carcinoma (83%). Nearly half of patients had pelvic lymph node metastasis (47%) and a tumor size superior to 5 cm on baseline MRI (47%). After a median follow-up of 75.5 months (6.3 years), estimated with Schemper method, 27 and 37 patients experienced pelvic and extra-pelvic relapses, respectively (Figure 1). Most extra-pelvic relapses occurred in lungs (n = 20, 54%), peritoneal cavity (n = 10; 27%), para-aortic lymph nodes (n = 8; 22%) and bones (n = 6; 16%). Among relapsing patients, 19 experienced both pelvic and extra-pelvic recurrences, at different times or simultaneously. 39 patients died and 38 deaths were preceded by recurrence: pelvic recurrence alone (N = 6; 16%), extra-pelvic recurrence alone (N = 15; 39%) and both (N = 17; 45%).

Pelvic recurrence-free survival (PRFS)

PRFS for all patients was 81% (CI 95%: 73–87%), 70% (CI 95%: 61–77%) and 64% (CI 95%: 55–72%), at 12, 24 and 60 months respectively (Figure 2). In univariate analysis, tumor size (p = 0.001), lymph node metastasis status (p = 0.002), neutrophil and leukocyte counts (p < 0.001 for both) and BM SUVmax (p < 0.001) were the factors

significantly associated with poor PRFS (Table 2). The hazard ratio corresponding to BM SUVmax from multivariable analysis was 2.9 (CI 95%: 1.3 to 6.2; p = 0.007) using a threshold of 2.8 (Table 2, Figure 2). In multivariate analysis, neutrophilia, defined by a neutrophils count >7 G/L, and tumor size superior to 5 cm at baseline remained independent statistically significant prognostic factors for PFRS (HR 2.6, p = 0.004 and HR 2.5, p = 0.006 respectively) (Table 2, Figure 2). These results were confirmed by models adapted to competing risks environment for cumulative incidence of pelvic relapse (Appendix 1 & 2) with HR equal to 2.3 for BM SUVmax (p = 0.05) and HR equal to 2.2 for neutrophilia (p = 0.05).

Extra-pelvic recurrence free survival (EPRFS)

EPRFS for all patients was 84% (CI 95%: 77–90%), 70% (CI 95%: 61–77%) and 62% (CI 95%: 55–71%), at 12, 24 and 60 months respectively. Several baseline factors were associated with reduced EPRFS in univariate analysis, including tumor size (p = 0.001), pelvic lymph node status (p = 0.001), FIGO stage (p = 0.002), neutrophil and leukocyte counts (p = 0.001 and p = 0.003), tumor SUVmax (p = 0.009) and BM SUVmax (p < 0.001) (Table 3). Among the factors associated with EPRFS in the univariate model, only tumor size >5 cm remained independently associated with poorer EPRFS in the multivariate model (HR 2.5, p = 0.006). The presence of pelvic lymph node metastasis (HR 2.2, p = 0.02), neutrophils >7 G/L (HR 1.9, p = 0.05) and BM SUVmax >2.8 (HR 2.5, p = 0.02) failed to reach the statistically significant threshold despite consequent hazard ratios and indicative confidence intervals (Table 2). Models adapted to competing risks environment for cumulative incidence of extra-pelvic relapse (Appendix 3) strengthened these results, with the remaining prognostic significance of tumor size (HR 2.6, p = 0.008) and highlighted the added prognostic value of FIGO stage (HR 2.9, p = 0.008) and neutrophilia (HR 2.5, p = 0.009).

Overall survival (OS)

OS for all patients was 94% (CI 95%: 88–97%), 77% (CI 95%: 68–84%) and 67% (CI 95%: 58–76%), at 12, 24 and 60 months respectively (Figure 2). FIGO stage (p = 0.002), tumor size (p = 0.001), pelvic lymph node metastasis (p = 0.001), neutrophil and leukocyte counts (p = 0.001 and p = 0.003), tumor SUVmax (p = 0.009) and BM SUVmax (p < 0.001) were the factors significantly associated with poor OS in univariate analysis (Table 4). The hazard ratio from multivariable analysis was 2.5 (CI 95%: 1.2 to 5.2; p = 0.009) for baseline MR tumor size using a threshold of 5 cm (Table 4). In multivariate analysis, BM SUVmax >2.8 (HR 2.7; CI 95%: 1.2 to 6.1; p = 0.02) and neutrophilia (HR 2.4, p = 0.02) did not remain independent statistically significant prognostic factors for OS (Table 4).

Correlation between PET biomarkers and hemogram blood parameters

Correlations between PET biomarkers (BM SUVmax, tumor SUVmax and MTV) and hemogram blood parameters

Table 1. Baseline characteristics of patients.

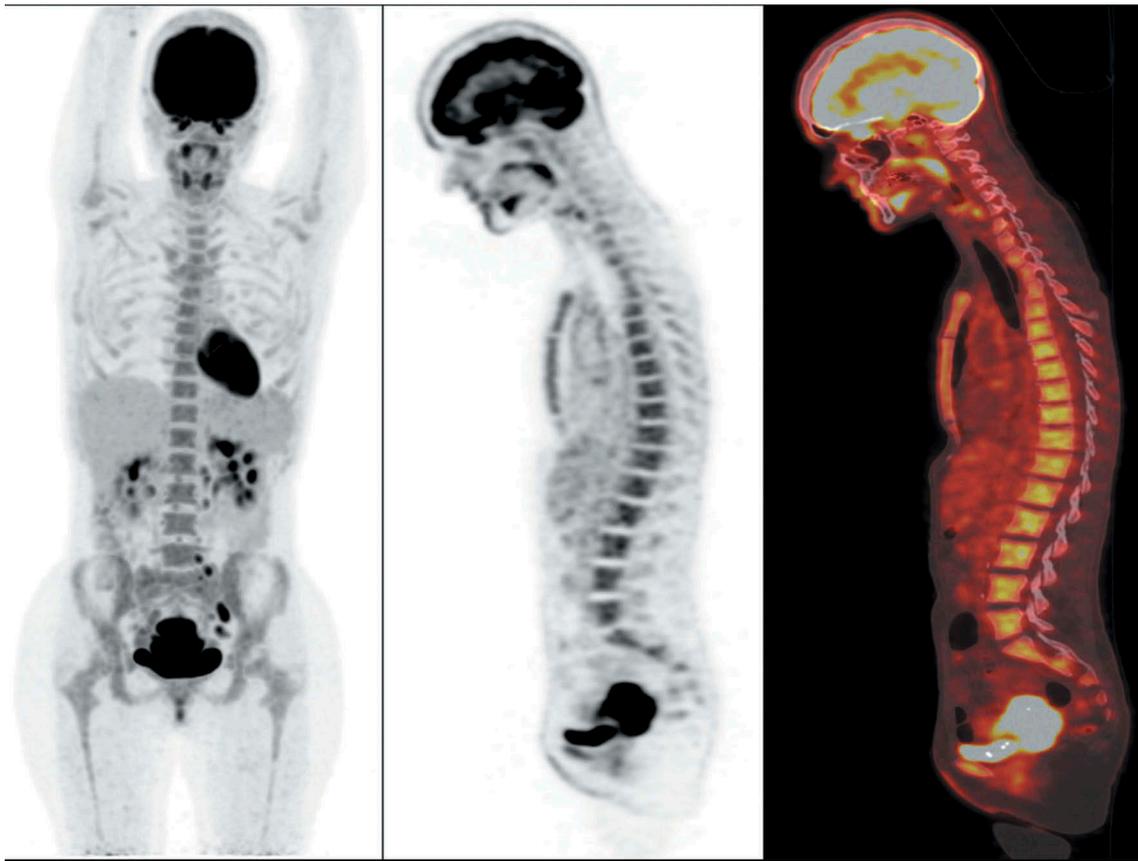| Baseline Patient Characteristics	Median (min-max)	n (%)
Age	47 (27–82)	-
Histopathology		
Adenocarcinoma	-	20 (17)
Squamous cell carcinoma	-	96 (83)
FIGO* stage		
Ib1	-	6 (5)
Ib2	-	30 (26)
IIa	-	7 (6)
IIb	-	60 (52)
IIIb	-	9 (8)
IVa	-	4 (3)
Tumor size >5 (cm)	-	54 (47)
Pelvic nodal metastases	-	54 (47)
Hematologic parameters		
Leukocytes (G/L)	7.7 (1.8–18.0)	-
Neutrophils (G/L)	5.4 (1.2–14.0)	-
Hemoglobin (g/dL)	12.3 (6.5–15.3)	-
Platelets (G/L)	285 (89–890)	-
Neutrophils to lymphocytes ratio (NLR)	3.4 (0.9–24.0)	-
FDG PET † parameters		
Tumor SUVmax‡	12.0 (4.9–28.6)	-
Metabolic tumor volume (cm^3)	29.9 (6.4–191.2)	-
BM§ SUVmax$^\square$	2.8 (1.9–4.5)	-

Abbreviations: *FIGO: International Federation of Gynecology and Obstetrics. †FDG PET: fluorodeoxyglucose positron emission tomography. ‡SUV$_{max}$: maximum standardized uptake value. §BM: bone marrow. $^\square$BM SUV$_{max}$: average of maximum standardized uptake values of each vertebral body in bone marrow.

Figure 1. Maximal intensity projection coronal (left) and sagittal (middle) FDG PET* images. Sagittal 18F-FDG PET/CT with bone window CT[†] on the spine (right); initial staging for a 44-year-old patient with squamous LACC revealing pelvic and para-aortic lymph node metastasis and showing an increased FDG uptake in the spine hematopoietic BM[‡] tissue (BM SUV_{max}[§] 3.5). Nearly 3 years after completion of brachytherapy, the patient relapsed locally and finally died one full-year after recurrence.

Abbreviations: *FDG PET: fluorodeoxyglucose positron emission tomography. †CT: computed tomography. SUV_{max}: maximum standardized uptake value. ‡BM: bone marrow. §BM SUV_{max}: average of maximum standardized uptake values of each vertebral body in bone marrow.
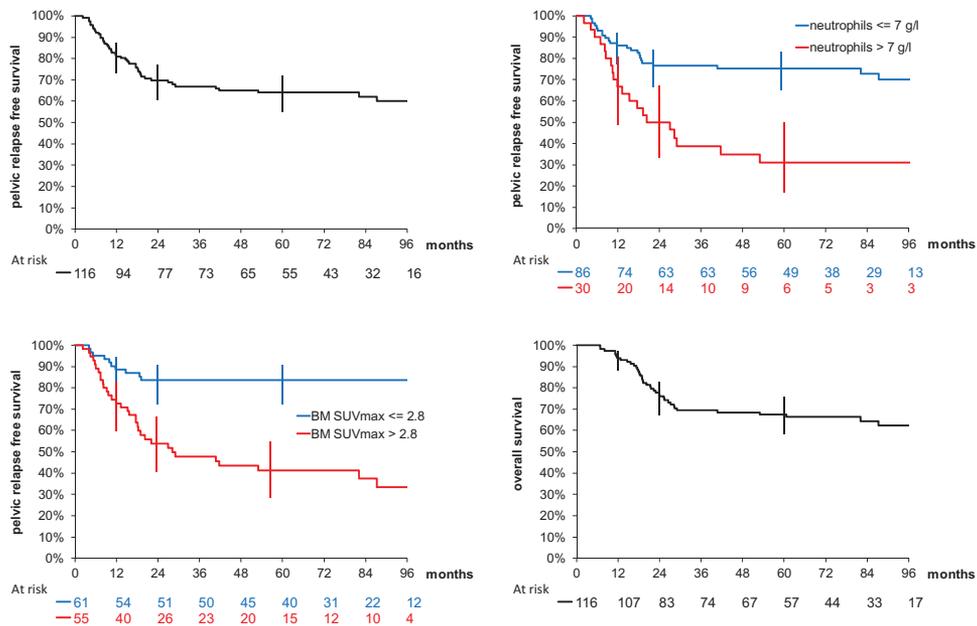
Figure 2. Kaplan-Meier curves for PRFS* (in the upper left) and OS[§] (in the lower right) in all patients (N = 116). Curves for PRFS* stratified according to BM SUV_{max}[‡] (in the lower left) and neutrophils count (in the upper right).

Abbreviations: *PRFS: pelvic recurrence-free survival. §OS: overall survival. ‡BM SUV_{max}: average of maximum standardized uptake values of each vertebral body in bone marrow.

Table 2. Prognostic significance of the hematologic and PET‡ biomarkers for pelvic recurrence-free survival in univariate and multivariate analyses.

	Pelvic recurrence-free survival						
Events (pelvic recurrence, death) = 43	Univariate				Multivariate		
Variable	p	p trend	HR*	CI‡ 95%	p	HR*	CI‡ 95%
Age (>47 vs ≤ 47)	0.03	-	2.0	1.1–3.6	0.09	1.7	0.9–3.2
Histopathology (ADK vs SCC)	0.6	-	0.8	0.4–1.8	-	-	-
FIGO stage (I-II vs III-IV)	0.03	-	2.4	1.1–5.2	-	-	-
Tumor size (>5 vs ≤ 5 cm)	0.001	-	2.8	1.5–5.4	0.006	2.5	1.3–4.9
Pelvic nodal metastasis (yes vs no)	0.002	-	2.7	1.4–5.1	0.09	1.8	0.9–3.5
Leukocytes (>10 vs ≤ 10 G/L)	<0.001	0.03	3.1	1.7–5.8	-	-	-
Neutrophils[a] (>7 vs ≤ 7 G/L)	<0.001	0.01	3.3	1.8–6.1	0.004	2.6	1.4–5.0
NLR[#] (>3.4 vs ≤ 3.4)	0.03	0.1	2.0	1.1–3.7	-	-	-
Tumor SUV_{max} (>12 vs ≤ 12)	0.01	0.004	2.3	1.2–4.3	-	-	-
MTV[†] (>30 vs ≤ 30 cm³)	0.01	0.01	2.2	1.2–4.2	-	-	-
BM SUV_{max} [§] (>2.8 vs ≤ 2.8)	<0.001	<0.001	3.9	2.4–9.9	0.007	2.9	1.3–6.2

Abbreviations: *HR: hazard ratio. ‡ CI: confidence interval. §BM SUV_{max}: average of maximum standardized uptake values of each vertebral body in bone marrow. †MTV: metabolic tumor volume. #NLR: neutrophils to lymphocytes ratio.

Table 3. Prognostic significance of the hematologic and PET‡ biomarkers for extra pelvic recurrence-free survival in univariate and multivariate analyses.

	Extra pelvic recurrence-free survival						
Events (extra-pelvic recurrence, death) = 44	Univariate				Multivariate		
Variable	p	p trend	HR*	CI‡ 95%	p	HR*	CI‡ 95%
Age (>47 vs ≤ 47)	0.02	-	2.1	1.1–3.8	0.09	1.7	0.9–3.2
Histopathology (ADK vs SCC)	0.7	-	0.9	0.4–1.8	-	-	-
FIGO stage (I-II vs III-IV)	0.002	-	3.2	1.5–6.7	0.08	2.0	0.9–4.2
Tumor size (>5 vs ≤ 5 cm)	0.001	-	3.0	1.6–5.7	0.006	2.5	1.3–4.9
Pelvic nodal metastasis (yes vs no)	0.001	-	2.9	1.5–5.4	0.02	2.2	1.1–4.4
Leukocytes (>10 vs ≤ 10 G/L)	0.003	0.1	2.6	1.4–4.9	-	-	-
Neutrophils[a] (>7 vs ≤ 7 G/L)	0.001	0.007	2.8	1.5–5.0	0.05	1.9	1.0–3.6
NLR[#] (>3.4 vs ≤ 3.4)	0.09	0.4	1.7	0.9–3.1	-	-	-
Tumor SUV_{max} (>12 vs ≤ 12)	0.009	0.002	2.3	1.2–4.3	-	-	-
MTV[†] (>30 vs ≤ 30 cm³)	0.01	0.006	2.3	1.2–4.3	-	-	-
BM SUV_{max} [§] (>2.8 vs ≤ 2.8)	<0.001	<0.001	3.5	2.2–8.9	0.02	2.5	1.2–5.3

Abbreviations: *HR: hazard ratio. ‡ CI: confidence interval. §BM SUV_{max}: average of maximum standardized uptake values of each vertebral body in bone marrow. †MTV: metabolic tumor volume. #NLR: neutrophils to lymphocytes ratio.

Table 4. Prognostic significance of the hematologic and PET‡ biomarkers for overall survival in univariate and multivariate analyses using a Cox model (significant factors in bold).

	Overall survival						
Events (death) = 39	Univariate				Multivariate		
Variable	p	p trend	HR*	CI‡ 95%	p	HR*	CI‡ 95%
Age (>47 vs ≤ 47)	0.05	-	1.9	1.0–3.5	-	-	-
Histopathology (ADK vs SCC)	0.5	-	0.8	0.4–1.6	-	-	-
FIGO stage (I-II vs III-IV)	0.006	-	3.0	1.4–6.5	0.1	2.0	0.9–4.4
Tumor size (>5 vs ≤ 5 cm)	0.001	-	3.0	1.5–6.0	0.009	2.5	1.2–5.2
Pelvic nodal metastasis (yes vs no)	0.003	-	2.7	1.4–5.2	0.1	1.7	0.9–3.5
Leukocytes (>10 vs ≤ 10 G/L)	<0.001	0.009	3.3	1.7–6.3	-	-	-
Neutrophils (>7 vs ≤ 7 G/L)	<0.001	0.003	3.5	1.9–6.7	0.02	2.4	1.2–6.1
NLR[#] (>3.4 vs ≤ 3.4)	0.03	0.1	2.1	1.1–4.1	-	-	-
Tumor SUV_{max} (>12 vs ≤ 12)	0.003	<0.001	2.8	1.4–5.6	0.08	2.0	0.9–4.3
MTV[†] (>30 vs ≤ 30 cm³)	0.02	0.007	2.3	1.2–4.4	-	-	-
BM SUV_{max} [§] (>2.8 vs ≤ 2.8)	<0.001	<0.001	4.0	2.4–10.6	0.02	2.7	1.2–6.1

Abbreviations: *HR: hazard ratio. ‡ CI: confidence interval. §BM SUV_{max}: average of maximum standardized uptake values of each vertebral body in bone marrow. †MTV: metabolic tumor volume. #NLR: neutrophils to lymphocytes ratio.

(leukocytes, neutrophils, hemoglobin and platelets) were studied (Appendix 4). BM SUVmax was weakly, but significantly correlated with tumor SUVmax (rank[rho] = 0.41; p < 0.01). Correlations between BM SUVmax and neutrophils were not considered as strong enough (rank [rho]<0,4 and p > 0,01). Furthermore, BM SUVmax was not significantly correlated with hemoglobin level or platelet count (p > 0.05).

Discussion

Our study shows that an increased BM SUVmax measured on baseline 18F-FDG PET predicts poorer PRFS following CRT plus IGABT in cervical cancer patients. Tumor size superior to 5 cm was prognostic for PRFS, EPRFS and OS. In addition, high BM SUVmax and neutrophilia were two independent prognostic biomarkers but only for pelvic recurrence. Both could however

be partly explained by the pro-inflammatory role of the microenvironment and G-CSF expressed by tumor cells.

Identifying tumor response biomarkers is important to predict success or failure of treatment. Several studies have revealed that tumor microenvironment with bone marrow derived pro-inflammatory cells, such as neutrophils, can promote cancer progression through an increased expression of inflammatory cytokines and growth factors, but also adversely affect response to therapy. [17–19] As many studies have found, neutrophil to lymphocyte ratio (NLR), [20] albumin level, [21] c-reactive protein (CRP) level [22] and Glasgow prognostic score (GPS) [23] may also predict the outcome for LACC patients who receive CRT plus IGABT. Additionally, the current hypothesis is that radiotherapy failure is related to increased levels of myeloid-derived suppressor cells. In that context, it was shown that high bone marrow glycolytic activities on 18F-FDG PET occurred more frequently in patients with leukocytosis and might therefore be predictor of radiotherapy failure. [16] Recently, Lee et al. showed that cervical cancer patients with elevated BM FDG uptake or high neutrophil count characterized respectively by BM to liver SUVmax ratio >0.82 and NLR >2.1, had an increased risk of distant recurrence after definitive radiotherapy or surgery treatment. [24]

In our study, BM SUVmax on staging PET was found to be an independent predictor of PRFS. Indeed, patients with BM SUVmax <2.8 showed prolonged pelvic relapse-free survival as compared to patients with BM SUVmax >2.8. Strikingly, baseline BM SUVmax tended to be a better predictor of pelvic and extra-pelvic recurrence and OS than tumor SUVmax. Similarly, the absolute number of neutrophils seems to be a better biomarker than NLR to identify patients at higher risk of pelvic relapse that could require dose escalation and might provide new targets for cancer therapy. [25]

In the recent study by Lee et al., [24] BLR, defined as the BM-to-Liver uptake Ratio, was an independent factor for predicting distant recurrence-free survival but was not significantly associated with worse progression-free survival for patient subgroup treated with CRT without brachytherapy (43% of the total number of included patients). Recommendations from the European SocieTy for Radiotherapy & Oncology states that high dose rate brachytherapy, associated with concomitant CRT, is the standard of care for LACC. [26] While surgery is often the main treatment for early stage cervical cancer, that is merely an ad hoc option for patients either with extensive pelvic and/or vaginal disease. The main advantage of our present work is that we studied specifically the PRFS in this specific population of patients, reflecting response to CRT plus brachytherapy used as sole definitive Standard of Care therapy. Lastly, previous study [24] might only have captured early recurrence or progression due to 26.2 months reported median follow-up, as compared to 75.5 months in our study.

In addition, our findings indicate the positive, linear but weak correlation between BM SUVmax and tumor SUVmax, recognized as an indicator of tumor aggressiveness and cancer cell proliferation. [27] These results support the hypothesis of a connection between more vigorous tumor cell metabolism and hematopoietic BM activation.

As previously noted, increased relapse risks were observed among patients with high BM glycolytic activities on 18F-FDG PET and/or with neutrophilia and leukocytosis.

A potential explanation is that BM derived pro-inflammatory myeloid cells, as myeloid-derived suppressor cells, under the action of G-CSF expressed by tumor cells play a key role in the promotion of tumorigenesis, neoangiogenesis, cancer cell proliferation, survival [17,28] and metastatic invasion, by modulating the adaptive immune system and shifting therapy response. [29] Tumor associated neutrophil density (TAN), obtained on biopsy samples, was associated with poor prognosis and a higher probability of therapy failure, in particular in radiotherapy. [18] Further studies could explore the correlation between BM glycolytic activities features on FDG-PET, TAN density within the primary site, serum levels of circulating MDSC and G-CSF expressed by cervical tumor cells.

Our results open further research opportunities. A potential approach for novel therapies is to block immune cells in the inflammatory microenvironment, such as tumor associated neutrophils or myeloid-derived suppressor cells. [30] This candidate approach may be used to potentiate radiotherapy and brachytherapy. [31–34] Tumor SUVmax on 18F-FDG PET detects immune (in) activation by targeted molecular agents. [35] Therefore, our methodology could be used as a tool to evaluate granulopoiesis by neutrophilia or BM SUVmax with the intent that it will predict response to neutrophils or myeloid-derived suppressor cells-blockade therapies.

Limitations of the study include the relatively small sample size but also its retrospective and monocentric natures. Our cohort was rather heterogeneous, including various FIGO stages of patients, with basal prognostic already different independently of FDG uptake in the bone marrow. Thus, outcome prediction must be validated on an independent external cohort. Additionally, we observed a high pelvic relapse rate (23%) that is worse than average levels, usually ranging from 10 to 15%. [25] This difference might be a consequence of scheduling considerations in local PET acquisitions, as the priority for nuclear imaging in our institution depends on the evolution and aggressiveness of the disease. Furthermore, we did not include the dosimetric parameters and the dosage of chemotherapy in this analysis. Unfortunately, CRP and albumin were not available for all patients due to the retrospective design of the study. Consequently, it was not possible to calculate Glasgow prognostic score, which need to be assessed in upcoming prospective evaluations. In the statistical analysis, some of the variables considered in the Cox model were correlated (for instance leucocytes, neutrophils and NLR). When considered simultaneously in the multivariate Cox model, redundancies were eliminated by the stepwise selection. Therefore, we thought reasonable to stick with a classical Cox analysis, without calling for dimension reduction techniques or more sophisticated approaches. Anyway, our study indicates that BM SUVmax remains a robust biomarker for predicting pelvic recurrence in LACC patients, although prospective confirmation is warranted in an independent prospective series of consecutive patients. In conclusion, since high BM SUVmax on 18F-FDG PET has worse pelvic recurrence-free survival following CRT plus BT, baseline 18F-FDG PET would be a relevant assay to select patients that require an intensified radiotherapy and/or a close monitoring during therapy. It could be a useful tool to predict response to potential novel therapies targeting pro-inflammatory cells in the tumor microenvironment.

Patients and methods

Patient selection

One hundred and sixteen patients who had pre-treatment 18F-FDG PET/CT scans, between 2005 and 2014 were selected retrospectively. The inclusion criteria were as follow: diagnosis of LACC proven by histopathology (FIGO Ib to IVa), no surgery performed except for para-aortic surgical staging, squamous cell carcinoma or adenocarcinoma histological subtypes and maximal time interval of 1 month between 18F-FDG PET/CT and therapy initiation. All patients included did not receive neoadjuvant chemotherapy, corticosteroids, lithium, G or GM-CSF over the last three months. None of them had in addition a history of chronic inflammatory, auto-immune disease, or hematologic disease (malignant hemopathy or hemolytic anemia) or presented with acute or chronic infection. Treatment consisted of a concomitant chemoradiation delivering 45 Gy in 25 fractions of 1.8 Gy each through a 3D conformal technique with high megavoltage photons to the pelvis $\pm$ the para-aortic area depending on the para-aortic lymph node status of the 18F-FDG PET or the primary surgical lymph node staging. This first treatment was followed by a pulse-dose rate image-guided adaptive boost of uterovaginal brachytherapy delivering 15 Gy to 95% of the intermediate risk clinical target volume. Concomitant chemotherapy was systematically administrated and the standard regimen was cisplatin 40 mg/m^2 weekly, five times during external radiotherapy delivery, with a sixth cycle administered during brachytherapy.

After treatment, patients were evaluated regularly with pelvic MRI, CT scans, clinical examinations and biopsies in case of relapse suspicion. No patients underwent completion surgery. Follow-up examinations were performed every three months for the first two years, then each semester for the next three years, and then once yearly. When recurrence was suspected, biopsy of the lesion was recommended. Pelvic relapse included local failure involving the true pelvis (cervix, parametria, vagina) and nodal failure within the pelvis. Extra-pelvic relapse included the remaining lymph node areas (in particular para-aortic and supraclavicular metastases) and/or systemic failure (any organ). The study has been approved by the institutional review board and performed in compliance with the Declaration of Helsinki.

18F-FDG PET/CT scans

18F-fluorodeoxyglucose PET/CT scans were performed from the skull base to the proximal femur using two different PET machines: a Siemens Biograph I (Siemens AG, Erlangen, Germany), mono-slice with LSO-based detectors installed in 2003 (N = 77, PET 1) and a General Electric Discovery-690 (GE Healthcare, Waukesha, WI) with LYSO-based detectors installed in 2011 (N = 39, PET 2). Patients fasted for at least six hours and were injected intravenously with 18F-FDG (mean dose: 334.5 MBq [137.5–676]). PET/CT imaging studies were performed 60 min after injection (median: 61.5 minutes [53–87]). Before PET acquisition, a non-contrast CT scan was performed to generate attenuation correction maps. PET images were reconstructed with a 2D Ordered Subset Expectation Maximization (OSEM) algorithm (8 subsets, 2 iterations, no post-filtering) for PET 1 and with a fully 3D time-of flight iterative reconstruction scheme (VPFX) (OSEM algorithm, 24 subsets, 2 iterations) for PET 2. Images were then converted in SUV units by normalization using the patient body weight.

18F-FDG PET/CT image analysis

Data from the 18F-FDG PET scans were calculated using 3D SLICER (version 4.6.2), an open source software platform for biomedical research. First, the primary tumor was delineated on the PET images, using a 40% threshold of SUVmax, within a manually drawn volume, assisted by CT data for anatomical location to extract tumor PET parameters (SUVmax and MTV volume). Secondly, a circular VOI with a 15-mm diameter was placed slice-by-slice within the center of T12 (thoracic) to L5 (lumbar) vertebral bodies to measure high BM glycolytic activities. The greatest value was chosen as the SUVmax of each vertebral body. BM metabolic uptakes (BM SUVmax) were defined as the average of maximum standardized uptake values of all vertebral bodies [9,10]. In several cases with severe lumbar osteoarthritis, vertebral fractures, hemangioma or lumbar spine surgery history, VOI were drawn in other vertebral bodies, mainly thoracic vertebrae. All the ROI placements were performed by a nuclear medicine physician.

Hemogram blood tests

Pretreatment blood samples taken before any chemotherapy were analyzed. According to World Health Organization (WHO) recommendations, leukocytosis and neutrophilia were defined as a leukocyte count or a neutrophil count exceeding 10 and 7 G/L, respectively. The NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes (G/L).

Statistical analysis

Continuous variables were dichotomized at their median value, except for leucocytes and neutrophils a priori dichotomized at 10 G/L and 7 G/L respectively. Tests for continuous variables dealt both with the binary form and the continuous form (trend test). Median follow-up was estimated using the inverse Kaplan-Meier method. [36] For PRFS, an event was defined as a pelvic relapse or a death with time corresponding to the earliest date of occurrence and patients with neither pelvic relapse nor death were censored at the date of last news. A similar definition was given for EPRFS. For overall survival, death from any cause was the event. The "total cumulative incidence" of pelvic relapse was estimated considering death without evidence of pelvic relapse as a competing risk, with extra pelvic relapses being completely ignored. Similarly, the "total cumulative incidence" of extra-pelvic relapse was estimated considering death without evidence of extra-pelvic relapse as a competing risk, with pelvic relapses being

completely ignored. The role of all factors measured at diagnosis on prognosis was studied with Cox models for survival and regression models adapted to competing risks environment for cumulative incidence. [37] A classical Cox model was used, with proportional hazard over all time and linear dependency of the log hazard function on covariates. For multivariate analyses, forward selection methods were used. For assessment of the relationships between blood cell count values, BM SUVmax, MTV and tumor SUVmax, Spearman's rank correlation coefficients were calculated. All reported p values are two-sided and significant p values below 1% were considered after multiple testing corrections. Analyses were performed with SAS® version 9.4.

Author Contributions

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(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,
(2) drafting the article or revising it critically for important intellectual content,
(3) final approval of the version to be submitted

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethical approval

All procedures performed in this study were in accordance with the institutional review board.

Informed consent

For this type of study (retrospective) formal consent is not required.

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