Baseline PET Radiomics for Non-Invasive Risk Stratification in Hodgkin Lymphoma

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2026 JULY 19–22 VANCOUVER, BC
JOINT AAPM | COMP MEETING

ABSTRACT

Purpose: To identify distinct subgroups of patients with classic Hodgkin lymphoma (cHL) using unsupervised clustering of PET/CT-derived radiomic features, and to evaluate their prognostic associations with freedom from progression (FFP).
Methods: Baseline 18FDG PET/CT images were processed using an automated segmentation and PyRadiomics-based pipeline, extracting 1,316 features. Each feature was log transformed, z-score standardized, with a redundancy reduction correlation coefficient filter applied. Principal component analysis and a Gaussian mixture model (GMM) were used to assign radiomic clusters. Freedom from progression (FFP) was measured using Kaplan–Meier. A multivariable Firth-penalized Cox regression model was constructed using cluster membership after adjustments for age, stage, and sex.
Results: We identified 197 patients with cHL diagnosed at Stanford University between 2015-2024, with median age of 32 (range=6-79), 64.5% with early vs 35.5% with advanced stage, median IPS of 2, and median follow-up of 3.98 years. The GMM model partitioned into three radiomic clusters: RC1 (n=104; 53%), RC2 (n=53; 27%), and RC3 (n=40; 20%). RC1 was defined by heterogeneous texture and low tumor volumes, RC2 by homogenous texture and low tumor volumes, and RC3 by heterogeneous texture and high tumor volumes. The 4-year FFP was 68.2%, 82.2%, and 48.4% for RC1, RC2, and RC3, respectively (P=0.015). In a multivariable Cox model adjusted for age, stage, and sex, both RC1 (HR 1.96, 95% CI 1.01–4.13, p = 0.046) and RC3 (HR 2.82, 95% CI 1.32–6.37, p = 0.007) had higher risk of a PFS event relative to RC2. Posterior probabilities from the GMM clustering provided each patient with a continuous probability of belonging to each radiomic cluster. In time-dependent survival analyses and receiver-operator curves, a clinical-radiomic risk model incorporating these GMM posterior probabilities and 5-fold cross-validation trials (500 iterations) yielded high area under curve performance (AUC=0.68 at 4 years), which outperformed total metabolic tumor volume alone (AUC=0.61).
Conclusion: Unsupervised clustering of PET/CT-derived radiomic features can reproducibly identify three prognostically distinct cHL subgroups. These clusters capture significant FFP differences of these subgroups that remain independent of established clinical covariates including age, stage, and sex, suggesting that radiomic phenotyping may provide independent and complementary prognostic value.

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INTRODUCTION

- Classic Hodgkin lymphoma (cHL) is highly treatable, but some patients still progress after frontline therapy highlighting the need for better risk stratification
- Current prognostic models (Ann Arbor stage, IPS, baseline PET/CT metabolic tumor volume) incompletely capture cHL's biological heterogeneity and poorly identify high risk patients
- Radiomics extracts quantitative imaging features, characterizing tumor phenotype (texture, morphology, spatial heterogeneity) beyond visual assessment
- Unsupervised machine learning (e.g., Gaussian mixture modeling) can use these high dimensional features to uncover latent patient subgroups without predefined labels
- This study applied an automated PET/CT radiomic pipeline to 197 cHL patients at Stanford to identify imaging based clusters and assess their independent association with freedom from progression

METHODS AND MATERIALS

- Image processing: Automated segmentation and PyRadiomics pipeline extracted 1,316 features from baseline 18FDG PET/CT (**Figure 1**)
- Preprocessing: Features log transformed, z-score standardized, and redundancy filtered by correlation coefficient
- Clustering: PCA and a Gaussian mixture model (GMM) assigned radiomic clusters
- Outcome: FFP measured by Kaplan Meier
- Modeling: Firth penalized multivariable Cox regression on cluster membership, adjusted for age, stage, and sex

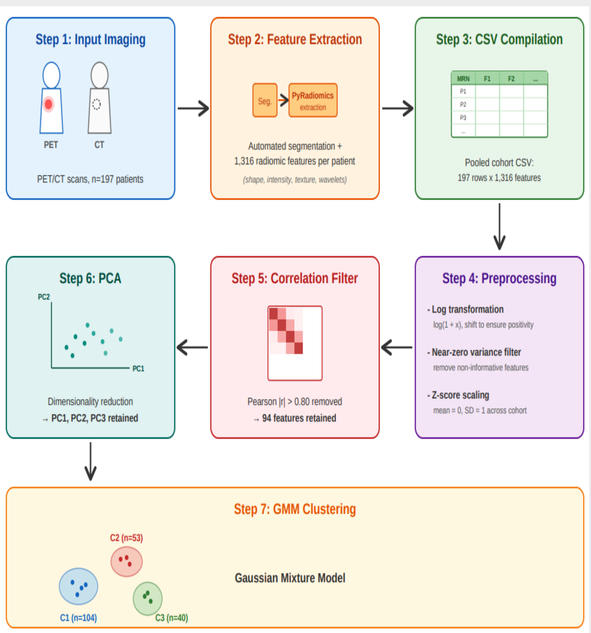

Figure 1. Study Design

RESULTS

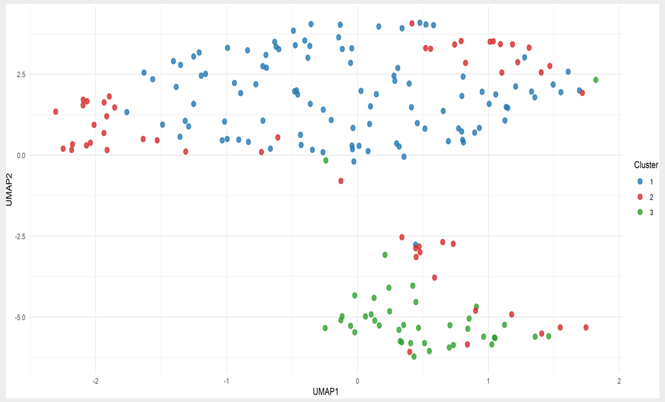

Figure 2. UMAP plot of the 3 GMM clusters

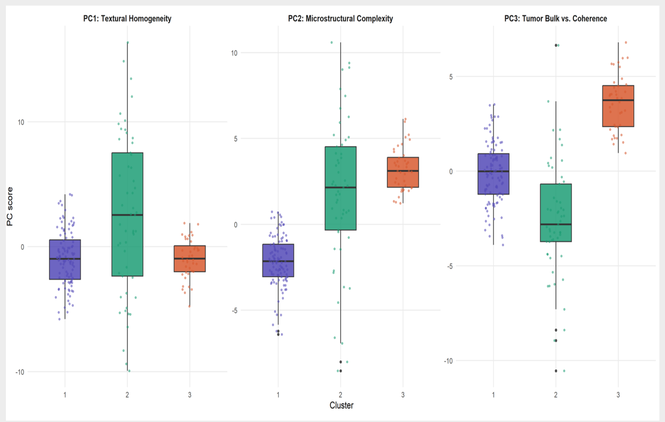

Figure 3. PC scores per cluster

	Overall							
	1-yr	2-yr	3-yr	4-yr	5-yr	6-yr	7-yr	8-yr
MTV alone (MeshVolume)	0.60	0.61	0.59	0.61	0.61	0.62	0.59	0.63
Cluster 1	0.53	0.53	0.54	0.54	0.54	0.54	0.57	0.56
Cluster 2	0.53	0.57	0.60	0.64	0.65	0.67	0.61	0.57
Cluster 3	0.55	0.56	0.59	0.60	0.61	0.63	0.60	0.64
3 Cluster Combined	0.56	0.57	0.60	0.64	0.62	0.65	0.60	0.58
Cluster + clinical	0.58	0.65	0.65	0.68	0.64	0.64	0.63	0.64

Table 1. AUC values at 1-8 years

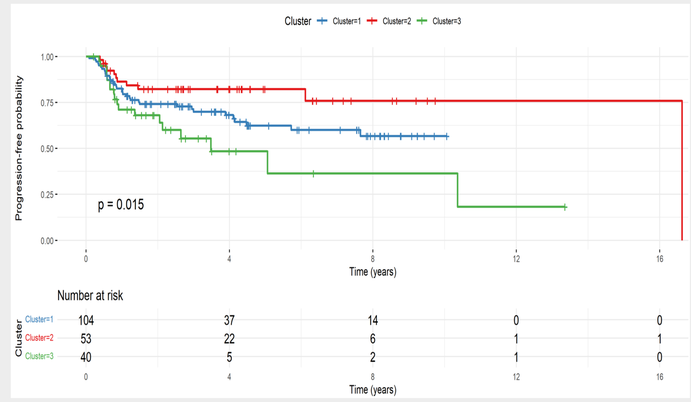

Figure 5. Kaplan-Meier curve of the 3 GMM clusters

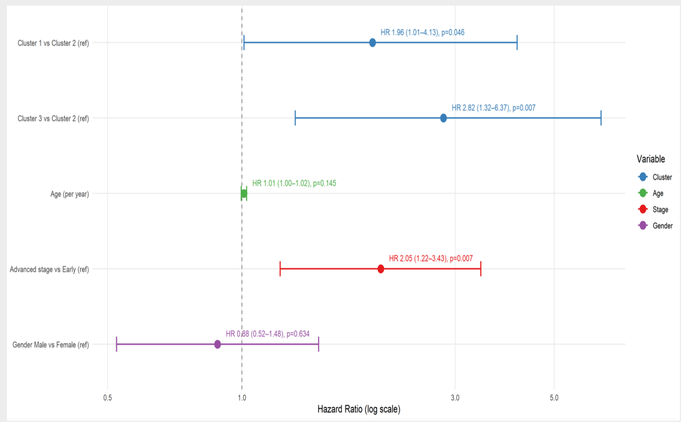

Figure 4. Multivariable Firth Cox – Hazard Ratios

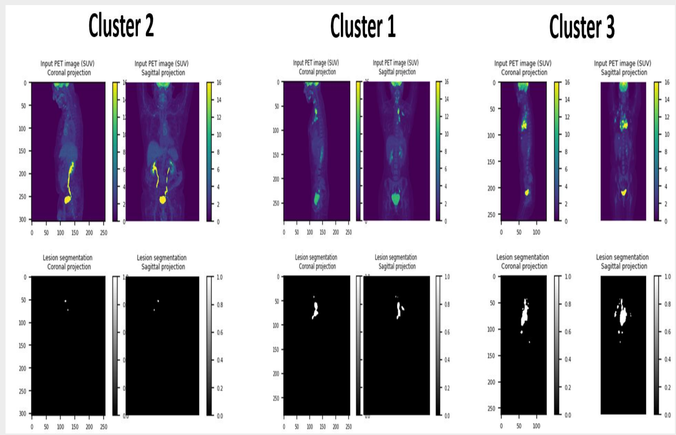

Figure 6. PET/CT segmentation scans of patients from each of the 3 clusters

- Cohort: 197 cHL patients diagnosed at Stanford (2015–2024); median age 32 (range 6–79), 64.5% early vs 35.5% advanced stage, median IPS 2, median follow-up 3.98 years
- Clusters: The GMM partitioned patients into three radiomic clusters — RC1 (n=104; 53%), RC2 (n=53; 27%), RC3 (n=40; 20%) (**Figure 2**)
- Cluster phenotypes: RC1 — heterogeneous texture, low tumor volume; RC2 — homogeneous texture, low tumor volume; RC3 — heterogeneous texture, high tumor volume (**Figure 3**)
- 4-year FFP: 68.2% (RC1), 82.2% (RC2), 48.4% (RC3); P=0.015 (**Figure 5**)
- Multivariable Cox (adjusted for age, stage, sex): Relative to RC2, both RC1 (HR 1.96, 95% CI 1.01–4.13, p=0.046) and RC3 (HR 2.82, 95% CI 1.32–6.37, p=0.007) had higher risk of a PFS event (**Figure 4**)
- Risk model: A clinical-radiomic model using GMM posterior probabilities (5-fold CV, 500 iterations) achieved AUC=0.68 at 4 years, outperforming total metabolic tumor volume alone (AUC=0.61) (**Table 1**)

CONCLUSION

- Unsupervised clustering of PET/CT radiomic features reproducibly identified three prognostically distinct cHL subgroups
- Clusters captured significant FFP differences independent of age, stage, and sex
- Radiomic phenotyping may offer independent, complementary prognostic value

REFERENCES

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2. van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, Beets-Tan RGH, Fillion-Robin JC, Pieper S, Aerts HJWL. Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Res. 2017 Nov 1;77(21):e104-e107. doi: 10.1158/0008-5472.CAN-17-0339. PMID: 29092951; PMCID: PMC5672828.