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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SCIT Research Fellow

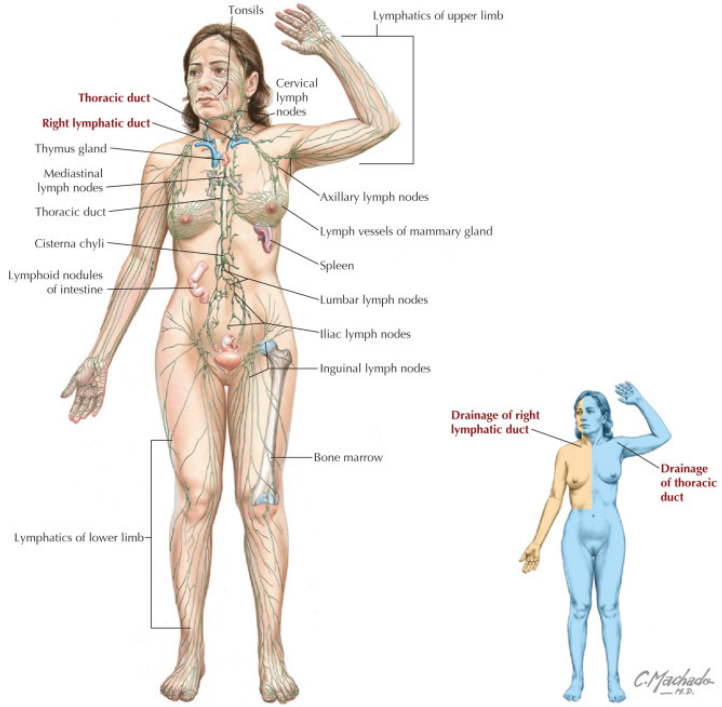
RSL Meeting

July 22nd, 2020

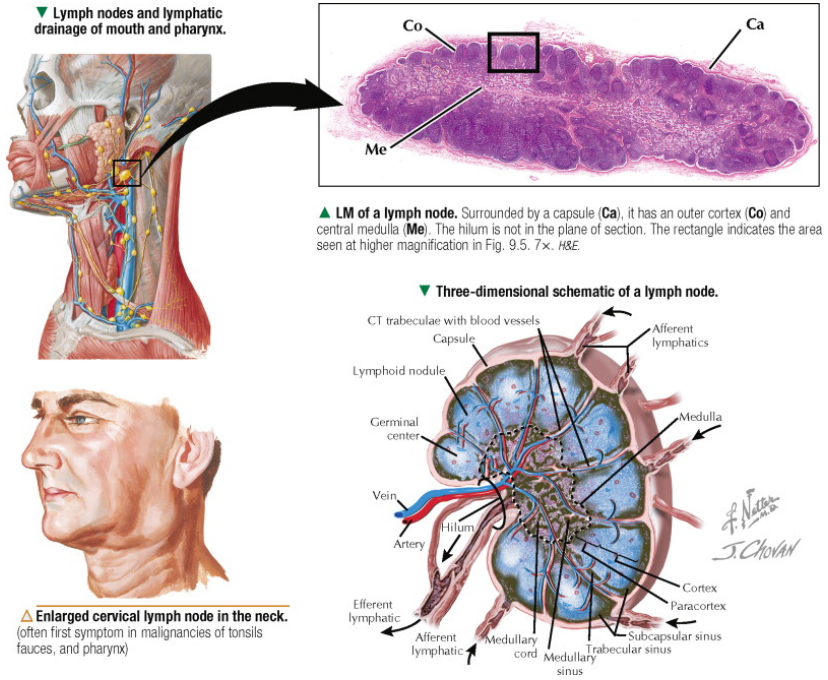
Roadmap

- Background
- Clinical Aspects
- Approach
- Preliminary Results
- Next Steps

Background: Lymphatic System



Hansen J.T (2018) *Netter' Clinical Anatomy: 4th Edition* Philadelphia, Pennsylvania: Elsevier



Ovalle WK (2013) *Netter's Essential Histology* Philadelphia, Pennsylvania: Saunders

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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).

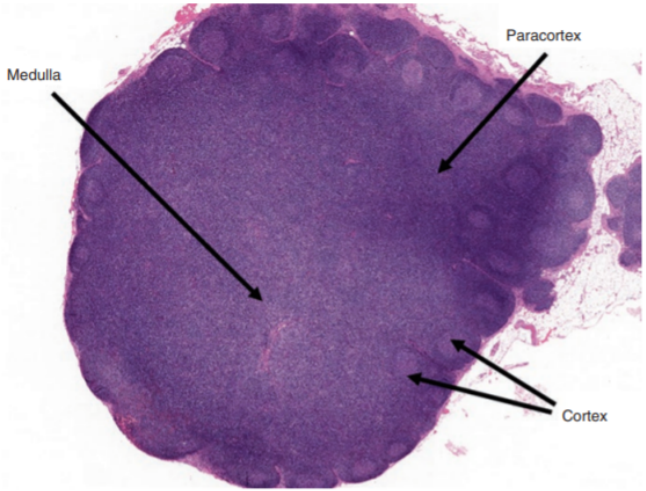

Fig. 2.1 Histology of a normal lymph node showing cortex (B-cell area), paracortex (T-cell area), and medulla

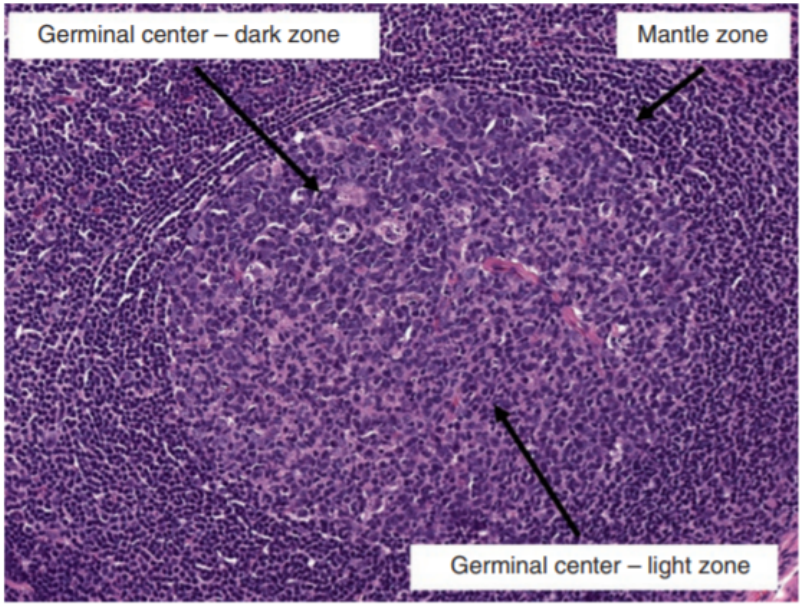

Fig. 2.2 Secondary follicle with germinal center and mantle zone. Marginal zone is not clearly visible in lymph nodes

Nasr M.R (2019) *Lymph Node Pathology For Clinicians* Cham, Switzerland: Springer Nature Switzerland AG

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Background: Lymph Node Histology

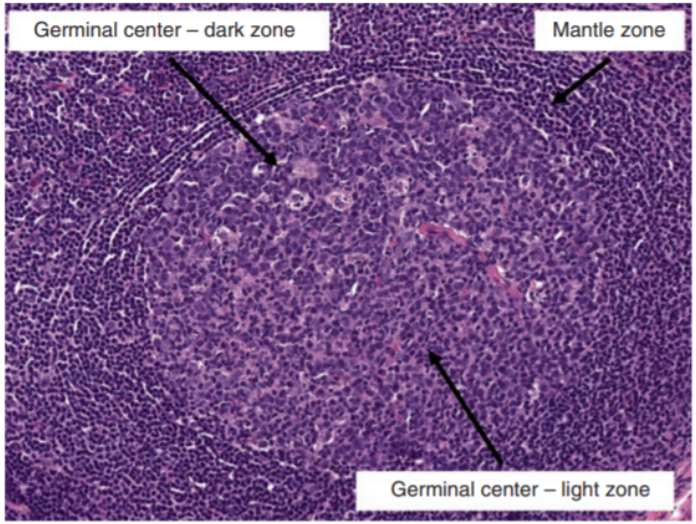

Fig. 2.2 Secondary follicle with germinal center and mantle zone. Marginal zone is not clearly visible in lymph nodes

Normal

Pathology

Involved lymph nodes or tissues show partial or complete effacement of architecture by diffuse infiltration of medium- to large-sized lymphoid cells (Fig. 5.20).

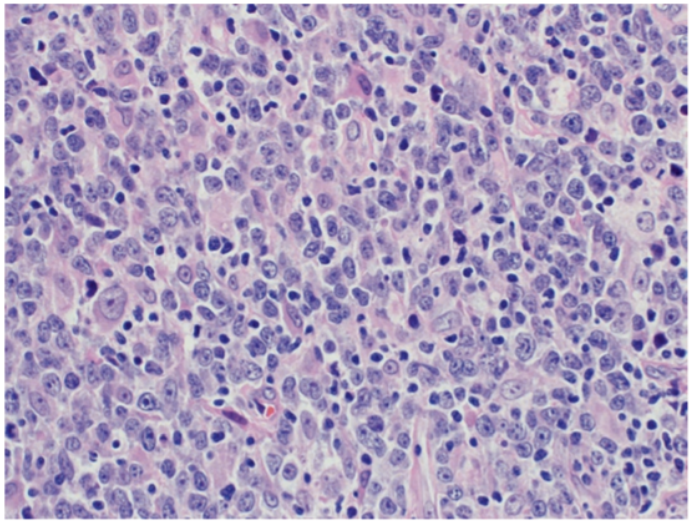

Fig. 5.20 Diffuse large B-cell lymphoma with sheets of large cells with irregular nuclei, open chromatin and one to several prominent nucleoli

Diffuse Large B-Cell Lymphoma (DLBCL)

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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[1]
- 10 percent will be deemed to have refractory disease[1]
- Heterogenous presentation[2]

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

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

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.

1. Gisselbrecht C et al (2018) *How I manage patients with relapsed/refractory diffuse large B cell lymphoma* British Journal of Haematology 182: 633-643
2. Li S et al (2018) *Diffuse large B-cell lymphoma* Pathology 50 (1): 74-87.

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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?

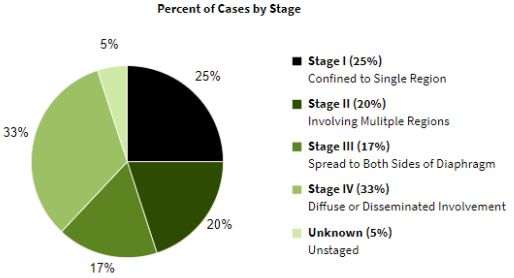
Relative survival statistics compare the survival of patients diagnosed with cancer with the survival of people in the general population who are the same age, race, and sex and who have not been diagnosed with cancer. Because survival statistics are based on large groups of people, they cannot be used 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.

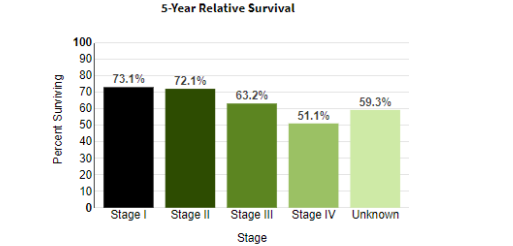
Percent Surviving 5 Years

63.2%

Based on data from SEER 18 2009-2015. 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





SEER 18 2009-2015, All Races, Both Sexes by Ann Arbor Stage

NIH National Cancer Institute (2019) Cancer Stats Facts: NHL- Diffuse Large B Cell Lymphoma (DLBCL) Retrieved from https://seer.cancer.gov/statfacts/html/dlbcl.html

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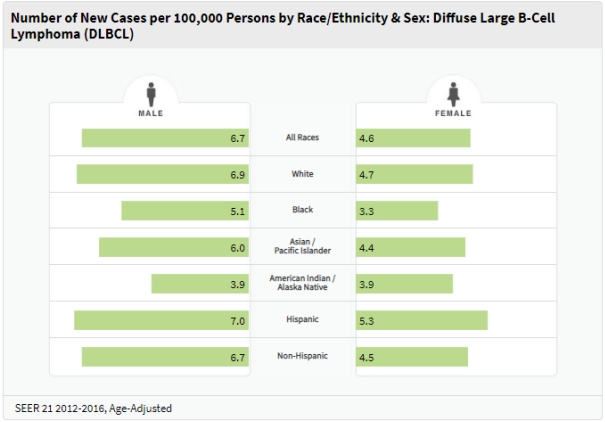
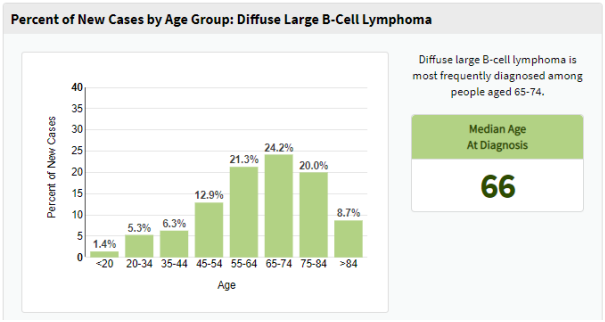
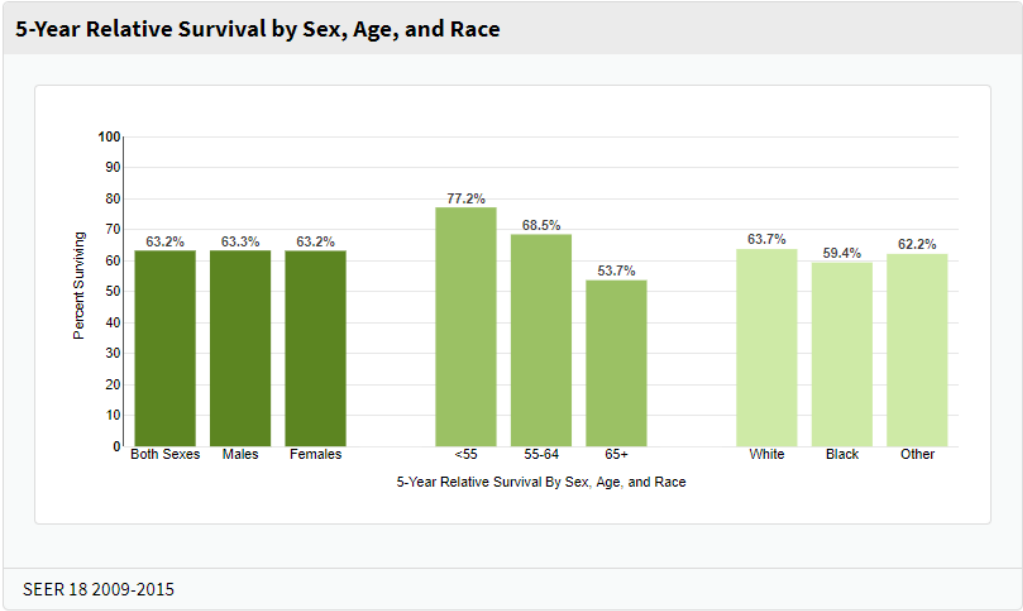
Clinical Problem: DLBCL Demographics







NIH National Cancer Institute (2019) Cancer Stats Facts: NHL- Diffuse Large B Cell Lymphoma (DLBCL) Retrieved from https://seer.cancer.gov/statfacts/html/dlbcl.html

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Clinical Problem: DLBCL Treatment & Quality of Life

Treatment[1]	Indication	Effectiveness	Regimen
R-CHOP	Standard Treatment	60 percent Success Rate in Advanced Disease	4-6 Cycles
R-ICE	Salvage Therapy	46 Percent Success Rate	3 Cycles
Allogenic Stem Cell Transplant (ASCT)	Last Option	50 percent will Qualify 50 percent will Relapse	Procedure

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

	Name	Mechanism of Action	Adverse Side Effect
R	Rituximab	Monoclonal Antibody	Immune Toxicity
C	Cyclophosphamide	DNA Alkylating Agent	Hemorrhagic Cystitis
H	Doxorubicin	DNA Intercalation	Cardiotoxicity
O	Vincristine	Microtubule Formation	Peripheral Neuropathy
P	Prednisone	Glucocorticoid	Immunosuppression

	Name	Mechanism of Action	Adverse Side Effect
R	Rituximab	Monoclonal Antibody	Immune Toxicity
I	Ifosfamide	DNA Alkylating Agent	Hemorrhagic Cystitis
C	Carboplatin	DNA Alkylating Agent	Nephrotoxicity
E	Etoposide Phosphate	DNA topoisomerase II Inhibitor	Bone Marrow Suppression

1. Gisselbrecht C et al (2018) *How I manage patients with relapsed/refractory diffuse large B cell lymphoma* British Journal of Haematology 182: 633-643

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Clinical Problem:
Current Clinical Prognostic Model

National Comprehensive Cancer Network- International Prognostic Index (NCCN-IPI)[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 on all predisease activities without restriction)
1 – Symptomatic but completely ambulatory (Restricted in 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 more 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

Extranodal Sites

No bone marrow, CNS, liver/GI tract, or lung involvement	0
Bone marrow, CNS, liver/GI tract, or lung involvement	1

Stage

Stage I/II	0
Stage III/IV	1

Overall Score	Prognosis	Percent 5 Year Progression Free Survival	Percent 5 Year Overall Survival
0-1	Low	91	96
2-3	Low-Intermediate	74	82
4-5	High-Intermediate	51	64
>=6	High	30	33

3. Diffuse Large B- cell Lymphoma Prognosis (NCCN-IPI) [2019] Retrieved from https://qxmd.com/calculate/calculator_311/diffuse-large-b-cell-lymphoma-prognosis-nccn-ipi
4. Zhou Z et al (2014) *An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era* Blood 124(6): 837-842

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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

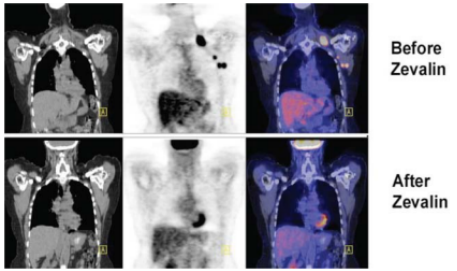

FIGURE 4.5 This set of "before and after" PET/CT images demonstrates the use of these nuclear imaging modalities to evaluate the clinical effects of radioimmunotherapy using radiopharmaceutical compounds such as yttrium-90 ibritumomab tiuxetan (Zevalin®) in the treatment of malignant lymphoma. SOURCE: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

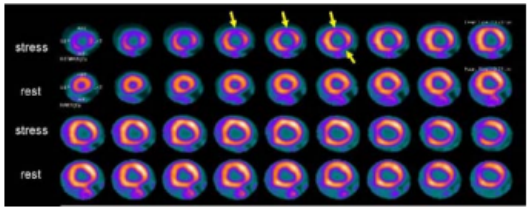

FIGURE 2 PET images of myocardial blood flow during stress and rest in a patient with coronary artery disease. Contiguous tomographic slices of the radiotracer uptake in the myocardium are shown (from left to right). Images in the upper row were obtained during stress and images at the bottom were obtained at rest. Light pink indicates normal and dark blue diminished blood flow. Note 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.

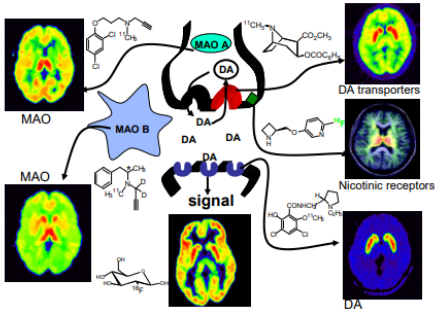

FIGURE 6.2 Radiotracers for imaging neurotransmitter function, as exemplified in the brain dopamine system. A simplified diagram of a dopamine (DA) synapse shows the dopamine transporter (red), dopamine receptors (blue), and monoamine oxidase (MAO) A and B, a nicotine binding site (green), and brain 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.

Committee on State of the Science of Nuclear Medicine(2007) *Advancing Nuclear Medicine Through Innovation* Washington, D.C. : The National Academies Press

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Positron Emission Tomography (PET): Principle

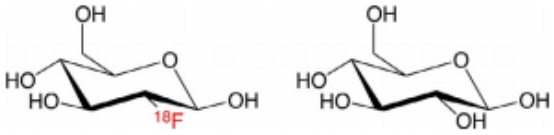

Fig. 11.3. The chemical structure of ^{18}F-fluorodeoxyglucose (FDG) (left) is very similar to glucose (right); in FDG the 2' hydroxyl group has been replaced by ^{18}F.

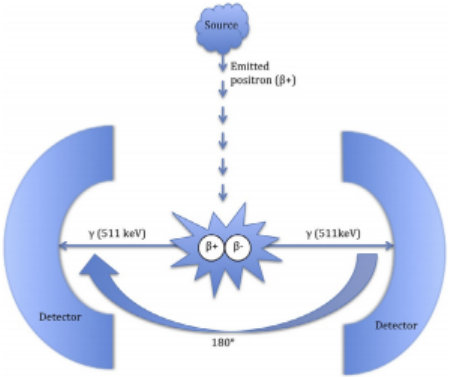

Fig. 11.1. After being emitted, positrons travel a distance before combining with an electron in an annihilation event. This results in the production of two antiparallel 511 keV photons which strike opposing detectors within a coincidence time window.

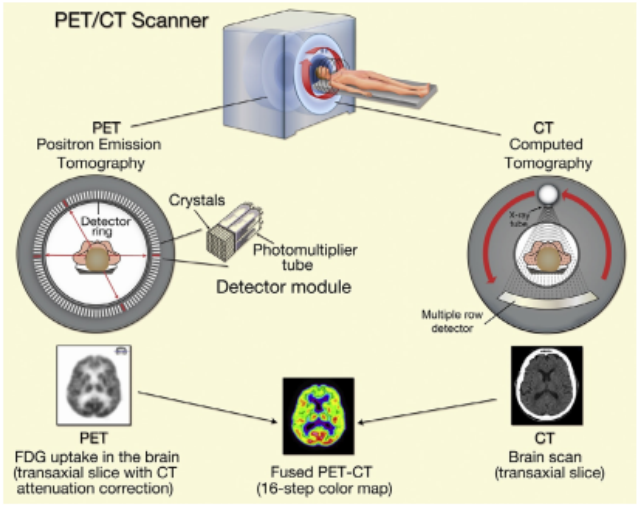

Fig. 11.4. Typical multimodality positron emission tomography (PET)/computed tomography (CT) imaging system combining a state-of-the-art PET scanner, for molecular imaging, with a multiple-detector-row CT scanner, for anatomic imaging. The software and hardware are optimized to acquire complementary 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 multicrystal scintillation detector and photomultiplier tubes. The electronics and detector localize annihilation-photon absorption to a single crystal. FDG, ^{18}F-fluorodeoxyglucose. (Reproduced with permission from Esser, 2009.)

Masdeu J.C. (2016) *Handbook of Clinical Neurology , Neuroimaging, Part I* Amsterdam, Netherlands : Elsevier B.V.

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Positron Emission Tomography (PET): Workflow

Pretreatment

Acquired before initiation of standard treatment

Baseline PET used for:

Risk stratification

NCCN-IPI using PET discriminates patients with very good prognosis from patients at high risk of treatment failure, mostly elderly patients unsuitable for salvage treatments for whom testing with novel agents may be appropriate

Parameters including number of extranodal sites and metabolic tumour burden, also combined with early response are promising predictors of prognosis.

Staging including bone marrow assessment

Can replace bone marrow biopsy in selected cases

Mapping initial disease sites for accurate response assessment

Differentiating lymphomatous involvement from other causes for increased FDG uptake, e.g. infection, inflammation, bone marrow hyperplasia

Response

Acquired 2- 4 cycles into standard treatment

Interim PET used for:

Prognosis

Early CMR has excellent prognosis and usually predicts CMR at end of treatment; such patients do not require end-of-treatment scans.

Patients with a positive interim PET and other high risk features, e.g. poor-risk IPI, may require close monitoring during treatment as they have higher risk of refractory disease and relapse.

PET is a more appropriate test for interim imaging assessment than CT.

Excluding disease progression on treatment

But should not be used to change standard treatment unless clear evidence of progression. To date, no evidence exists that response adaptation at interim on the basis of positive PET improves patient outcomes and risks over-treating many patients.

Post treatment

Acquired up to 8 weeks after last cycle of standard treatment

End of treatment PET used for:

Remission assessment

Using Deauville criteria. Patients with end-of-treatment Deauville scores 4 and 5 should be considered for further treatment with biopsy confirmation wherever feasible but particularly if salvage treatment ± ASCT is being considered.

Decision making as to suitability for ASCT following high-dose chemotherapy

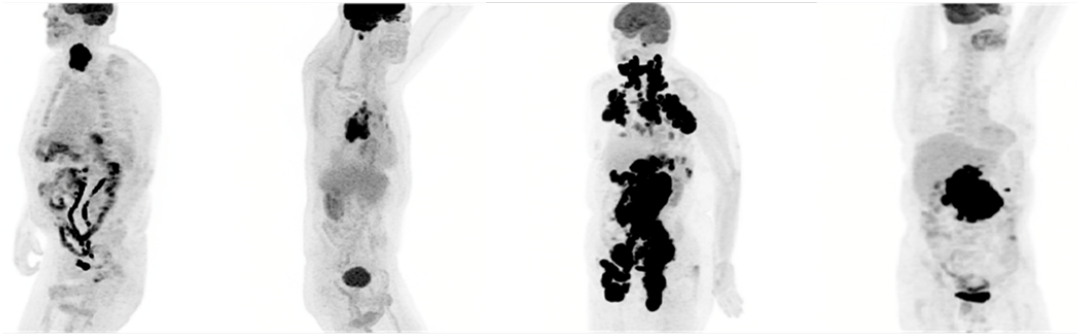
In preference to CT

5. Barrington S.F et al (2016) *PET Scans for Staging and Restaging in Diffuse Large B-Cell and Follicular Lymphomas* Current Hematologic Malignancy Reports 11: 185-195

Positron Emission Tomography (PET): Staging of Disease

Ann Arbor Staging System	
Stage	Area of Involvement
Stage I	Involvement of a single lymph node region or single organ
Stage II	≥ 2 lymph node regions on the same side of the diaphragm
Stage III	≥ 2 lymph node regions on both sides of the diaphragm
Stage IV	Widespread disease in multiple organs. Does not need lymph node involvement

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



IE IIA IIIB IVX

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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].

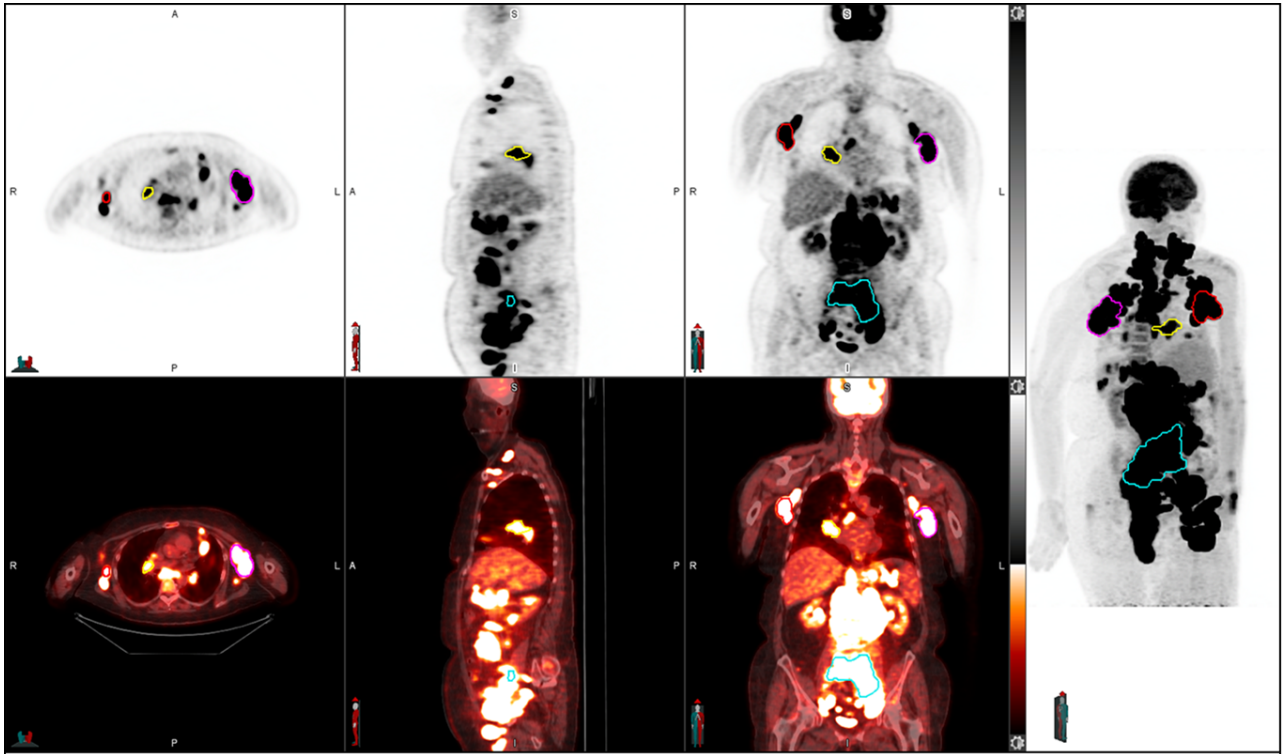
Radiomic Features
14 first order statistics: Energy, entropy, kurtosis, maximum, mean, mean absolute deviation, median, minimum, range, root mean square, skewness, standard deviation (Std), uniformity, variance.
8 shape- and size-based features: Compactness 1, compactness 2, maximum 3D diameter, spherical disproportion, sphericity, surface area, surface to volume ratio, volume.
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 low gray-level emphasis (LRLGLE), long run high gray-level emphasis (LRHGLE).
384 wavelet features: Wavelet features consist of the first order statistics and textural features extracted from eight wavelet decompositions (X_{HHH}, X_{HHL}, X_{HLH}, X_{HLL}, X_{LHH}, X_{LHL}, X_{LLH}, and X_{LLL}). For example, Energy_HHL represents the energy feature calculated from decomposition X_{HHL}.

Table 1. The detailed radiomic features.

Example of Radiomic Features[8]

7. Napel S et al (2018) *Quantitative imaging of cancer in the postgenomic era: Radio (geno) mics, deep learning, and habitats* Cancer 124(24): 4633-4649
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



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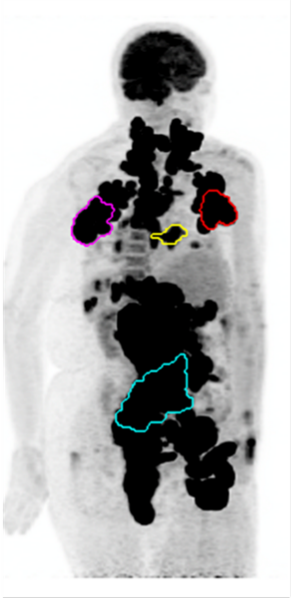
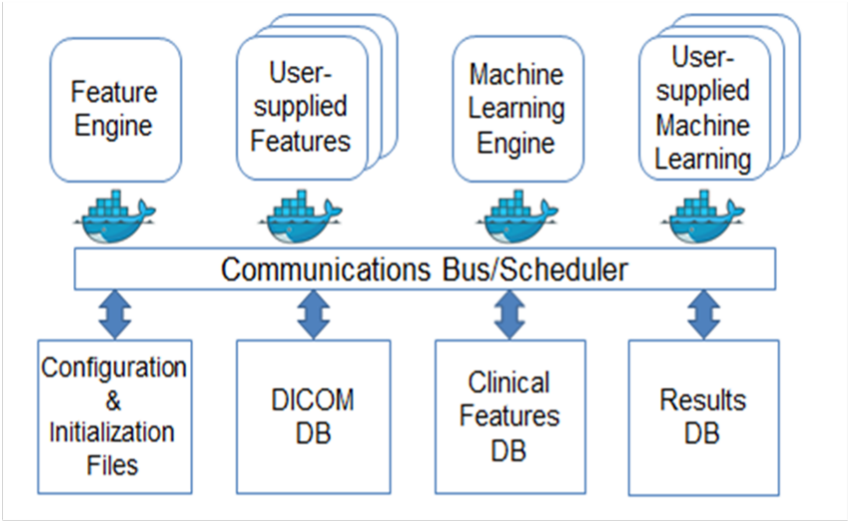
Prognostic Model: Feature Extraction Pipeline





Quantitative Imaging Feature Pipeline

Types of Radiomic Features Extracted
Morphology
Texture
Size
Intensity

Feature Engine Results

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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

Molecular Marker of DLBCL[2]

Markers	Frequency	Significance
CD19	Often	Diagnosis, target
CD20	Often	Diagnosis, target
CD22	Often	Diagnosis, target
CD79a/CD79b	Often	Diagnosis
PAX5	Often	Diagnosis
sIG or cytoIG	50–75%, IgM more common	Diagnosis
CD5	5–10%	Prognosis
CD30	Variably expressed, more in anaplastic	Prognosis, target
CD10	30–60%	All 3 markers (CD10, BCL6, MUM1) combined to define GCB vs non-GCB
BCL6	60–90%	
MUM1	35–65%	
Ki67	Variably expressed in every case, usually >40%	Proliferative marker
MYC	20–40%	Coexpression define
BCL2	Often	Prognosis, target
P53	Variable depending on cut-off	Prognosis

DLBCL, diffuse large B-cell lymphoma.

2. Li S et al (2018) *Diffuse large B-cell lymphoma* Pathology 50 (1): 74-87

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

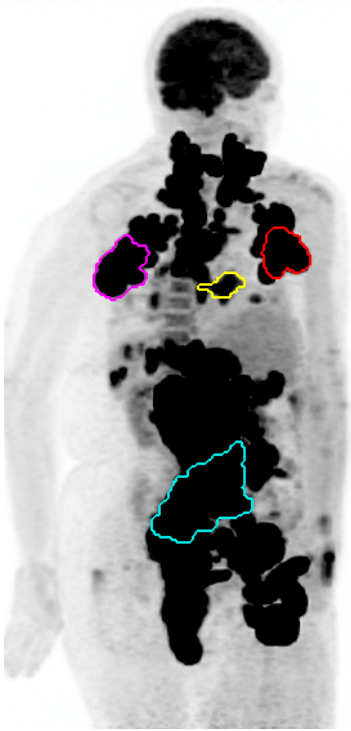
–5.8 percent yield

- 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

Radiomic Features

This section contains the definitions of the various features that can be extracted using PyRadiomics. They are subdivided into the following classes:

- `First Order Statistics` (19 features)
- `Shape-based (3D)` (16 features)
- `Shape-based (2D)` (10 features)
- `Gray Level Cooccurence Matrix` (24 features)
- `Gray Level Run Length Matrix` (16 features)
- `Gray Level Size Zone Matrix` (16 features)
- `Neighbouring Gray Tone Difference Matrix` (5 features)
- `Gray Level Dependence Matrix` (14 features)

All feature classes, with the exception of shape can be calculated on either the original image and/or a derived image, obtained by applying one of several filters. The shape descriptors are independent of gray value, and are extracted from the label mask. If enabled, they are calculated separately of enabled input image types, and listed in the result as if calculated on the original image.

Most features defined below are in compliance with feature definitions as described by the Imaging Biomarker Standardization Initiative (IBSI), which are available in a separate document by Zwanenburg et al. (2016) [1]. Where features differ, a note has been added specifying the difference.

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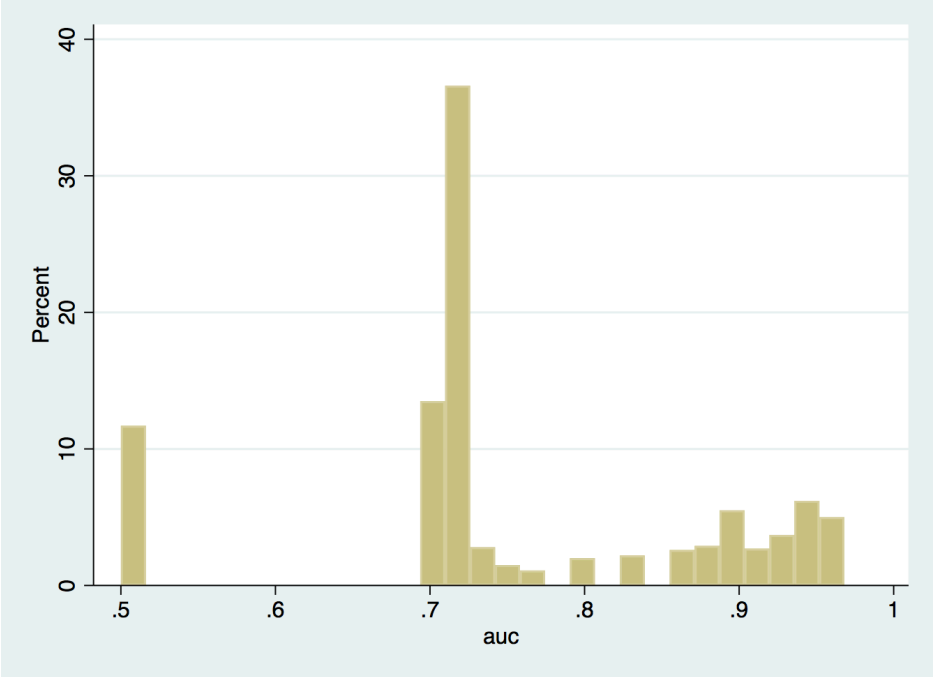
Preliminary Results: LASSO Regression Analysis

- 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



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Next Steps: Standardization of Approach

Factors	Strategy
Sample Size	1. Single Lesion 2. Increase Number of Lesions 3. Optimize Lesion Size
Selection of Lesion	1. Standardized Quantitative Approach 2. Non Standardized Qualitative Approach 3. No Criteria
Segmentation	1. Semi- Automated 2. Manual 3. Fully Automated

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