Combination of FDG PET/CT Radiomics and Clinical Parameters for Outcome Prediction in Patients with Hodgkin's Lymphoma

Claudia Ortega (claudia.ortega@uhn.ca)
University of Toronto https://orcid.org/0000-0003-3357-1849
Yael Eshet
Chaim Sheba Cancer Research Centre: Sheba Medical Center
Anca Prica
Princess Margaret Hospital Cancer Centre
Reut Anconina
Sunnybrook Health Sciences Centre
Sarah Johnson
University of Toronto
Danny Constantini
University of Toronto
Sareh Keshavarzi
Princess Margaret Hospital: Princess Margaret Hospital Cancer Centre
Kulanthaivelu Roshini
University of Toronto
Ur Metser
University of Toronto
Patrick Veit-Haibach
University of Toronto

Research Article

Keywords: Hodgkin Lymphoma, predictor models, radiomics, PET/CT

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1340117/v1

Abstract

Purpose:

The aim of the study is to evaluate the prognostic value of joint evaluation of PET- and CT radiomics combined with standard clinical parameters in patients with HL.

Methods:

Overall, 88 patients (42 female and 46 male) with a median age of 43.3 (range 21-85 years) were included. Textural analysis of the PET/CT images was performed using a freely available software (LIFE X). 65 radiomics features (RF) were evaluated. Univariate and Multivariate models were used to determine the value of clinical characteristics and FDG PET/CT radiomics in outcome prediction. A binary logistic regression model was used to determine potential predictors for radiotherapy and odds ratios (OR) with 95% confidence intervals (CI) were reported. Features relevant for survival outcome were assessed with Cox proportional hazards to calculate hazard ratios with 95% CI.

Results:

Overall, Albumin + ALP + CT radiomic features (Area under curve (AUC): 95.0 (86.9;100.0) – Brier: 3.9 (0.1;7.8) remained as significant independent predictors for outcome prediction. PET- SHAPE Sphericity (1.9 (1.05,3.42) p=0.033); CT grey level zone length matrix high gray-level zone emphasis (GLZLM SZHGE mean (2 (1.08,3.73) p=0.028)) and PARAMS XSpatial Resampling (2.1 (1.2,3.68) p=0.0091) as well as hemoglobin results (p=0.016) remained as independent features in the final model for binary outcome as predictors of need of radiotherapy. (AUC = 0.79)

Conclusion:

We evaluated the value of baseline clinical parameters as well as combined PET and CT radiomics in HL patients for survival and prediction of need of radiotherapy. We found that different combinations of all three factors/features were independently predictive of the here evaluated endpoints.

Introduction

Hodgkin lymphoma (HL) is one of the most common malignancies involving the lymphatic system. The 5-year survival rate for all people with Hodgkin lymphoma is high, overall rate of around 87%. [1]

Given the bimodal peak incidence with high rates of presentation at a young age, an individualized, risk-adapted therapy is desirable to maintain high cure rates while minimizing treatment-related toxicity. [2, 3]

Correct identification of predictive biomarkers that correlate with poor therapy response and overall poor prognosis are essential for a personalized therapy approach, which is crucial to select patients that would benefit from an initial more aggressive therapy, while avoiding over-treatment in patients with a high likelihood of good prognosis.. [4–7]

Molecular imaging with clinical standard positron emission tomography (PET)/computed tomography (CT) using the radiopharmaceutical ^{18}F-fluoro-deoxy-glucose (FDG) is the main imaging procedure for baseline staging of lymphoma, interim response assessment and evaluation of residual disease in many jurisdictions worldwide. [8]

Standardized uptake value (SUV) obtained from FDG PET/CT scans is the most widely used parameter for lesion depiction and characterization and it provides a reliable assessment of tumor activity, of tumor aggressiveness and response to treatment. [9]

However, SUV is not reflective of the underlying spatial distribution of tracer activity within a tumor itself, which can be particularly heterogeneous in lymphoma [10]. The unequal distribution of tracer activity within a tumor on FDG PET/CT is a manifestation of this ‘intra-tumor heterogeneity’, which can be measured by analyzing the variation in the spatial arrangements of voxel intensities. [11]

In recent years, there has been increasing interest in Radiomics, the science of extracting and analyzing quantitative and mineable features from standard-of-care biomedical images to create texture analysis of cross-sectional images (CT, MRI and PET) which may provide detailed information of the underlying pathophysiology. Radiomics features of a tumor may provide additional information regarding tumor biology and behavior. [12–16]

Numerous studies have investigated intra-tumor heterogeneity on PET/CT in patients with tumors of the brain, head and neck, thyroid, lung, breast, esophagus, pancreas, colon, cervix, as well as in patients with sarcomas and lymphomas. [17–21]

Current clinical lymphoma biomarkers incorporate cellular and molecular data to classify specific disease subtypes and predict clinical behavior [22].

The association between intra-tumor image-based heterogeneity and biological heterogeneity has been shown to correlate with clinical outcomes such as treatment response and survival in a variety of tumor types, including lymphoma. This suggests that radiomic biomarkers can be developed and cross-referenced with established clinical cellular and molecular biomarkers to better predict outcomes and influence evidence based clinical decision making in patients with lymphoma. [22–30]

The aim of this study is to evaluate the prognostic value of joint PET- and CT radiomics combined with standard clinical parameters in patients with HL. We hypothesize that some hidden radiomics features content within the baseline PET/CT may predict survival outcomes.

Materials And Methods

Study cohort

Within this REB - approved retrospective study 88 patients diagnosed and treated in a tertiary referral center with HL) from September 2012 to June 2016 were evaluated.

All patients had complete clinical records including pathology reports from either nodal or extra nodal biopsy, or descriptions of sites of involvement, presence of bulky disease, Ann Arbor Stage, and B symptoms. Furthermore, all standard of care bloodwork, systemic treatment planned and received, as well as provision of radiotherapy treatment along with response assessment for each line of therapy was recorded. Follow up times; Progression free survival and Overall survival were recorded.

Imaging acquisition

^{18}F FDG PET/CT was performed in these patients as a component of baseline staging. Images were obtained according to our institutional protocol as follows: [23]

PET was performed on a Siemens mCT40 PET/CT scanner (Siemens Healthcare). Patients were positioned supine with arms outside the region of interest. Images were obtained from the top of the skull to the upper thighs. Iodinated oral contrast material was administered for bowel opacification; no intravenous iodinated contrast material was used. Overall, 5–9 bed positions were obtained, depending on patient height, with an acquisition time of 2–3 min per bed position. CT parameters were 120 kV; 3.0 mm slice width, 2.0 mm collimation; 0.8 sec rotation time; 8.4 mm feed/rotation. A PET emission scan using time of flight with scatter correction was obtained covering the identical transverse field of view. PET parameters were as follows: image size: 2.6 pixels; slice: 3.27; and 5-mm full width at half maximum (FWHM) gaussian filter type.

Textural analysis

Textural analysis of the PET/CT images was performed using a freely available software LIFE X (lifexsoft.org) [31]. Primary contour on FDG-avid nodal and extranodal lesions was performed semi-automatically by the software (with minor manual correction when needed) using a thresholding method to define each volume of interest (VOI). PET VOI were subsequentially defined based on background pre-defined thresholds including threshold at 40% of the and at 70% of SUVmax as commonly used in clinical setting. [26]

Individual lesions were selected and measured two per organ, maximum five different sites [32] and then labeled as nodal or extranodal involvement for each specific site (Figure 1). Lesions smaller than 64 voxels were excluded since they did not fulfill the minimum size criteria for feature extraction by the software.

Since a thresholding method is not available for the CT-component, the contours for the CT derived volume of interest were performed manually, slice-by-slice to cover the entire tumor volume as previously

describe in the literature.

65 radiomics features (RF) were obtained by the software including: conventional metrics features reporting the mean, median, maximum, minimum values of the voxel intensities on the image; size and shape histogram-based features such as volume, compacity and sphericity including their asymmetry (skewness), flatness (kurtosis), uniformity, and randomness; and additional textural features, such as GLCM- Gray-Level Co-occurrence Matrix, GLRLM- Grey-Level Run Length Matrix, NGLDM- Neighborhood Grey-Level Different Matrix, GLZLM- Grey-Level Zone Length Matrix.

Statistical analysis

In this study, two main outcomes were considered. First, Survival Outcome, which corresponds to a composite combination of Progression Free Survival (PFS) + Overall Survival (OS), given the small number of adverse events in our cohort. A second endpoint named radiotherapy outcome", defined as evaluation if radiomics at baseline PET can predict the need for radiotherapy after completion of chemotherapy. The latter endpoint is a binary outcome, where those who received radiation are assigned a score of 1, while those who did not receive radiation are assigned a score of 0.

The characteristics of patients were presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Univariate and multivariate models were used to determine the role of baseline demographics, clinical characteristics, and FDG PET/CT radiomics in predicting the outcome of patients with lymphoma. A binary logistic regression model was used to determine potential risk factors for Radiotherapy Outcomes and the odds ratios (OR) with 95% confidence intervals (CI) were reported. The Cox proportional hazards regression, on the other hand, was used to determine Survival Outcome factors and to calculate hazard ratios (HR) with 95% CI. In both logistic and Cox models, variables with a p-value of less than 0.10 in the univariate analysis were considered for inclusion in the multivariate analysis, and variables with a p value of less than 0.05 were retained in the final model. Pearson correlation is calculated to check the correlation between clinical, PET, and CT radiomics factors. In addition, predictors with high variance inflation factors are excluded from the models to avoid multicollinearity caused by correlated predictors. The area under the receiver operating characteristic curve (AUC), which indicates the predictive accuracy of a model, was used to determine if the CT and PET variables would improve predictive accuracy over the demographic and clinical risk factors. AUC of 0.5 represents random predictions, and AUC of 1 represents perfect predictions. The R package (version 3.6.3, R Foundation for Statistical Computing, https://www.R-project.org/) was used primarily for statistical analysis.

Results

Study population

Overall, 88 patients, 42 women (48%) and 46 men (52%) with a median age of 43.3 (range 21-85 years) were included. A summary of the patient population is presented in Table 1.

Table 1
Summary of patient population

Population	**Age years [range]**
88 patients	43.3 [21-85]
Distribution	**N (%)**
Female	42 (48)
Male	46 (52)
Pathology	**N (%)**
Classical Hodgkin's lymphoma	16 (18)
Mixed cellularity classical Hodgkin lymphoma	5 (6)
Nodular lymphocyte predominant Hodgkin lymphoma	11 (12)
Nodular sclerosis classical Hodgkin lymphoma	56 (64)
Disease location	**N (%)**
Nodal disease	87 (98)
Extranodal disease	56 (63)
Bulky presentation	5 (5)
Overall stage	**N (%)**
Stage IA	5 (6)
Stage IIA	33 (39)
Stage IIB	8 (9)
Stage IIIA	14 (16)
Stage IIIB	4 (5)
Stage IVA	10 (11)
Stage IVB	13 (15)
B-symptoms	25 (28)

Initial curative treatment was intended for all the patients. Combined doxorubicin + bleomycin + vinblastine + dacarbazine (ABVD) was the initial therapy of choice in 91% (n=79) of patients, with 62% (n=54/88) receiving 6 cycles and 94% of them (n=82/88) completing therapy as initially planned. Of those, 84% (n=72/88) achieved complete metabolic response (CMR) at end of therapy PET/CT defined by Deauville score criteria below 4. [34–40]

Overall, 48% (n=43/88) underwent additional radiotherapy for residual FDG-avid disease or to sites of bulky disease, achieving complete metabolic response in 95% (n= 41/43).

At a mean follow-up of 33.9 months (range 6-65), response to treatment was complete response (CR) in 88% (n=76), progressive disease (PD) in 8% (n=7); partial response (PR) in 2% (n=2) and stable disease (SD) in 1% (n=1) and not evaluated 2% (n=2) because of loss of follow-up. There were 10 adverse events during the follow up period (defined as death, progression based on follow up CT or PET/CT, or relapse).

Univariate analysis

The statistically significant results of the Univariable Cox regression analysis for CT and PET parameters when considering either nodal-only involvement or when considering all sites of disease involvement, as well as correlation with composite survival as previously described and predictors of radiotherapy, are summarized in Table 2 and 3. Of note, only one CT- parameter (GLZLM SZHGE mean) was found to be significant for prediction of need for radiotherapy in both categories (nodal vs. all sites), whereas several yet similar parameters (Shape and GLRLM) were found to be significant for prediction of the composite outcome endpoint. The results for PET showed similar trends: Shape, GLRLM- as well as GLZLM features were found to be significant in all evaluation categories. Interestingly, a rather ‘standard’ feature like TLG was found to be predictive as well.

Table 2
UVA for CT parameters when correlated with PFS and radiotherapy prediction

Parameter	HR	95%CI	p value
CT parameters for NODAL involvement to PFS			
SHAPE Volume mL	1.99	1.22 - 3.26	0.0061
SHAPE Volume vx mean	1.97	1.16 - 3.34	0.012
GLRLM GLNU mean	2.06	1.25 - 3.4	0.0045
GLRLM RLNU mean	1.84	1.08 - 3.13	0.025
GLZLM GLNU mean	1.65	1.0 - 2.73	0.048
CT parameters for NODAL involvement to radiotherapy outcome			
GLZLM SZHGE mean	1.84	1.07 - 3.15	0.026
CT parameters for ALL SITES involvement to PFS			
SHAPE Volume mL mean	1.96	1.19 - 3.22	0.008
SHAPE Volume vx mean	1.97	1.17 - 3.33	0.011
GLRLM GLNU mean	1.99	1.24 - 3.19	0.0043
GLRLM RLNU mean	1.88	1.09 - 3.25	0.023
GLZLM GLNU mean	1.77	1.01 - 3.09	0.046
CT parameters for ALL SITES involvement to radiotherapy outcomes			
	OR	95% CI	P value
GLZLM SZHGE mean	1.67	1.01 - 2.76	0.047

Table 3. Univariate analysis (UVA) for PET parameters when correlated with PFS and radiotherapy prediction

	Parameter	HR	95% CI	p value
PET volume 100% threshold for NODAL and PFS				
CONVENTIONAL TLG mean	1.89	1.15 - 3.12	0.013	
SHAPE Volume mL mean	2.1	1.24 - 3.54	0.0055	
GLRLM LRE mean	1.77	1.04 - 3.01	0.035	
GLZLM LZE mean	1.66	1.15 - 2.4	0.0072	
PET volume 100% threshold ALL SITES and PFS				
CONVENTIONAL TLGm mean	1.79	1.09 - 2.95	0.022	
SHAPE Volume mean	1.96	1.16 - 3.32	0.012	
GLZLM LZE mean	1.65	1.14 - 2.39	0.0085	
NO predictors of radiotherapy outcome using PET volume 100% threshold were found				
PET volume 70% threshold for NODAL and PFS				
CONVENTIONAL TLG mean	1.94	1.15 - 3.27	0.013	
SHAPE Volume mL mean	2.16	1.29 - 3.64	0.0037	
GLRLM GLNU mean	2.1	1.08 - 4.09	0.028	
GLZLM LZE mean	1.53	1.08 - 2.17	0.016	
PET volume 70% threshold for NODAL and radiotherapy outcome				
	OR	**95% CI**	**p value**	
HISTO Entropy log10 mean	0.6	0.36 - 0.99	0.047	
PET volume 70% threshold ALL SITES and PFS				
CONVENTIONAL TLG mean	1.84	1.09 - 3.09	0.022	
SHAPE Volume mL mean	2.02	1.2 - 3.42	0.0086	
GLRLM GLNU mean	2.02	1.06 - 3.87	0.033	
GLZLM LZE mean	1.53	1.08 - 2.17	0.018	

PET volume 70% threshold ALL SITES and radiotherapy outcomes			
HISTO Entropy log10 mean	0.6	0.36 – 1.0	0.049
PET volume 40% threshold NODAL and PFS			
CONVENTIONAL TLG mean	1.53	1.03 - 2.28	0.036
SHAPE Volume mean	1.9	1.23 - 2.92	0.0037
GLRLM GLNU mean	2.27	1.3 - 3.96	0.0039
GLRLM RLNU mean	2.59	1.44 - 4.66	0.0015
PET volume 40% threshold ALL SITES and PFS			
CONVENTIONAL TLG mean	1.51	1.0 - 2.27	0.048
SHAPE Volume mean	1.87	1.2 - 2.91	0.006
GLRLM GLNU mean	1.79	1.09 - 2.95	0.022
GLRLM RLNU mean	1.71	1.09 - 2.68	0.019
GLZLM LZE mean	2.22	1.1 - 4.49	0.025
NO predictors of radiotherapy outcome using PET volume 40% threshold were found			

Multivariate Analysis (MVA) parameters correlated with survival composite outcome

Multivariable Cox regression analysis was performed based on significant parameters from univariate analysis (UVA). The parameters with the lowest p-value (clinical as well as imaging parameters) were used for model building for the composite outcome which included Albumin (p= 0.034); ALP (p=0.028) and CT gray scale parameter grey level run length matrix non-uniformity for run (GLRLM GLNU mean (2.52 (1.22, 5.18) p=0.012)). It was found that ALP + CT (AUC: 85.0 (61.1;100.0) – Brier: 5.1 (0.8;9.4), Albumin + ALP (AUC: 90.8 (83.4;98.3) – Brier: 6.6 (1.6;11.6), Albumin + CT (AUC: 91.8 (83.0;100.0) – Brier: 5.2 (0.4;10.0) and Albumin + ALP + CT (AUC: 95.0 (86.9;100.0) – Brier: 3.9 (0.1;7.8) remained as significant independent predictors for composite outcome prediction.

MVA parameters predictors of need for Radiotherapy

For the prediction of need for radiotherapy, a few parameters were significant in the UVA including Overall Stage 3. This parameter was however excluded from the MVA given that this was already predefined by the images and could potentially introduce bias.

Therefore, first order PET parameters SHAPE Sphericity (1.9 (1.05,3.42) p=0.033); CT parameter grey level zone length matrix high gray-level zone emphasis (GLZLM SZHGE mean (2 (1.08,3.73) p=0.028)) and PARAMS XSpatial Resampling (2.1 (1.2,3.68) p=0.0091) as well as abnormal hemoglobin results (p=0.016) remain as independent features in the final model for binary outcome as predictors of radiotherapy. (AUC = 0.79). Figure 2.

Discussion

In our study, we evaluated the utility of combined PET/CT radiomics features as well as clinical parameters for outcome prediction of patients with Hodgkin's lymphoma (HL).

So far, only a few radiomics studies have been performed in HL populations addressing outcome prediction and even fewer have considered clinical parameters as well as combined PET *and* CT features for outcome prediction. We found that CT as well as PET radiomics combined with clinical parameters might be able to help predict outcome endpoints like PFS and OS as well as the need for additional radiotherapy.

We found several radiomics parameters from baseline FDG PET/CT to be predictors of survival and predictors for the need for radiotherapy in the univariable analysis. However, when multivariable models were designed, considering the parameter with the lowest p-value for the model building, no PET-related parameter was found to be an independent predictor for the composite survival. This is concordant with a few earlier studies that evaluated a similar question, including first order parameters such as SUVmax. For example, Frood et al [27] recently published a meta-analysis for baseline PET/CT imaging parameters as predictor of treatment outcome in Hodgkin and diffuse large B-cell lymphomas (DLBCL). In the meta-analysis 10 studies assessing SUVmax as predictor of response, however, none none of the studies evaluated radiomics features. The largest study, by Akharti et al. [38] demonstrated that SUVmax could not be applied to predict either PFS or OS in 267 patients. Interestingly, in our study, a CT second order parameter was a predictor of survival when combined with clinical parameters such as albumin and ALP.

Driessen, J et al. [25] recently presented a radiomics analysis in a larger cohort of patients with relapsed HL. They found that a combination of radiomics and clinical features results in a strong prediction model for 3-year time to progression. The model uses robust PET features that address inter-lesional heterogeneity in distance, metabolic volume and SUV, but did not include any second or higher order radiomic features, as compared to our study. In addition, this investigation did not include radiomics evaluation of the CT- component of the PET/CT.

A recent study by Zhou and co-workers evaluated if the radiomic features of baseline FDG PET could predict the prognosis of Hodgkin lymphoma [39]. They found that Long-zone high gray-level emphasis and Dmax were independently correlated with 2-year progression-free survival. Again, however, this study

did not evaluate the complementary CT-radiomics, and did not integrate any clinical information into their AUC analysis. Furthermore, they evaluated a smaller number of patients, which were further divided into a training and validation data set which likely decreases statistical robustness.

Another study has taken a somewhat different approach, evaluating 45 patients receiving R-CHOP (Rituximab+ Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) chemotherapy for DLBCL, evaluating the ability to predict therapy response [40]. Here, the authors concluded that that SUV_{max} and gray level co-occurrence matrix dissimilarity were independent predictors of lesions with incomplete response.

Milgrom, S.A. et al. [29] analyzed a cohort of 251 mediastinal HL patents using another freely available software (IBEX). They found that first order parameters MTV and TLG are associated with disease progression in HL. None of the second order parameters were predictors of progression in their cohort either.

Lue et al. [24] investigated 11 first order, 39 higher order features in 42 patients with HL to predict PFS and OS. With 21 events in the cohort (12 relapses, 9 deaths) it was demonstrated that SUV, kurtosis, stage and intensity non-uniformity (INU) derived from Grey-Level Run Length Matrix (GLRLM) were independent predictors of PFS and only disease stage and INU derived from GLRLM were independent predictors of OS.

Overall, compared to the relatively sparse, directly comparable literature, in our study none of the PET-derived radiomic features were found to be independent features in the MVA for composite survival prediction. Since several PET-radiomic features were found to be significant in the UVA, if we had evaluated only PET radiomics features, it might be that those parameters would have been significant in the MVA and therefore, we would have more comparable results to other studies. However, in our investigation, PET radiomics parameters were ‘outperformed’ by the CT-radiomic features (which consequently ended up in the MVA) and were therefore not directly compared to the available studies. We feel that, since PET/CT is a hybrid imaging modality in clinical routine, both components (the PET *and* the CT) should be evaluated in a complementary fashion and as demonstrated, there appears to be value in CT-derived textural features as well.

However, in our cohort, a PET first order parameter, SHAPE Sphericity, and the CT second order features, GLZLM SZHGE mean and PARAMS XSpatial Resampling, were independent predictors for the need of radiotherapy when combined with hemoglobin result at baseline lab work (AUC=0.79) which again underlines the values for *combined* radiomic evaluation of PET and CT. It has to be pointed out that the clinical decision to apply additional radiotherapy is often multifactorial and that not only one clinical scenario indicates the need for radiotherapy in HL patients. However, based on our analysis, the integration of combined CT and PET radiomics features might be of further guidance/help to decide which patients might profit from additional radiotherapy for improvement of their disease outcome.

Again, similar to other studies cited above, only first order and morphologic PET radiomic features were found to be significant and thus, not necessarily intrinsically related with voxel characteristics. For CT, however, two second order features were found to be of value (i.e. GLZLM SZHGE). As for the comparable literature, no other studies evaluated predictors for the need for radiotherapy, besides the bulkiness of the tumor and therefore this finding may open a window for further analysis in larger cohorts.

Several other new studies have evaluated different aspects of radiomics i.e. in MRI or in PET, but those studies concentrated on technical aspects of the analysis itself rather than the ability of radiomics for prediction. Also, PET/CT radiomics has been thoroughly evaluated in non-Hodgkin lymphoma and in the context of prediction for bone marrow involvement, but as this was done for follicular lymphoma these studies are not specifically relevant for HL patients [41–44].

Concerning the integration of clinical parameters, it has been shown in the literature that ALP is not necessarily a predictive clinical parameter on its own. While that is certainly valid from a dedicated clinical perspective, in our cohort it has been found to be of predictive value in conjunction with the here evaluated imaging features. Thus, the integration of combined PET and CT radiomics features may elevate the value of specific clinical parameters when evaluated in conjunction.

Limitations

This study has several limitations.. First, this is a retrospective analysis of data acquired in a single tertiary oncology center so transferability to secondary centers might be limited. Second, the patient population is relatively small However, we do evaluate partly unique endpoints which have not been assessed in many other investigations. Third, few adverse events were observed, but this is expected in this malignancy and population. Thus, a composite survival outcome including OS + PFS was created. Results may vary in larger cohorts with more potential adverse events, which might allow evaluation of separate outcomes as TTP or OS. Further prospective analysis to confirm our concepts and findings would be valuable.

Conclusion

We evaluated the value of baseline clinical parameters as well as combined PET and CT radiomics in HL patients for survival and prediction of need of radiotherapy. We found that different combinations of all three factors/features were independently predictive of the survival outcome and radiotherapy outcome as outlined above.

Declarations

FUNDING: This study did not receive any funding.

CONFLICT OF INTEREST: No conflict of interest for the authors to disclose.

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

INFORMED CONSENT: Informed consent was obtained from all individual participants included in the study.

References

1. Statistics adapted from the American Cancer Society's (ACS) publication, Cancer Facts & Figures 2021, and the ACS website. Additional source was: Seigel R, et al.: Cancer Statistics 2021. CA: A Cancer Journal for Clinicians. 2021 Jan; 71(1):7-33. doi/full/10.3322/caac.21654
2. Engert, A. et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 363, 640–652, https://doi.org/10.1056/NEJMoa1000067 (2010).
3. Eich, H. T. et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 28, 4199–4206, https://doi.org/10.1200/JCO.2010.29.8018 (2010)
4. Bonfante, V. et al. Outcome of patients with Hodgkin's disease failing after primary MOPP-ABVD. J Clin Oncol 15, 528–534, https://doi.org/10.1200/JCO.1997.15.2.528 (1997).
5. Moskowitz, C. H. et al. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. Br J Haematol 124, 645–652 (2004)
6. Allen, P. B. & Gordon, L. I. Frontline Therapy for Classical Hodgkin Lymphoma by Stage and Prognostic Factors. Clin Med Insights Oncol 11, 1179554917731072, https://doi.org/10.1177/1179554917731072 (2017)
7. Shanbhag S, Ambinder RF. Hodgkin lymphoma: a review and update on recent progress. CA Cancer J Clin. 2018;68:116–32.
8. Wright CL, Maly JJ, Zhang J, Knopp MV. Advancing Precision Nuclear Medicine and Molecular Imaging for Lymphoma. PET Clin. 2017;12:63-82.
9. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. *Eur J Nucl Med Mol Imaging*. 2017;44(Suppl 1):97-110. doi:10.1007/s00259-017-3690-8
10. Schürch CM, Federmann B, Quintanilla-Martinez L, Fend F. Tumor Heterogeneity in Lymphomas: A Different Breed. Pathobiology. 2017.
11. Hatt M, Majdoub M, Vallières M, et al. 18F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. J Nucl Med. 2015;56:38-44.
12. Fang YH, Lin CY, Shih MJ, et al. Development and evaluation of an open-source software package "CGITA" for quantifying tumor heterogeneity with molecular images. Biomed Res Int. 2014;2014:248505.

13. Mayerhoefer M, Materka A, Langs G, et al. Introduction to Radiomics. J Nucl Med April 1, 2020 vol. 61 no. 4 488-495.
14. Lee JW, Lee SM. Radiomics in Oncological PET/CT: Clinical Applications. Nucl Med Mol Imaging. 2018 Jun.
15. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology. 278 (2): 563-77. doi:10.1148/radiol.2015151169.
16. Hatt M, Tixier F, Visvikis D and Le Rest C. Radiomics in PET/CT: More Than Meets the Eye?. J Nucl Med 2017 58:365-366 10.2967.
17. Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-Welsch C, Hellwig D, Rube C, et al. Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-small cell lung cancer. J Nucl Med. 2005;46(8):1342–1348.
18. Sah BR, Owczarczyk K, Siddique M, et al. Radiomics in esophageal and gastric cancer. Abdom Radiol (NY). 2018 Aug.
19. Werner RA, Weich A, Kircher M, et al. The theranostic promise for Neuroendocrine Tumors in the late 2010s - Where do we stand, where do we go? Theranostics. 2018;8(22):6088-6100. Published 2018 Nov 29. doi:10.7150/thno.30357.
20. Ha S, Park S, Bang JI, Kim EK, Lee HY. Metabolic radiomics for pretreatment (18)F-FDG PET/CT to characterize locally advanced breast cancer: histopathologic characteristics, response to neoadjuvant chemotherapy, and prognosis. Sci Rep. 2017;7(1):1556.
21. Hong R, Halama J, Bova D, Sethi A, Emami B. Correlation of PET standard uptake value and CT window-level thresholds for target delineation in CT-based radiation treatment planning. Int J Radiat Oncol Biol Phys. 2007;67(3):720–726.
22. Sun R, Medeiros LJ, Young KH. Diagnostic and predictive biomarkers for lymphoma diagnosis and treatment in the era of precision medicine. Mod Pathol. 2016;29:1118-1142.
23. Parvez A, Tau N, Hussey D, et al. 18 F-FDG PET/CT metabolic tumor parameters and radiomics features in aggressive non-Hodgkin's lymphoma as predictors of treatment outcome and survival. Ann Nucl Med. 2018 Jul;32(6):410-416.
24. Lue KH, Wu YF, Liu SH, Hsieh TC, Chuang KS, Lin HH, Chen YH. Prognostic Value of Pretreatment Radiomic Features of 18F-FDG PET in Patients with Hodgkin Lymphoma. Clin Nucl Med. 2019 Oct;44(10):e559-e565. doi: 10.1097/RLU.0000000000002732. PMID: 31306204.
25. Driessen, J., Zwezerijnen, G.J.C., Schöder, H., Moskowitz, A.J., Kersten, M.J., Moskowitz, C.H., Eertink, J.J., van de Brug, T., de Vet, H.C.W., Hoekstra, O.S., Zijlstra, J.M. and Boellaard, R. (2021), Predictive value of quantitative ^{18}F-FDG-PET-CT radiomics analysis in 174 patients with relapsed/refractory classical Hodgkin lymphoma. Hematological Oncology, 39:. https://doi.org/10.1002/hon.21_2879.
26. Orlhac F, Soussan M, Maisonobe JA, Garcia CA, Vanderlinden B, Buvat I. Tumor texture analysis in 18F-FDG PET: relationships between texture parameters, histogram indices, standardized uptake values, metabolic volumes, and total lesion glycolysis. J Nucl Med. 2014;55(3):414–422.

27. Frood, R., Burton, C., Tsoumpas, C. et al. Baseline PET/CT imaging parameters for prediction of treatment outcome in Hodgkin and diffuse large B cell lymphoma: a systematic review. Eur J Nucl Med Mol Imaging 48, 3198–3220 (2021). https://doi.org/10.1007/s00259-021-05233-2.
28. Eertink, J.J., van de Brug, T., Wiegers, S.E. et al. 18F-FDG PET baseline radiomics features improve the prediction of treatment outcome in diffuse large B-cell lymphoma. Eur J Nucl Med Mol Imaging (2021). https://doi.org/10.1007/s00259-021-05480-3.
29. Milgrom SA, Elhalawani H, Lee J, Wang Q, Mohamed ASR, Dabaja BS, Pinnix CC, Gunther JR, Court L, Rao A, Fuller CD, Akhtari M, Aristophanous M, Mawlawi O, Chuang HH, Sulman EP, Lee HJ, Hagemeister FB, Oki Y, Fanale M, Smith GL. A PET Radiomics Model to Predict Refractory Mediastinal Hodgkin Lymphoma. Sci Rep. 2019 Feb 4;9(1):1322. doi: 10.1038/s41598-018-37197-z. PMID: 30718585; PMCID: PMC6361903.
30. Hanaoka K, Hosono M, Tatsumi Y, et al. Heterogeneity of intratumoral (111)In-ibritumomab tiuxetan and (18)F-FDG distribution in association with therapeutic response in radioimmunotherapy for B-cell non-Hodgkin's lymphoma. EJNMMI Res. 2015;5:10.
31. C Nioche, F Orlhac, S Boughdad, S Reuzé, J Goya-Outi, C Robert, C Pellot-Barakat, M Soussan, F Frouin, and I Buvat. LIFEx: a freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity. Cancer Research 2018; 78(16):4786-4789.
32. Revised RECIST Guideline Version 1.1: What Oncologists Want to Know and What Radiologists Need to Know. Mizuki Nishino, Jyothi P. Jagannathan, Nikhil H. Ramaiya, and Annick D. Van den Abbeele. American Journal of Roentgenology 2010 195:2, 281-289.
33. Radiomics in Pulmonary Lesion Imaging. Cameron Hassani, Bino A. Varghese, Jorge Nieva, and Vinay Duddalwar. American Journal of Roentgenology 2019 212:3, 497-504.
34. Barrington SF, Mikhaeel NG, Kostakoglu L et-al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J. Clin. Oncol. 2014;32 (27). doi:10.1200/JCO.2013.53.5229.
35. Cheson BD, Fisher RI, Barrington SF et-al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J. Clin. Oncol. 2014;32 (27): . doi:10.1200/JCO.2013.54.8800.
36. Gallamini A, Barrington SF, Biggi A et-al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. Haematologica. 2014;99 (6): 1107-13. doi:10.3324/haematol.2013.103218.
37. Biggi A, Gallamini A, Chauvie S et-al. International validation study for interim PET in ABVD-treated, advanced-stage hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. J. Nucl. Med. 2013;54 (5): 683-90. doi:10.2967/jnumed.112.110890.
38. Akhtari M, Milgrom SA, Pinnix CC, Reddy JP, Dong W, Smith GL, Mawlawi O, Abou Yehia Z, Gunther J, Osborne EM, Andraos TY, Wogan CF, Rohren E, Garg N, Chuang H, Khoury JD, Oki Y, Fanale M, Dabaja

BS. Reclassifying patients with early-stage Hodgkin lymphoma based on functional radiographic markers at presentation. Blood. 2018 Jan 4;131(1):84-94. doi: 10.1182/blood-2017-04-773838. Epub 2017 Oct 16. PMID: 29038339; PMCID: PMC5755043.

39. Zhou Y, Zhu Y, Chen Z, Li J, Sang S, Deng S. Radiomic Features of ^{18}F-FDG PET in Hodgkin Lymphoma Are Predictive of Outcomes. Contrast Media Mol Imaging. 2021 Nov 22;2021:6347404. doi: 10.1155/2021/6347404. PMID: 34887712; PMCID: PMC8629643.
40. Coskun N, Okudan B, Uncu D, Kitapci MT. Baseline 18F-FDG PET textural features as predictors of response to chemotherapy in diffuse large B-cell lymphoma. Nucl Med Commun. 2021 Nov 1;42(11):1227-1232. doi: 10.1097/MNM.0000000000001447. PMID: 34075009.
41. Driessen J, Zwezerijnen GJ, Schöder H, Drees EE, Kersten MJ, Moskowitz AJ, Moskowitz CH, Eertink JJ, De Vet HC, Hoekstra OS, Zijlstra JM, Boellaard R. The impact of semi-automatic segmentation methods on metabolic tumor volume, intensity and dissemination radiomics in ^{18}F-FDG PET scans of patients with classical Hodgkin lymphoma. J Nucl Med. 2022 Jan 6:jnumed.121.263067. doi: 10.2967/jnumed.121.263067. Epub ahead of print. PMID: 34992152.
42. Faudemer J, Aide N, Gac AC, Damaj G, Vilque JP, Lasnon C. Diagnostic value of baseline ^{18}FDG PET/CT skeletal textural features in follicular lymphoma. Sci Rep. 2021 Dec 10;11(1):23812. doi: 10.1038/s41598-021-03278-9. PMID: 34893676; PMCID: PMC8664828.
43. Angelopoulou MK, Mosa E, Pangalis GA, Rondogianni P, Chatziioannou S, Prassopoulos V, Moschogianni M, Tsirkinidis P, Asimakopoulos JV, Konstantinou I, Tsourouflis G, Sachanas S, Yiakoumis X, Boutsikas G, Arapaki M, Gainaru G, Kyrtsonis MC, Siakantaris MP, Datseris I, Panayiotidis P, Konstantopoulos K, Vassilakopoulos TP. The Significance of PET/CT in the Initial Staging of Hodgkin Lymphoma: Experience Outside Clinical Trials. Anticancer Res. 2017 Oct;37(10):5727-5736. doi: 10.21873/anticanres.12011. PMID: 28982893.
44. Song MK, Chung JS, Lee JJ, Jeong SY, Lee SM, Hong JS, Chong A, Moon JH, Kim JH, Lee SM, Kim SJ, Shin HJ. Metabolic tumor volume by positron emission tomography/computed tomography as a clinical parameter to determine therapeutic modality for early-stage Hodgkin's lymphoma. Cancer Sci. 2013 Dec;104(12):1656-61. doi: 10.1111/cas.12282. Epub 2013 Oct 23. PMID: 24033666; PMCID: PMC7653520.

Figures

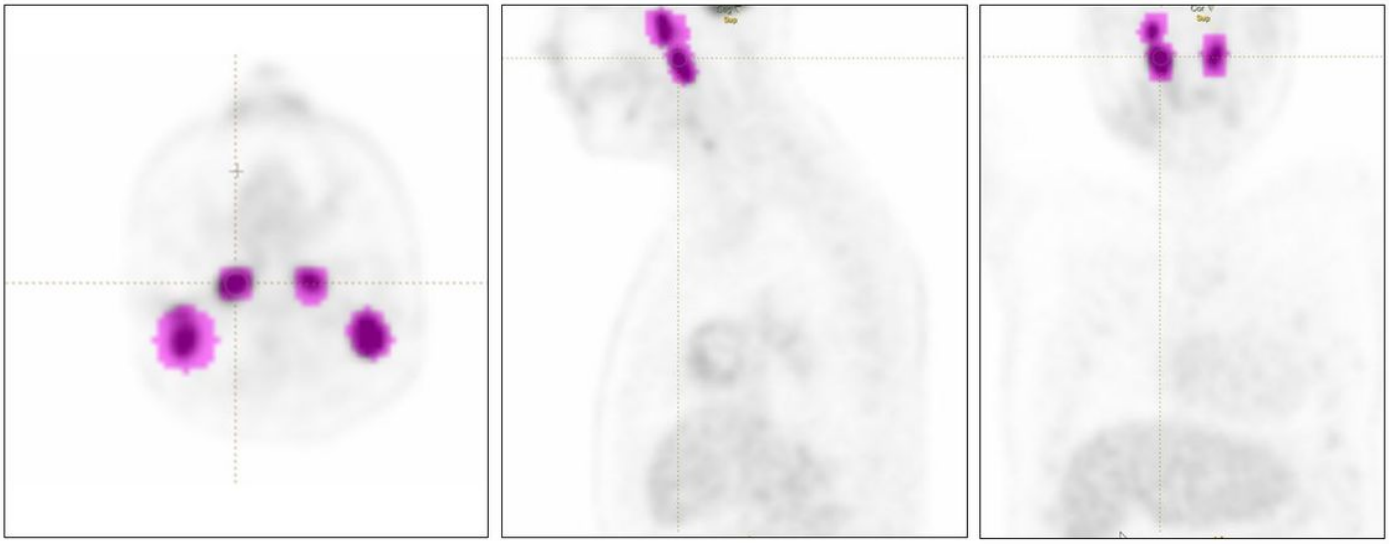

Figure 1

PET contouring using LifeX software of an 18-year-old male patient with Stage I Hodgkin Lymphoma.

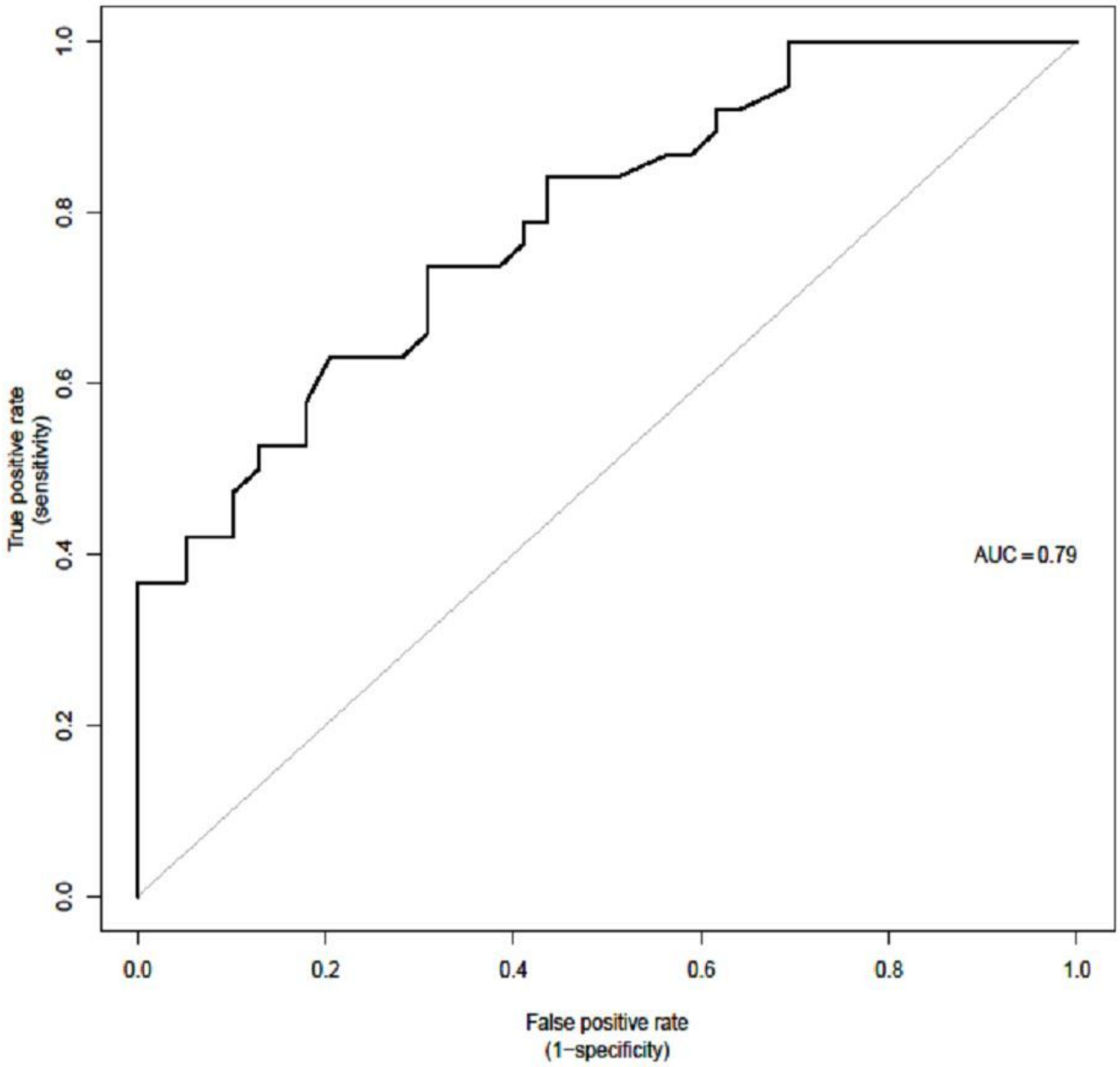

Figure 2

MVA for prediction of Radiotherapy