Prediction of Clinical Outcomes in Diffuse Large B-Cell Lymphoma (DLBCL) Utilizing Radiomic Features Derived from Pretreatment Positron Emission Tomography (PET) Scan

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Roadmap

- Background
- Clinical Aspects
- Approach
- Preliminary Results
- Next Steps
Background: Lymphatic System


Background: Lymph Node Histology

Normal Lymph Node Histology

Lymph nodes are part of the lymphatic pathway with connections via afferent and efferent lymphatics. A lymph node is surrounded by a capsule and structurally divided into three areas – cortical, paracortical, and medullary (Fig. 2.1).

Fig. 2.1 Histology of a normal lymph node showing cortex (B-cell area), paracortex (T-cell area), and medulla

Fig. 2.2 Secondary follicle with germinal center and mantle zone. Marginal zone is not clearly visible in lymph nodes

Background: Lymph Node Histology

Normal

Diffuse Large B-Cell Lymphoma (DLBCL)

Nasr M.R (2019) Lymph Node Pathology For Clinicians Cham, Switzerland: Springer Nature Switzerland AG
Background: Diffuse Large B-Cell Lymphoma (DLBCL)

- Highly aggressive cancer
- Is the most common subtype of Non-Hodgkin’s Lymphoma (NHL)
- Accounts for a quarter of new lymphoma cases
- 30 to 40 percent of patients will relapse after standard treatment
- 10 percent will be deemed to have refractory disease

Table 1 2016 update of WHO classification of DLBCL: subtypes and related entities

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma, NOS</td>
<td>GCB versus ABC/non-GCB, MYC and BCL2 double expressor, CD5+</td>
</tr>
<tr>
<td>DLBCL subtypes</td>
<td>T-cell/mixedcytology-rich large B-cell lymphoma</td>
</tr>
<tr>
<td>Primary DLBCL of the central nervous system</td>
<td>Primary cutaneous DLBCL, leg type</td>
</tr>
<tr>
<td>EBV positive DLBCL, NOS</td>
<td></td>
</tr>
<tr>
<td>Other lymphomas of large B-cells</td>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
<td>DLBCL associated with chronic inflammation</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>ALK-positive LBCL</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>HHV8+ DLBCL, NOS</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>Borderline cases</td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations</td>
<td>High-grade B-cell lymphoma, NOS</td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

ABC, activated B-cell like; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell like; HHV8, human herpesvirus 8; NOS, not otherwise specified; WHO, World Health Organization.

Clinical Problem:
DLBCL Survival Statistics

Number of New Cases and Deaths per 100,000: The number of new cases of diffuse large B-cell lymphoma was 5.6 per 100,000 men and women per year. The number of deaths was 1.8 per 100,000 men and women per year. These rates are age-adjusted and based on 2012-2016 cases and deaths.

How Many People Survive 5 Years Or More after Being Diagnosed with Diffuse Large B-Cell Lymphoma?

Relative survival statistics compare the survival of patients diagnosed with cancer with the survival of people in the general population who are the same age, race, and sex and who have not been diagnosed with cancer. Because survival statistics are based on large groups of people, they cannot be used to predict exactly what will happen to an individual patient. No two patients are entirely alike, and treatment and responses to treatment can vary greatly.

Based on data from SEER 18 2003-2015. Gray figures represent those who have died from diffuse large B-cell lymphoma. Green figures represent those who have survived 5 years or more.

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Diffuse Large B-Cell Lymphoma

Clinical Problem: DLBCL Demographics

Clinical Problem: DLBCL Treatment & Quality of Life

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Effectiveness</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>Standard Treatment</td>
<td>60 percent Success Rate in Advanced Disease</td>
<td>4-6 Cycles</td>
</tr>
<tr>
<td>R-ICE</td>
<td>Salvage Therapy</td>
<td>46 Percent Success Rate</td>
<td>3 Cycles</td>
</tr>
<tr>
<td>Allogenic Stem Cell Transplant (ASCT)</td>
<td>Last Option</td>
<td>50 percent will Qualify 50 percent will Relapse</td>
<td>Procedure</td>
</tr>
</tbody>
</table>

### Common Side Effects of Chemotherapy

- Appetite
- Constipation
- Nausea
- Vomiting
- Fatigue
- Weight Loss
- Infection
- Hair Loss
- Urinary Changes
- Mouth Sores
- Swallowing
- Chemo Brain
- Numbness
- Pain
- Sexual Function
- Fertility

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Adverse Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Rituximab</td>
<td>Monoclonal Antibody</td>
</tr>
<tr>
<td>C</td>
<td>Cyclophosphamide</td>
<td>DNA Alkylating Agent</td>
</tr>
<tr>
<td>H</td>
<td>Doxorubicin</td>
<td>DNA Intercalation</td>
</tr>
<tr>
<td>O</td>
<td>Vincristine</td>
<td>Microtubule Formation</td>
</tr>
<tr>
<td>P</td>
<td>Prednisone</td>
<td>Glucocorticoid</td>
</tr>
</tbody>
</table>


[Stanford Medicine logo]
Clinical Problem: Current Clinical Prognostic Model

National Comprehensive Cancer Network- International Prognostic Index (NCCN-IPI)\textsuperscript{3,4}

### Age
- 40 Years: 0
- 41-60 Years: 1
- 61-75 Years: 2
- >75 Years: 3

### Performance Status
ECOG scale:
0 - Asymptomatic (Fully active, able to carry out all predisease activities without restriction)
1 - Symptomatic but completely ambulatory (Restricted or physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2 - Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about less than 50% of waking hours)
3 - Symptomatic, <50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4 - Bedbound (Completely disabled, cannot carry on any self-care. Totally confined to bed or chair)
ECOG 0-1: 0
ECOG 2-4: 1

### LDH
- Normal: 0
- Elevated, Up To 3x Upper Limit of Normal: 1
- >3x Upper Limit of Normal: 2

### Extraneous Sites
- No bone marrow, CNS, liver/GI tract, or lung involvement: 0
- Bone marrow, CNS, liver/GI tract, or lung involvement: 1

### Stage
- Stage III: 0
- Stage III/IV: 1

### Overall Score
<table>
<thead>
<tr>
<th>Overall Score</th>
<th>Prognosis</th>
<th>Percent 5 Year Progression Free Survival</th>
<th>Percent 5 Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Low</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>2-3</td>
<td>Low-Medium</td>
<td>74</td>
<td>82</td>
</tr>
<tr>
<td>4-5</td>
<td>High-Medium</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>&gt;6</td>
<td>High</td>
<td>30</td>
<td>33</td>
</tr>
</tbody>
</table>

Clinical Problem: Issues with NCCN-IPI

- Given that near half of DLBCL patients present with advanced disease (Stage III/IV), a disease specific prognostic model is needed.

- Older age and ECOG may be a poor prognostic factors as a result of inability to tolerate chemotherapy.

- Lactate Dehydrogenase (LDH) is a non-specific biomarker.

- The majority of relapses in DLBCL occur within the first 2 years after completion of standard treatment.

- Clinical prognostic models, such as NCCN-IPI, are not built to guide treatment by design.
Clinical Need: Versatile Prognostic Model

- The heterogeneity of DLBCL makes it challenging to choose alternative therapies outside of standard treatment.
- Due to the high risk of relapse, a “wait and see” treatment approach is problematic in this patient population as it leads to a “trial and error” approach that is detrimental to patient quality of life.
- These challenges demonstrate a clinical need for: A versatile prognostic model with the ability to predict clinical outcomes and guide treatment at initial staging of disease.
Approach: Positron Emission Tomography (PET)

Examples of PET Capabilities

1. Clinical Diagnosis
2. Clinical Prognosis
3. Treatment Response
4. Verification of Molecular Targets
5. Efficacy of Pharmaceuticals
6. Theranostics

FIGURE 2 PET images of myocardial blood flow during stress and rest in a patient with coronary artery disease. Contiguous tomographic slices of the radiotracer uptake in the myocardium are shown (from left to right). Images in the upper row were obtained during stress and images at the bottom were obtained at rest. Light pink indicates normal and dark blue diminished blood flow. Net is the area of reduced blood flow on the stress images (arrows) which is no longer seen on the rest images, indicating the presence of coronary artery disease. SOURCE: Courtesy of Marcelo Di Carli, Harvard University.

FIGURE 4.5 This set of “before and after” PET/CT images demonstrates the use of these nuclear imaging modalities to evaluate the clinical effects of radiolabeled tumor therapy using radiopharmaceutical compounds such as yttrium-90 ibritumomab tiuxetan (Zevalin®) in the treatment of malignant lymphoma. SOURCE: Courtesy of Peter Conti, University of Southern California.

FIGURE 6.2 Radiotracers for imaging neurotransmitter function, as exemplified in the brain dopamine system. A simplified diagram of a dopamine (DA) synapse shows the dopamine transporter (red), dopamine receptors (blue), and monoamine oxidase (MAO) A and B, a monoamine binding site (green), and brain glucose metabolism along with radiotracer structures and human brain images corresponding to each of these molecular targets. SOURCE: Courtesy of Joanna Fowler, Brookhaven National Laboratory.
Fig. 11.3. The chemical structure of $^{18}$F-fluorodeoxyglucose (FDG) (left) is very similar to glucose (right); in FDG the 2’ hydroxyl group has been replaced by $^{18}$F.

Fig. 11.4. Typical multimodality positron emission tomography (PET) computed tomography (CT) imaging system combining a state-of-the-art PET scanner, for molecular imaging, with a multiple-detector-row CT scanner, for anatomic imaging. The software and hardware are optimized to acquire complementary information from a patient bed moving through both scanners. For the CT component of the scan, lasting seconds, the table moves uninterrupted while a continuous volume is acquired in spiral scan mode. For PET images, the bed moves in incremental steps based on the PET detectors’ field-of-view (typically 16.2 cm) with each acquisition typically taking 3–6 minutes. The PET detector ring is shown with a multielement scintillation detector and photomultiplier tubes. The electronics and detector localize annihilation-photon absorption to a single crystal. FDG, $^{18}$F-fluorodeoxyglucose.

Positron Emission Tomography (PET): Workflow

**Pretreatment**
Acquired before initiation of standard treatment

**Response**
Acquired 2-4 cycles into standard treatment

**Post treatment**
Acquired up to 8 weeks after last cycle of standard treatment

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Positron Emission Tomography (PET): Staging of Disease

<table>
<thead>
<tr>
<th>Ann Arbor Staging System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
</tbody>
</table>

A: Absence of B Symptoms
B: Presence of B Symptoms
- Unintentional Weight Loss >10 percent body weight in six month period
- Recurrent or Persistent Fever > 100.4 °F
- Presence of Night Sweats
E: Involvement of extranodal region that is contiguous or proximal to known nodal region
X: Bulky Disease
- mass > 10 cm in diameter or > 1/3 of mediastinal diameter
Prognostic Model: Radiomics

• **Definition:** Radiomics is predicated on the beliefs that these images reflect underlying pathophysiologies, and that they can be converted into mineable data for improved diagnosis, prognosis, prediction, and therapy monitoring\(^7\).

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**Example of Radiomic Features**\(^8\)

<table>
<thead>
<tr>
<th>Radionic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 first order statistics: Energy, entropy, kurtosis, maximum, mean, mean absolute deviation, median, minimum, range, root mean square, skewness, standard deviation (Std), uniformity, variance.</td>
</tr>
<tr>
<td>8 shape- and size-based features: Compactness 1, compactness 2, maximum 3D diameter, spherical disproportion, sphericity, surface area, surface to volume ratio, volume.</td>
</tr>
<tr>
<td>34 textural features: Autocorrelation, cluster prominence, cluster shade, cluster tendency, contrast, correlation, difference entropy, dissimilarity, difference variance, energy(_C), entropy(_C), homogeneity 1, homogeneity 2, informational measure of correlation 1 (IMC1), informational measure of correlation 2 (IMC2), inverse difference moment normalized (IDMN), inverse difference normalized (IDN), inverse variance, maximum probability, sum average, sum entropy, sum variance, variance, short run emphasis (SRE), long run emphasis (LRE), gray-level non-uniformity (GLN), run length non-uniformity (RLN), run percentage (RP), low gray-level run emphasis (LGLRE), high gray-level run emphasis (HGLRE), short run low gray-level emphasis (SRLGLE), short run high gray-level emphasis (SRHGLE), long run gray-level emphasis (LRLGLE), long run high gray-level emphasis (LRHGLE).</td>
</tr>
<tr>
<td>384 wavelet features: Wavelet features consist of the first order statistics and textural features extracted from eight wavelet decompositions (X(<em>{HLH}), X(</em>{HHL}), X(<em>{HLL}), X(</em>{HHH}), X(<em>{HHL}), X(</em>{HLL}), X(<em>{LLL}), and X(</em>{LLL})). For example, Energy(<em>{HLH}) represents the energy feature calculated from decomposition X(</em>{HLH}).</td>
</tr>
</tbody>
</table>

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8. Xiong J et al (2018) *The Role of PET-Based Radiomic Features in Predicting Local Control of Esophageal Cancer treated with Concurrent Chemoradiotherapy* Scientific Reports 8: 9902
Prognostic Model: Selection of Lymph Node
Prognostic Model: Feature Extraction Pipeline

Types of Radiomic Features Extracted
- Morphology
- Texture
- Size
- Intensity
- Feature Engine
- Results

Quantitative Imaging Feature Pipeline
Prognostic Model: Purpose Use for Stratification

- The clinical outcome is 2-Year Progression Free Survival (2-yr PFS)
- The prognostic model will be able to group patients based on whether or not they achieve 2-yr PFS
- Will compare the molecular pathology, clinical prognostic scores, demographics, and risk factors between the two subgroups
- Will allow for the isolation of non-imaging attributes that can possibly guide treatment

Patient Cohort:
Stanford Hospital and Clinics (SHC)

- SHC is a referral center
- Stanford Research Repository (STARR) system used to isolate DLBCL patients based on ICD Code
- Overall Hits: ~2400
- Unique Patients: ~1900 pts
- Patients meeting Inclusion Criteria:
  - 110 Patients

- 5.8 percent yield

Inclusion Criteria

1. Must have a confirmed diagnosis of DLBCL
2. Must have an accessible pretreatment PET scan
3. Must have clinical follow up for at least 2 years
MIM Software Gradient Based PET Edge

- Commercial Software
- Semi-Automated Approach
- Largest Lesion Selected
- Standardized Algorithm
- Independent of Thresholds
- Integrated into clinical software
- Minimal Interruption in Workflow
Feature Extraction: PyRadiomics

- Out of the 110 patients that met inclusion criteria, radiomic features were extracted from 85 patients
  - 77 percent yield
  - Breakdown of Clinical Outcome
    - 26 patients Relapsed
    - 59 patients achieved 2 yr PFS
- 910 radiomic features were extracted from each patient using PyRadiomics
- Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis applied to help with variable selection
Preliminary Results: LASSO Regression Analysis

- Algorithm ran 1000 times
- 5 Fold Cross Validation
- Variables with the Greatest Frequency were Related to Texture properties
- Current Issue
  – Sample Size

Corresponding AUC histogram
Next Steps: Standardization of Approach

<table>
<thead>
<tr>
<th>Factors</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>1. Single Lesion</td>
</tr>
<tr>
<td></td>
<td>2. Increase Number of Lesions</td>
</tr>
<tr>
<td></td>
<td>3. Optimize Lesion Size</td>
</tr>
<tr>
<td>Selection of Lesion</td>
<td>1. Standardized Quantitative Approach</td>
</tr>
<tr>
<td></td>
<td>2. Non Standardized Qualitative Approach</td>
</tr>
<tr>
<td></td>
<td>3. No Criteria</td>
</tr>
<tr>
<td>Segmentation</td>
<td>1. Semi- Automated</td>
</tr>
<tr>
<td></td>
<td>3. Fully Automated</td>
</tr>
</tbody>
</table>
References


8. Xiong J et al (2018) *The Role of PET-Based Radiomic Features in Predicting Local Control of Esophageal Cancer treated with Concurrent Chemoradiotherapy* Scientific Reports 8: 9902