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Author/s:

Subramaniam, S;Callahan, J;Bressel, M;Hofman, MS;Mitchell, C;Hendry, S;Vissers, FL;Van der Hiel, B;Patel, D;Van Houdt, WJ;Tseng, WW;Gyorki, DE

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Suren Subramaniam ORCID iD: 0000-0002-9821-0270

William Tseng ORCID iD: 0000-0002-0360-6871

The role of ^{18}F -FDG PET/CT in retroperitoneal sarcomas – A multicenter retrospective study.

Authors

Suren Subramaniam FRACS¹; Jason Callahan PhD²; Mathias Bressel MSc³; Michael S. Hofman FRACP. ²; Catherine Mitchell FRACP⁴; Shona Hendry FRACP⁵; Frederique L. Vissers MD⁷; Bernies Van der Hiel MD⁸; Dakshesh Patel MD⁹; Winan J. Van Houdt MD, PhD⁶; William W. Tseng MD¹⁰; David E. Gyorki MD¹

Affiliations: 1. Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. 2. Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. 3. Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. 4. Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. 5. Department of Pathology, St Vincents Hospital, Melbourne, VIC, Australia. 6. Department of Surgical Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands. 7. Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands 8. Department of Nuclear Medicine, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The

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Netherlands. 9. Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States. 10. Department of Surgery, Division of Breast, Endocrine and Soft Tissue Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States.

Correspondance

David E. Gyorki, MD

Division of Cancer Surgery,

Peter MacCallum Cancer Centre,

305,Grattan Street,

Melbourne, VIC 3000. Australia.

Email: david.gyorki@petermac.org

Short Title: FDG PET in RPS

Synopsis

The paper presents a series of patients with primary retroperitoneal sarcoma with preoperative staging PET scans and describes the correlation of standard uptake variable (SUV) and tumour grade, therefore presenting a non-invasive surrogate for tumour grade.

Data Availability Statement

The Data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abstract

Background:

The role of ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) in the evaluation of retroperitoneal sarcomas (RPS) is poorly defined. We evaluated the correlation of maximum standardised uptake value (SUVmax) with pathologic tumor grade in the surgical specimen of primary retroperitoneal dedifferentiated liposarcoma (DDLPS) and leiomyosarcoma (LMS).

Methods:

Patients with the above histological subtypes in 3 participating institutions with preoperative ^{18}F -FDG PET/CT scan and histopathological specimen available for review were included. The association between SUVmax and pathological grade was assessed. Correlation between SUVmax and relapse free survival (RFS) and overall survival (OS) were also studied.

Results:

Of the total 58 patients, final pathological subtype was DDLPS in 44(75.9%) patients and LMS in 14 (24.1%). The mean SUVmax was 8.7 with a median 7.1 (range 2.2 to 33.9). The tumors were graded I, II, III in 6(10.3%), 35(60.3%) and 17(29.3%) patients respectively. There was an association of higher histological grade with higher SUVmax ($r_s=0.40$, $p=0.002$). Increasing SUVmax was associated with worse RFS ($p=0.003$) and OS ($p=0.003$).

Conclusion:

There is a correlation between SUVmax and pathologic tumor grade; increasing SUVmax was associated with worse OS and RFS, providing a preoperative non-invasive surrogate marker of tumour grade and biological behavior.

Keywords: Retroperitoneal, soft tissue tumour, PET scan

Introduction:

Retroperitoneal sarcoma (RPS) is a rare disease, with an incidence of around 0.5–1 case per 100 000(1, 2) and accounts for about 15% of all soft tissue sarcomas (STS) (1). Liposarcoma is the most frequent histological subtype (50-63%), followed by leiomyosarcoma (LMS) (19–23%) (3, 4). Other less frequent soft tissue sarcoma subtypes in the retroperitoneum include solitary fibrous tumour (SFT), malignant peripheral nerve sheath tumour (MPNST), synovial sarcoma and undifferentiated pleomorphic sarcoma (UPS)(3, 4)]. Recently, collaborations between individual centers have led to an unprecedented collection of retrospective and prospective data and successful completion of the first randomized controlled trial specifically targeting patients with RPS (5). Consensus guidelines have been published in the management of these rare tumors [(6).Careful preoperative planning with appropriate imaging (e.g. contrast-enhanced CT) is essential to ensure optimal cancer outcomes.

Functional imaging with ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) has improved

preoperative staging in a number of tumour types(7, 8). However data is lacking in patients with RPS. Preoperative CT guided biopsies in RPS have been shown to be oncologically safe(9, 10) and reliable but the accuracy in the identification of histological subtype and grade is less than optimal, identifying the grade correctly only in 50% of the cases(9, 11).

The consensus guidelines issued by the TransAtlantic and Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) proposed the use of ^{18}F -FDG PET/CT when available to target biopsy to areas of highest SUV uptake(2). Given the large size of many retroperitoneal sarcomas, targeting the biopsy to the highest-grade component of the tumour may help to tailor treatment. This is particularly the case for decision making regarding neoadjuvant systemic therapy which may be considered in high grade RPS, a therapeutic approach being assessed in the upcoming prospective STRASS 2 trial, which will evaluate the role of neoadjuvant chemotherapy in patients at high risk of distant relapse (12)]. In addition, a high value of SUVmax on PET may in itself represent unfavourable tumour biology, but this has never been formally studied in RPS.

To evaluate whether a PET/CT scan may help to target the biopsy in order to obtain a reliable grade estimation in RPS, this study evaluates the potential correlation of SUVmax in the tumor on preoperative PET with the pathological FNCLCC (Fédération National des Centres de Lutte Contre le Cancer) grade of the tumor in the surgical resection specimen in patients with primary retroperitoneal dedifferentiated liposarcoma (DDLPS) or Leiomyosarcomas (LMS). These two histologic subtypes encompass the

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vast majority of high-grade disease in RPS. A second aim of the study is to evaluate the correlation between SUVmax and the relapse free survival (RFS) and overall survival (OS).

Materials and Methods

Patients

Patients undergoing definitive surgery for primary retroperitoneal LMS or DDLPS at Peter Mac Callum Cancer Centre (PMCC), Melbourne, Australia; The Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands and the University of Southern California (USC), Keck school of Medicine, Los Angeles, United States between July 2013 and June 2018 were identified from the units databases. The case notes of all the patients were reviewed from the electronic database available. Patients were included if they underwent pre-operative ^{18}F -FDG PET/CT and had a pre-operative biopsy and subsequent pathology from the resection specimen available for review.

Patients with well-differentiated liposarcoma without evidence of dedifferentiation were excluded from the study. The DDLPS group was divided as WD/DD liposarcoma (WD/DDLPS) if both well-differentiated and de-differentiated component were present and de-differentiated liposarcoma (DDLPS) if no well-differentiated component was present. Anyone without a preoperative ^{18}F -FDG PET/CT scan was excluded from the study. Patients in which the ^{18}F -FDG PET/CT scan was not performed prior to neoadjuvant therapy were also excluded. Patients with recurrent

sarcoma were excluded or patients with well-differentiated liposarcoma without a dedifferentiated component were excluded.

RFS was defined as the time from surgery to the date of first relapse or date of death, whichever occurs first and OS was defined as the time from surgery to the date of death from any cause.

Histopathologic grading

All pathology samples were reviewed by an experienced sarcoma pathologist in each participating institution and the grade allocated according to the final pathology sample at each institution. Grading was done as per FNCLCC grading. The highest grade of the tumor which was usually in the resection specimen was used for the purposes of analysis.

¹⁸F-FDG PET/CT

The ¹⁸F-FDG PET/CT scans were done as per the EANM guidelines in all the participating centres. This included: Fasting for at least 6 hours, BGL <11 mmol/L, Weight base dose 3.6 MBq/kg, Uptake time between 60-75 mins. There were some studies where the scanning was done elsewhere in which case the images were imported and reviewed.

All PET/CT scans were reviewed by an experienced nuclear medicine physician at each institution. SUVmax of the primary tumour was determined.

Statistical analysis

All statistical analyses were performed in R 3.4.2(13). The SUVmax per pathological grade was displayed using box-plots and jitter plots. The association between SUVmax and pathological grade was assessed using Spearman's correlation. A Cox proportional-hazards model was created to assess the impact of SUVmax on OS and RFS. Linear and non-linear effects were assessed using penalised splines with 2, 3 and 4 degrees of freedom. Penalised splines with 3 degrees of freedom provided best-fit using AIC criteria. The assumption of proportional hazards was verified.

Results

A total of 58 patients who met the inclusion criteria were included in the analysis. 31 patients were from Peter MacCallum Cancer Centre, 13 from the Netherlands Cancer institute and 14 from University of Southern California. The median age was 63.5 years (range 32 - 86 years) with 57% males. Median tumour size was 18.4cm (range 4-50cm). The patient and tumour characteristics are described in Table 1.

The final pathological subtype was DD LPS in 21(36.2%) patients, WD/DD LPS in 23(39.7%) and LMS in 14(24.1%). The tumour FNCLLC grades 1,2, 3 were noted in 6(10.3%), 35(60.3%) and 17(29.3%) patients.

The median SUVmax of grade 1, 2 and 3 sarcomas were 3.2, 7.1 and 9.5 respectively (Table 2). The median SUVmax for liposarcoma and leiomyosarcoma were 6.8 (range 2.2 to 33.9) and 7.8 (range 2.2 to 19.9) respectively. Within the liposarcoma subgroup, the median SUV max for

WD/DD LPS and DD LPS were 4.2 (range 2.2 to 33.9) and 7.8 (range 3.2 to 24) respectively. Examples of PET/CT scans from two patients included in the study are shown in Figure 1, comparing cross sectional imaging from contrast enhance CT with FDG-PET/CT. There was a correlation between SUVmax and tumour grade (spearman correlation: $r_s = 0.40$, $p=0.002$) (Figure 2. This correlation applied to both patients with liposarcoma and leiomyosarcoma.

After a median follow up of 2.9 years, the three-year relapse free and overall survival was 60% (95% CI: 45-72) and 75% respectively (95% CI: 60-85) (Figure 3A and Figure 4A). Using a SUVmax of 5.0 as a reference (HR=1), the relative hazard of recurrence (Figure 3B) and death (Figure 4B) were plotted as a function of the SUVmax. Increasing SUVmax was associated with worse RFS ($p=0.003$) and OS ($p=0.003$)

Discussion:

This study represents the largest series to date analysing the correlation between ^{18}F -FDG PET/CT and tumour grade in patients with primary retroperitoneal DD-LPS and LMS. The measurement of SUVmax on preoperative PET/CT correlates strongly with tumour grade. This provides a non-invasive, preoperative surrogate for tumour biology that adds to the tumor grade.

Median SUVmax in this study was 6.8 and 7.8 for liposacoma and leiomyosarcoma respectively, and we were able to show that SUVmax is associated with OS and RFS ($p = 0.003$) which may be a reflection of the correlation of SUVmax and the grade, however the small sample size with

only 6 grade 1 patients did not allow to explore this further in a multivariable model. We restricted our study population to include only patients with DDLPS and LMS to keep the population more homogeneous and we focussed on those patients where functional imaging was most likely to impact on management.

These findings are in line with the only other paper evaluating the role of PET/CT for RPS (14). This study by Rhu et al. demonstrated an SUVmax cutoff > 4.5 to be associated with a higher grade and worse prognosis in retroperitoneal liposarcomas. The median SUVmax of 3.3 (IQR of 4.4) in this series [(14)] was lower compared to our study, this lower median score can be explained by the inclusion of pure well differentiated liposarcoma as well as myxoid and pleomorphic liposarcoma by Rhu et al, and also the inclusion of recurrent and metastatic retroperitoneal LPS which contributed to 53.2% of their patients. This heterogeneous population may have distorted the findings in that study.

The recent development of prognostic nomograms for patients with retroperitoneal sarcoma has demonstrated the inherent heterogeneity of this patient population, which until recently was poorly represented by the AJCC staging system(15). The AJCC 8th edition has addressed some of the limitations of previous staging systems for RPS (3), in particular that most cases are large and by-definition deep and therefore staging had little stratification other than by tumour grade. Recognizing the difference of anatomical locations, subcategorizing the location of STS; introducing more T stages and including nomograms to better predict the individual

patients prognosis are recent developments. Nomograms have also been developed to predict disease free survival (DFS) and overall survival (OS) OS after surgical resection following first local recurrence in RPS(16). Without optimally targeting the preoperative biopsy, and thereby the most important prognostic factor, tumour grade, we may underestimate the risk (15). Also not including the histological subtype as part of the staging system is a disadvantage (17). For the first time, STS was not considered a single entity and site-specific staging systems were developed.

For retroperitoneal sarcomas, it has been shown that pre-operative biopsies tend to under estimate the final grade probably due to sampling error(10, 11, 18-20). It has been shown that percutaneous biopsy has low accuracy in the diagnosis ofDDLPS and thereby could potentially impact decision making in neoadjuvant treatment (21). Therefore, PET/CT might be of added value when there is doubt regarding grading. The images in figure 1 show how an FDG PET/CT can identify the area of a tumour which a percutaneous biopsy should ideally target to ensure an accurate and representative sample. Other areas where PET/CT may be of benefit include accurate initial staging, neoadjuvant therapy planning, and it may also help to evaluate post-therapy response assessment and prognostication in sarcoma patients(22, 23).

Studies of STS have confirmed the utility of ^{18}F -FDG PET in predicting treatment response(23, 24). In a study of 46 patients with STS, including 10 RPS patients with histology types LPS and LMS, it has been shown that a reduction of metabolic activity following neoadjuvant chemotherapy

is a better predictor than the change in size and hence ^{18}F -FDG PET/CT was proposed to monitor treatment response in patients with high-grade soft-tissue sarcoma [(24). Studies looking for treatment response assessment using ^{18}F -FDG PET/CT in RPS alone are lacking.

Tumour size, histological tumour grade and margin status are currently the routinely applied factors for recurrence free and overall survival(2, 25, 26). In the largest series of primary RPS that included all histologic subtypes (n = 1007), the Trans-Atlantic RPS Working Group (TARPSWG) reported that tumor grade was associated with local recurrence, distant metastasis, and overall survival(4). In this multi-institutional study, 370 DDLPS were stratified by Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade. Interestingly, they show that the pattern of failure differs based on the FNCLCC grade of DDLPS. Grade II DDLPS had an 8-year overall survival of 50%, a local recurrence risk of 50% and distant metastasis risk less than 10%. Grade III DDLPS, on the other hand, had an 8-year overall survival of 30%, a local recurrence risk of 35%, and a distant metastasis risk of 30%.

Preoperative prognostic assessment is important for optimal patient selection for neoadjuvant therapy as well as to stratify for clinical trials. Future studies of neoadjuvant therapy should consider including a baseline PET/CT to allow optimal risk stratification and ensure that patients are staged as accurately as possible. This may help to ensure homogeneity of the study population. The planned STRASS 2 study

[12,(27)] will include a PET/CT substudy, which will further contribute to this body of knowledge.

The current study is limited by its retrospective nature and the small patient numbers. A larger study is required to assess the effect of SUVmax adjusting for known prognostic factors. Alternative volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been correlated with outcome in soft tissue sarcomas(28)] but were not routinely reported in our study population and therefore were not included in the current analysis.

Conclusion

The SUVmax measured by ^{18}F -FDG PET/CT provides a preoperative non-invasive surrogate marker of tumour grade and biological behavior of the tumor in patients with retroperitoneal DDLPS and LMS. This data supports the use of this imaging modality to help guide patient selection for neoadjuvant therapies and for stratifying patients in future clinical trials. Future studies correlating changes in SUVmax and other volumetric parameters with response to neoadjuvant therapy could be considered.

Acknowledgements:

Australia and New Zealand Sarcoma Association (ANZSA) for the data support.

Abbreviations list:

¹⁸F-Fluorodeoxyglucose positron emission tomography /computed tomography – ¹⁸F-FDG PET/CT; Metabolic tumor volume - MTV; Total lesion glycolysis – TLG; Retroperitoneal sarcomas -RPS; Soft tissue sarcoma – STS; Dedifferentiated liposarcoma – DDLPS; Well differentiated/Dedifferentiated liposarcoma - WD/DD LPS; Leiomyosarcoma – LMS; Solitary fibrous tumour – SFT; Malignant peripheral nerve sheath tumour – MPNST; Undifferentiated pleomorphic sarcoma – UPS; Peter MacCallum Cancer Centre (Australia) – PMCC; The Netherlands Cancer Institute (Netherlands) – NKI; The University of Southern California (USA) - USC; French Fédération Nationale des Centres de Lutte Contre le Cancer Grading- FNCLCC Grade; Relapse free survival –RFS; Overall survival – OS; TransAtlantic and Australasian Retroperitoneal Sarcoma Working Group – TARPSWG; AJCC – American Joint Committee of Cancer; Mean tumour volume - MTV; Total lesion glycolysis - TLG

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Figure Legends

Figure 1: Contrast enhanced CT and PET scan of: A) DDLPS - SUVmax 13.5 & pathological grade 2; B) DDLPS - SUVmax 15.6 & pathological grade 3

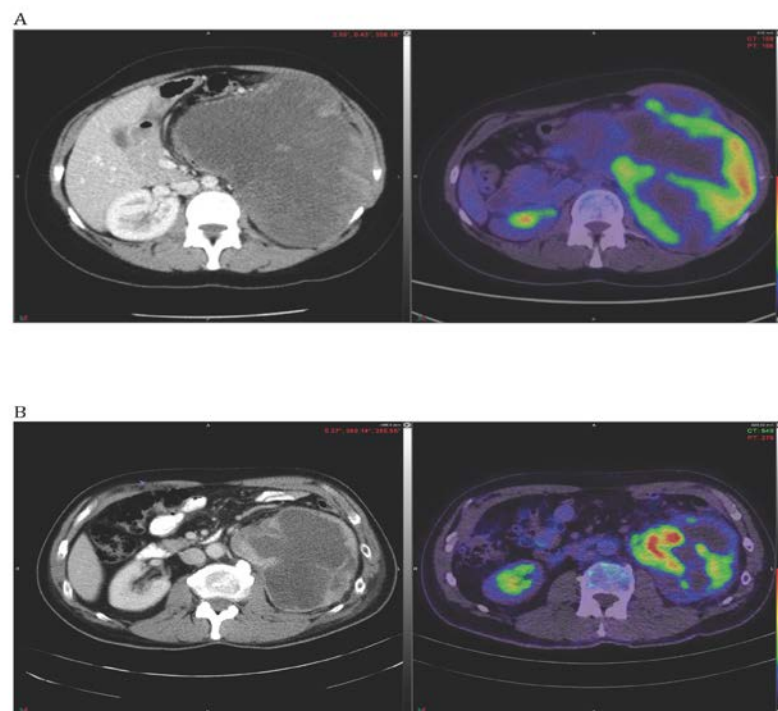


Figure 1: Contrast enhanced CT and PET scan of: A) DDLPS - SUVmax 13.5 & pathological grade 2; B) DDLPS - SUVmax 15.6 & pathological grade 3

Figure 2. SUV max by Histological Grade

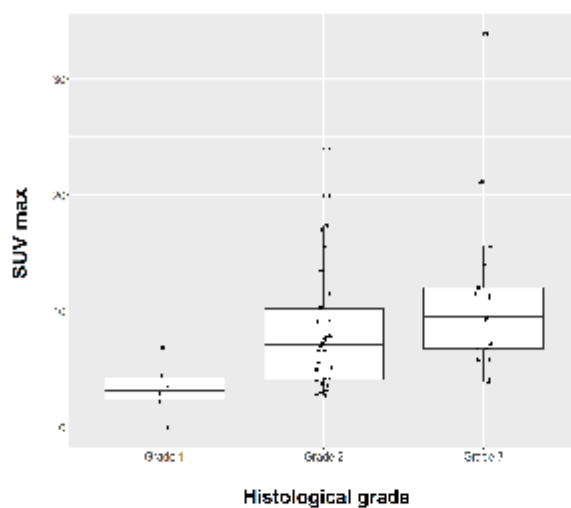


Figure 2: SUV max by Histological Grade

Figure 3: A) Kaplan-Meier plot for Recurrence free survival (95% CI in grey) and B) plot of HR of relapse by SUVmax

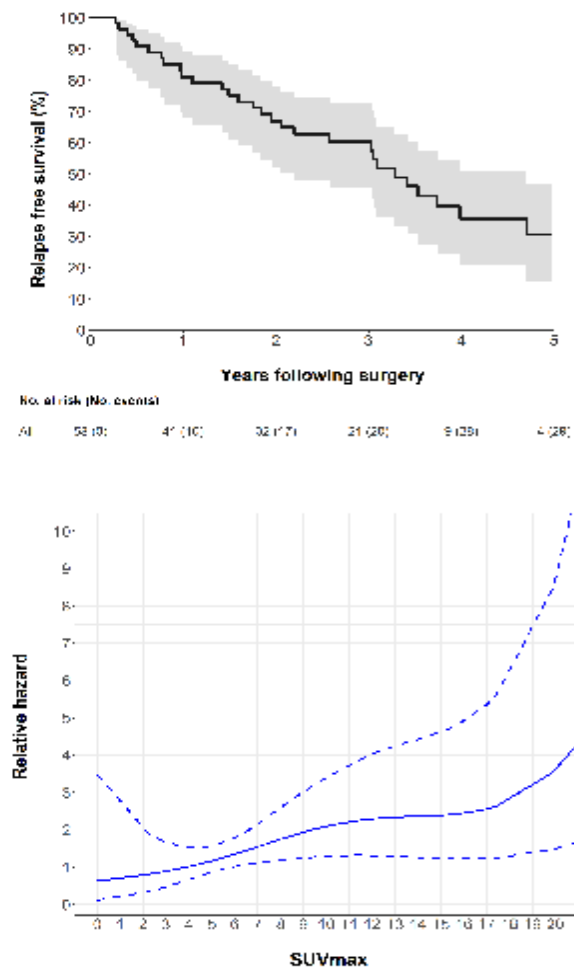


Figure 3: A) Kaplan-Meier plot for Recurrence free survival (95% CI in grey) and B) plot of HR of relapse by SUVmax

Figure 4. A) Kaplan-Meier curves for OS (95% CI in grey) B) plot of HR of death by SUVmax

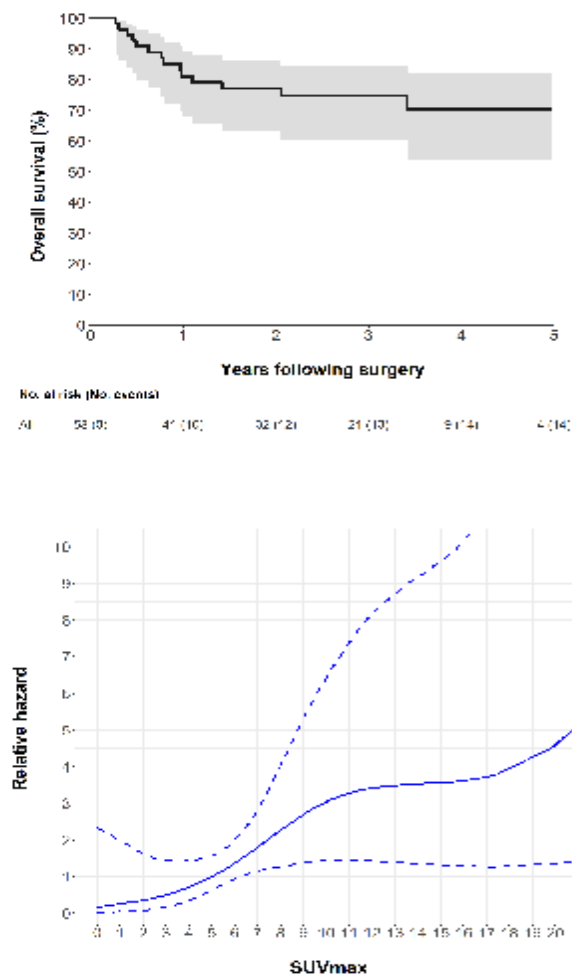


Figure 4: A) Kaplan-Meier curves for OS (95% CI in grey) B) plot of HR of death by SUVmax

Table 1. Patient Tumor Characteristics

Characteristic	Total (n = 58)
Institution	
NKI	13 (22%)
PM	31 (53%)
USC	14 (24%)
Sex, n (%)	
Female	25 (43%)
Male	33 (57%)
Age, years	
Mean (SD)	61 (14)
Median [range]	64 [32 - 86]
IQR	53 - 71
Chemotherapy, n (%)	
No	51 (88%)
Yes	7 (12%)
Radiotherapy, n (%)	
No	31 (53%)

Characteristic	Total (n = 58)
Yes	27 (47%)
SUVmax	
Mean (SD)	9 (6)
Median [range]	7 [0 - 34]
IQR	4 - 11
Histology, n (%)	
DD LPS	21 (36%)
LMS	14 (24%)
WD/DD LPS	23 (40%)
Grade, n (%)	
Grade 1	6 (10%)
Grade 2	35 (60%)
Grade 3	17 (29%)
Size, mm	
Mean (SD)	22 (11)
Median [range]	18 [4 - 50]
IQR	14 - 26

Table II. SUVmax descriptive statistics by histological grade

Characteristic	Histological grade		
	Grade 1 (n = 6)	Grade 2 (n = 35)	Grade 3 (n = 17)
SUVmax			
Mean (SD)	3.3 (2.3)	8.3 (5.3)	11.2 (7.4)
Median [range]	3.2 [0.0 - 6.9]	7.1 [2.8 - 24.0]	9.5 [3.9 - 33.9]
IQR	2.4 - 4.2	4.1 - 10.2	6.8 - 12.0