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ORIGINAL ARTICLE

A score combining baseline neutrophilia and primary tumor SUV_{peak} measured from FDG PET is associated with outcome in locally advanced cervical cancer

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Abstract
Purpose We investigated whether a score combining baseline neutrophilia and a PET biomarker could predict outcome in patients with locally advanced cervical cancer (LACC).
Methods Patients homogeneously treated with definitive chemoradiation plus image-guided adaptive brachytherapy (IGABT) between 2006 and 2013 were analyzed retrospectively. We divided patients into two groups depending on the PET device used: a training set (TS) and a validation set (VS). Primary tumors were semi-automatically delineated on PET images, and 11 radiomics features were calculated (LIFEx software). A PET radiomic index was selected using the time-dependent area under the curve (td-AUC) for 3-year local control (LC). We defined the neutrophil SUV grade (NSG = 0, 1 or 2) score as the number of risk factors among (i) neutrophilia (neutrophil count >7 G/L) and (ii) high risk defined from the PET radiomic index. The NSG prognostic value was evaluated for LC and overall survival (OS).
Results Data from 108 patients were analyzed. Estimated 3-year LC was 72% in the TS (n = 69) and 65% in the VS (n = 39). In the TS, SUV_{peak} was selected as the most LC-predictive biomarker (td-AUC = 0.75), and was independent from neutrophilia (p = 0.119). Neutrophilia (HR = 2.6), high-risk SUV_{peak} (SUV_{peak} > 10, HR = 4.4) and NSG = 2 (HR = 9.2) were associated with low probability of LC in TS. In multivariate analysis, NSG = 2 was independently associated with low probability of LC (HR = 7.5, p < 0.001) and OS (HR = 5.8, p = 0.001) in the TS. Results obtained in the VS (HR = 5.2 for OS and 3.5 for LC, p < 0.02) were promising.
Conclusion This innovative scoring approach combining baseline neutrophilia and a PET biomarker provides an independent prognostic factor to consider for further clinical investigations.

Keywords Cervical carcinoma · Brachytherapy · Radiomics · Prognostic factor · Biomarkers · Neutrophilia

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Introduction

Although screening of cervical cancer has reduced its incidence in developed countries, it remains the fourth most common cause of cancer mortality worldwide in women [1]. And while cervical cancer has been reduced globally, especially in developed countries, its incidence among young women has risen [2]. The most relevant tumor-related prognostic factors for locally advanced cervical cancer (LACC) are tumor size at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, and lymph node metastases [3].

Five-year overall survival (OS) ranges from 80% (stage IB) to 15% (stage IVA–B) [4]. Despite carefully implemented treatment, approximately 30–40% of patients will suffer relapse of their cancer [5].

18-Fluorodeoxyglucose positron emission tomography (^{18}F–FDG PET) plays an essential role in the initial evaluation of these patients. The main indications are staging and detection of nodal and distant metastases [6]. An elevated maximum standard uptake value (SUV_{max}) within the primary tumor at baseline is a predictor of poorer response to therapy (5-year disease-free survival was ~50% for patients with $SUV_{max} \geq 10$ vs. ~70% for $SUV_{max} < 10$), although it is not associated with poorer OS [7]. Tumor-related leukocytosis and neutrophilia are likewise independently associated with a threefold increase in the risk of local failure in LACC [8–10].

Image-guided adaptive brachytherapy (IGABT) makes personalized treatment possible after residual tumor definition based on MRI or PET imaging. Implementation of IGABT in patients with LACC has improved rates of local control in patients with locally advanced tumors at diagnosis [11, 12]. Although several factors—both tumor- and dosimetry-related—are associated with a higher local control rate, there remains a crucial need for refining prognosis prediction and identifying patients who would benefit most from dose escalation [11, 13, 14].

Radiomics is based on the conversion of digital medical images into minable high-dimensional data that can be interrelated with patient characteristics via statistical analyses [15]. A combination of biological parameters and PET radiomics analysis could improve current outcome prediction to drive therapeutic strategies.

This study aimed to develop and validate an original score combining prognostic values from two criteria—neutrophilia and a PET imaging feature—for predicting outcomes in patients with LACC treated with definitive chemoradiation and IGABT.

Materials and methods

Patients and tumors

We examined the clinical records of consecutive patients treated for histologically confirmed LACC in our institution between 2006 and 2013, who received concurrent chemoradiation followed by IGABT. Patients should have had ^{18}F–FDG PET in our institution as part of their initial staging prior to any surgery, chemotherapy or radiotherapy. Patients with PET-positive para-aortic lymph nodes or histological evidence of para-aortic metastases were excluded. No surgery was performed other than for para-aortic surgical staging. This study was approved by the institutional review board.

Treatment characteristics and follow-up

Patients received pelvic external beam radiotherapy (EBRT, 45 Gy), delivered in 25 fractions of 1.8 Gy each through a 3D conformal technique. Concurrent chemotherapy with cisplatin or carboplatin was delivered weekly. Sequential EBRT boosts were delivered to macroscopically involved pelvic lymph nodes, excluding para-aortic lymph nodes. The pulsed-dose-rate brachytherapy boost was based on MRI computer-assisted treatment planning. The vaginal mold technique was used, as previously described [16]. Further details have been published previously [8, 17, 18].

PET-CT acquisition and radiomic analysis

Two PET datasets were defined, a training set (TS) and a validation set (VS), according to the PET device used for image acquisition [19]. Patients in TS underwent a baseline PET scan using a Siemens Biograph scanner (Siemens AG, Erlangen, Germany). Images were reconstructed using a 2D ordered subset expectation maximization (OSEM) algorithm (8 subsets, 2 iterations). Images for patients in the VS were acquired using a GE Discovery 690 device (GE Healthcare, Waukesha, WI, USA). In this group, a fully 3D time-of-flight iterative reconstruction scheme was used (VUE Point FX, 24 subsets, 2 iterations) [20]. The voxel size was 5.3 mm × 5.3 mm × 3.4 mm (matrix size: 128 × 128, 4 min/bed position) for the TS and 2.7 mm × 2.7 mm × 3.4 mm (matrix size: 256 × 256, 2 min/bed position) for the VS. Images were resampled to a 2 mm × 2 mm × 2 mm grid using a trilinear interpolation to reduce bias in image analysis due to differences between reconstruction grids [21, 22].

The primary tumor was delineated on the PET images using a 40% threshold of SUV_{max} within a manually drawn volume to define the tumor volume of interest (VOI-T). The entire radiomic feature extraction was performed using Local Image Features Extraction (LIFEx) software (www.lifexsoft.org) [23].

For each VOI-T, five typical features were first extracted: SUV_{mean} (mean SUV in the VOI), SUV_{max}, SUV_{peak} (mean SUV in the 1-mL sphere located in the VOI so that the mean SUV in that sphere was maximum), metabolic volume (MV), and total lesion glycolysis (TLG, product of SUV_{mean} and MV).

Then, SUV values in each VOI-T were resampled in 128 bins between 0 and 40 SUV units using an absolute method to avoid a correlation between textural features and metabolic tumor volume, and to reduce the impact of noise and matrix size [24]. The higher bound was chosen to include all tumor SUV values [25]. Three texture matrices were calculated in each VOI-T: the gray-level co-occurrence matrix (GLCM), the gray-level run length matrix (GLRLM) and the gray-level zone length matrix (GLZLM). GLCM and GLRLM were computed in 13 directions, and each textural feature extracted from these matrices corresponds to the average

value over the 13 directions. Six 3D textural indices (homogeneity; entropy from GLCM; short-run emphasis [SRE]; long-run emphasis [LRE] from GLRLM; low gray-level zone emphasis [LGZE]; high gray-level zone emphasis [HGZE] from GLZLM) were analyzed [26].

Complete blood count analysis

Complete blood counts used for analysis were obtained prior to any surgical staging, chemotherapy or radiotherapy, and were all performed in our institution. The optimal neutrophil cut-off for assessing biological inflammation was >7.0 G/L [27]. Anemia was defined as hemoglobin count below 12.0 g/dL. These cut-off points were chosen because they have been recognized as standard pathological definitions. Patients who received corticosteroids, were treated for an immune disease, or presented with chronic inflammation or acute or chronic infection (including human immunodeficiency virus) were excluded.

Score definition

We defined a prognostic score using two features: neutrophilia and a PET radiomic index associated with LC. From the TS, we selected the PET radiomic index that maximized the area under the receiver operating characteristic (ROC) curve (td-AUC) for 3-year LC, and determined its correlation with neutrophil count. The cut-off for the selected index was derived using the Youden index, which maximizes the sum of sensitivity and specificity.

The combined score from neutrophilia and the single selected PET index was defined as follows: 0 = absence of neutrophilia and low-risk defined from the selected PET radiomic index; 1 = neutrophilia or high risk defined from the selected index; 2 = neutrophilia and high risk defined from the selected index.

Statistical analysis

Differences in patient characteristics between the TS and VS were compared with chi-squared and Student's *t* tests. Outcomes were defined as the length of time between the date of initiation of radiotherapy and time of death for OS and local failure for LC. Patients were censored at the time of the most recent follow-up. Pearson's test was performed to explore correlations between PET-derived features and neutrophil count in the TS. Survival curves were compared using the log-rank test for univariate analysis. A *p*-value of less than 0.05 was interpreted as significant. Multivariate analyses were performed using variables with $p < 0.15$ in univariate analysis, according to the Cox proportional hazards model. This analysis was first performed in the TS, then in two cohorts extracted from the TS (G1) and VS (G2) and manually matched in terms of FIGO stage and nodal status, and finally in the VS, to evaluate the robustness of the results. Statistical analyses were performed using R (version 3.3.2).

Results

Patients and tumors

From the original 186 patients, we first excluded patients who did not undergo ^{18}F–FDG PET in our institution (68/186). A total of 118 consecutive patients were thus identified, with missing baseline blood counts in 10. From the remaining 108 patients (63% of 186), 69 patients (64%) included in the training set were treated during the period from March 2006 to April 2011, and 39 patients (36%) included in the validation set were treated between October 2011 and December 2013. Histologies (squamous cell carcinoma or adenocarcinoma) were well balanced between TS and VS ($p = 0.367$). Patient characteristics are summarized in Table 1. Matched patient characteristics are summarized in supplementary Table S1.

Survival and disease control

In the TS, the median follow-up was 57.0 months (6.8–100.6). Twenty patients (29%) died, all of their disease, and 21 patients (30%) had local failure. Estimated 3-year OS and LC were 70% (95% CI: 60–82%) and 72% (95% CI: 62–84%), respectively.

In the VS, the median follow-up was 30.8 months (5.0–60.0). Thirteen patients (33%) died, all of their disease, and 14 patients (36%) had local failure. Estimated 3-year OS and LC were 65% (95% CI: 51–82%) and 65% (95% CI: 51–82%), respectively.

Prediction of LC using biological biomarkers

Nineteen (27%) and 12 (31%) patients from the TS and VS, respectively, had baseline neutrophilia ($p = 0.721$). The td-AUC for neutrophil count in predicting 3-year LC was 0.61 in the TS. Twenty-eight (41%) and 15 (38%) patients from the TS and VS, respectively, had baseline anemia ($p = 0.829$). The hemoglobin count td-AUC at 3 years for LC was 0.55 in the TS. There was no association between neutrophilia and age ($p = 0.847$).

Choice of PET radiomic index

Delineated MV were comparable between the TS (median 29 mL; range 9–115) and VS (median 26 mL; range 6–191; $p = 0.369$). SUV_{peak} was the PET radiomic index with the highest td-AUC (td-AUC = 0.753, supplementary Table S2). The optimal SUV_{peak} cut-off defined using the Youden index

Table 1 Patient characteristics

Characteristics		Overall population	Training set	Validation set	p (χ^2 & t test)
		No. (%) or median [range]			
Patient characteristics					
Number of patients		108	69	39	
Histology	ADK	17 (16%)	13 (19%)	4 (10%)	*0.367*
	SCC	91 (84%)	56 (81%)	35 (90%)	
FIGO stage	IB1	6 (6%)	3 (4%)	3 (8%)	*0.022*
	IB2	29 (27%)	24 (35%)	5 (13%)	
	IIA	7 (7%)	7 (10%)	0 (0%)	
	IIB	55 (51%)	29 (42%)	26 (67%)	
	IIIB	8 (7%)	5 (7%)	3 (8%)	
	IVA	3 (2.8%)	1 (1%)	2 (5%)	
Age (years)		47 [27–82]	45 [28–71]	50 [27–82]	*0.004*
Tumor size	≤ 5 cm	61 (57%)	37 (54%)	24 (62%)	*0.552*
	> 5 cm	47 (43%)	32 (46%)	15 (38%)	
Nodal status	Negative	60 (56%)	46 (67%)	14 (36%)	*0.004*
	Positive	48 (44%)	23 (33%)	25 (64%)	
Patient biology					
Hemoglobin (g/dL)		12.3 [6.5–15.3]	12.2 [6.5–15.3]	12.5 [7.7–14.6]	*0.358*
Platelet count (G/L)		286 [146–890]	286 [156–890]	286 [146–491]	*0.370*
Leukocytes (G/L)		7.8 [3.3–18]	7.8 [4.1–16.3]	7.8 [3.3–18]	*0.769*
Neutrophils (G/L)		5.5 [1.4–14]	5.5 [2.3–12.2]	5.2 [1.4–14]	*0.694*
Lymphocytes (G/L)		1.6 [0.2–4.1]	1.6 [0.7–3]	1.7 [0.2–4.1]	*0.228*
Monocytes (G/L)		0.6 [0.2–1.5]	0.5 [0.2–1.3]	0.6 [0.3–1.5]	*0.416*

ADK adenocarcinoma, *SCC* squamous cell carcinoma

was 10.0 (specificity 0.78, sensitivity 0.72 in TS). There was no significant correlation between neutrophilia and SUV_{peak} in the TS (p = 0.119, R = 0.19; supplementary Fig. S1). SUV_{peak} was therefore used to create the score.

Prediction of LC using neutrophilia and selected PET radiomic index

At 3 years, the estimated LC in the TS was 80% (95% CI: 65–97%) for patients who had no initial neutrophilia vs. 33% (95% CI: 15–74%) for those who had (p = 0.025). The estimated LC was 90% (95% CI: 81–99%) for patients with low SUV_{peak} values vs. 50% (95% CI: 35–72%) with high SUV_{peak} values (p < 0.001; Fig. 1).

In univariate analysis in the TS, high SUV_{peak} (HR = 4.4, p = 0.001), neutrophilia (HR = 2.6, p = 0.025), pelvic nodal involvement (HR = 3.5, p = 0.005) and tumor size measured on baseline MRI ≥ 5 cm (HR = 3.3, p = 0.008) corresponded to decreased LC. In multivariate analysis, both neutrophilia and SUV_{peak} independently yielded reduced LC (HR = 3.8, p = 0.017 and HR = 4.1, p = 0.006) in the TS.

In the matched VS, high SUV_{peak} (p = 0.012) and neutrophilia (p = 0.018) decreased LC. Similarly, in the VS, high SUV_{peak} (p = 0.029) and neutrophilia (p = 0.018) were associated with worse LC.

Prediction of LC using NSG (neutrophil SUV_{peak} grade) score

In the TS, 29 (42%), 31 (45%) and 9 (13%) patients had NSG scores of 0, 1 and 2, respectively. Estimated 3-year LC was 90%, 74% and 11% (p = 0.001) for patients with NSG = 0, 1 and 2, respectively. In the VS, 8 (20%), 19 (49%) and 12 (31%) patients had NSG scores of 0, 1 and 2, respectively. Estimated 3-year LC was 100%, 63% and 39% in patients with NSG = 0, 1 and 2, respectively (p = 0.020; Fig. 2 and supplementary Fig. S2).

In univariate analysis in the TS, NSG = 2 was associated with worse LC (HR = 9.2, p < 0.001). In multivariate analysis, NSG = 2 remained an independent prognosis biomarker for LC (HR = 7.5, p < 0.001 compared with HR = 3.8 and HR = 4.1 for neutrophilia and SUV_{peak} respectively). N-stage and tumor size ≥5 cm were also independently associated with poor LC (HR = 3.7, p = 0.007 and HR = 4.6, p = 0.003 respectively).

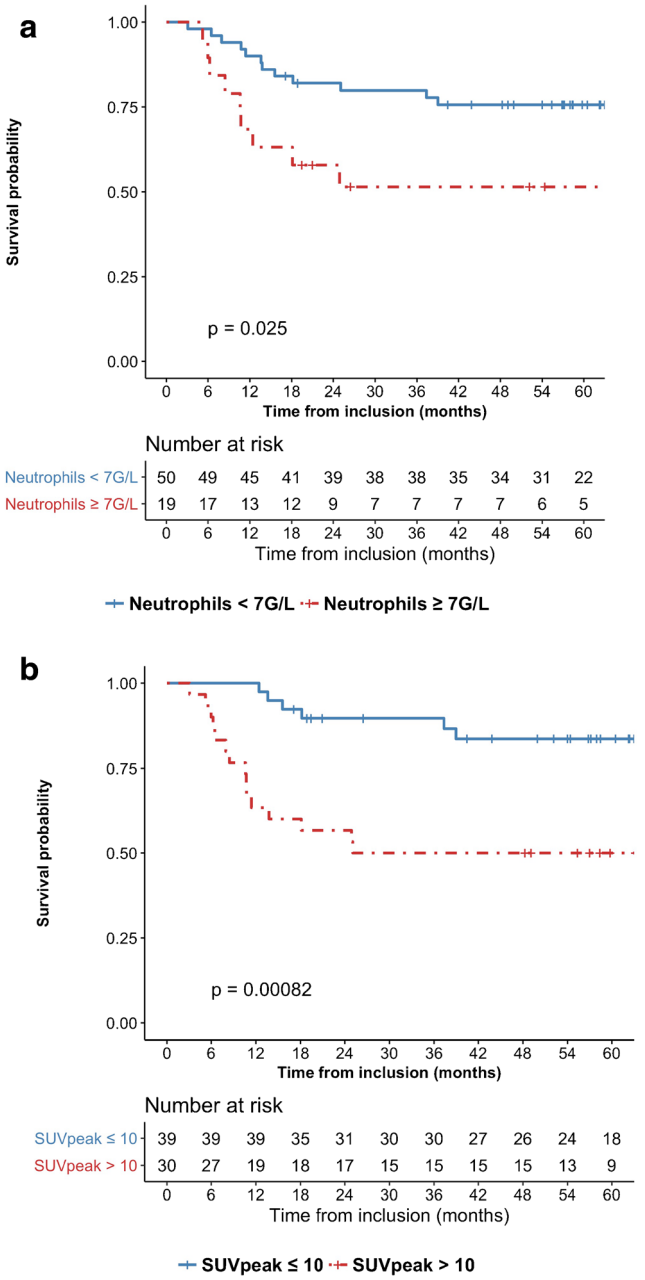

Fig. 1 A. Estimated local control in training set patients, with or without neutrophilia. B. Estimated local control in training set patients, with or without high-risk SUV_{peak}

In univariate analysis, NSG = 2 was also related to decreased LC in both the matched VS (HR = 5.7, p = 0.018) and VS (HR = 3.3, p = 0.030; supplementary Fig. S3). In multivariate analysis, NSG = 2 remained an independent prognostic factor for poor LC (HR = 3.5, p = 0.023) in the VS.

The results regarding the association of neutrophilia, SUV_{peak} and NSG score with patient OS were comparable. Univariate and multivariate analysis, including survival analysis, are summarized in Table 2 and supplementary Table S3.

Discussion

This study evaluated factors for predicting LC and OS in patients with LACC treated with definitive chemoradiation plus IGABT. LACC patients with baseline neutrophilia and high FDG PET SUV_{peak} values within the primary tumor have poorer outcomes, even after adjusting for other factors.

The current radiomics paradigm consists of adding quantitative information to visual analysis rather than replacing it entirely [28]. In the field of oncology and radiotherapy, translational approaches are increasingly studied—for example, radiogenomics analyzing associations between genetic alterations and normal tissue toxicity after radiotherapy. Such studies need "big data" approaches and collaborative research [29]. In this work, we aimed to propose a new approach, translational but able to be quickly implemented for clinicians. To our knowledge, this is the first study integrating one accessible hematological parameter and a single PET radiomic index in a robust score comprising two binary variables.

To date, several groups of indices derived from PET images have been used to characterize intratumoral metabolic heterogeneity, including conventional and histogram-derived (first order) and textural features (second order). Previous studies have found these features to be associated with patient outcomes in LACC [5, 7, 30–33]. Conventional indices, i.e., SUV_{max} (5, 10.2 or 11.2 cut-off), TLG (562 cut-off) and metabolic tumor volume (MTV), have been used to predict disease-free survival [5, 7, 32, 33]. A prognostic score for LACC has also been proposed, using nodal status, tumor SUV_{max} and tumor volume combined in a nomogram [34]. In our study, where all patients had $SUV_{max} > 5$ (min 5.2), a 10.2 cut-off predicted LC in the TS (p = 0.005) and almost reached significance in the VS (p = 0.072), and a 11.2 cut-off predicted LC in both TS and VS (p = 0.009 and p = 0.029). The prognostic value of the sum of tumor and lymph node MTV using ^{18}F–FDG PET has also been reported [35].

More recently, textural features, i.e., gray-level non-uniformity from GLRLM, have been associated with outcomes in studies of patients with LACC [30]. Others have assessed the predictive value of PET textural features for tumor staging and categorizing early (FIGO I–II) vs. advanced stages (FIGO III–IV), using automatic classification with support vector machines [36]. Tumor heterogeneity analysis through PET radiomic indices and relation to treatment outcome gives rise to many methodological questions in defining a roadmap for robust analysis. As reported previously, differences in acquisition and reconstruction parameters can cause substantial variation in conventional and texture PET index values [37]. In this work, all images were resampled to the same voxel grid. As shown by Orlhac et al., in extreme cases (comparison between PET images and autoradiography images), this parameter can in fact lead to large differences in absolute values

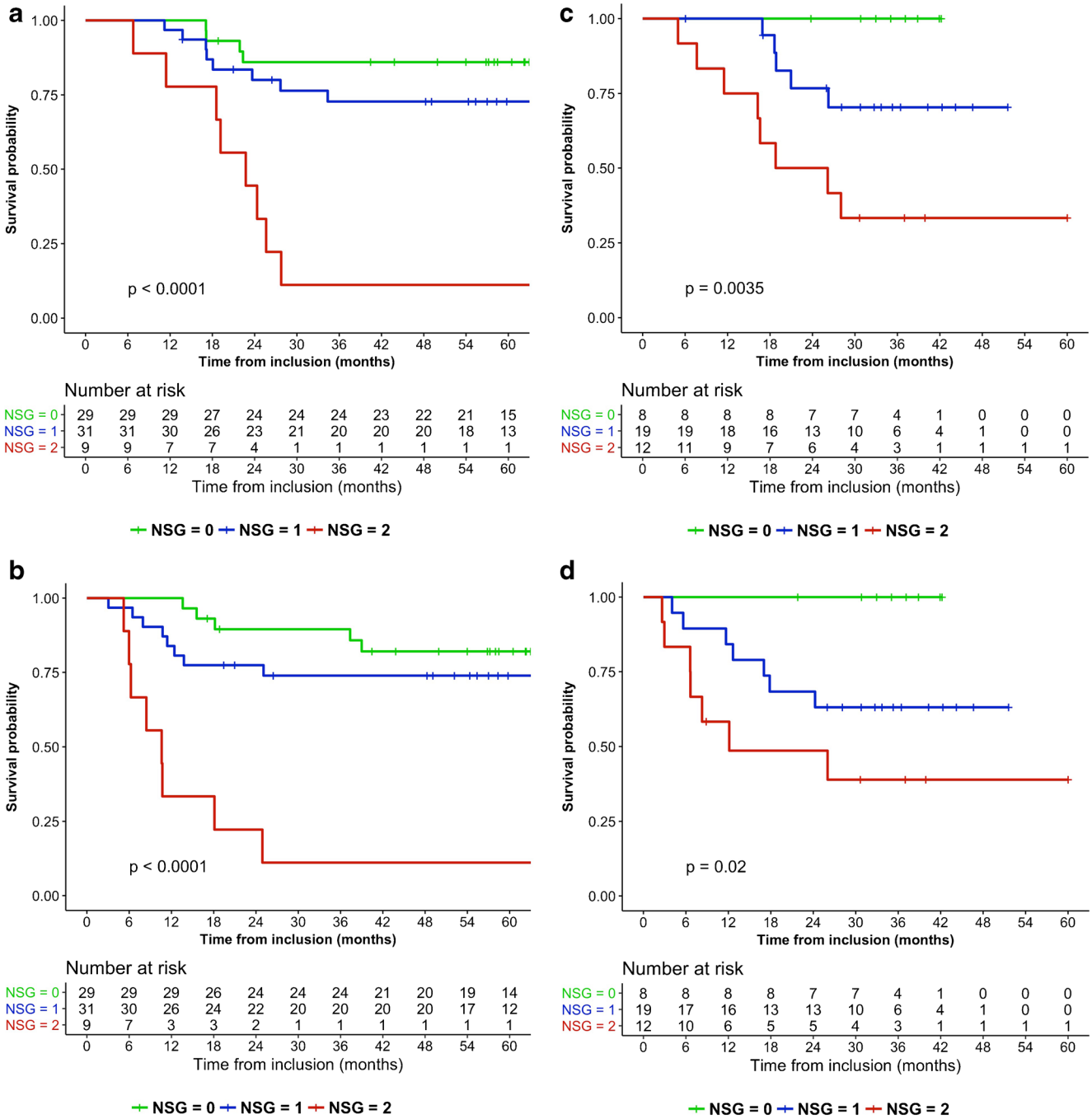

Fig. 2 A. Estimated overall survival in training set patients based on NSG score. B. Estimated local control in training set patients based on NSG score. C. Estimated overall survival in validation set patients based on NSG score. D. Estimated local control in validation set patients based on NSG score. NSG: neutrophil SUV grade, defined as 2 = neutrophil >7 G/L AND SUV_{peak} > 10; 1 = neutrophil >7 G/L OR SUV_{peak} > 10; 0 = neutrophil ≤7 G/L AND SUV_{peak} ≤ 10 PNN 7: neutrophil count ≥7 G/L; SUV_{peak}: > 10

of texture indices [22]. In many cases, however, this preliminary step is not sufficient to completely standardize images, due to additional differences in spatial resolution and efficiency among scanners. In the present study, SUV_{peak} was selected in the TS as a promising index for LC prediction. This index has the solid advantage of being robust to the delineation of and less dependent on acquisition and reconstruction parameters than SUV_{max} [26]. In a previous study [19], it was shown to be comparable between the two cohorts in a healthy liver VOI. We first attributed the differences in SUV_{peak} observed in VOI-T to differences in FIGO stage between the two cohorts: 80% patients from the VS vs. 51% from the TS had FIGO stage IIB or higher (p = 0.022; Table 1). Therefore, we conducted the same analysis for

Table 2 Results of univariate and multivariate (Cox) analyses on training set (significant values in bold)

Training set: 69 patients

Variable	Overall survival						Local control					
	Univariate Cox analysis			Multivariate Cox analysis			Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	*p*	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
NSG = 2 (vs. NSG < 2)	**6.8**	**2.7–16.9**	**< 0.001**	**5.8**	**2.1–15.8**	**0.001**	**9.2**	**3.7–23.0**	**< 0.001**	**7.5**	**2.8–19.6**	**< 0.001**
N-positive (vs. N0)	**3.1**	**1.3–7.6**	**0.007**	–	–	0.051	**3.5**	**1.4–8.2**	**0.005**	**3.7**	**1.4–9.4**	**0.007**
T size ≥5 cm (vs. < 5 cm)	–	–	0.070	–	–	0.14	**3.3**	**1.3–8.6**	**0.008**	**4.6**	**1.7–12.5**	**0.003**
Anemia (vs. absence)	–	–	0.494				–	–	0.352			
FIGO III–IV (vs. I–II)	**4.0**	**1.0–15.5**	**0.012**	–	–	0.054	–	–	0.597			
NSG = 2 (vs. NSG < 2)	**5.1**	**1.7–15.6**	**0.004**	**5.2**	**1.6–16.8**	**0.006**	**3.3**	**1.2–9.5**	**0.030**	**3.5**	**1.2–10.1**	**0.023**
FIGO III–IV (vs. I–II)	**3.9**	**1.0–6.4**	**0.049**	4.5	1.1–19.7	**0.041**	–	–	0.148	–	–	0.110
N-positive (vs. N0)	–	–	0.552				–	–	0.165			
T size ≥5 cm (vs. < 5 cm)	–	–	0.132	–	–	0.607	–	–	0.228			
Anemia (vs. absence)	–	–	0.177				–	–	0.270			

All variables with a *p* value <0.15 in univariate analysis were analyzed in the multivariate analysis

HR for non-significant variables ($p > 0.05$) are not displayed;

NSG score: 2 = neutrophil >7 G/L AND $SUV_{peak} > 10$; 1 = neutrophil >7 G/L OR $SUV_{peak} > 10$; 0 = neutrophil ≤7 G/L AND $SUV_{peak} \leq 10$; T size: maximum tumor size on T2-weighted MRI

FIGO stage and nodal status on matched cohorts (G1 and G2). The results remained similar in both groups (supplementary Fig. S3), supporting the predictive value of the cut-off defined in TS for SUV_{peak} (Fig. 2).

In the present study, SUV_{peak} was combined with neutrophilia. We tested the same score using SUV_{max} or entropy instead of SUV_{peak} (supplementary Table S4). Both indices had a high td-AUC for predicting 3-year LC (> 0.70) and did not correlate with neutrophil count ($p = 0.110$ and $p = 0.173$, respectively; supplementary Table S2). The results revealed the robustness of a score consisting of a biological index and a PET radiomic index. SUV_{peak} has the considerable advantage of being readily available in everyday practice using clinical software. SUV_{peak} corresponds to the maximum carbohydrate metabolism observed in the tumor. From this perspective, our results are consistent with biological knowledge [38].

Research is increasingly focusing on the involvement of neutrophils in the initiation and progression of cancer, and their potential as clinical biomarkers and therapeutic targets [39]. However, the cut-off for defining neutrophilia still varies [8, 9]. Neutrophilia is also analyzed through the neutrophil-to-lymphocyte ratio (NLR). In a recent meta-analysis, elevated pretreatment NLR was shown to be associated with worse OS (HR = 1.375) [40]. From our results, SUV_{peak} and neutrophilia independently predicted worse LC in multivariate analysis (Table S3). Moreover, based on the NSG score, their prognostic impact might be cumulative (HR = 7.5 for NSG score = 2, compared with HR = 3.8 and HR = 4.1 for neutrophilia and SUV_{peak}, respectively in TS). Neutrophil-targeting agents are being developed for the treatment of inflammatory and autoimmune diseases [39]. They represent a promising therapeutic route, with multiple paths for investigation [41].

Limitations of our study include its retrospective design and the small number of patients. We could not compute hazard ratios corresponding to neutrophilia and SUV_{peak} as independent factors in our VS, since there was no patient with an SUV_{peak} below 10 who experienced local relapse or death. Still, both our training and VS analysis displayed potential associations between patient outcome and multiple pretreatment characteristics, including hematological parameters. We determined and validated that baseline neutrophilia associated with high SUV_{peak} values calculated using an NSG score was the strongest independent prognostic factor—ahead of FIGO stage, tumor length evaluated on pretreatment MRI, pelvic nodal involvement and anemia—of poorer OS and LC. Finally, by validating the NSG score in two cohorts (the FIGO-matched cohort and the VS), we investigated the impact of patient and tumor characteristics on the predictive power of the score. Even if our results need to be confirmed in a larger cohort, we have proposed an innovative methodology. Lastly, selecting SUV_{peak}, an accessible PET radiomic index measurable in daily practice, is another strength. The next step is to confirm these data in an independent prospective cohort before translating these results to the clinic. This score may be used for adaptive strategies to improve patient outcome.

Conclusion

These findings suggest a prognostic value of baseline NSG score, combining neutrophilia and SUV_{peak}, in patients with LACC treated with definitive chemoradiation and IGABT. To our knowledge, this is the first study to combine an easily accessible PET index and a biological feature in a score. This promising approach should be considered for further clinical investigation.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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