FDG-PET RADIOMIC ANALYSIS PREDICTS SURVIVAL IN PATIENTS WITH SOFT TISSUE SARCOMAS

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Case Study: Introduction

- Introduction
- FDG PET
- Current Interpretation
- Radiomics

- Photos - **Measures thousands of coloured squares** (**pixels**)
- Modern medical imaging- consists of 3D digital information made up of (**voxels**)
- Process of colour mapping allows us to see this

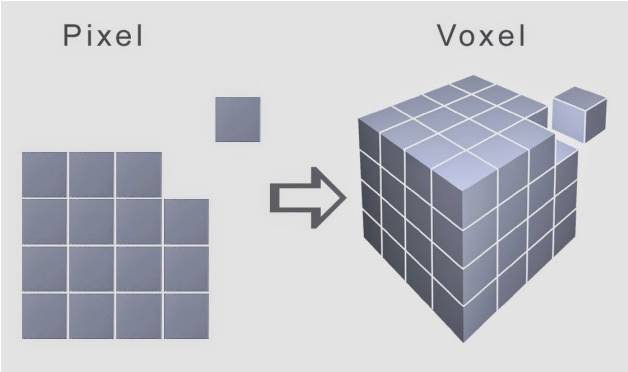
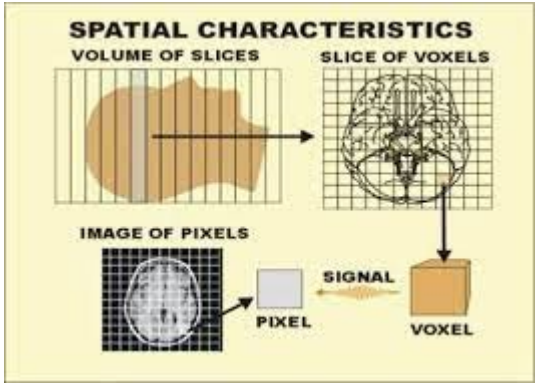


Figure 1. Pixel vs Voxel in radiology



Background: FDG PET

- Introduction
- **FDG PET**
- Current Interpretation
- Radiomics

Increased FDG uptake is correlated with more **aggressive tumour cells**

Plays an essential role in assessing local and distant disease spread and evaluating response to treatment [1]

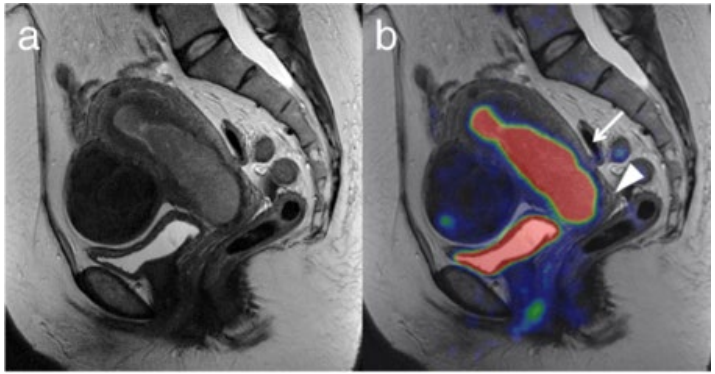


Figure 2. PET/CT of a large endometrial cancer

[1] Manganaro, L., Nicolino, G. M., Dolciami, M., Martorana, F., Stathis, A., Colombo, I., & Rizzo, S. (2021). Radiomics in cervical and endometrial cancer. *The British journal of radiology*, *94*(1125), 20201314. https://doi.org/10.1259/bjr.20201314

Background: Current Interpretation

- Introduction
- FDG PET
- **Current Interpretation**
- Radiomics

Currently **qualitative assessment** with **simple quantitation** (SUV Maximum) [2]

SUV (standardised uptake value) **is a measure of FDG uptake**

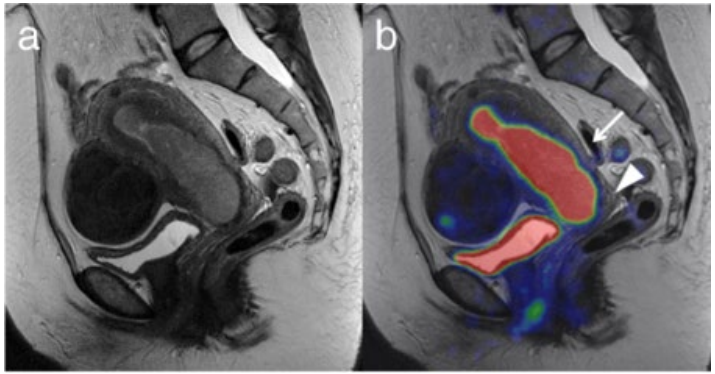


Figure 2. PET/CT of a large endometrial cancer

[2] Walentowicz-Sadlecka, M., Malkowski, B., Walentowicz, P., Sadlecki, P., Marszalek, A., Pietrzak, T., & Grabiec, M. (2014). The preoperative maximum standardized uptake value measured by 18F-FDG PET/CT as an independent prognostic factor of overall survival in endometrial cancer patients. *BioMed research international*, *2014*, 234813. https://doi.org/10.1155/2014/234813

Background: Radiomics

- Introduction
- FDG PET
- Current Interpretation
- **Radiomics**

Definition: the process of extracting **multiple quantitative** imaging biomarkers [3]

Described using **radiomic features**

Radiomic features can capture **image characteristics**

E.g. image texture, tumour heterogeneity, tumour shape

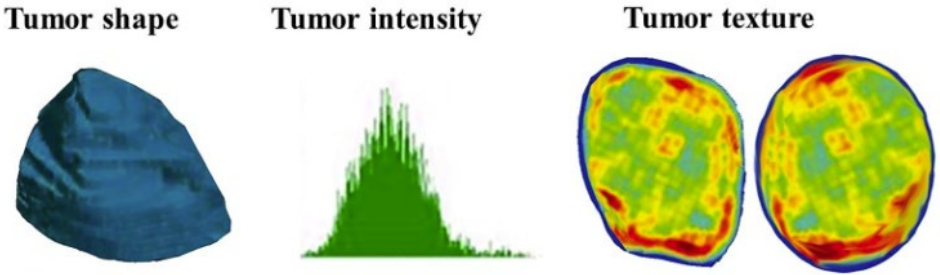


Figure 3. Image characteristics described by radiomic features

[3] Gu, H., Zhang, X., di Russo, P., Zhao, X., & Xu, T. (2020). The Current State of Radiomics for Meningiomas: Promises and Challenges. *Frontiers in oncology*, *10*, 567736. https://doi.org/10.3389/fonc.2020.567736

Background: Radiomics

Quantification In Imaging

FDG PET

Current Interpretation

Radiomics

More biological heterogeneity = poorer prognosis

Tumour Heterogeneity in FDG PET is a known prognostic marker

This heterogeneity can be **quantified**

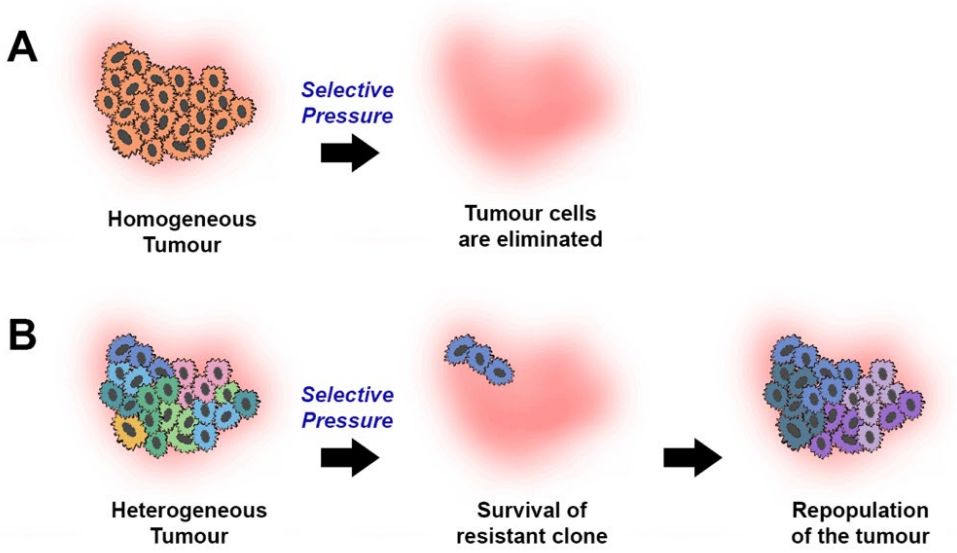
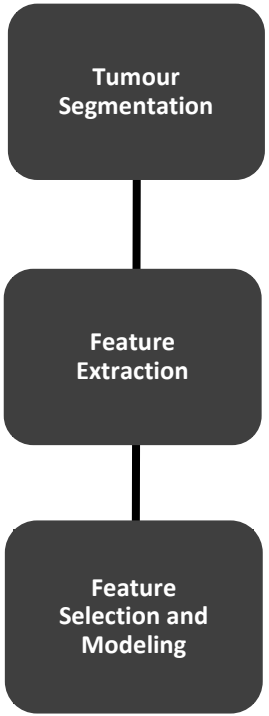


Figure 4. Demonstration of tumour heterogeneity [4]

[4] Gay L, Baker AM and Graham TA. Tumour Cell Heterogeneity [version 1; peer review: 5 approved]. F1000Research 2016, 5(F1000 Faculty Rev):238 (https://doi.org/10.12688/f1000research.7210.1)

Radiomics


Tumour Segmentation
Feature Extraction
Feature Selection and Modeling

Tumour Segmentation

- **Tumour Segmentation**
- **Feature Extraction**
- **Feature Selection and Modeling**

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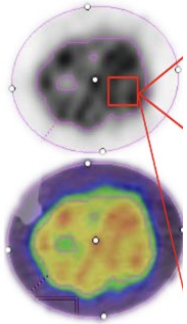
Tumour Segmentation

Tumour Segmentation

Feature Extraction

Feature Selection and Modeling

Radiomic Features can be separated into **first, second and higher order features**



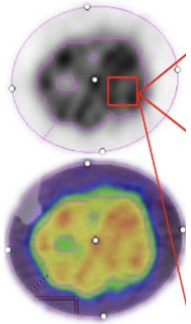
Tumour Segmentation

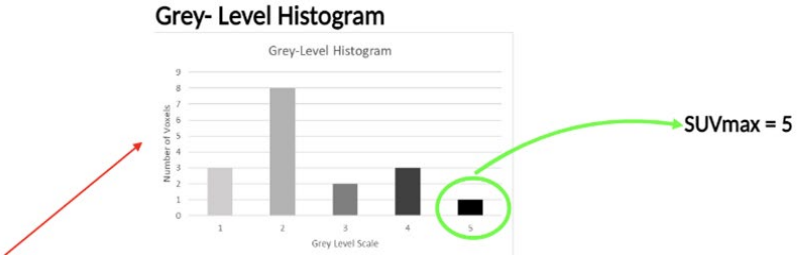
Tumour Segmentation

Feature Extraction

Feature Selection and Modeling

Radiomic Features can be separated into **first, second and higher order features**





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Tumour Segmentation

Tumour Segmentation

Feature Extraction

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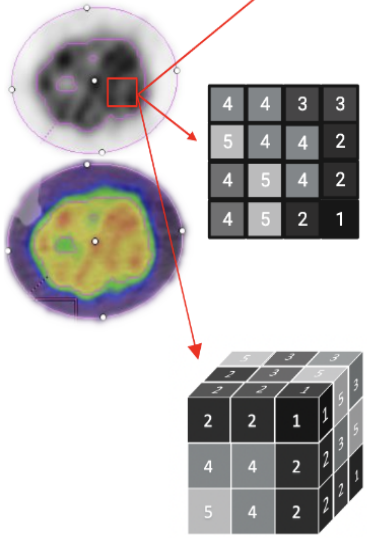
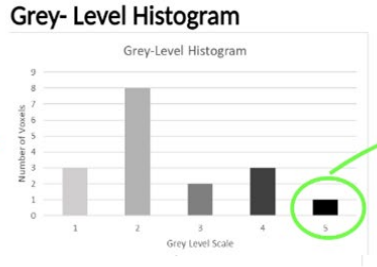
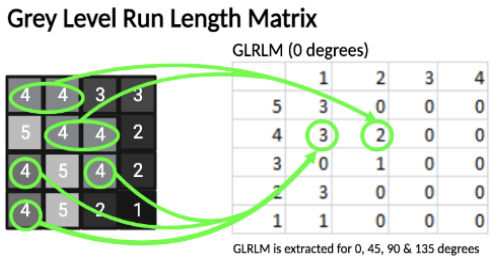
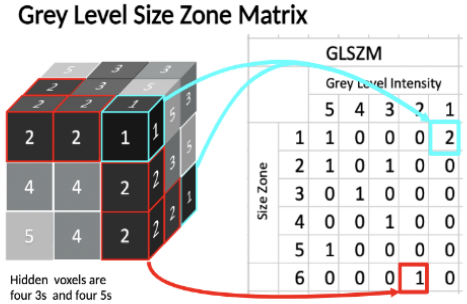






GLRLM fraction

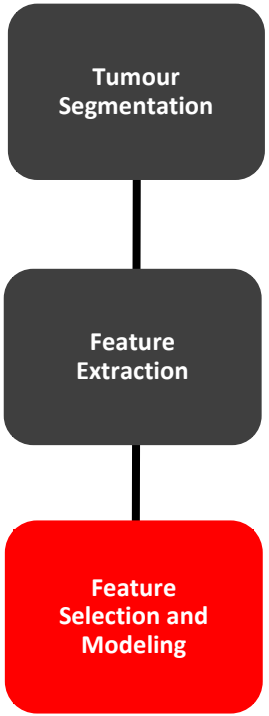
% of voxels within VOI that are part of runs



GLSZM - Zone Percentage

Ratio of number of zones to number of voxels: measures the coarseness of the texture

Feature Selection and Modelling



Radiomic Features can essentially act as tumour **biomarkers**

- **This is COMPLEMENTARY to current practice**

- **Diagnosis** e.g. presence of bone metastases
- **Prognosis**
  - Survival endpoints
  - Grade
  - Gene markers
- **Response to treatment**

Aim

Assess the **prognostic value** of pre-treatment FDG **PET quantitative parameters** for patients with **soft tissue sarcoma**

Methods

1. Patient Identification
2. Tumour Segmentation
3. Radiomic Feature Extraction
4. Statistical Analysis

Methods

1. Patient Identification
2. Tumour Segmentation
3. Radiomic Feature Extraction
4. Statistical Analysis

Inclusion Criteria	Primary soft tissue sarcoma
	Pre-treatment PET
Exclusion Criteria	Treatment prior to PET
	PET data not available for review
	Age <18
	Treatment with palliative intent
	GIST (gastrointestinal stromal tumor)

Methods

1. **Patient Identification**
2. **Tumour Segmentation**
3. **Radiomic Feature Extraction**
4. **Statistical Analysis**

186 Patients identified from cross-referencing POWH PET/Nuclear Med Databases with POWH STS database

Exclusions

No Initial PET (70)

Treatment with palliative intent (25)

Age at diagnosis <18 (6)

Other Cancers (9)

GIST (1)

Initial PET elsewhere (29)

48 Patients

Exclusions

PET Image Unavailable (4)

44 Patients

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Methods

1. Patient Identification
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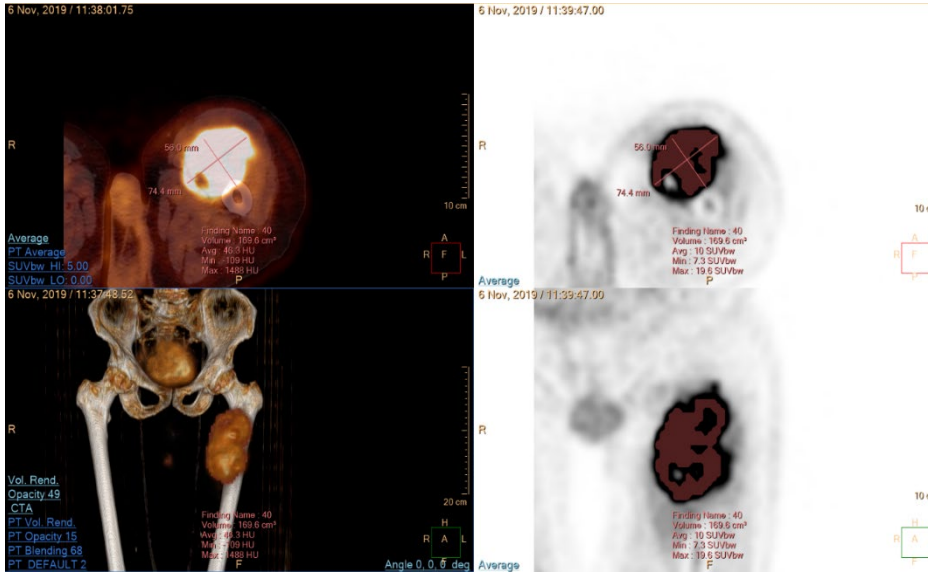

Figure 3. PET scan segmented using 40% of SUVmax on IntelliSpace Portal

- Software: **IntelliSpace Portal**
- Threshold: 40% of SUVmax

Methods

1. Patient Identification
2. Tumour Segmentation
3. Radiomic Feature Extraction
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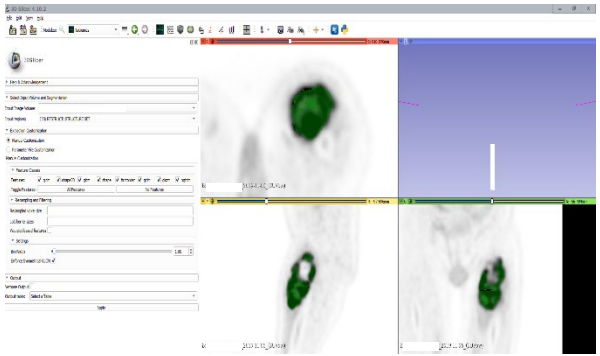
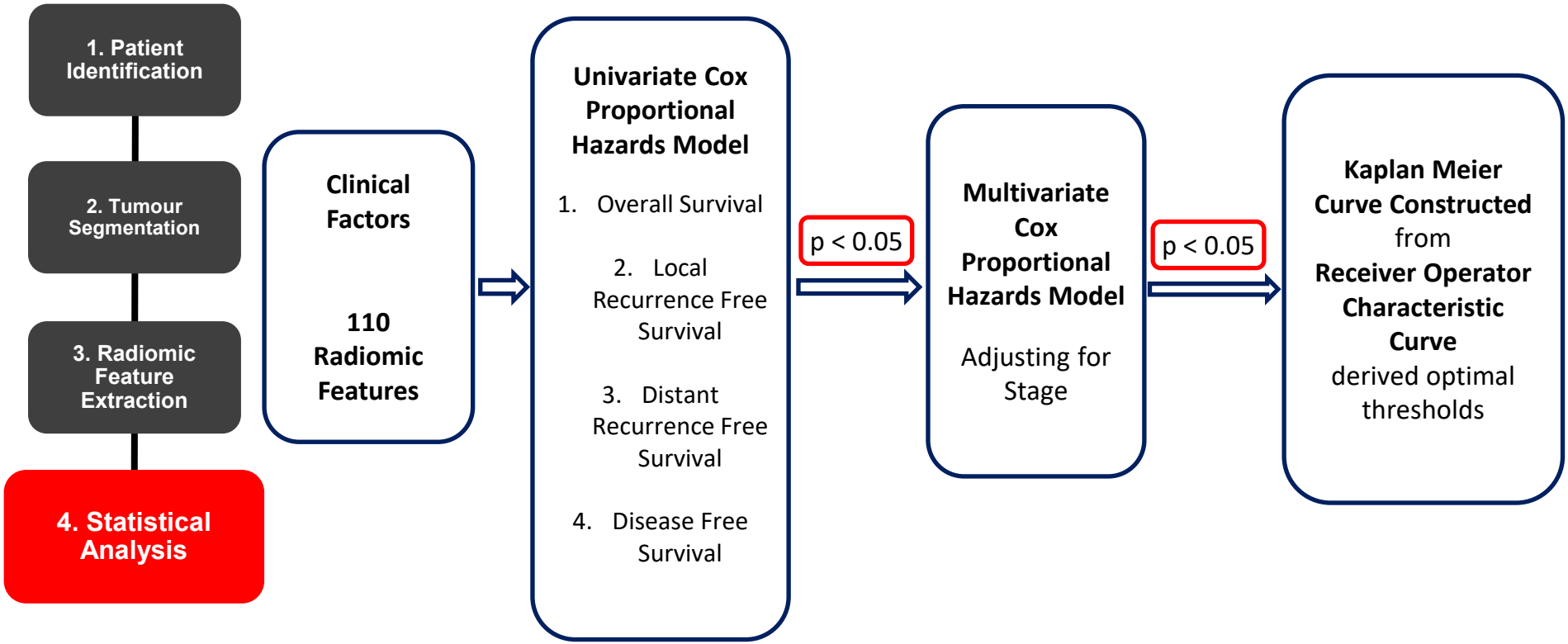


Figure 4. Feature Extraction on 3D Slicer

- Images exported into 3DSlicer 4.10.2
- Pyradiomics Plugin utilized to extract features
- Total Features = **110**
  i. First Order Statistics (19 features)
  ii. Shape-based (3D) (16 features)
  iii. Shape-based (2D) (10 features)
  iv. Gray Level Cooccurence Matrix (24 features)
  v. Gray Level Run Length Matrix (16 features)
  vi. Gray Level Size Zone Matrix (16 features)
  vii. Neighbouring Gray Tone Difference Matrix (5 features)
  viii. Gray Level Dependence Matrix (14 features)

Methods


1. Patient Identification
2. Tumour Segmentation
3. Radiomic Feature Extraction
4. Statistical Analysis
Clinical Factors
110 Radiomic Features
Univariate Cox Proportional Hazards Model
1. Overall Survival
2. Local Recurrence Free Survival
3. Distant Recurrence Free Survival
4. Disease Free Survival
p < 0.05
Multivariate Cox Proportional Hazards Model
Adjusting for Stage
p < 0.05
Kaplan Meier Curve Constructed from Receiver Operator Characteristic Curve derived optimal thresholds

Patient Characteristics

- Demographics
- Histology
- Treatment
- Grade & Stage
- Follow Up

Patient Characteristics

- **Demographics**
- Histology
- Treatment
- Grade & Stage
- Follow Up

Gender	Male no. (%)	19 (43%)
	Female no. (%)	25 (57%)
Age at Diagnosis	Mean (Standard Deviation)	57 (18)
	Range	19 – 85

Patient Characteristics

- Demographics
- **Histology**
- Treatment
- Grade & Stage
- Follow Up

Histology		
	Liposarcoma	10
	Leiomyosarcoma	6
	Fibromyxosarcoma	5
	Myxoid fibrosarcoma	4
	Undifferentiated pleomorphic sarcoma	4
	Sarcomatoid tumour	2
	Peripheral nerve sheath tumour	2
	Angiosarcoma	2
	Synovial sarcoma	1
	Giant Cell sarcoma	1
	Undifferentiated sarcoma	1
	Rhabdomyosarcoma	1
	Spindle cell sarcoma	1
	Unknown	3

Patient Characteristics

- Demographics
- Histology
- Treatment
- Grade & Stage
- Follow Up

Treatment	Surgery	11
	RT + Surgery	22
	Chemotherapy + Surgery	2
	RT + Chemotherapy + Surgery	5
	Chemotherapy	1
	Unknown	3

Patient Characteristics

- Demographics
- Histology
- Treatment
- Grade & Stage
- Follow Up

Grade	1	8
	2	10
	3	25
AJCC Clinical Stage	Ia	2
	Ib	7
	II	3
	IIIa	11
	IIIb	18
	IV	2
	Unknown	1
Follow Up	Mean (Standard Deviation)	28.58 months (18 months)
	Range	6.2 months – 76 months

Survival Analysis

Outcome	Feature	Multivariate	
		HR (95% CI)	P value
Overall Survival	*$SUV_{Maximum}$	*1.1 (1-1.2)	*0.042
	$SUV_{Kurtosis}$	1.4 (1.0 - 1.8)	0.044
Local Recurrence Free Survival	$GLSZM_{SZNUN}$	3.45e5 (5.2e-11 - 0.75)	0.045
Distant Recurrence Free Survival	$GLSZM_{SZNUN}$	1.5 (2.8e-07-0.35)	0.024
Disease Free Survival	$Shape_{SurfaceVolumeRatio}$	1.6 (0.095-1.3e5)	0.035
	$SUV_{Skewness}$	1.5 (0.0096-16)	0.017
	$SUV_{Kurtosis}$	1.6 (0.012-3.7)	0.025
	$GLSZM_{SZNUN}$	1.6 (0.95-1.5)	0.011

* Univariate Analysis

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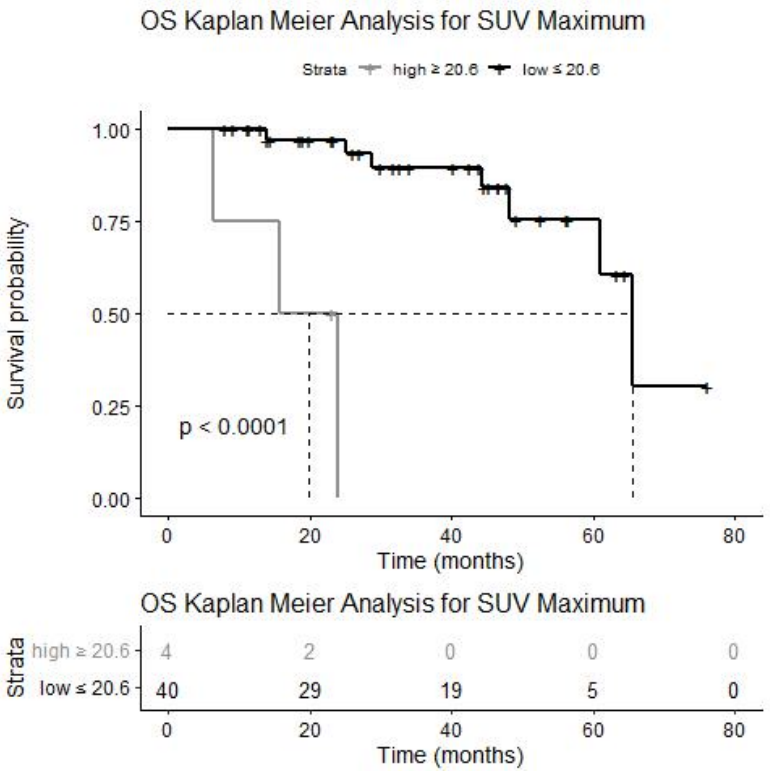

Survival Median: 19.7 months vs 65.6 months

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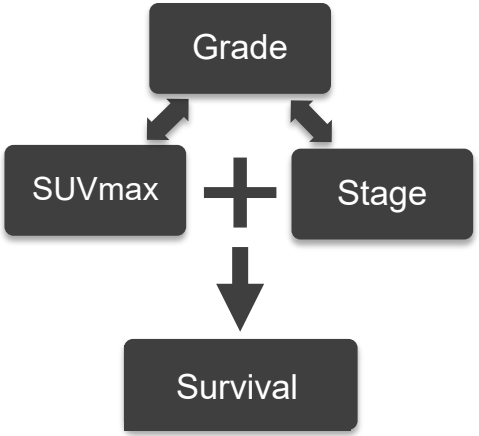

Insignificance on multivariate likely due to correlation between **grade and SUVmax (p = 0.002)**

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Survival Analysis: Intratumoural Heterogeneity

- Radiomic features which measured **intratumoural heterogeneity** were associated with **survival**
  - Intratumoural heterogeneity has been shown to be correlated with prognosis[4-6]
  - Can measure heterogeneity across the **entire tumour**

[5] Ramón, Y.C.S., et al. Clinical implications of intratumor heterogeneity: challenges and opportunities. *J. Mol. Med. (Berl.)* **98**, 161-177 (2020).
[6] Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science. 2014;344(6190):1396–1401
[7] Zhang, J., et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* **346**, 256-259 (2014).

SUV Kurtosis

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* Univariate Analysis

Measures the **peakedness of SUV distribution**

Higher values indicate **greater heterogeneity**

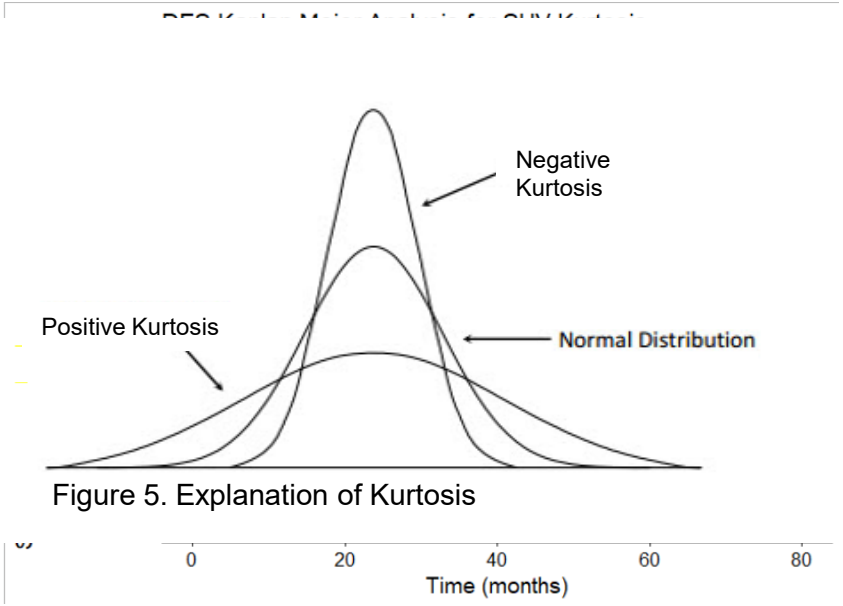

Figure 5. Explanation of Kurtosis

Survival Median: not reached vs 21 months

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Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

Outcome	Feature	Multivariate	
		HR (95% CI)	P value
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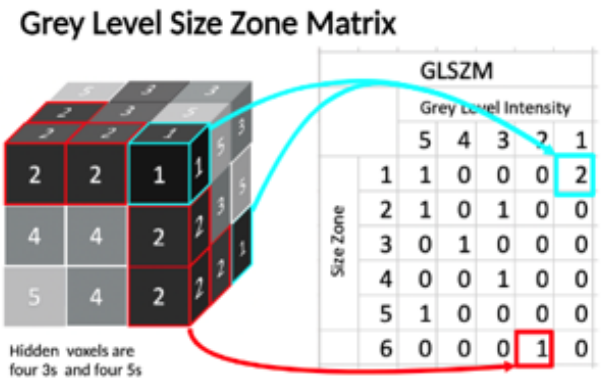

Figure 6. Explanation of GLSZM

$GLSZM_{SZNUN}$ measures the **variability of size zone volumes** throughout the image

Lower values indicate **more homogeneity among zone size volumes** in the image.

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Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

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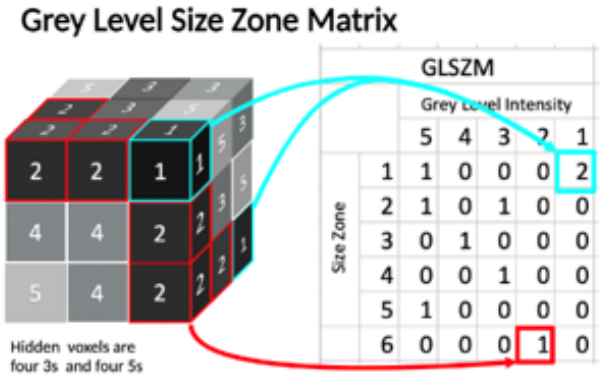

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Grey Level Size Zone Matrix

Size Zone \ Grey Level Intensity	5	4	3	2	1
1	1	0	0	0	2
2	1	0	1	0	0
3	0	1	0	0	0
4	0	0	1	0	0
5	1	0	0	0	0
6	0	0	0	1	0

Lower $GLSZM_{SZNUN}$ could represent

1. Numerous small but approximately equal size zones, representing increased tumour heterogeneity (multiple equal sized subpopulations of cancer)

Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

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4	0	0	1	0	0
5	1	0	0	0	0
6	0	0	0	1	0

Lower $GLSZM_{SZNUN}$ could represent

1. Numerous small but approximately equal size zones, representing increased tumour heterogeneity (multiple equal sized subpopulations of cancer)

2. Numerous large (approximately equal) size zones indicating less heterogeneity

Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

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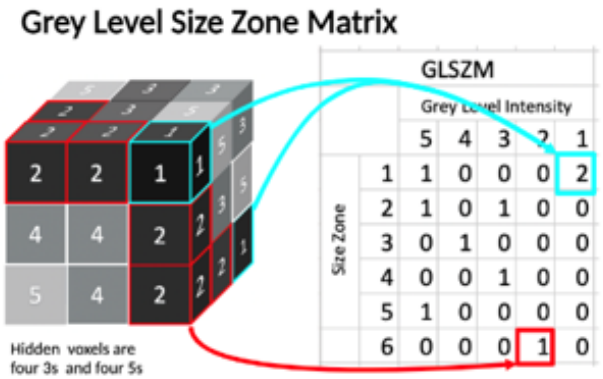
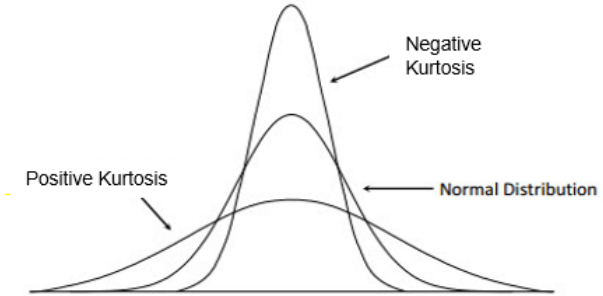
Lower values indicate **more homogeneity among zone size volumes** in the image.



Lower $GLSZM_{SZNUN}$ could represent

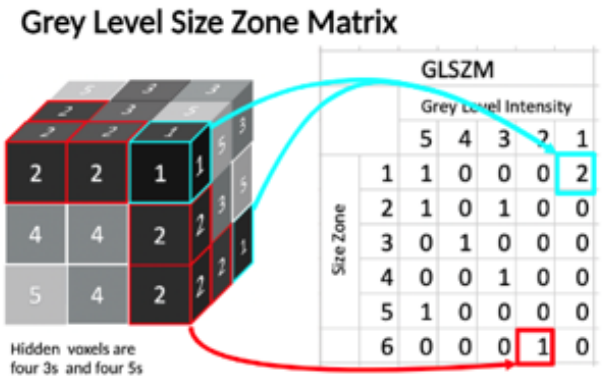
1. Numerous small but approximately equal size zones, representing increased tumour heterogeneity (multiple equal sized subpopulations of cancer)
2. Numerous large (approximately equal) size zones indicating less heterogeneity



Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

$GLSZM_{SZNUN}$ measures the **variability of size zone volumes** throughout the image

Lower values indicate **more homogeneity among zone size volumes** in the image.



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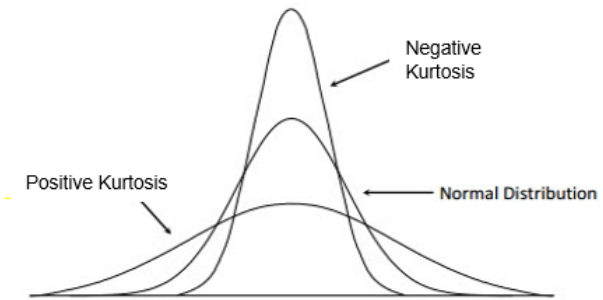

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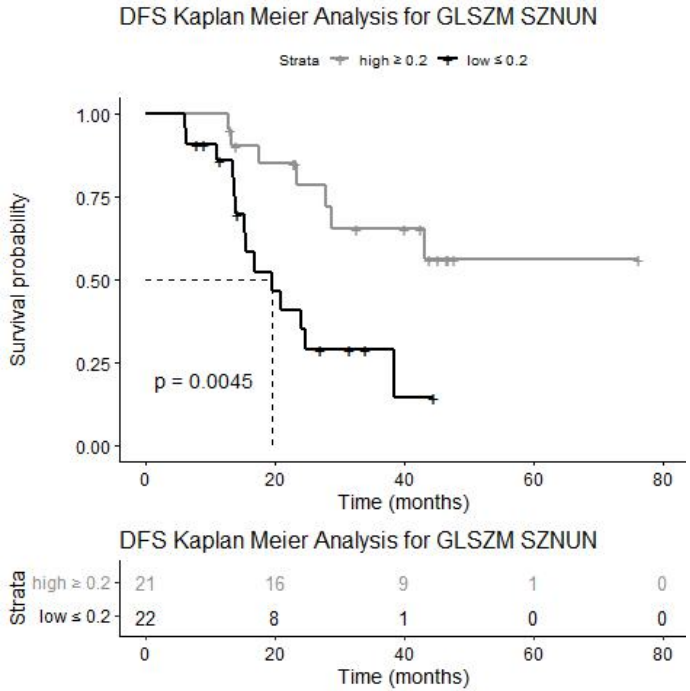
Grey Level Size Zone Matrix Size Zone Non-Uniformity Normalised

Outcome	Feature	Multivariate	
		HR (95% CI)	P value
Overall Survival	*$SUV_{Maximum}$	*1.1 (1-1.2)	*0.042
	$SUV_{Kurtosis}$	1.4 (1.0 - 1.8)	0.044
Local Recurrence Free Survival	$GLSZM_{SZNUN}$	3.45e5 (5.2e-11 - 0.75)	0.045
Distant Recurrence Free Survival	$GLSZM_{SZNUN}$	1.5 (2.8e-07-0.35)	0.024
Disease Free Survival	$Shape_{SurfaceVolumeRatio}$	1.6 (0.095-1.3e5)	0.035
	$SUV_{Skewness}$	1.5 (0.0096-16)	0.017
	$SUV_{Kurtosis}$	1.6 (0.012-3.7)	0.025
	$GLSZM_{SZNUN}$	1.6 (0.95-1.5)	0.011

* Univariate Analysis



Survival Median: 19.6 months vs not reached

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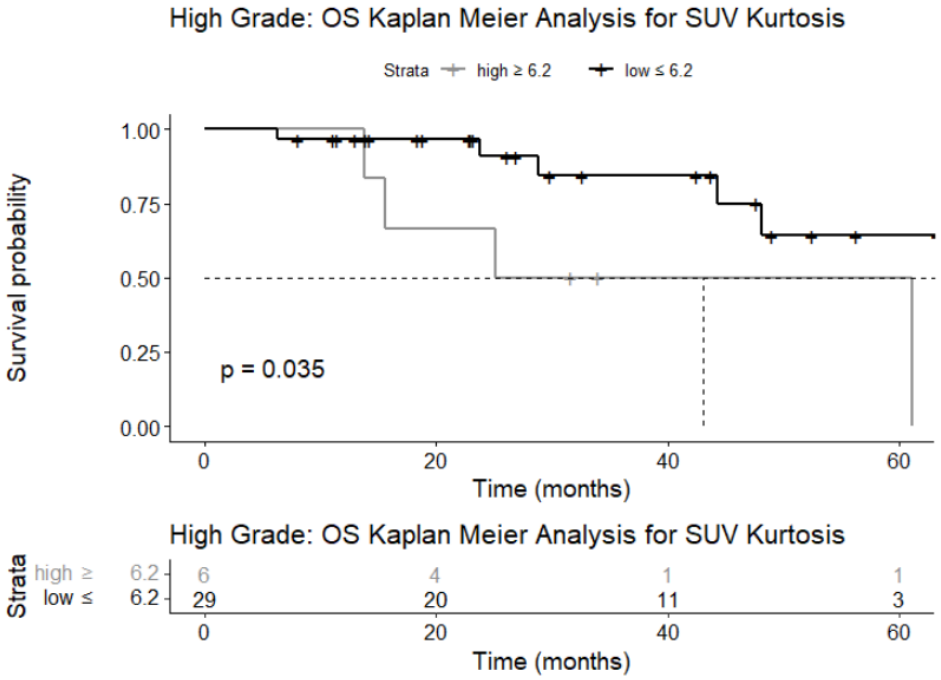
High – Grade Subgroup Analysis (Grade 2/3: n = 35)

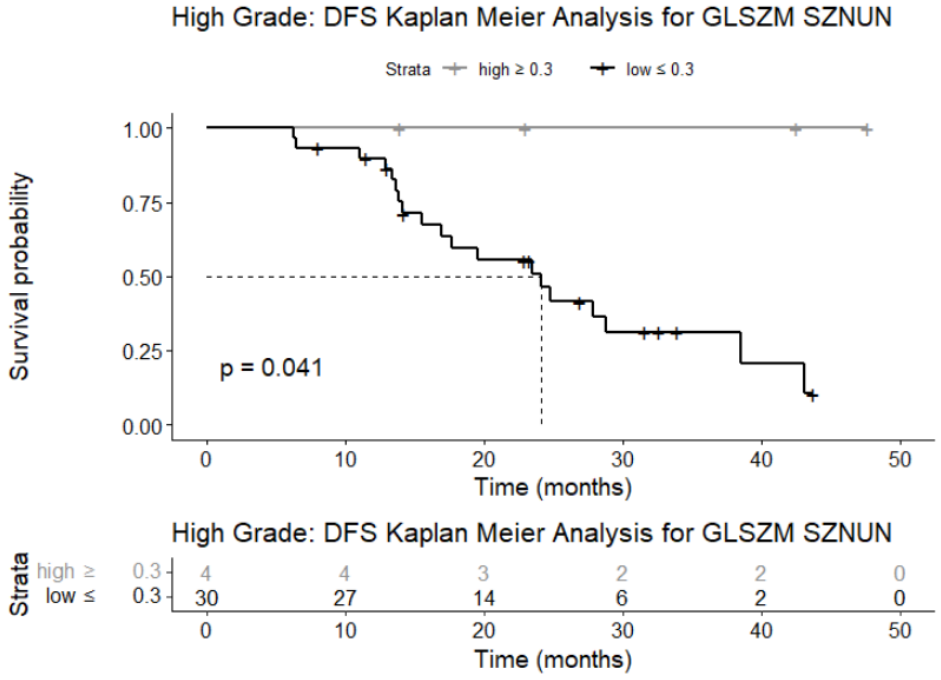
Outcome	Feature	Multivariate	
		HR (95% CI)	P value
Overall Survival	$SUV_{Kurtosis}$	1.4 (1.0 - 1.8)	0.044
Distant Recurrence Free Survival	$GLSZM_{SZNUN}$	1.5 (2.8e-07-0.35)	0.024
Distant Recurrence Free Survival	$GLSZM_{SZNUN}$	1.6 (0.95-1.5)	0.011

Features could **stratify survival** even amongst **high grade tumours**

High – Grade Subgroup Analysis (Grade 2/3: n = 35)



Survival Median: 65.6 months vs 43.1 months



Survival Median: 24.2 months vs not reached

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Limitations

Retrospective nature

Patient Cohort

- **Small patient cohort** (n = 44)
- Relatively **short follow up** (mean = 28.6 months)

High correlation between features

- SUVKurtosis & SUVSkewness
  - (cor = 0.76, $p < 0.001$)

Conclusion

In this cohort, radiomic features, especially **measures of heterogeneity**, demonstrated significant prognostic utility **independent of clinical stage** and could **predict all measured survival outcomes**.

Discussion: Future Directions

Identified PET radiomic features need to be tested for robustness and reproducibility in **large, prospective, multi-centre studies**

Incorporated directly into clinical practice and **guide treatment** & determine **follow up intervals**

Machine learning algorithms and deep learning approaches

Questions/Discussion?