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ORIGINAL ARTICLE



# Metabolic parameters of [$^{18}$F]FDG PET-CT before and after radiotherapy may predict survival and recurrence in cervical cancer

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**ABSTRACT**

**Background:** Cervical cancer is the fourth most common female malignancy. [$^{18}$F]-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET-CT) is routinely performed in patients with locally advanced cervical cancer for staging and treatment response evaluation. With this retrospective, observational cohort study, we wanted to investigate the prognostic value of the maximum standardised uptake value (SUVmax) and the volumetric parameters of metabolic tumour volume (MTV) and total lesion glycolysis (TLG) before and after treatment in women with cervical cancer, with overall survival (OS) and recurrence as outcome measures.

**Methods:** Women with cervical cancer referred for curative radiotherapy and who underwent two PET-CT scans (before treatment and approximately 7 months post-treatment) were included. SUVmax, MTV and TLG were measured at baseline and post-treatment on the primary tumour, pelvic and distant lymph node metastases, distant organ metastases, and on total tumour burden. The PET parameters were associated with OS by Cox regression and recurrence by multivariable logistic regression. Kaplan-Meier curves and C-index were used to visualise the prognostic potential of the different measures.

**Results:** A total of 133 patients were included. At the primary tumour level and on total tumour burden, age- and clinical-stage adjusted analyses showed a significant association between PET parameters and OS and recurrence when measured post-treatment. At baseline (pre-treatment), MTV and TLG were associated with OS and recurrence, whereas SUVmax was not. C-index from adjusted Cox models on total tumour burden showed higher values for the post-treatment PET compared to baseline. Kaplan-Meier curves demonstrated a greater prognostic potential for MTV and TLG compared to SUVmax, both at baseline and post-treatment.

**Conclusions:** The FDG PET-CT-derived parameters SUVmax, MTV, and TLG measured post-treatment can predict OS and recurrence in cervical cancer. Parameters measured before treatment had overall lower prognostic potential, and only MTV and TLG showed significant association to OS and recurrence.

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FDG PET-CT; prognostic value; cervical cancer; positron emission tomography

## Introduction

Cervical cancer is the fourth most common female cancer worldwide, causing more than 300 000 deaths annually [1,2]. The disease is staged according to the International Federation of Gyneacology and Obstetrics (FIGO), and the FIGO stage is a major prognostic factor, constituting the basis for the choice of intended treatment [3,4].

[$^{18}$F]fluorodeoxyglucose (FDG) positron emission tomography integrated with computed tomography (PET-CT) is a nuclear medicine imaging modality widely used for diagnosis, clinical staging, and response evaluation in cervical cancer and other malignancies [4,5]. In clinical practice, the most frequently used parameter is the maximum standardised uptake value (SUVmax), a semi-quantitative parameter, extracted from a single "hottest" voxel, thus not reflecting the whole tumour metabolism. Volume-based PET parameters such as metabolic tumour volume (MTV) and total lesion glycolysis (TLG) are suggested to better represent the total tumour burden and have been proven superior to SUVmax as prognostic markers for overall survival (OS) in head-and-neck cancer [6], non-small cell lung carcinoma [7–10] and ovarian cancer [11] and shown promising results in several other malignancies [12–15]. Regarding cervical carcinoma, some studies exist that have addressed this issue. A recent meta-analysis concluded that a high pre-treatment SUVmax had a significant correlation with OS in patients with locally advanced cervical cancer, but due to limited data no conclusions could be drawn regarding the association between TLG

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and MTV and OS [16]. Another meta-analysis, however, found that volume-based pre-treatment PET-CT parameters were significant prognostic factors of OS [17]. One meta-analysis found that response evaluation using post-radiotherapy FDG-PET CT was a prognostic factor for overall survival and progression-free survival [18]. However, no analysis of different PET parameters was done.

To the best of our knowledge, no studies exist that assess the prognostic value of the different PET parameters both pre- and post-treatment. With this retrospective, observational cohort study [19], we will investigate the prognostic value of three PET-derived metabolic parameters in women with locally advanced cervical cancer, both at baseline before treatment and at follow-up after treatment with OS and recurrence as outcome measures.

## Materials and methods

### Patients

All patients with locally advanced cervical cancer referred to the Department of Oncology at Skåne University Hospital, Sweden for combined chemoradiotherapy with curative intention were eligible for retrospective inclusion. The inclusion period was 2011–2021. Patients who had performed two PET-CT scans, one at baseline before treatment start and one at follow-up after treatment and who were included in the Swedish Quality Register for Gynaecologic Cancer were eligible for inclusion.

A total of 134 patients fulfilled the inclusion criteria. One patient was later excluded due to imaging analysis difficulties (necrosis in the cervical tumour with connection to the urinary bladder, causing contamination of the tumour area by FDG-containing urine), rendering a total of 133 patients and 266 PET-CT scans. Data on recurrence, FIGO stage and time between examinations were retrieved from clinical records. FIGO stage was set according to the classification of 2009.

In accordance with regional and national guidelines, external beam radiotherapy using a volumetric modulated arc therapy technique with 1.8–2.0 Gy per fraction and high dose rate brachytherapy to a total dose of $\geq$80 Gy was administered to the primary tumour. Concomitant weekly-based cisplatin 40 mg/m$^2$, optimally 6 cycles with a maximum dose of 70 mg per treatment was administered according to the protocol [20–22]. The second PET-CT was performed approximately 5 months after the end of treatment, according to regional clinical practice [20,23]. In essence, all patients followed the same treatment protocol and had the same treatment intention (curative). Small deviations from the protocol were sometimes necessary, for example, if a patient had low blood platelet levels, a treatment round of chemotherapy could be omitted.

### PET-CT imaging

Two different PET-CT systems were used for image acquisition: Discovery MI (GE Healthcare, Milwaukee, WI, USA) and Philips Gemini TF (Philips Healthcare, Cleveland, OH, USA). Patients were in general examined on the same PET-CT system both before and after treatment. Time-of-flight was used on all systems. Patients received 4 MBq/kg body weight of [$^{18}$F]FDG intravenously. Accumulation time was 60 min before imaging. Fasting for at least 4 h before the examination and a glucose level $\leq$ 180 mg/dl was required.

For the baseline examination, a PET scan was performed from the upper thigh level to the base of the skull. A high-dose CT from the abdomen to upper thigh level for radiotherapy treatment dose planning, anatomic orientation and attenuation correction was usually performed, complemented by a low-dose CT from the base of the skull to the thorax.

For the follow-up examinations, a whole-body PET from the upper thigh level to the base of the scull was performed, either combined with a low-dose CT or a diagnostic CT with intravenous and oral contrast.

### Image analysis

PET-CT scans were analysed retrospectively (by MM) using the HERMES Software System (Hermes Medical Solutions, Stockholm, Sweden) for volume segmentation of the primary tumour, pelvic lymph node metastases, suspected distant lymph node metastases, and distant organ metastases.

Patients with suspected distant lymph nodes or organ metastases on PET/CT were included if they fulfilled the inclusion criteria described above.

For complicated cases, a second observer (ET) reviewed the segmentations. Lesions suspected to be malignant or of unclear origin were marked. The analyses were performed without knowledge of the patient's outcome.

When possible, lesions were segmented semi-automatically using the fixed relative threshold method, defined as 41% of the SUVmax of the lesion. If not possible, e.g., due to heterogenous tumour mass or proximity to the FDG-containing urine bladder, or in small lesions with a low signal to background ratio with a risk of overestimation of the MTV, manual delineation for segmentation was used instead. From these volumes of interest, SUVmax, MTV (the metabolically active tumour volume) and TLG (the metabolically active tumour volume multiplied by the SUV mean of that volume, i.e. MTV X SUVmean) were obtained. The PET parameters were measured on the primary tumour, pelvic lymph node metastases (i.e. lymph nodes up to the aortic bifurcation), distant lymph node metastases (all other lymph nodes), distant organ metastases as well as on total tumour burden (the sum of all lesions). An example of tumour and lymph node segmentation is shown in Supplementary Material 1.

### Statistics

Descriptive statistics were used to illustrate patient characteristics and the PET parameters (median and range for the continuous variables age, follow-up time (years) and time between examinations (months)). SUVmax, MTV and TLG were analysed for the primary tumour lesion, pelvic lymph nodes, distant lymph nodes, distant organ metastases, and total tumour burden respectively. Unadjusted and multivariable (adjusted for

age and clinical stage) Cox regression model was used for survival analysis. Unadjusted and multivariable (adjusted for age and clinical stage) logistic regression model was used for analysis of recurrence since data on the time to recurrent disease was not available.

When adjusting for clinical stage, we dichotomised into low (FIGO I-II) and high (FIGO III-IV) FIGO stage. A few patients could not be classified according to FIGO and were annotated as FIGO stage X, and were classified to the high FIGO stage group.

Kaplan-Meier curves were used to illustrate survival between high and low values for the PET-parameters for primary tumour and total tumour burden. The PET parameters were dichotomised into two groups using the median as cut-off, rendering two groups for each PET variable, with low and high SUVmax, TLG, and MTV, respectively.

Harrel's Concordance-index (C-index) was used for model prediction. A C-index $= 1$ corresponds to a perfect model prediction and C-index $= 0.5$ represents a random prediction (no better than a coin toss).

Statistical significance was set to $p < 0.05$ and two-sided analyses were performed.

All analyses were performed in R v.4.1.0.

## Results

### Patient characteristics

A total of 133 patients underwent one baseline PET-CT scan before treatment and one follow-up scan after treatment. Patient characteristics are summarised in Table 1.

### Pet parameters

The median values of the PET-parameters for primary tumour, pelvic lymph node metastases, distant lymph node metastases, and distant organ metastases were generally higher for patients who died. The values are shown in Supplementary Material 2.

### Survival

#### Total tumour burden

Survival analysis showed a significant association for MTV and TLG at both baseline and post-treatment. For SUVmax, there was a statistically significant association post-treatment but not at baseline (Table 2).

C-index on dichotomised PET-parameter values (by the median) were higher post-treatment compared to baseline. Post-treatment, TLG had the highest index, followed by SUVmax and then MTV (Table 3).

#### Primary tumour

Unadjusted and adjusted (for age and clinical stage) Cox regression analysis showed a statistically significant association between the three PET parameters and survival at both baseline and post-treatment, except for SUVmax at baseline, as shown in Table 2.

C-index values were essentially equal at baseline and post-treatment for MTV and TLG, but for SUVmax the value was slightly higher post-treatment. MTV and TLG had higher values than SUVmax, as shown in Table 3.

#### Pelvic lymph node metastases

All PET parameters at baseline and post-treatment showed a statistically significant association (Table 2). C-index values are shown in Table 3.

**Table 1.** Patient characteristics.

| | Alive N (%) | Dead N (%) | Total N (%) |
|---|---|---|---|
| | 104 (78.2) | 29 (21.8) | 133 (100) |
| FIGO | | | |
| IA1 | 2 (1.9) | 0 (0.0) | 2 (1.5) |
| IA2 | 1 (1.0) | 0 (0.0) | 1 (0.8) |
| IB1 | 10 (9.6) | 1 (3.4) | 11 (8.3) |
| IB2 | 16 (15.4) | 7 (24.1) | 23 (17.3) |
| IIA1 | 8 (7.7) | 1 (3.4) | 9 (6.8) |
| IIA2 | 4 (3.8) | 2 (6.9) | 6 (4.5) |
| IIB | 47 (45.2) | 7 (24.1) | 54 (40.6) |
| IIIA | 1 (1.0) | 1 (3.4) | 2 (1.5) |
| IIIB | 6 (5.8) | 6 (20.7) | 12 (9.0) |
| IVA | 1 (1.0) | 2 (6.9) | 3 (2.3) |
| X | 8 (7.7) | 2 (6.9) | 10 (7.5) |
| Missing | 0 | 0 | 0 |
| FIGO | N (%) | N (%) | N (%) |
| I + II | 88 (84.6) | 18 (62.1) | 106 (79.7) |
| X + III + IV | 16 (15.4) | 11 (37.9) | 27 (20.3) |
| Recurrent disease | 11 (10.6) | 26 (92.9) | 37 (28.0) |
| Missing | 0 | 1 | 1 |
| Age | 48 [23, 86] | 52 [24, 85] | 48 [23, 86] |
| Follow-up time, years | 3.1 [0.4, 8.8] | 1.5 [0.7, 3.8] | 2.7 [0.4, 8.8] |
| Time between examinations, months | 6.8 [3.7, 45.5] | 5.8 [1.1, 14.7] | 6.8 [1.1, 45.5] |

Follow-up-time calculated from 1st Positron Emission Tomography with Computed Tomography (PET-CT) until death, censoring or end-of-follow-up.
Unless otherwise stated data is presented as median [range].
FIGO – International Federation of Gynaecology and Obstetrics.

**Table 2.** Unadjusted and adjusted* Cox regression for mortality (blue) and unadjusted and adjusted* logistic regression for recurrent disease (green), evaluating each variable one at a time. Unadjusted values are to the left (darker shade) and adjusted to the right (lighter shade), for each outcome analysis.

| | Cox regression for mortality | | | | Logistic regression for recurrent disease | | | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | $HR_{Adj}$ (95% CI) | *p*-value | OR (95% CI) | *p*-value | $OR_{Adj}$ (95% CI) | *p*-value |
| **Total Tumour Burden** | | | | | | | | |
| 1st PET-CT MTV | 1.013 (1.007–1.018) | <0.001 | 1.010 (1.004–1.016) | 0.001 | 1.003 (1.001–1.004) | <0.001 | 1.003 (1.001–1.004) | 0.002 |
| 2nd PET-CT MTV | 1.043 (1.031–1.056) | <0.001 | 1.045 (1.029–1.061) | <0.001 | 1.012 (1.009–1.015) | <0.001 | 1.012 (1.008–1.015) | <0.001 |
| 1st PET-CT TLG | 1.0009 (1.0005–1.0013) | <0.001 | 1.001 (1.000–1.001) | 0.002 | 1.0002 (1.0001–1.0003) | 0.005 | 1.0002 (1.0000–1.0003) | 0.020 |
| 2nd PET-CT TLG | 1.004 (1.003–1.006) | <0.001 | 1.004 (1.002–1.005) | <0.001 | 1.0010 (1.0009–1.0018) | <0.001 | 1.0013 (1.0008–1.0018) | <0.001 |
| 1st PET-CT $SUV_{max}$ | 1.021 (0.973–1.072) | 0.395 | 1.030 (0.981–1.082) | 0.238 | 0.999 (0.988–1.011) | 0.959 | 0.999 (0.987–1.010) | 0.799 |
| 2nd PET-CT $SUV_{max}$ | 1.129 (1.086–1.174) | <0.001 | 1.123 (1.078–1.170) | <0.001 | 1.038 (1.024–1.051) | <0.001 | 1.038 (1.025–1.052) | <0.001 |
| **Primary Tumour** | | | | | | | | |
| 1st PET-CT MTV | 1.012 (1.006–1.017) | <0.001 | 1.009 (1.003–1.015) | 0.003 | 1.003 (1.001–1.004) | 0.003 | 1.002 (1.001–1.004) | 0.011 |
| 2nd PET-CT MTV | 1.053 (1.031–1.076) | <0.001 | 1.041 (1.017–1.065) | 0.001 | 1.017 (1.008–1.026) | <0.001 | 1.016 (1.007–1.025) | 0.001 |
| 1st PET-CT TLG | 1.001 (1.000–1.001) | <0.001 | 1.001 (1.000–1.001) | 0.004 | 1.0002 (1.0000–1.0003) | 0.011 | 1.0002 (1.0000–1.0003) | 0.034 |
| 2nd PET-CT TLG | 1.008 (1.005–1.012) | <0.001 | 1.007 (1.003–1.010) | <0.001 | 1.002 (1.001–1.004) | <0.001 | 1.002 (1.001–1.003) | 0.001 |
| 1st PET-CT $SUV_{max}$ | 1.000 (0.971–1.025) | 0.874 | 0.998 (0.973–1.024) | 0.878 | 0.998 (0.992–1.004) | 0.552 | 0.999 (0.993–1.004) | 0.607 |
| 2nd PET-CT $SUV_{max}$ | 1.190 (1.091–1.297) | <0.001 | 1.176 (1.077–1.285) | <0.001 | 1.042 (1.020–1.067) | <0.001 | 1.041 (1.019–1.065) | <0.001 |
| **Pelvic Lymph Node Metastases** | | | | | | | | |
| 1st PET-CT MTV | 1.063 (1.022–1.105) | 0.002 | 1.066 (1.021–1.112) | 0.004 | 1.022 (1.011–1.034) | <0.001 | 1.021 (1.009–1.033) | 0.001 |
| 2nd PET-CT MTV | 1.052 (1.028–1.077) | <0.001 | 1.045 (1.020–1.070) | <0.001 | 1.012 (1.003–1.021) | 0.011 | 1.011 (1.002–1.020) | 0.019 |
| 1st PET-CT TLG | 1.007 (1.002–1.012) | 0.008 | 1.006 (1.000–1.012) | 0.037 | 1.002 (1.001–1.004) | 0.009 | 1.002 (1.000–1.004) | 0.038 |
| 2nd PET-CT TLG | 1.003 (1.001–1.005) | <0.001 | 1.002 (1.000–1.004) | 0.015 | 1.001 (1.000–1.002) | 0.026 | 1.001 (1.000–1.002) | 0.048 |
| 1st PET-CT $SUV_{max}$ | 1.096 (1.037–1.158) | 0.001 | 1.079 (1.019–1.143) | 0.009 | 1.019 (1.004–1.034) | 0.016 | 1.015 (0.999–1.031) | 0.061 |
| 2nd PET-CT $SUV_{max}$ | 1.116 (1.066–1.169) | <0.001 | 1.091 (1.041–1.144) | <0.001 | 1.042 (1.021–1.063) | <0.001 | 1.038 (1.017–1.060) | <0.001 |
| **Distant Lymph Node Metastases** | | | | | | | | |
| 1st PET-CT MTV | 1.084 (0.999–1.176) | 0.051 | 1.070 (0.983–1.165) | 0.117 | 1.032 (1.004–1.061) | 0.027 | 1.030 (1.002–1.059) | 0.036 |
| 2nd PET-CT MTV | 1.030 (1.016–1.044) | <0.001 | 1.022 (1.006–1.038) | 0.007 | 1.011 (1.004–1.018) | 0.002 | 1.010 (1.003–1.017) | 0.006 |
| 1st PET-CT TLG | 1.010 (0.995–1.025) | 0.195 | 1.007 (0.992–1.024) | 0.363 | 1.003 (0.998–1.008) | 0.197 | 1.003 (0.998–1.008) | 0.223 |
| 2nd PET-CT TLG | 1.004 (1.002–1.006) | <0.001 | 1.003 (1.001–1.005) | 0.014 | 1.001 (1.000–1.002) | 0.009 | 1.001 (1.000–1.002) | 0.018 |
| 1st PET-CT $SUV_{max}$ | 1.080 (1.002–1.165) | 0.045 | 1.047 (0.963–1.138) | 0.283 | 1.033 (1.008–1.058) | 0.010 | 1.029 (1.004–1.054) | 0.025 |
| 2nd PET-CT $SUV_{max}$ | 1.108 (1.066–1.155) | <0.001 | 1.100 (1.050–1.151) | <0.001 | 1.037 (1.020–1.056) | <0.001 | 1.037 (1.018–1.056) | <0.001 |
| **Distant Organ Metastases** | | | | | | | | |
| 1st PET-CT MTV | 1.584 (0.953–2.635) | 0.076 | 1.254 (0.898–1.751) | 0.183 | 1.018 (0.995–1.042) | 0.130 | 1.014 (0.990–1.038) | 0.264 |
| 2nd PET-CT MTV | 1.043 (1.022–1.064) | <0.001 | 1.048 (1.026–1.070) | <0.001 | 1.012 (1.005–1.019) | 0.001 | 1.012 (1.005–1.019) | 0.001 |
| 1st PET-CT TLG | 1.233 (0.985–1.542) | 0.067 | 1.094 (0.863–1.387) | 0.456 | 1.002 (0.999–1.005) | 0.114 | 1.002 (0.999–1.005) | 0.233 |
| 2nd PET-CT TLG | 1.008 (1.004–1.013) | <0.001 | 1.009 (1.005–1.014) | <0.001 | 1.002 (1.001–1.003) | 0.003 | 1.002 (1.001–1.003) | 0.002 |
| 1st PET-CT $SUV_{max}$ | 1.594 (1.256–2.023) | <0.001 | 1.480 (1.157–1.894) | 0.002 | 1.041 (0.998–1.085) | 0.062 | 1.033 (0.990–1.077) | 0.135 |
| 2nd PET-CT $SUV_{max}$ | 1.178 (1.121–1.237) | <0.001 | 1.164 (1.103–1.228) | <0.001 | 1.049 (1.030–1.068) | <0.001 | 1.049 (1.030–1.067) | <0.001 |

*Adjusted for age and FIGO X + III + IV vs I + II.
HR: Hazard Ratio. OR: Odds Ratio. PET-CT: Positron Emission Tomography with Computed Tomography. SUV: standardised uptake value. MTV: Metabolic Tumour Volume. TLG: Total Lesion Glycolysis. FIGO: International Federation of Gynaecology and Obstetrics.

**Table 3.** Harrell's concordance index (C-index) from adjusted Cox models.

| | 1st PET-CT | 2nd PET-CT |
|---|---|---|
| | Primary Tumour | |
| MTV | 0.702 | 0.701 |
| TLG | 0.693 | 0.695 |
| $SUV_{max}$ | 0.629 | 0.686 |
| | Pelvic Lymph Node Metastases | |
| MTV | 0.697 | 0.688 |
| TLG | 0.679 | 0.667 |
| $SUV_{max}$ | 0.720 | 0.733 |
| | Distant Lymph Node Metastases | |
| MTV | 0.633 | 0.702 |
| TLG | 0.679 | 0.681 |
| $SUV_{max}$ | 0.720 | 0.711 |
| | Distant Organ Metastases | |
| MTV | 0.643 | 0.705 |
| TLG | 0.644 | 0.701 |
| $SUV_{max}$ | 0.654 | 0.815 |
| | Total | |
| MTV | 0.714 | 0.810 |
| TLG | 0.703 | 0.832 |
| $SUV_{max}$ | 0.641 | 0.831 |

PET-CT: Positron Emission Tomography with Computed Tomography; SUV: standardised uptake value.;MTV: Metabolic Tumour Volume; TLG: Total Lesion Glycolysis.

### *Distant lymph node metastases*

At the baseline PET, 21 patients had lesions that were designated possible distant lymph node metastases by the interpreting nuclear medicine physician (MM). As histopathological verification was not possible, and the clinical suspicion of malignancy was low enough not to alter the FIGO stage or disqualify the patients from curative intent. All PET parameters measured post-treatment but not at baseline showed a statistically significant association (Table 2). C-index values are shown in Table 3.

### *Distant organ metastases*

At the baseline PET, 6 patients had undesignated lesions, not possible to verify histologically, and as the clinical suspicion of malignancy was low the findings did not alter the FIGO stage nor disqualify the patients from chemoradiotherapy with curative intent. The lesions were however designated as distant metastases by the interpreting nuclear medicine physician.

SUVmax at both baseline and post-treatment showed a significant association to survival, as did MTV and TLG for the follow-up PET. MTV and TLG at baseline showed no significant association to survival (Table 2). C-index values are shown in Table 3.

### *Kaplan-Meier analyses*

Kaplan-Meier curves on total tumour burden showed a statistically significant difference in survival between high and low

MTV ($p = 0.0086$) and TLG ($p = 0.019$) but not SUVmax ($p = 0.2$) at baseline. At follow-up, the difference in survival was greater between high and low value for all three parameters and the difference was statistically significant for all (Figure 1). At primary tumour level, there was a statistically significant difference between the high and low TLG ($p = 0.044$) at baseline, whereas the difference was not statistically significant for MTV ($p = 0.062$) and SUVmax ($p = 0.33$), as shown in Figure 2. At follow-up, the difference increased but remained statistically insignificant for SUVmax ($p = 0.15$).

### *Recurrent disease*

Adjusted and unadjusted logistic regression analysis for recurrent disease is shown in Table 2. For total tumour burden, primary tumour and pelivc lymph nodes, all parameters showed a statistically significant association to recurrent disease except SUVmax at baseline. For distant lymph nodes, TLG at baseline failed to show a statistically significant association. For distant organ metastases, all PET-parameters at follow-up were associated to recurrence, whereas at baseline, there was no significant association.

## Discussion

In this study we have evaluated both basic and advanced PET parameters and shown significant associations between tumour burden and OS as well as recurrent disease. Further, we have evaluated image information at two time points, both at baseline before treatment and post-treatment. Taken

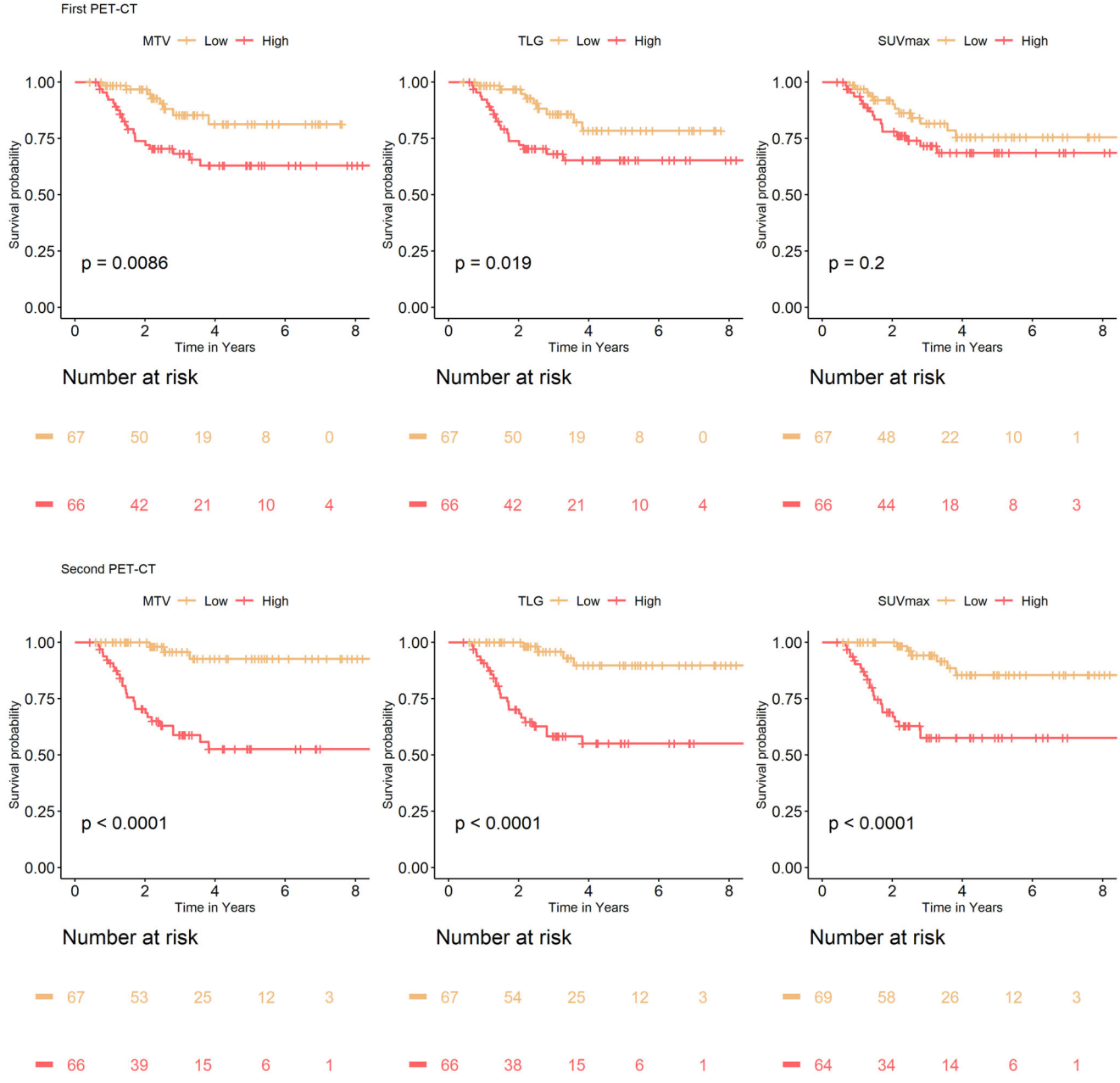


**Figure 1.** Kaplan-Meier Curves on the three PET-variables (left MTV, middle TLG, right SUVmax) on total tumour burden measured at baseline (top row) and follow-up (lower row), divided by the median into high (red) and low (yellow).

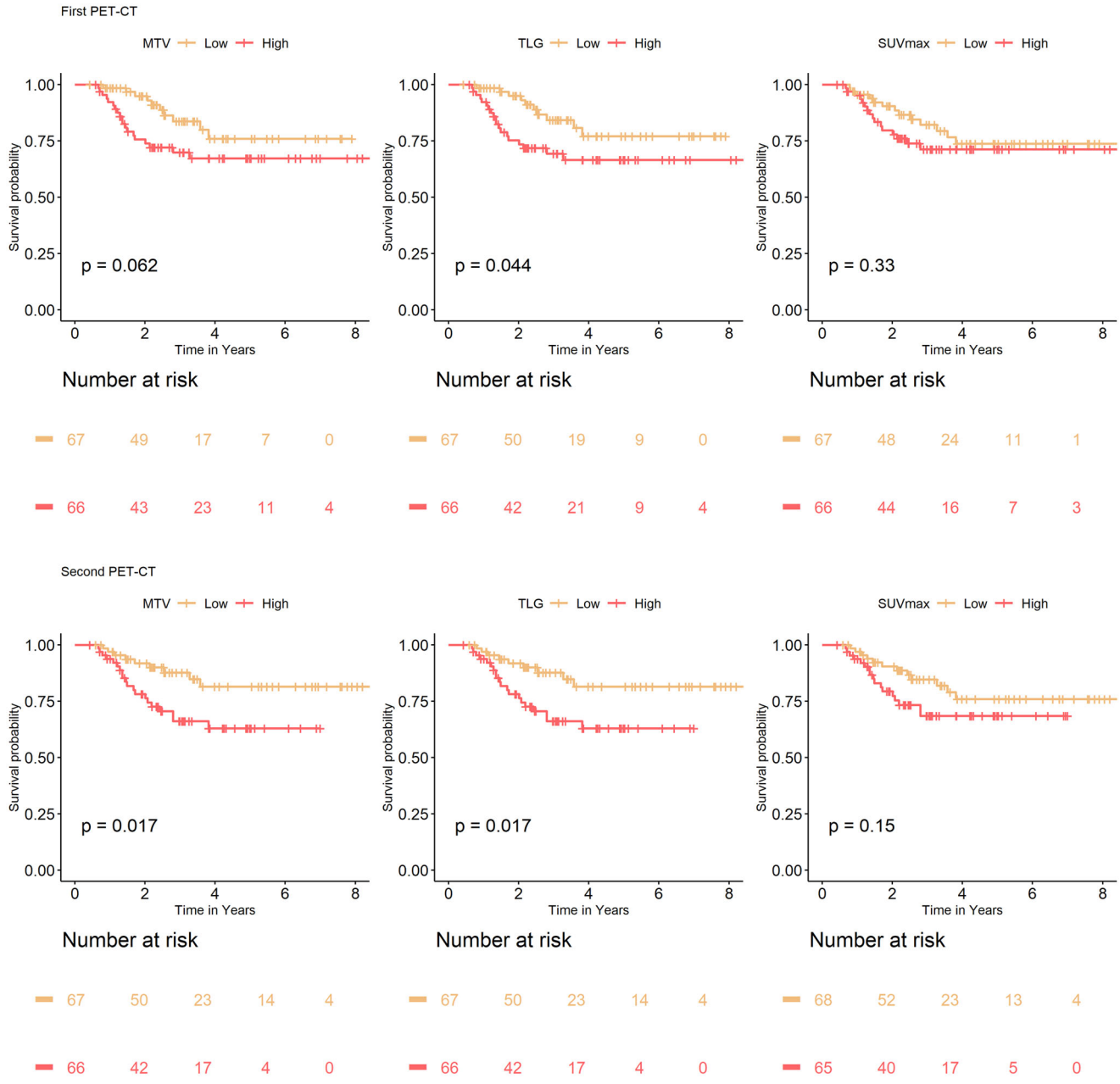


**Figure 2.** Kaplan-Meier Curves on the three PET-variables (left MTV, middle TLG, right SUVmax) on primary tumour measured at baseline (top row) and follow-up (lower row), divided by the median into high (red) and low (yellow).

together, the prognostic value of the PET parameters were in general stronger post-treatment compared to baseline. The more advanced volumetric parameters MTV and TLG showed similar or better predictive potential compared to the standard parameter SUVmax.

To the best of our knowledge, our study is the only one to evaluate both basic and advanced parameters at both baseline and post-treatment, as well as at various tumour/-metastases levels, including total tumour burden.

### *Comparison with previous studies*

Even though PET-CT is an essential part of the diagnostic work-up for cervical cancer and many other malignancies, there is still potential prognostic information in the images that have not yet been fully studied. As has been shown previously for many other malignancies such as non-small cell lung carcinoma [8,9], head-and-neck cancer [6,13], oesophageal cancer [14] and ovarian cancer [11], the volumetric PET-parameters MTV and TLG have shown promising prognostic potential.

Our literature search found two meta-analyses investigating the prognostic value of different PET parameters measured before treatment in cervical cancer, both with event-free survival and overall survival as primary and secondary outcome measures. In a meta-analysis by Han et al. [17] from 2018, the authors concluded that the volumetric PET-CT parameters were significant prognostic factors in patients with cervical cancer and that patients with high MTV and TLG showed higher risk of adverse events or death. Another meta-analysis from 2021 by Han et al. [16] included studies on patients with

locally advanced cervical cancer treated with concomitant chemoradiotherapy. The authors concluded that a high primary tumour SUVmax was associated with a shorter overall survival and event-free survival but due to limited data, publication bias, and heterogeneity between the included studies, no certain association was found between TLG or MTV and survival. Both groups highlighted the small number of included studies (12 and 14, respectively) and the small samples in included studies (mean 55 and 94 patients, respectively). Our results indicate that TLG and MTV are superior to SUVmax as prognostic markers for both survival and recurrence when measured at the baseline PET, as SUVmax was the only parameter that failed to show a statistically significant association to both outcome measures, when measured at the primary tumour level and on total tumour burden.

One meta-analysis from 2019 investigated the prognostic potential of FDG-PET CT performed after radiotherapy treatment and found that treatment response evaluated with PET was a significant prognostic factor [18]. However, in this meta-analysis, only the response (measured as complete metabolic response, partial metabolic response or progressive metabolic disease) was correlated to outcome, but the isolated post-treatment parameter values were not directly correlated to outcome, thus no comparison between pre- and post-treatment values was made. Also, there was no comparison between the different PET-parameters.

Other imaging modalities can be used for prediction analysis. Dynamic contrast-enhanced CT can be used for the assessment of hypoxia through blood flow analysis to predict treatment response according to studies by Capaldi et al. and Banks et al. [24–25]. Toita et al. found that cervical size assessed by CT had limited prognostic value [26]. In contrast, Ogino et al. found that CT-measured cervix size was a pretreatment prognostic marker [27].

### PET parameters

The simple and observer-independent SUVmax is the most used PET parameter for the quantification of metabolic activity in a tumour. However, as it only represents the value of a single voxel, it does not necessarily represent the total tumour burden or volume. The more advanced volumetric parameters MTV and TLG can overcome this issue. However, there are potential drawbacks with these methods as well. First, retrieving these parameters requires the segmentation of the tumour. This can be done manually, which is time-consuming and observer-dependent. Many software programmes have developed semi-automatic segmentation algorithms that can be based either on a fixed absolute threshold (such as SUV $>$ 2.5) or a fixed relative threshold (e.g., $>$ 41% of SUVmax). In cervical cancer, the proximity of the FDG-containing urinary bladder makes automatic delineation between the organs difficult. Also, tumours can be heterogeneous with varying FDG uptake intensity due to for example necrosis. In this study, we aimed to use the semi-automatic function using a fixed relative threshold to the largest possible extent. Whenever not possible, manual segmentation was performed instead.

Interpretation and comparison of different PET parameters may be challenging. Since the SUVmax, MTV and TLG have different units, the resulting HRs and ORs are not directly comparable. Also, although statistically significant, the resulting HRs and ORs were small and close to 1, which can be explained by the small digits for each unit increase on the continuous scale for the PET parameters. For this reason, C-index and Kaplan-Meier curves were used to illustrate and compare the predictive value of the different parameters.

### Clinical implementation

This study has several clinical implementations. First, a deeper knowledge of the PET parameters in relation to clinical outcomes and the implementation of more advanced PET parameters in clinical practice may increase the utility of PET-CT as a method. Further, taken the whole patient into account, the concept of total tumour burden may be a comprehensive way of communication imaging results to the treating physician.

### Limitations

Some limitations require consideration. First, the retrospective nature of the study inevitably leads to possible bias in patient selection. Second, even though PET-CT is used for diagnosis and staging, all findings suspicious of malignancy have not been verified through histopathological examination at the time of the PET-CT-examination and could therefore be false positive lesions. Likewise, the sensitivity of PET-CT is not 100%, why all malignant lesions may not have been detected. Also, we acknowledge the weakness of using two different PET systems, which could lead to inter-patient variability for the different PET-parameter values due to different reconstruction algorithms. Another limitation is related to the method of lesion segmentation itself, as this is an observer-dependent procedure and reproducibility is thus limited. When adjusting for age and clinical stage, we were obliged to stratify for two different groups (FIGO stage I + II vs FIGO stage III + IV + X), instead of for each FIGO stage separately, due to the small sample size this would render for each FIGO stage. Also, a few patients could not be classified according to FIGO and were annotated as FIGO stage X. Finally, we acknowledge that it was not possible to compare the PET variables to tumour volume measured on the CT alone, since most CT images were low-dose and not contrast-enhanced.

## Conclusions

For women with cervical cancer, all studied PET parameters of total tumour burden were associated with overall survival as well as to recurrent disease. PET parameters measured post-treatment showed a stronger association compared to values at baseline. When measured at baseline, the advanced, volumetric parameters MTV and TLG appeared superior to SUVmax.

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## Ethical approval

This study was approved by the Regional Ethical Review Board at Lund (#2016/417, #2018/753 and #2020-02524) and was performed in accordance with the Declaration of Helsinki. All patients included from 2016 signed a written informed consent. Informed consent before 2016 was waived by the Ethical Review Board. Patients signed informed consent regarding publishing their data and photographs.

## Author contributions

All authors participated in the design of the study. Data collection was done by HS and MB. MM performed the imaging segmentations. Statistical analyses were performed by statistician AÅ. The manuscript was written by MM with significant contribution from ET, as well as HS and MB. All authors read and approved the final manuscript.

## Disclosure statement

The authors declare that they have no competing interests.

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## Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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