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Combination of FDG PET/CT radiomics and clinical parameters for outcome prediction in patients with non-Hodgkin's lymphoma

Claudia Ortega[a], Reut Anconina[b], Sayali Joshi[c], Ur Metser[a], Anca Prica[d], Sarah Johnson[a], Zhihui Amy Liu[e,f], Sareh Keshavarzi[e,f] and Patrick Veit-Haibach[a]

Purpose **The purposes was to build model incorporating PET + computed tomography (CT) radiomics features from baseline PET/CT + clinical parameters to predict outcomes in patients with non-Hodgkin lymphomas.**

Methods **Cohort of 138 patients with complete clinical parameters and follow up times of 25.3 months recorded. Textural analysis of PET and manual correlating contouring in CT images analyzed using LIFE X software. Defined outcomes were overall survival (OS), disease free-survival, radiotherapy, and unfavorable response (defined as disease progression) assessed by end of therapy PET/CT or contrast CT. Univariable and multivariable analysis performed to assess association between PET, CT, and clinical.**

Results **Male ($P = 0.030$), abnormal lymphocytes ($P = 0.030$), lower value of PET entropy ($P = 0.030$), higher value of SHAPE sphericity ($P = 0.002$) were significantly associated with worse OS. Advanced stage (III or IV, $P = 0.013$), abnormal lymphocytes ($P = 0.032$), higher value of CT gray-level run length matrix (GLRLM) LRLGE mean ($P = 0.010$), higher value of PET gray-level co-occurrence matrix energy angular second moment ($P < 0.001$), and neighborhood gray-level different matrix (NGLDM) busyness mean ($P < 0.001$) were significant predictors of shorter DFS. Abnormal lymphocyte ($P = 0.033$), lower value of CT NGLDM coarseness ($P = 0.082$), and higher value of PET GLRLM gray-level nonuniformity zone mean ($P = 0.040$) were significant predictors of unfavorable response to chemotherapy. Area under the curve for the three models (clinical alone, clinical + PET parameters, and clinical + PET + CT parameters) were 0.626, 0.716, and 0.759, respectively. *Nucl Med Commun* 45: 1039–1046**

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Keywords: non-Hodgkin lymphoma, PET/computed tomography, predictor models, radiomics

[a]Department Medical Imaging, University Medical Imaging Toronto, University Health Network – Mount Sinai Hospital – Women College Hospital, University of Toronto, Toronto, Ontario, Canada, [b]Department of Diagnostic Imaging, Chaim Sheba Medical Center, Ramat Gan, Israel, [c]Department of Diagnostic Imaging, The Hospital for Sick Children, [d]Division of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, [e]Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network and [f]Biostatistics Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Correspondence to Claudia Ortega, MD, Department Medical Imaging, Princess Margaret Cancer Center, 610 University Ave, 3-950, Toronto, ON M5G2M9, Canada
Tel: +1 416 946 4501x4833; fax: +1 416 946 6564; e-mail: Claudia.Ortega@uhn.ca

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Introduction

Non-Hodgkin's lymphomas (NHL) accounts for about 4% of all cancers. ^{18}F-fluorodeoxyglucose (FDG) PET/computed tomography (PET/CT) is the recommended imaging modality for the staging and restaging of FDG-avid lymphoma, including aggressive NHL according to Deauville score criteria [1].

NHL includes a variety of subtypes, with diffuse large B-cell lymphoma (DLBCL) been the most common aggressive subtype [2]. Despite recent improvements in chemotherapy, the average 5-year progression-free survival (PFS) is about 60% with nearly a third of patients treated with standard chemotherapy having refractory disease or relapse [3]. Early identification of these high-risk patients using traditional prognostic factors is very limited, currently based in International Prognostic Index (IPI) score, among others [4].

Radiomics is a rapidly evolving field in medical imaging. The term refers to extraction and analysis of large volume quantitative imaging data from medical images, such as CT or PET in a minable form to build predictive models associating texture features to phenotypes, genetic and proteomic signatures, and even treatment outcomes

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[5]. These parameters can capture intra-tumoral biological heterogeneity associated with cellular and molecular characteristics such as cellular proliferation, fibrosis, necrosis, metabolism, angiogenesis, hypoxia, and receptor expression to name a few [6].

Recently, radiomics analysis has been used for extraction of a wide variety of quantitative data that reflect biological characteristics of disease providing additional promising prognostic biomarkers in lymphomas. In recent years, several studies have explored the prognostic value of PET/CT radiomics in lymphoma [7–11].

It has been found that the pattern of ^{18}FDG uptake in different cancers can represent several different biological characteristics, that is, vascularization, cellularity, hypoxia, metabolism, cell density, or necrosis. However, despite a large number of PET/CT radiomic studies in solid tumors, very few data is available on prognostic value of radiomics in malignant lymphomas [11]. Furthermore, only a few publications are taking into account the hybrid nature of PET/CT and are evaluating mostly the radiomic features of the PET component. Finally, the standard of care clinical parameters are often not reported in radiomics evaluation studies. However, since they contain crucial (and already used) clinical prognostic value, ideally those should be integrated in the prognostic model together with radiomics features.

The aim of our study was to create and evaluate a model incorporating PET and CT radiomics features from baseline diagnostic PET/CT in conjunction with clinical parameters to build a combined method for predicting outcomes in patients with NHL.

Table 1 Summary of patient population

Population	Age years [range]
138 patients	54.6 [18.2–89]
Sex	*N* (%)
Female	65 (47)
Male	73 (53)
Pathology	*N* (%)
Anaplastic CLL	4 (2.2)
T-cell	9 (6.5)
B-cell (indolent/unclassifiable/mantle)	23 (16.7)
DLBCL	102 (73.9)
Disease location	*N* (%)
Nodal disease	87 (98)
Extranodal disease	56 (63)
Bulky presentation	5 (5)
Overall stage	*N* (%)
Stage I–II	77 (56)
Stage III–IV	61 (44)
Presence of B-symptoms	27 (20)
Chemotherapy regimen	*N* (%)
ABVD	5 (3.5)
R-CHOP	125 (90.5)
LY-EPOCH	5 (3.5)
GDP/PRED/rituximab alone	8 (5.7)
Response to chemotherapy*	*N* (%)
CR	106 (77)
PD	10 (7)
PR	19 (14)
SD	3 (2)
Radiotherapy treatment	*N* (%)
Yes	68 (49)
No	70 (51)
Response assessment after radiotherapy	*N* (%)
CR	63 (90)
Follow-up times	Months (range) 25.3 [3–44]

ABVD, doxorubicin hydrochloride (adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine; CLL, Chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; LY_EPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin); PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; SD, stable disease.

Materials and methods

Study cohort

This institutional ethics board-approved retrospective analysis included 151 patients diagnosed and treated in a tertiary referral center with NHL from September 2012 to June 2016 (Princess Margaret Cancer Center, University Health Network, Toronto, Canada).

All included patients underwent baseline staging PET/CT as per standard of care practice. Complete clinical records including pathology reports from either nodal or extra nodal biopsy, descriptions of sites of involvement, presence of bulky disease, Ann Arbor stages, and presence of B symptoms were recorded (summarized in Table 1). Furthermore, all standard of care blood work, systemic treatment, planned and received, as well as provision of radiotherapy treatment along with response assessment at the end of each line of therapy was recorded as part of the IPI score [12].

Follow up times, PFS, and overall survival (OS) outcomes were collected (Supplementary Data 1, Supplemental digital content 1, *http://links.lww.com/NMC/A303*). Progression was defined as per Lugano classification at resting FDG PET/CT Deauville 5-point scale and when not available, morphologic assessment in follow-up CT.

Imaging acquisition

^{18}F FDG PET/CT was performed in these patients at baseline staging as part of their standard of care. Images were obtained according to our institutional protocol as follows.

PET/CT was performed on a Siemens mCT40 PET/CT scanner (Siemens Healthcare, Siemens Healthineers AG Siemensstr, Forchheim, Germany). Patients were positioned supine with arms outside the region of interest. Images were obtained from the skull base to the upper thighs. Iodinated oral contrast material was administered for bowel opacification; no intravenous iodinated contrast material was used. Overall, five to nine bed positions were obtained, depending on patient height, with an acquisition time of 2 min per bed position. CT parameters were 120 kV; 3.0 mm slice width, 2.0 mm collimation; 0.8 s 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 Gaussian filter type.

Textural analysis

Textural analysis of the PET images was performed using a freely available software LIFE X version 5.10 (lifexsoft.org) in compliance with the Image Biomarker Standardization Initiative.

Primary contour on FDG-avid nodal and extranodal lesions was performed semiautomatically by the software (with minor manual correction when needed) using a thresholding method to define each volume of interest (VOI) by three radiologists with >5 years of experience (C.O., R.A., and S.J.) and supervised by a senior radiologist with more than 15 years of experience (P.V-H.). PET VOI were subsequentially defined based on background predefined SUV max thresholds including threshold at 40%, 70%, and whole volume [13].

All the representative lesions in the patient were selected as per RECIST guidelines (https://recist.eortc.org). Lesions smaller than 64 voxels were excluded since they did not fulfill the minimum size criteria for feature extraction by the radiomics software.

Since a thresholding method is not available for the CT component, the contours for the CT-derived VOI were performed manually, slice-by-slice to cover the entire volume of the lymphoma lesion as previously describe in the literature.

Sixty-five radiomics features were obtained by the software including: conventional metrics features reporting the SUV 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 (gray-level run length matrix), NGLDM (neighborhood gray-level different matrix), and GLZLM (gray-level zone length matrix).

Statistical analysis

Summary statistics were used to describe patient, disease, and treatment characteristics. Frequency and percentage were provided for categorical variables, and median and range were presented for continuous variables.

Four outcomes were assessed: (i) OS, defined from date of diagnosis to death date or last follow up date, (ii) disease-free survival (DFS), defined from date of diagnosis to date of progression, death, or last date of follow up, (iii) whether or not the patient received radiotherapy after completion of chemotherapy and (iv) whether the patient had a favorable response (complete response or partial response) or an unfavorable response (stable disease or progressive disease) in post therapy contrast CT or end of therapy PET/CT.

For the PET and for the non-contrast CT (NCCT) analysis, two separate datasets were analyzed: nodal and nodal + extranodal combined. For the PET analysis, three datasets were analyzed; including 70% defined thresholds, 40% threshold, and the whole contoured (100%) volume.

Univariable and multivariable analyses (MVA) were performed to assess the association of clinical, PET, and CT variables with each of the four outcomes. Cox proportional hazards models were fitted for OS and DFS outcomes; logistic regression models were fitted for radiotherapy outcome and for chemotherapy response. Clinical, PET, and CT variables with a *P*-value of less than 0.1 in the univariable were eligible for inclusion in the MVA. MVA were carried out using backward selection with a stay criteria of *P*-value <0.05. To avoid multicollinearity, one of the two correlated variables remained in the model, and variables that had a variance inflation greater than 5 were excluded from the final model. Model performance was quantified and displayed using area under the receiver operating characteristic (ROC) curve (AUC). All statistical analyses were carried out in R version 4.3.0 [14], and ROC curves were generated using R packages survivalROC [15] and pROC [16].

Results

Study population

From the initial cohort of $n = 151$ patients, 13 were excluded due to the following reasons: no baseline PET available ($n = 5$); no FDG-avid disease ($n = 5$); PET performed post chemotherapy or surgery with no residual avid disease ($n = 2$); corrupted digital storage and transmission of medical images and related information ($n = 1$).

A final cohort of 138 patients, 65 women (47%) and 73 men (53%) with a median age of 48.6 years (range 25.1–94.9) were included in our final cohort for analysis. Follow up times were 25.3 months on average [range 3–44 months].

Initial treatment, chemotherapy regimen, and its completion and response achieved are detailed in Table 1, alongside demographic information.

Univariable analysis

The statistically significant variables resulted from the univariable Cox or logistic regression analysis for NCCT and PET parameters using 70%, 40%, and whole volume when considering either nodal-only involvement or when considering all sites of disease involvement, were

presented in Supplementary Data 1, Supplemental digital content 1, *http://links.lww.com/NMC/A303*.

Multivariable analysis

Overall survival

In the final model, male patient ($P = 0.030$), abnormal lymphocytes results ($P = 0.030$), lower value of PET parameter entropy ($P = 0.030$), and higher value of first order shape features sphericity parameter ($P = 0.002$) were significantly associated with worse OS.

Disease-free survival

In the final model, advanced stage (III or IV, $P = 0.013$), abnormal lymphocytes results ($P = 0.032$), higher value of CT parameter GLRLM long-run low-gray-level emphasis mean ($P = 0.010$), higher value of PET parameters GLCM energy angular second moment ($P < 0.001$,) and NGLDM busyness mean ($P < 0.001$) were significant predictors of worse DFS.

Radiotherapy outcome

In the final model, female ($P = 0.050$), higher stage ($P < 0.001$), and abnormal hemoglobin results ($P = 0.029$) were associated with a higher likelihood of needing radiotherapy. No PET or CT parameters were predictive.

Response to chemotherapy

Abnormal lymphocyte results ($P = 0.033$), lower value of CT parameter NGLDM coarseness mean ($P = 0.082$), and higher value of PET parameter GLRLM gray-level nonuniformity zone mean ($P = 0.040$) were significant predictors of unfavorable response to chemotherapy (summarized in Table 2).

Receiver operating characteristic and area under the curve analysis

For OS outcome, the model combining clinical and PET features performed better than the model with clinical variables alone (Fig. 1 with corresponding AUCs at various time points in Supplementary Data 2, Supplemental digital content 2, *http://links.lww.com/NMC/A304*).

For DFS outcome, the model including clinical, PET, and CT variables performed the best (Fig. 2, with corresponding AUC values in Supplementary Data 3, Supplemental digital content 3, *http://links.lww.com/NMC/A305*).

For chemotherapy response, presented in Fig. 3, the model combining clinical, PET, and CT variables had the best performance.

Discussion

Our study aim was to evaluate whether combined PET and CT radiomic features in conjunction with clinical parameters are predictive of response to chemotherapy, can predict need of consolidative radiotherapy, and long-term outcomes. Our study showed that standard of care clinical parameters in conjunction with combined PET and CT radiomics performs best in terms of outcome prediction in patients with NHL and therefore PET and CT features when added to clinical information significantly can increase the efficiency of clinical trials.

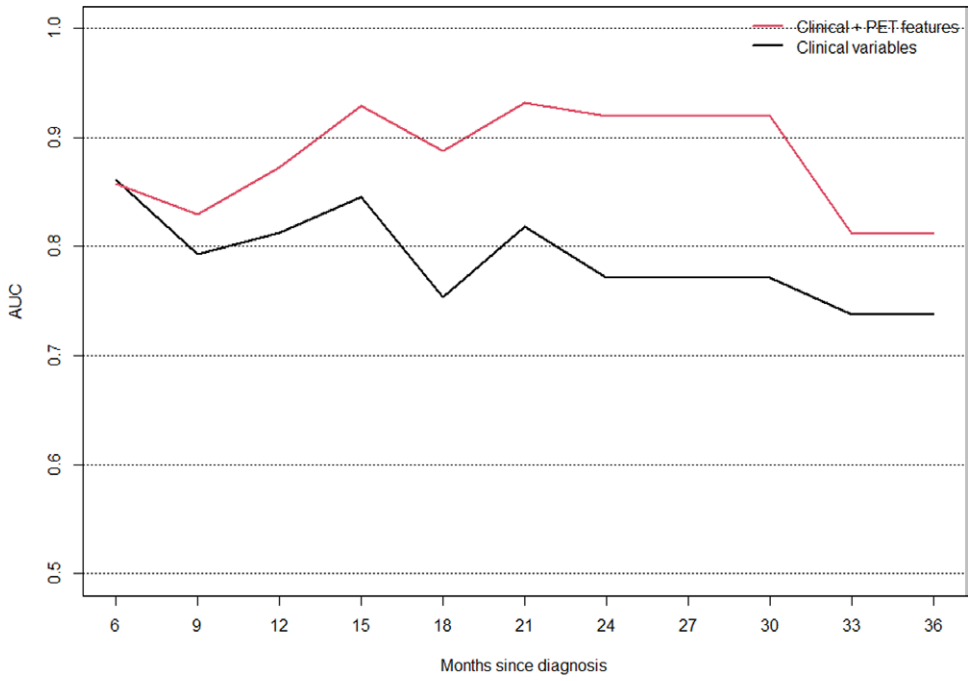
Accurately predicting the prognosis of patients is of great importance for optimizing therapy of aggressive lymphomas, such as DLBCL. Only few studies have attempted to assess the predictive value of radiomics

Table 2 Multivariable analysis

Variable	Hazard ratio	95% CI	*P* value
Predictors of OS			
HISTO entropy in PET	0.4	0.18–0.91	0.03
SHAPE sphericity in PET	3.09	1.51–6.3	0.002
Male (vs female)	4.07	1.11–14.96	0.03
Normal lymphocytes result (vs abnormal)	0.19	0.04–0.85	0.03
Predictors of DFS			
Stage III–IV (vs Stage I–II)	4.32	1.36–13.72	0.013
Normal lymphocytes result (vs abnormal)	0.17	0.03–0.86	0.032
GLRLM LRLGE mean in CT	1.67	1.13–2.47	0.01
GLCM energy angular second moment in PET	3.05	1.6–5.82	<0.001
NGLDM busyness mean in PET	1.98	1.39–2.8	<0.001
Predictors of need of radiotherapy			
Male (vs female)	0.43	0.19–1	0.05
Stage III–IV (vs Stage I–II)	0.13	0.06–0.31	<0.001
Normal hemoglobin results (vs abnormal)	2.59	1.11–6.08	0.029
Predictors of unfavorable response to chemotherapy			
Normal lymphocytes results (vs abnormal)	0.33	0.12–0.92	0.033
NGLDM coarseness mean in CT	0.48	0.21–1.1	0.082
GLRLM GLNU mean in PET	1.64	1.02–2.61	0.04

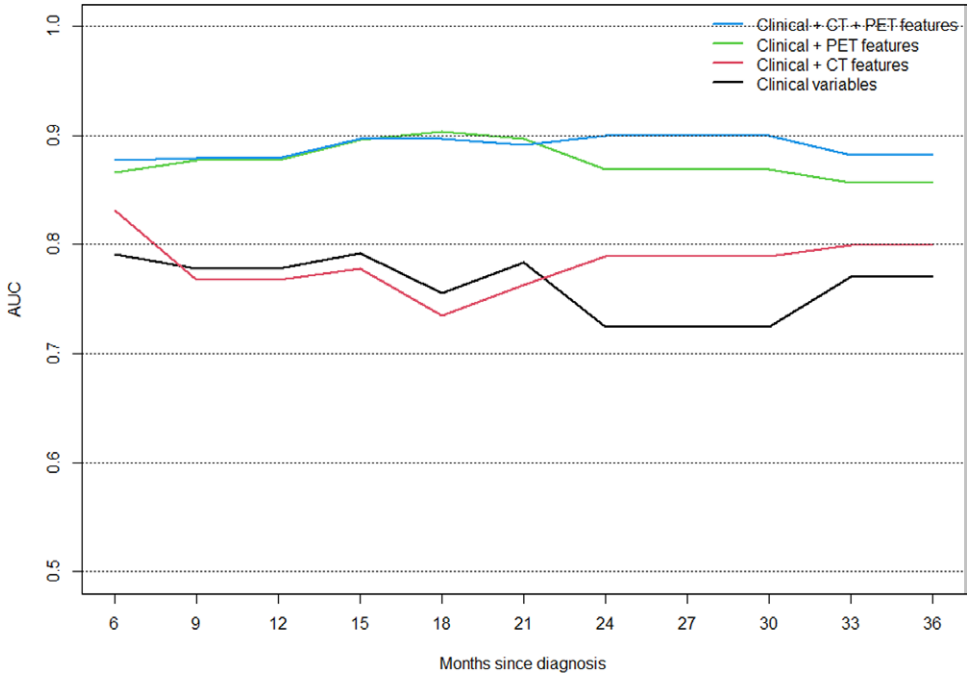
CI, confidence interval; CT, computed tomography; DFS, disease-free survival; GLCM, gray-level co-occurrence matrix; GLNU, gray-level non-uniformity; GLRLM, gray-level run length matrix; HISTO, histogram; LRLGE, long-run low-gray-level emphasis; NGLDM, neighborhood gray-level different matrix; OS, overall survival; SHAPE, shape features.

Fig. 1



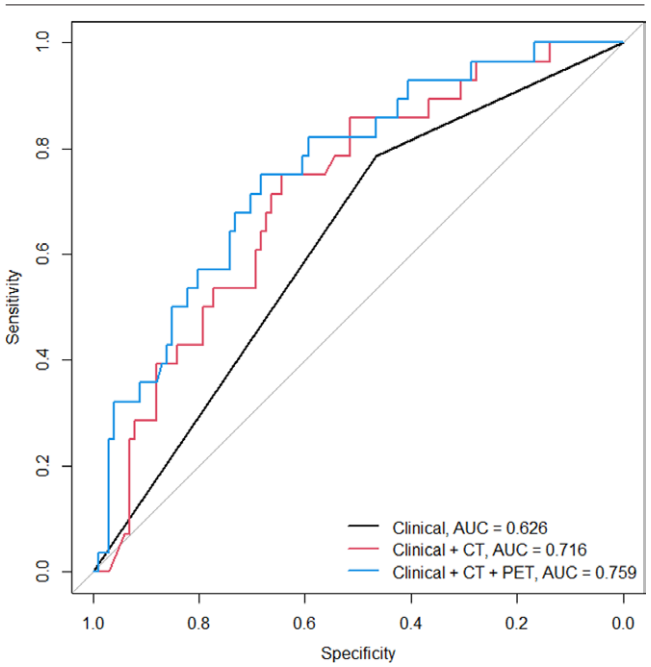
Comparison of AUC values of two OS models (i) including clinical variables only and (ii) including both clinical and PET variables. The latter model had higher AUCs. AUCs, areas under the curve; OS, overall survival.

Fig. 2



Comparison of AUC values of four DFS models, including (i) clinical variables only, (ii) clinical and CT variables, (iii) clinical and PET variables, and (iv) clinical, CT, and PET variables. Model (iv) had the highest AUCs. AUCs, areas under the curve; CT, computed tomography; DFS, disease-free survival.

Fig. 3



Comparison of ROC and AUC of three models for favorable response to chemotherapy: including (i) clinical variables only, (ii) clinical and CT variables, and (iii) clinical, CT, and PET variables. Model (iii) had the highest AUCs. AUCs, areas under the curve; CT, computed tomography; ROC, receiver operating characteristic.

information, mostly from PET imaging in DLBCL so far [17–19].

Relatively few studies have investigated the predictive value of other radiomics features in DLBCL. Moreover, due to the wide variability in the methodology and population of the studies in the literature, direct comparison is challenging. Only a few retrospective studies thus far have addressed the use of radiomics for a comprehensive disease evaluation in malignant lymphomas, exploring the application of textural analysis. Thus, these studies included different radiomic features, utilized different extraction methods, different software for radiomics analysis, and obtained controversial results as described by Parvez *et al*., who found that radiomics features of the higher FDG avid lesion have limited predictive value.

Literature has explored the prognostic value of PET/CT radiomics in lymphoma, including Hodgkin lymphoma, nasal-type extranodal natural killer/T cell lymphoma, mantle cell lymphoma, and DLBCL, respectively [7–9,20]. The results of these studies have shown that certain radiomics features may be predictors of some of the proposed outcomes.

Eertink *et al*. found that PET radiomics features extracted from the largest lesion of DLBCL was able to predict the 2-year time to progression (AUC = 0.67) [10]

Our study found that two first order parameters, PET-based entropy histogram ($P = 0.029$) and PET-based shape sphericity ($P = 0.0019$) were independent predictors of OS when correlated with male sex, anemia, and abnormal lymphocytes counts. These parameters represent intrinsic cellular and tumoral heterogeneity which has also been proved to be a predictor of poor outcome in other studies such us Ceriani *et al*. study analyzing 103 patients with primary mediastinal B-cell lymphoma enrolled in a prospective multicenter clinical trial (IELSG26). They demonstrated that metabolic heterogeneity (estimated using AUC of cumulative standardized uptake value-volume histograms) were a predictor of PFS at 5 years (total lesion glycolysis and metabolic heterogeneity with $P < 0.01$) [20].

When combining advanced stages of disease with abnormal lymphocytes counts at baseline, the CT parameter GLRLM ($P = 0.011$) was a predictor of shorter DFS. Additionally, two PET-related parameters GLCM and neighborhood gray-level dependence matrix (GLRLM) (both with $P = 0.001$) were also predictors of shorter times for relapse. Similarly, Lue *et al*. extracted 80 PET-based radiomics features from 171 patients with DLBCL and also found that RLN_{GLRLM} was independently associated with PFS (hazard ratio = 15.7, $P = 0.007$) and OS (hazard ratio = 8.64, $P = 0.040$), similar to our CT parameter [7].

In our study, CT radiomic gray level size zone-related features long-zone low gray-level emphasis (LZLGE, $P = 0.013$) and zone length nonuniformity ($P = 0.012$) were identified as predictors of shorter PFS when combined with advanced stages of disease and the presence of B-symptoms. Interestingly, Aide *et al*. study also found that LZLGE was the only independent predictor of 2-year event-free survival (hazard ratio = 2.84, $P = 0.01$, AUC = 0.76) when analyzing the PET component in a similarly sized cohort of 132 patients [21]. Similar predictive parameters (RLN_{GLRLM} in PET) were found in the study by Lue *et al*. in a smaller cohort of 83 patients, using a whole-tumor image analysis.

Additionally we encountered one CT-derived parameter (NGLDM coarseness with $P = 0.082$) and one PET-derived parameter (GLRLM gray-level nonuniformity; $P = 0.04$) as predictors of unfavorable response to first line of chemotherapy, when combined with abnormal lymphocytes count. An additional PET-derived parameter predictor of shorter PFS in our cohort was NGLDM busyness ($P = 0.0028$), which has not been described in any comparable literature to our knowledge, and would require further comparative analysis to be proven.

No CT nor PET-derived parameter was predictor of the eventual need of consolidative radiotherapy, in line with other published results.

As demonstrated above, a combined model including PET-derived features adding the CT-derived radiomic features with the clinical parameters perform better as predictors of survival models than each individual model separate. Furthermore, PET-derived parameters added information in prediction of response to chemotherapy than solely clinical parameters alone. This is line with the still limited available literature to date supporting the hypothesis that multi-omics approaches (clinical parameters plus imaging) might be superior to building predictor models than parameters from only one source independently. The unique approach combining clinical algorithms and imaging derived-features is a novel approach used in this project.

Baseline ^{18}F-FDG PET/CTs are already part of clinical practice and therefore, radiomics features can potentially be obtained and calculated at minimal additional costs/effort and most importantly without any adverse risk for the patient. With self-learning segmentation software anticipated to becoming widespread available, it might be a door to add radiomics features to clinical scoring systems in the future. To be able to get there an effort to collect larger prospective multicenter data and establish a minimal common ground on analysis, contouring methods and data collection and extraction is still needed.

Limitations

We acknowledge several limitations in this study. First, this is an analysis of data acquired in a single tertiary oncology center so transferability to smaller centers might be limited. Second, there are inherent limitations of a retrospective analysis. Third, the cohort includes different NHL types, including some indolent lymphomas or localized lymphomas that have different biology behaviors and outcomes than aggressive types, which may influence the validation of some features in these cases. Fourth, no cross validation cohort analysis was performed, and although validation analysis cannot overcome the absence of a validation cohort, it can describe the variability in the findings and indicate the expected performance of the model in a distinct dataset. Another limitation of this study is that we used a single method to segment the lymphoma lesions which were also contoured by three different radiologists, which may introduce confounding factors. To this date, there is no consensus on the tumor segmentation method for radiomic feature calculation in patients with DLBCL. Due to the high distribution variability of nodal and extranodal lesions with heterogeneous volumes and variable metabolic activity, lymphoma segmentation is more challenging than that of primary tumor lesions. Lastly, there was significant delay in completing the contouring phase and data analysis due to intervening restriction during COVID times.

Conclusion

Radiomics applies advanced computational methods to convert medical imaging data into quantitative descriptors of biological lymphoma characteristics that may predict patient survival and response to chemotherapy. Growing evidence indicates that prognostic models incorporating radiomics features would more accurately predict outcomes than volumetric PET parameters alone, therefore, radiomics seems a promising tool to identify imaging biomarkers that may help tailor treatment for a personalized medicine. For example, discriminating those who would benefit from escalation versus de-intensification of therapy, and contributing to improve outcomes, as was demonstrated in this analysis were a combined model outperforming in predicting disease behavior than each model individually.

Nevertheless, the few studies published so far produced inconclusive results due mainly to small cohorts. In fact, a consensus on several critical steps in the radiomics workflow is an unmet need to ensure comparability of results from different studies. Our hope is that in a near future new studies could confirm potential role of PET/CT radiomics in selecting robust imaging biomarkers that, alone or combined with clinical characteristics and or genetic profiles, may enhance the disease characterization and generate novel useful tools to tailor treatments.

However, the differences in biological and clinical characteristics of different lymphoma subtypes and the variable treatment options require ideally prospective studies to better understand the role of radiomics in this very heterogeneous group of disease.

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All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by C.O., R.A., and S.J. and statistical analysis by S.K. and Z.A.L. The first draft of the manuscript was written by C.O. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The University Health Network Research Ethics Board approves the above-mentioned study as it has been found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004 (REB 18-5223). Consent was waived given retrospective nature of the study.

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

Conflicts of interest

There are no conflicts of interest.

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