# ARRO Case: Pediatric High Risk Classical Hodgkin Lymphoma

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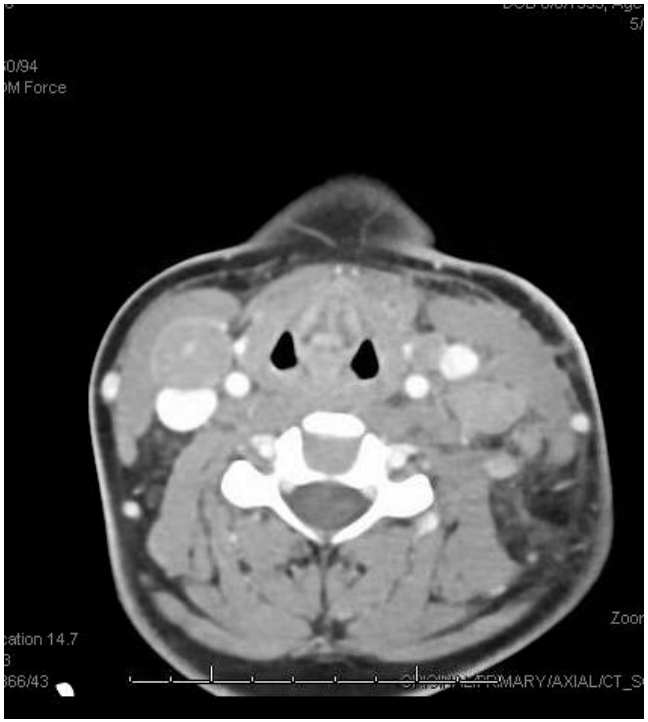
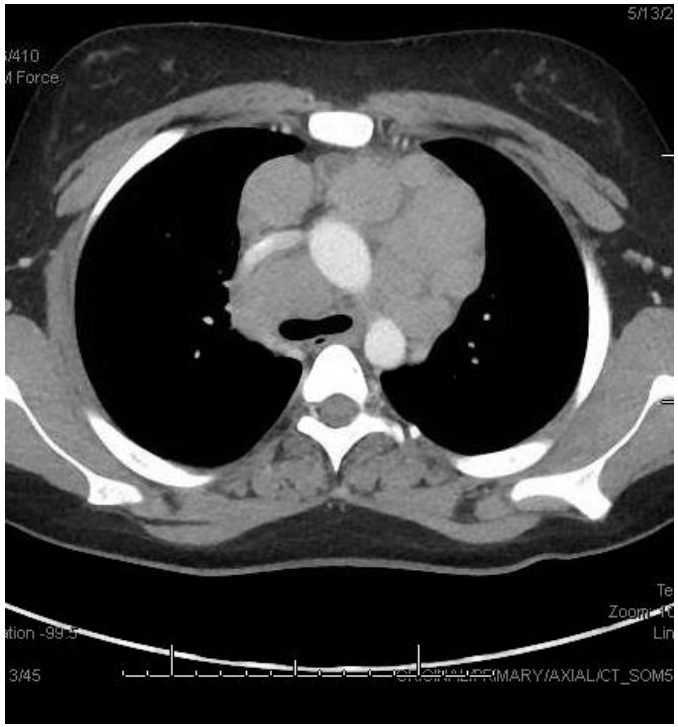
# Case Presentation

- 16 y/o F with no significant PMHx
- **4/2016:** Low grade fevers with night sweats but no weight loss
- **5/2016:** Presented to PCP with neck pain and 5 cm left sided neck mass. Referred to local ENT performed needle biopsy suggestive for lymphoma which led to imaging studies

# CT Neck and Chest





- Impression: Bulky bilateral cervical and supraclavicular and mediastinal lymphadenopathy

# Differential Diagnosis for Mediastinal Mass in Children

- Prominent thymus (pseudomass)
- Thymic hyperplasia
- Thymoma
- Thymic carcinoma
- Lymphoma (Hodgkin or Non-Hodgkin)
- Teratoma
- Thyroid tumors
- ALL

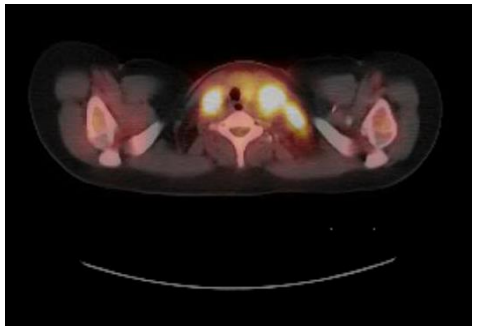
Ranganath et al Am J Roent 2012

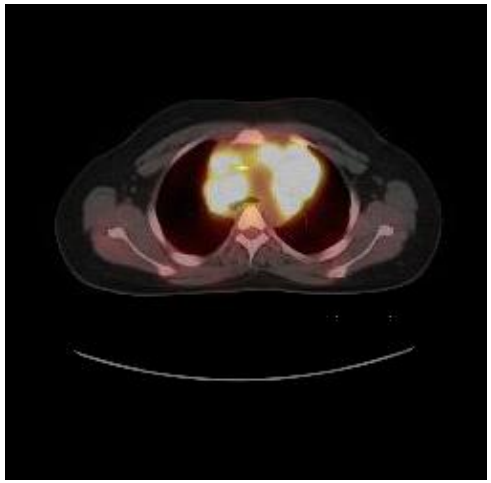
# Pathology

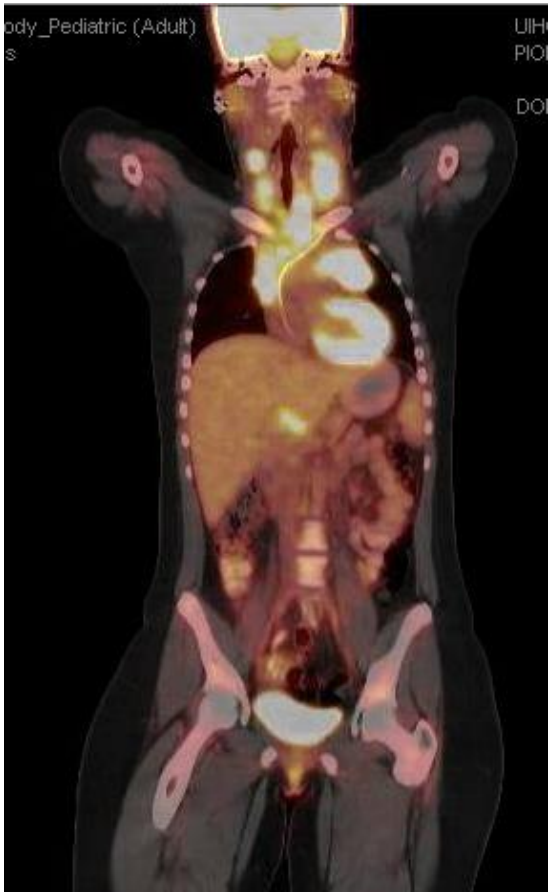
- Excisional biopsy:
  - Classical Hodgkin lymphoma, nodular sclerosis type
  - +CD30, +CD15, -CD20, -CD45

- Markers
  - CD30: Reed Sternberg cells
  - CD15: Hodgkin Lymphoma
    - CD15 negative: suggestive of anaplastic large cell lymphoma
  - CD20: B-cells

# PET/CT







**Findings:**

**Neck:** Extensive bulky hypermetabolic lymphadenopathy in neck levels, including left level II, bilateral levels III, IV, and V, with SUVmax of 12.7.

**Chest:** Extensive hypermetabolic confluent mediastinal lymphadenopathy, including the paratracheal, precarinal, subcarinal, prevascular, and AP window nodes, SUVmax of 15.5. No lung nodules identified.

**Abdomen and pelvis:** Hypermetabolic lesion in the left lobe of the liver with an SUVmax of 4.4. Hypermetabolic periportal lymphadenopathy with SUVmax of 6.7. Normal spleen and adrenal glands. No hypermetabolic pelvic lymphadenopathy.

# Epidemiology

- Incidence:
  - Age 0-14: 280 cases/year
  - Age 15-19: 800 cases/year
- F > M
- Risk factors: EBV (or hx of mono), HIV, single child family
- 30% higher in Caucasians

B&P Principles of Radiation Oncology 2014
Terezakis et al Pediatr Blood Cancer 2014
Ward et al CA: Cancer J Clin 2014

# Clinical Presentation

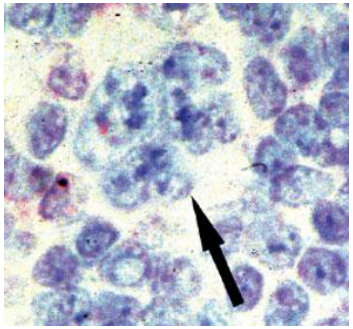
- Painless cervical lymphadenopathy (80%)
  - 75% involving mediastinum
- B symptoms: about 1/3 of cases
  - Temp > 38C
  - Night sweats
  - > 10% weight loss in 6 months
- Isolated mediastinal or infradiaphragmatic disease (spleen, liver) < 5%

Terezakis et al Pediatr Blood Cancer 2014
B&P Clinical Radiation Oncology 2014

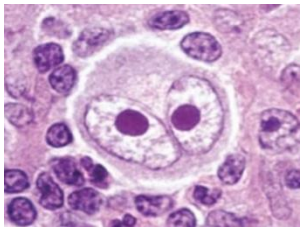
# Work Up

- H&P
- Labs: CBC, CMP, ESR, CRP, LDH
- Excisional biopsy
  - FNA doesn't preserve lymph node architecture
- Bone marrow biopsy: Stage III/IV
- Imaging
  - CT C/A/P with IV contrast (PO if concern for retroperitoneal/pelvic LNs)
  - PET/CT

# Histological subtypes



- Classic HD (cHD) 90%
  - CD30+, CD15+
    - Mnemonic: 30/15 = 2 (HD = 2 letters)
  - Classic RS cells (owl eyes)



- Lymphocyte-predominant HD (10%)
  - CD20+, CD45+, CD79+
  - Popcorn cells
  - Younger patients
  - ~15% transform to more aggressive B-cell lymphoma

# Classic HD subtypes

- Nodular sclerosis classical (most common)
- Mixed cellularity
- Lymphocyte rich classic
- Lymphocyte-depleted (LD) classic
- Interfollicular lymphoma

# Ann Arbor Staging

- Stage I: 1 lymph node region or localized involvement of a single extralymphatic organ or site (IE)
- Stage 2: does not cross diaphragm
  - Two or more lymph node regions OR
  - Single local invasion of extralymphatic organ or site and regional lymph node (IIE)
- Stage III: Stage II, but disease crosses the diaphragm. Includes spleen involvement (Stage IIIS)
- Stage IV: Diffuse or disseminated involvement for 1 or more extralymphatic organs/tissues
- Suffix: Absence (A) or presence (B) of B symptoms at diagnosis

# (Worse) Prognostic Factors

- Stage (most prognostic)
- Bulky disease
  - Mass > 10 cm or > 1/3 of transthoracic diameter
- B symptoms
- Classical subtype (vs lymphocyte predominant)
- Age > 10
- Slow response to initial therapy

Terezakis et al Pediatr Blood Cancer 2014
B&P Clinical Radiation Oncology 2014

# COG Risk Stratification

- Low Risk: Stage IA/IIA without bulky disease
- Intermediate Risk: Bulky I-IIA, I-IIAE, I-IIB, and IIIA/IVA
- High Risk: IIIB and IVB

# Treatment Paradigm

- Low Risk:
  - Chemotherapy alone
  - +/- Involved Site RT (ISRT) 21 Gy /14 fx (dependent on response to chemo)
- Intermediate Risk
  - Chemotherapy
  - +/- ISRT 21 Gy /14 fx  (same as low risk)
- High Risk
  - Chemotherapy + ISRT 21 Gy/14 fx

*Bulky disease requires ISRT

Hodgson et al PRO 2015
Terezakis et al Pediatr Blood Cancer 2014

# Chemotherapy

- ABVEC: most commonly used chemotherapy in US but not only one
- A: Adriamycin
- B: Bleomycin
- V: Vincristine
- E: Etoposide
- C: Cyclophosphamide
- Brentuximab vedotin (Bv): anti-CD-30 monoclonal antibody (experimental)

# IFRT vs INRT vs ISRT

- **Involved field RT (IFRT):** involved nodes at time of diagnosis plus those immediately sup and inf to primary (based on 2D imaging)
- **Involved node RT (INRT):** individual lymph nodes at time of diagnosis with involvement based on anatomic (CT) and functional (PET) imaging. Only used in Europe where pre-chemotherapy PET is performed in treatment position.
- **Involved site RT (ISRT):** similar to INRT where imaging leaves uncertainty to exact location of nodal disease (i.e. pre-treatment imaging not performed in RT positioning). ISRT CTV may include nodal tissue immediately adjacent to what appear to be involved nodes. Current recommendation by International Lymphoma Radiation Oncology Group.

Hodgson et al PRO 2015

# Radiation Treatment Planning

- Pre-chemo GTV
- Post-chemo GTV: any imaging abnormalities on PET or CT
- Post-chemo CTV: lymph nodes from pre-chemo GTV but take into account chemo reduction in axial diameter
- ITV if 4D-CT obtained
- PTV = CTV + margin
  - If IGRT present: 5-10 mm expansion
  - If IGRT not present: minimum 1 cm expansion
- Treat to 21 Gy/14 fx

Hodgson et al PRO 2015

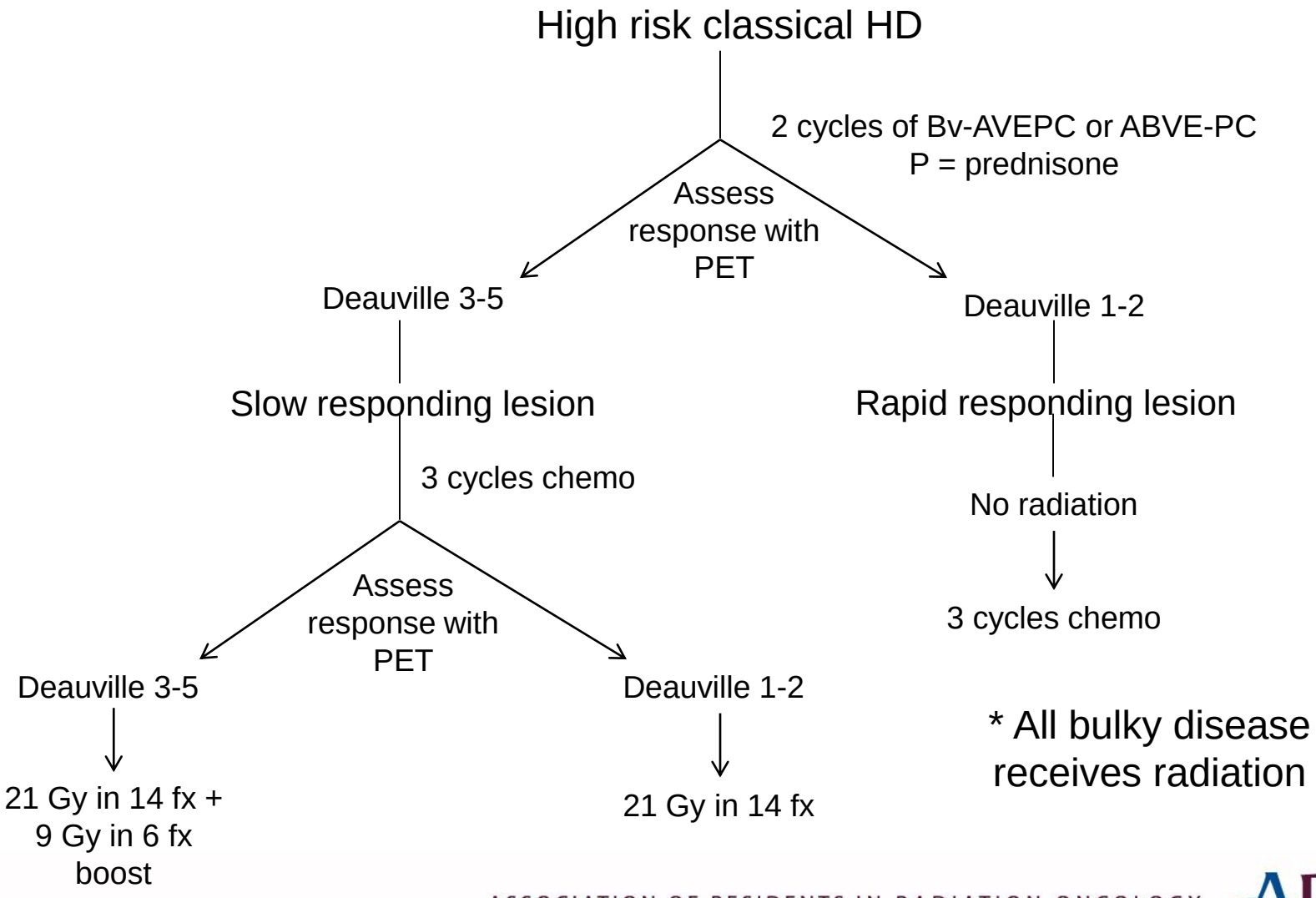
# Treatment for Our Patient

- Our patient: Stage IVBE (bulky)
  - Bone marrow biopsy was negative
- Enrolled in AHOD1331 for high risk classical lymphoma testing role of Bv
- Received 5 cycles of AVEC + Bv
- FDG-avid disease resolved after 2 cycles of chemotherapy (Deauville 2)

# Deauville Criteria

- Visual PET criteria scored 1-5
  - 1: No uptake
  - 2: Uptake ≤ mediastinal blood pool
  - 3: Uptake > mediastinal blood pool and ≤ normal liver
  - 4: Moderately increased uptake > normal liver
  - 5: Markedly increased uptake > normal liver

# AHOD 1331

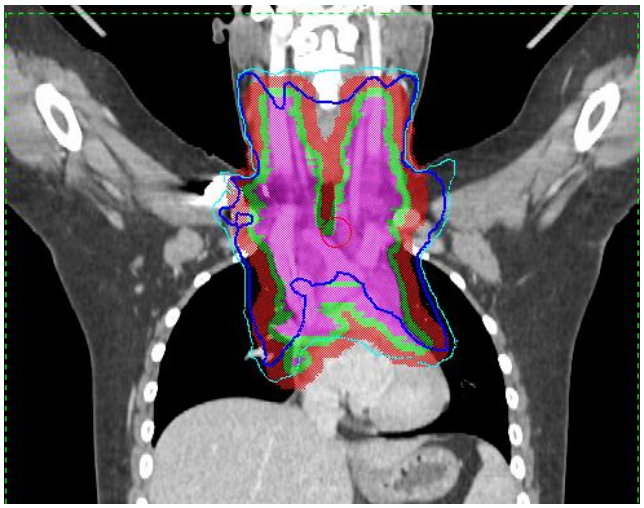

High risk classical HD
2 cycles of Bv-AVEPC or ABVE-PC
P = prednisone
Assess response with PET
Deauville 3-5
Deauville 1-2
Slow responding lesion
Rapid responding lesion
3 cycles chemo
No radiation
3 cycles chemo
Assess response with PET
Deauville 3-5
Deauville 1-2
21 Gy in 14 fx + 9 Gy in 6 fx boost
21 Gy in 14 fx
* All bulky disease receives radiation

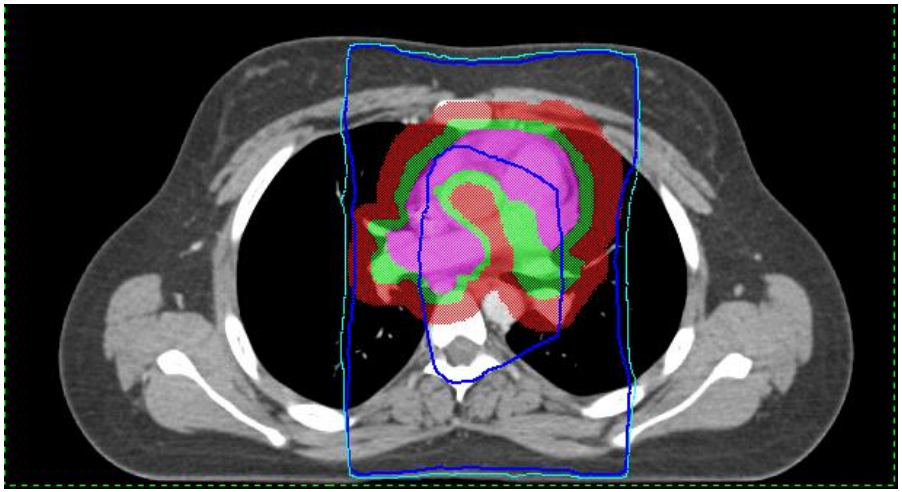
# Simulation and Planning (this case)

- Simulation
  - Position: supine, arms up
  - Immobilization: arm board
- Volume delineation
  - Post-chemotherapy CTV
  - ITV = CTV-postchemo + 5 mm sup/inf and 3 mm radial for account for 4D motion
  - PTV = ITV + 8 mm

# Contours/Plan

- Contours
  - Purple: Post-chemo CTV
  - Green: ITV
  - Red: PTV
- AP/PA 6x
  - Prescribed to 96% IDL (teal)
  - 100% IDL in dark blue





# Recommended Dose Constraints

- Heart: mean < 15 Gy
- Liver: V15 < 50%
- Kidneys
  - Ipsilateral: mean < 15 Gy
- Spinal cord: max point < 45 Gy
- Lung: V20 < 35%

AHOD 1331

- Thyroid
  - > 15 Gy increases risk of abnormal thyroid fxn
- Breast
  - 5-10 Gy can cause hypoplasia
  - Linear relationship with risk of cancer
- Skeletal growth: > 8 Gy affects epiphyseal chondroblasts
- Soft tissues: Muscle growth and subcutaneous fat impaired by doses > 25-30 Gy

Hodgson et al PRO 2015

# Dosimetry

| | ROI | Type | Primary Goal Dose cGy | Primary Goal Volume | Secondary Goal Dose cGy | Secondary Goal Volume |
|---|---|---|---|---|---|---|
| ◆ | Lung_Combined | Max DVH (%) | 2000 | 35 % | 0 | 0 % |
| ◇ | Lung_Combined | Mean Dose | 1500 | | 0 | |
| ◇ | Kidney_combined | Mean Dose | 1200 | | 0 | |
| ◇ | Liver | Max DVH (%) | 1500 | 50 % | 0 | 0 % |
| ◇ | Liver | Max DVH (%) | 2100 | 25 % | 0 | 0 % |
| ◇ | Cord | Max Dose | 4500 | | 0 | |
| ◇ | Heart | Mean Dose | 1500 | | 0 | |
| ◇ | PTV | Min DVH (%) | 2100 | 95 % | 1995 | 95 % |
| ◇ | ITV | Min DVH (%) | 1995 | 95 % | 0 | 0 % |
| ◇ | PTV | Max DVH (%) | 2310 | 10 % | 0 | 0 % |

# Follow-up 1st 5 years

- H&P:
  - Years 1-2: every 3-6  months
  - Year 3: every 6-12 months
  - Annually after
- Labs: annual TSH if neck irradiated
- Imaging
  - CT with contrast at 6, 12, and 20 months
  - Add PET if Deauville 4-5 after 5 cycles of chemo

NCCN Guidelines Version 2.2018

# Follow-up beyond 5 years

- Breast cancer:
  - Females who received chest RT greater than 20 Gy before age 30 yo should undergo breast MRI and mammogram yearly starting at age 25 or 8 years after RT (whichever occurs last)
- Cardiovascular disease:
  - Consider stress test/ECHO 10 years after tx
  - Consider carotid U/S at 10 years if neck irradiated
- Infertility: rare with ABVD regimen
- Labs: TSH, annual fasting glucose, biannual lipids

NCCN Guidelines Version 2.2018

# Outcome

- Completed RT in 10/2016
- Last CT Neck/Chest/Abdomen/Pelvis in 6/16/2017 was negative for recurrence

# Summary

- Excisional biopsy needed for confirmation
  - Classical HD: CD30+/CD15+
- PET-CT recommended for staging
- Treatment of high-risk classical HD is chemo followed by radiation
- ISRT is recommended in the 3D imaging era (rather than IFRT)
- Radiation planning requires consideration of pretreatment GTV and residual post-volume