LYMPHOMA

Dr. Eyad F. Alsaeed

Associate Professor , Consultant Radiation Oncologist

Department Of Medicine

WHO Classification of Hematological Neoplasms

Myeloid Lymphoid Histiocytic Mast Cell

B cell neoplasms *

T cell neoplasms

Hodgkin's lymphoma

* Includes plasma cell myeloma

Proposed WHO Classification of. Lymphoid Neoplasms - 1

B-Cell neoplasms

Precursor B-cell neoplasm

Precursor B-lymphoblastic leukemia/Iymphoma (precursor B-cell acute lymphoblastic leukemia)

Mature (peripheral) B-cell neoplasm*

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Splenic marginal zone B-cell lymphoma (+/— villous lymphocytes)

Hairy cell leukemia

Plasma cell myeloma**/plasmacytoma**

Extranodal marginal zone B-cell lymphama of MALT type

Nodal marginal zone B-cell lymphoma *(+1*— monocytoid B cells)

Follicular lymphoma

Mantle-cell lymphoma

Diffuse large B-cell lymphama

Mediastinal large B-cell lymphoma

Primary effusion lymphoma

Burkitt's lymphoma/Burlcitt cell leukemia

Proposed WHO Classification of. Lymphoid Neoplasms (cont'd)

T-cell and NK-cell neoplasms

Precursor T-cell neoplasm

Precursor T-lymnphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

Mature (peripheral) T-cell neoplasms

T-cell prolymphocytic leukemia

T-cell granular lymphocytic leukemia

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia (HTLV1 +)

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-type T-cell lymphoma

Hepotosplenic gamma-delta T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides**/Sezary syndrome**

Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type

Peripheral T-cell lymphoma, not otherwise characterized

Angioimmunoblastic T-celllymphoma

Amaplastic large-cell lymphoma, T/null cell, primary systemic type

Hodgkin's lymphoma (Hodgkin's disease)

Nodular lymphocyte-predominant Hodgkin's)ymphoma

Classical Hodgkin's lymphoma

Nodular sclerosis Hodgkin's Iymphoma (grades 1 and 2)

Lymphocyte-rich classical Hodgkin's lymphoma

Mixed cellularity Hodgkin's lymphoma

Lymphocyte depletion Hodgkin's lymphoma

NOTE: Only major categories are included. Subtypes and variants will be discussed in the WHO book[2] and are listed in Tables *7 through* 16. Common entities are shown in boldface type.

Abbreviations: HTLV1 +, human T-cell leukemia virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

***B-and T-/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).**

Clinical Grouping of Lymphomas

1. Indolent
2. Aggressive
3. Highly aggressive

Formerly

1. Low Grade
2. Intermediate Grade
3. High Grade

Clinical Grouping of Lymphomas

1. Indolent (≡ "low grade")

	Approximate International Incidence
– Follicular lymphoma Grade 1,2	22%
– Marginal zone lymphoma	
• Nodal	1%
• Extranodal (MALT)	5%
– Small lymphocytic lymphoma	6%
– Lymphoplasmacytic*	1%

*association with Waldenstrom's macroglobulinemia

Clinical Grouping of Lymphomas

2. Aggressive (≡ "intermediate grade")

	Approximate International Incidence
– **Diffuse large B-cell lymphoma**	**21%**
– **Primary mediastinal large B cell lymphoma**	**2%**
– **Anaplastic large T / null cell lymphoma**	**2%**
– **Peripheral T cell lymphoma**	**6%**
– **Extranodal NK / T cell lymphoma, nasal type**	
– **Follicular lymphoma Gd 3**	
– **Mantle cell lymphoma**	**6%**

Clinical Grouping of Lymphomas

3. Highly Aggressive (≡ ”High grade”)

	Approximate International Incidence
– Lymphoblastic lymphoma	2%
– Burkitts lymphoma	1%
– Burkitt-like lymphoma	2%

Clinical Grouping of Lymphomas
(further simplified for radiation oncology exam purposes)

- INDOLENT
  - Follicular lymphoma Gd 1, 2
  - MALT (marginal zone lymphoma, extranodal (MALT type))

- AGGRESSIVE
  - Diffuse large cell

Lymphoma – Staging System

(Cotswold's Meeting modification of Ann Arbour Classification

I	Single lymph node region (or lymphoid structure) *
II	2 or more lymph node regions
III	Lymph node regions on both sides of diaphragm
IV	Extensive extranodal disease (more extensive then "E")

Lymphoma – Staging System

Subscripts

A	Asymptomatic	
B	Fever	> 38^{o}, recurrent
	Night sweats	drenching, recurrent
	Weight loss	> 10% body wt in 6 mos
X	Bulky disease	≥ 10 cm
	or	> 1/3 internal transverse diameter @ T5/6 on PA CXR
E	Limited extranodal extension from adjacent nodal site	

Lymphoma – Essential Staging Investigations

- Biopsy – pathology review
- History – B symptoms, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC
- creatinine, liver function tests, LDH, calcium
- Bone marrow aspiration & biopsy
- CT neck, thorax, abdomen, pelvis

Additional Staging Investigations

- PET or ^{67}Ga scan
- CT / MRI of head & neck
- Cytology of effusions, ascites
- Endoscopy
- Endoscopic U/S

} for gastric lymphoma

- MRI - CNS, bone, head & neck presentation
- HIV
- CSF cytology - testis, paranasal sinus, peri-orbital, paravertebral, CNS, epidural, stage IV with bone marrow involvement

International Prognostic Index for NHL

Age	> 60
Stage	3, 4
PS	ECOG ≥ 2
LDH	> normal
Extranodal	> 1 site

	Number of Risk Factors	5 yr OS*
Low Risk	0-1	75%
Low-Intermediate	2	51%
High-Intermediate	3	43%
High Risk	4-5	26%

*Diffuse large cell lymphoma

Indolent Lymphoma

e.g. Follicular Gd 1/2, small lymphocytic, marginal zone

Limited Disease

(Stage 1A, 2A if 3 or less adjacent node regions)

- IFRT* 30-35 Gy
- Expect ~ 40% long term FFR
- Alternate:
  - CMT
  - Observation. Treat when symptomatic.

* Involved Field Radiotherapy. Use 35 Gy for follicular. 30 Gy for SLL, marginal

Indolent Lymphoma

e.g. Follicular Gd 1/2, small lymphocytic, marginal zone

Advanced Stage

(some Stage 2, Stage 3, 4)

- Palliative RT* for localized symptomatic disease
- Palliative chemotherapy** for disseminated symptomatic disease
- Observation only if low bulk, asymptomatic
  - Treat when symptomatic

* IFRT 15 – 20 Gy / 5

** CVP, chlorambucil

Aggressive Lymphoma (e.g. Diffuse large B cell)

Stage I, some Stage II

- CHOP* x 3 + IFRT (35-45 Gy)**

  Expect ~ 75% long term FFR

Stage III, IV, B symptoms, or bulky disease

CHOP* x 6-8

IFRT (35-45 Gy) to - sites of initial bulk

- residual disease (i.e. PR)

*or CHOP-R (see next slide)

** higher radiation dose if residual disease

Aggressive Lymphoma (e.g. Diffuse large B cell)

CHOP q 21 days

- Cyclophosphamide
- doxorubicin (formerly Hydroxydaunorubicin)
- vincristine ("Oncovin")
- Prednisone (p.o. x 5 days)

CHOP-R x 8 $\rightarrow$ ~40 % $\uparrow$ 3 yr EFS, OS (vs. CHOP x 8)

Extranodal Lymphoma

- Same treatment as nodal lymphoma

Notable Exceptions:

- Gastric MALT
- Testis
- CNS
- Skin

MALT = “mucosa associated lymphoid tissue”

MALT Lymphoma

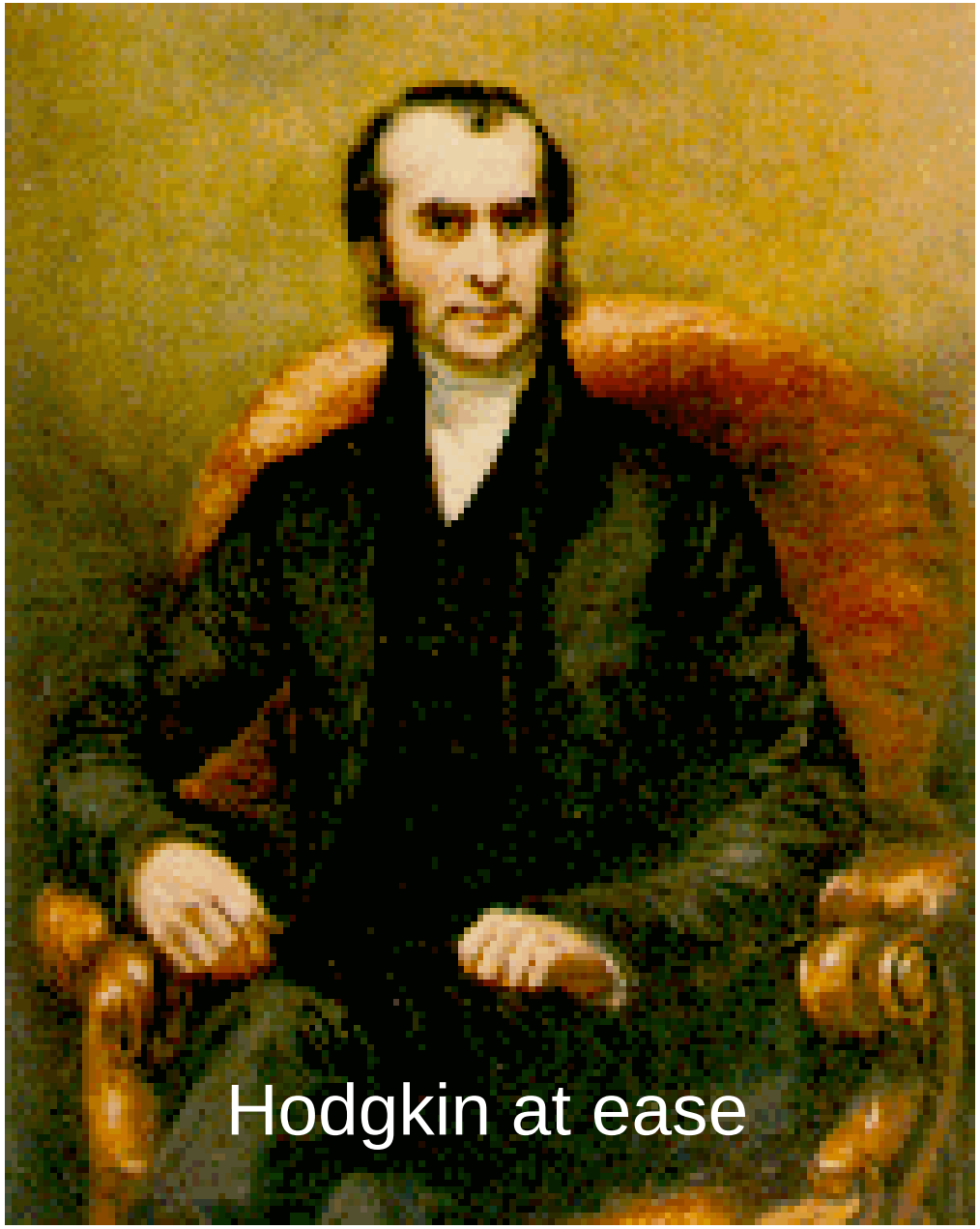
≡ Marginal zone B-cell lymphoma of extranodal (MALT) type

- Stomach. assoc. with Helicobacter pylori infection*
- Salivary Gland. assoc with Sjogren’s syndrome*
- Thyroid. assoc with Hashimoto’s thyroiditis*
- Orbital (lacrimal, conjunctiva)
- Other: Waldeyer’s ring, breast, bladder, lung, skin

* $\rightarrow$ chronic antigen stimulation

Gastric MALT Lymphoma

- Stage I_E , H. pylori +
  - → PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin)
    F/U gastroscopy + Bx q6mo for 2 yrs, then q1yr
- Stage I_E, H. pylori - or antibiotic failure
  - → IFRT 30 Gy (95% local control)
- Stage 2 or higher
  - → Treat as indolent lymphoma + H. pylori eradication


Hodgkin at ease

WHO Classification of Lymphoid Neoplasms

Hodgkin's Lymphoma (≡ Hodgkin's disease)

1. Nodular lymphocyte-predominant HL*
2. Classical HL
    - Nodular sclerosis HL
    - Lymphocyte-rich classical HL*
    - Mixed cellularity HL
    - Lymphocyte depletion HL

* formerly, both of these were classified as lymphocyte predominance Hodgkin's Disease

Hodgkin's Disease - Staging Investigations

- Biopsy – pathology review
- History – B symptoms, pruritis, alcohol pain, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC, ESR
- creatinine, liver function tests, LDH, calcium, albumin
- Bone marrow aspiration & biopsy
  - if abnormal CBC, Stage 2B or higher
- CT thorax, abdomen, pelvis

Hodgkin's Disease - Other Investigations

- PET scan
- ^{67}Ga scan
- Lymphangiogram – if expertise available, no PET

- Pregnancy test
- oophoropexy / semen cryopreservation
  - if chemotherapy or pelvic RT
- Dental assessment – if oropharyngeal RT

Hodgkin's Lymphoma

Early Stage

1A, 2A

Advanced

III, IV

Bulky Disease

B Symptoms

Hodgkin's Lymphoma

Early Stage

1A, 2A

Advanced

III, IV

Bulky Disease

B Symptoms

FAVOURABLE*

- 1-3 sites
- Age ≤ 40
- ESR < 50
- NS, LRCHL

UNFAVOURABLE*

- > 3 sites
- Age > 40
- ESR > 50
- Mixed cellularity

*NCIC HD6 Study Criteria reflecting prognosis when treated with radiation only

Early Stage Hodgkin's Lymphoma
Favourable Prognosis

- ABVD X 3 - 4
- IFRT 30 Gy / 20

- **Fewer cycles ABVD may be adequate**. GHSG HD10 study, in progress, compares ABVD x 2 vs. ABVD x 4

- **Lower radiation dose may be adequate**. GHSG HD10 study and EORTC H9 study, in progress, compare IFRT 20 Gy with 30 Gy (HD10) and 36 Gy (H9)

- **Caution: late toxicity data awaited**

Favourable Prognosis – Early Stage Hodgkin's Lymphoma

Some Other Treatment Options

- STNI

  Mantle + Para-aortic nodes,spleen 35 Gy/20

  - **historical gold standard**
  - **survival ≡ CMT**
  - **use if CTx containdicated**
  - **<u>but</u>: high risk late toxicity**

- ABVD x 2 + IFRT

  - **as per BCCA guidelines**
  - **awaiting clinical trial results** (GHSG HD10)

- ABVD x 6

  - **awaiting NCIC HD.6 results**

Early Stage Hodgkin's Lymphoma
Unfavourable Prognosis

- ABVD X 4 - 6
- IFRT 30 Gy / 20

- **NB: Overlap with favourable prognosis ESHL**

Advanced Stage Hodgkin's Lymphoma
Stage 3, 4, B symptoms, bulky disease

- ABVD X 6 – 8*
- IFRT
  - sites of bulky disease
  - sites of residual disease (35 Gy / 20)

* ABVD until 2 cycles past maximum response

ABVD

- doxorubicin (Adriamycin)
- Bleomycin
- Vinblastine
- Dacarbazine

IV Days 1, 15

Very Favourable Prognosis Hodgkin's Lymphoma

- Stage 1A NLPHL*
- Stage 1A high neck NS, LRCHL

→ IFRT 35 Gy / 20

*Nodular Lymphocyte Predominant HL

–usually localized, peripheral nodal sites

–good prognosis, but some late relapses (>10yr)

Hodgkin's Lymphoma
Rough Approximation of Prognosis

	DFS	OS
Early	80 – 90%	85 – 95%
Advanced	40 – 80%*	

If RT only (STNI): Deaths from 2nd malignancy > deaths from Hodgkin's disease by 15 – 20 yrs

* Depending on Hasenclever Prognostic Index: based on Age>45, male, Stage 4, albumin < 4, Hb < 10.5, WBC<600 or >15000

Side Effects of Radiotherapy for Hodgkin's Lymphoma

1. Depend on
   - Dose/fractionation
   - Site
   - Irradiated volume
   - Chemotherapy

2. - Acute
   - Subacute
   - Late

Toxicity of STNI for Hodgkin's Lymphoma

ACUTE

- Skin erythema
- Local alopecia
- Xerostomia
- Dysphagia
- Fatigue
- ↓ WBC, platelets
- Para-aortic RT - nausea, vomiting
  - diarrhea

Toxicity of EFRT for Hodgkin's Lymphoma

SUBACUTE

- Fatigue
- Xerostomia
- Pneumonitis < 5%, dependent on lung volume treated
- Herpes Zoster
- Lhermitte's Syndrome

Toxicity of STNI for Hodgkin's Lymphoma

LATE

- Hypothyroidism
- Cardiac
  - (CAD, valvular disease, pericarditis)
  - 5% risk cardiac death in 20 yrs (2-3 x expected)
- 2nd malignancy (↑ risk of most solid tumors)
  - esp. breast ca if < 25 yrs at time of RT
  - Lung ca in smokers
  - Solid tumour risk rises after 10 years from RT
  - Absolute Excess Risk ~1% per year

52 y.o. male with dysphagia

Exam: posterior oropharyngeal mass involving L tonsil, L base of tongue, crossing over midline to involve R base of tongue.

Biopsy: “large cell lymphoma of T-cell derivation with differential diagnosis between nasal type extranodal T-cell lymphoma, and peripheral T-cell lymphoma of unspecified type.”


PANIC

General Principles of Answering Lymphoma Questions - 2

- "First of all, I would take a complete history and perform a full physical examination…"
- "The pathology should be reviewed by an experienced lymphoma pathologist…"
- "This patient's management should be discussed in a multidisciplinary setting*…"

*At least by haematologist / medical oncologist and radiation oncologist

Clinical Grouping of Lymphomas

2. Aggressive (≡ "intermediate grade")

	Approximate International Incidence
– **Diffuse large B-cell lymphoma**	**21%**
– **Primary mediastinal large B cell lymphoma**	**2%**
– **Anaplastic large T / null cell lymphoma**	**2%**
– **Peripheral T cell lymphoma**	**6%**
– **Extranodal NK / T cell lymphoma, nasal type**	
– **Follicular lymphoma Gd 3**	
– **Mantle cell lymphoma**	**6%**

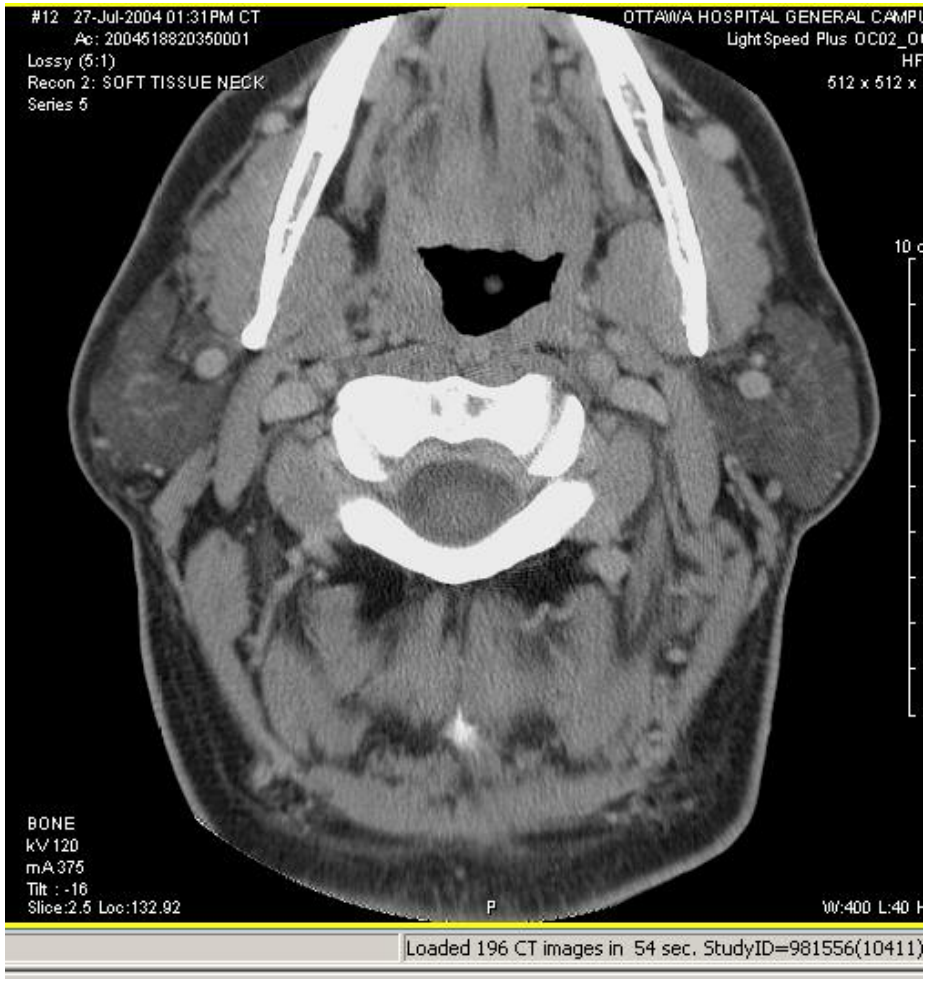
“Aggressive” lymphoma

- CT head, neck, thorax, abdo, pelvis
- MRI head & neck
- CBC, creatinine, LDH, liver enzymes
- Bone marrow aspiration & biopsy
- HIV testing
- Dental consult

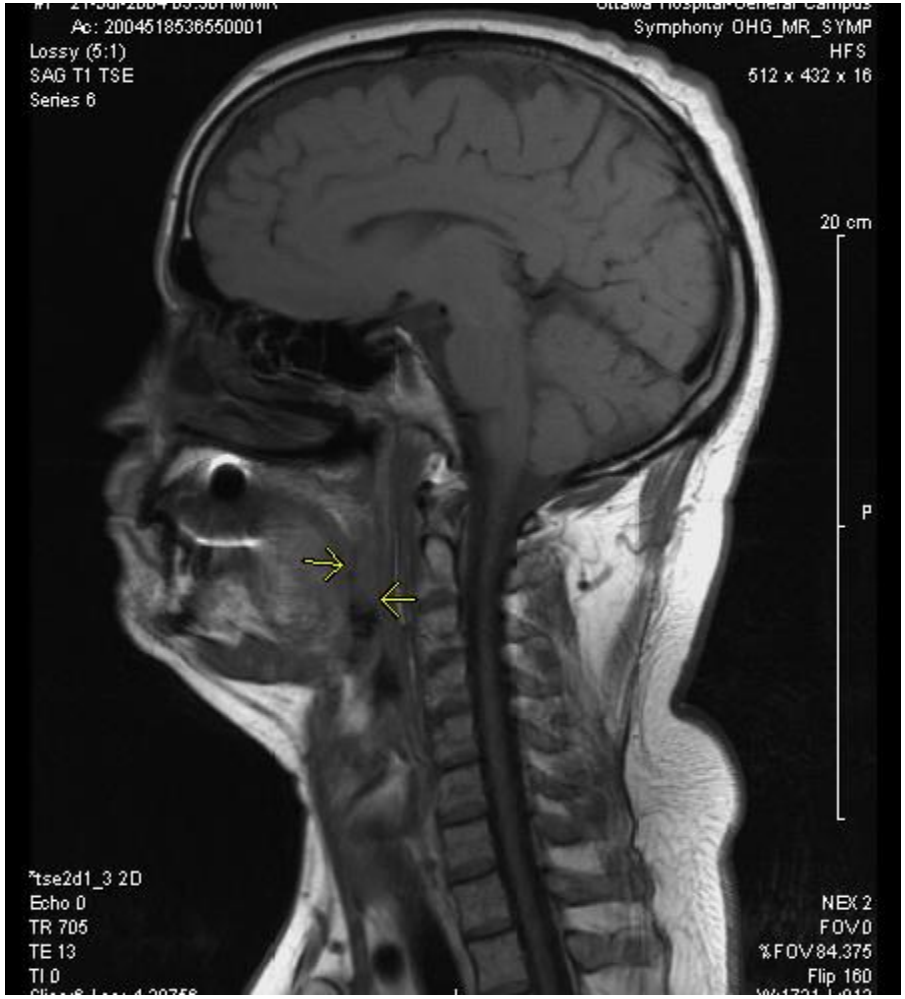
DM 005676

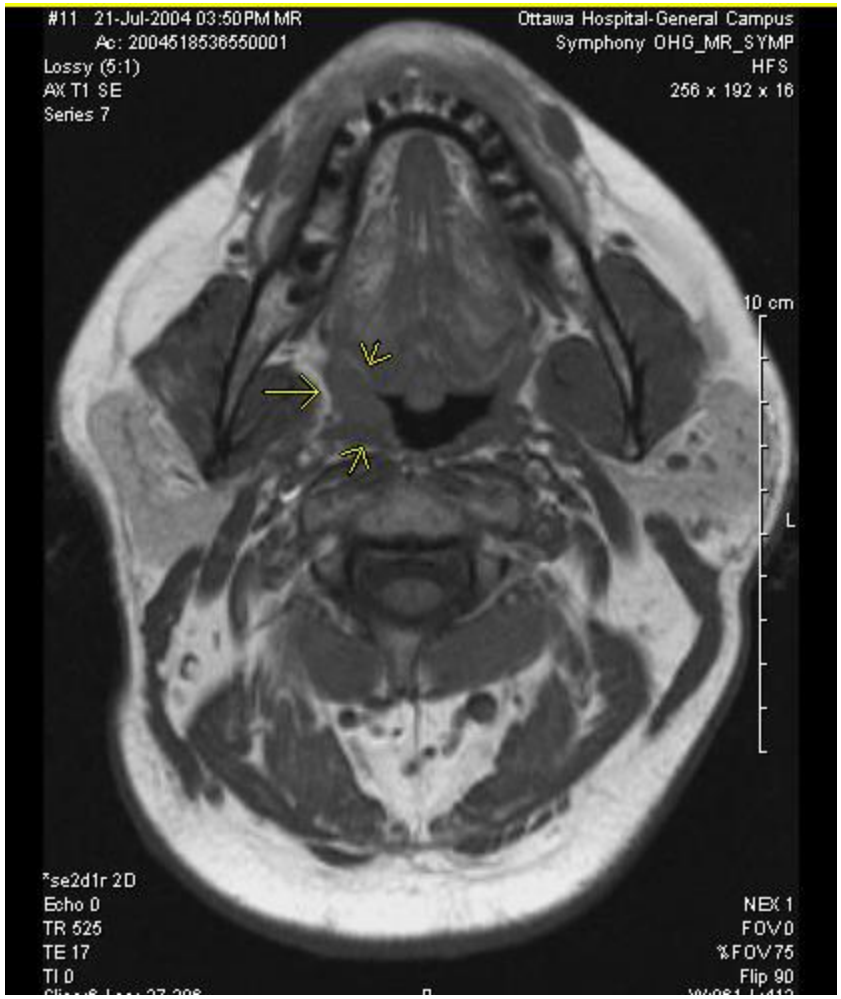
CT: “nodular defect arising from posterior aspect of pharynx extending into tonsillar region…3.5 x 1.5 cm…also a prominent nodular structure extending through base of tongue 3.5 x 2.5 cm…. Non-specific cervical lymph nodes, the largest 11 mm…”

No evidence of disease at other sites, normal lab work.



DM 005676


Ac: 2004518536550001
Lossy (5:1)
SAG T1 TSE
Series 6
Symphony OHG_MR_SYMP
HFS
512 x 432 x 16
20 cm
P
*tse2d1_3 2D
Echo 0
TR 705
TE 13
TI 0
NEX 2
FOV 0
%FOV 84.375
Flip 160


#11 21-Jul-2004 03:50PM MR
Ac: 2004518536550001
Lossy (5:1)
AX T1 SE
Series 7
Ottawa Hospital-General Campus
Symphony OHG_MR_SYMP
HFS
256 x 192 x 16
10 cm
L
*se2d1r 2D
Echo 0
TR 525
TE 17
TI 0
NEX 1
FOV 0
%FOV 75
Flip 90

DM 005676

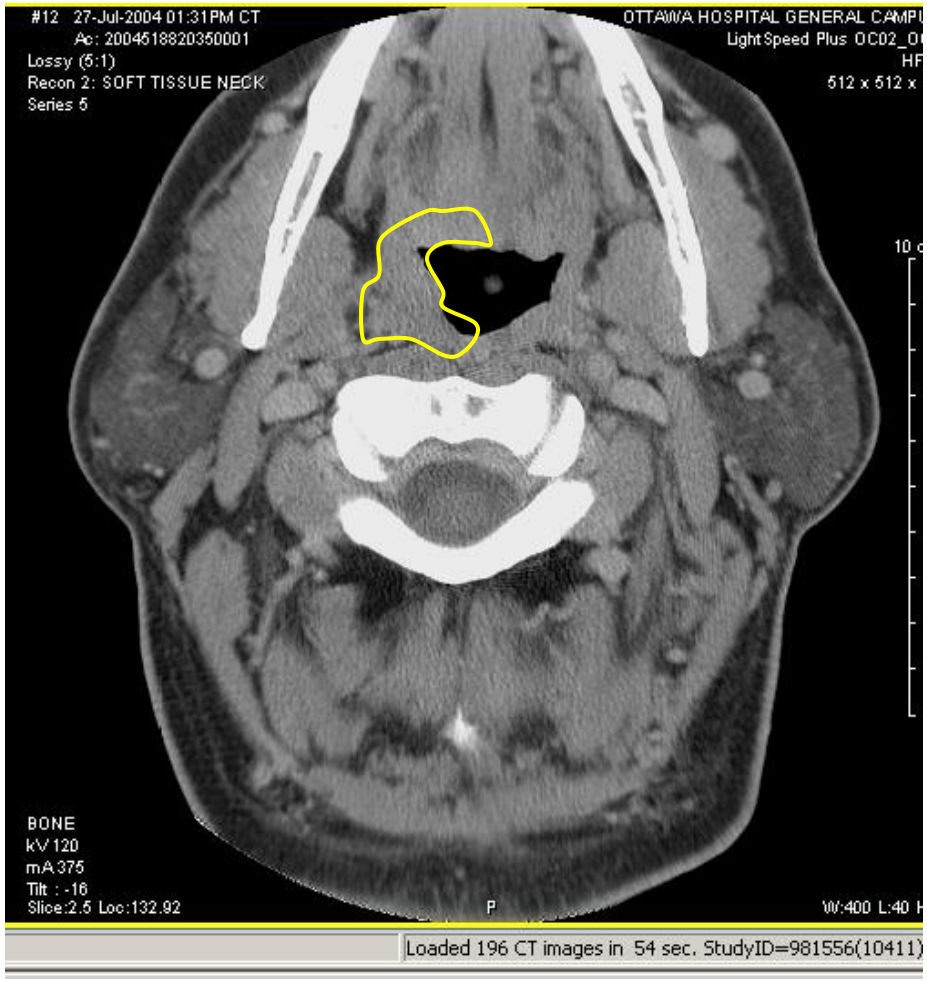
CHOP x 3

Why not CHOP-R?

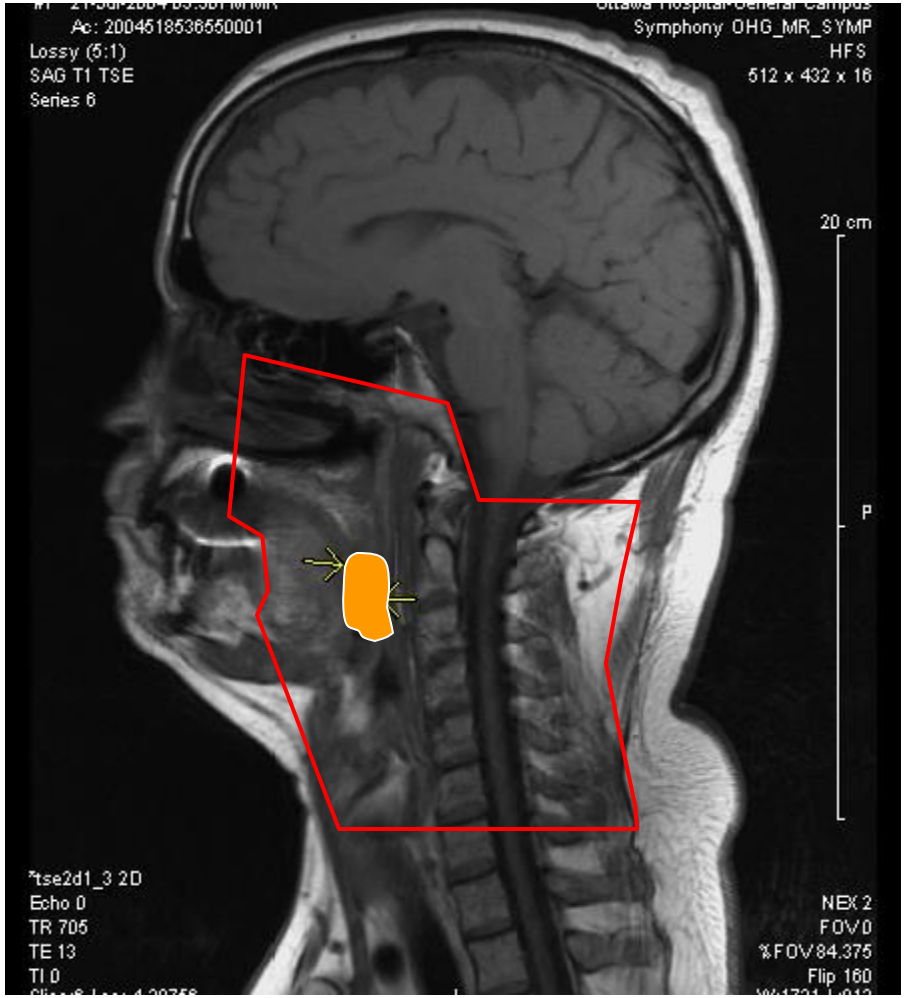
Planning CT

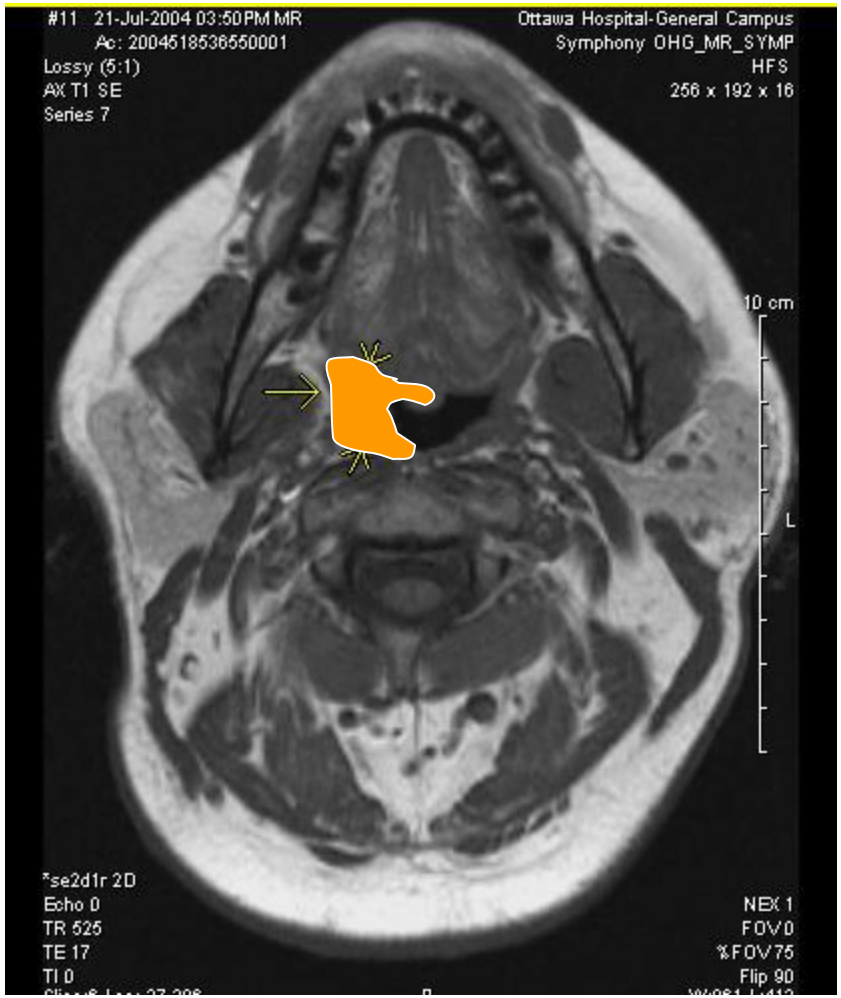
Supine, in immobilization shell

GTV contoured



DM 005676





PTV: Waldeyer's Ring. Lateral POP, 6 MV photons, compensators for dose homogeneity, 40 Gy / 20 / 4 wks

31 y.o. female with recent onset fatigue, night sweats, and mass in right neck

Seen in ER: R supraclavicular node ~2 cm

CXR: Huge ant mediastinal mass

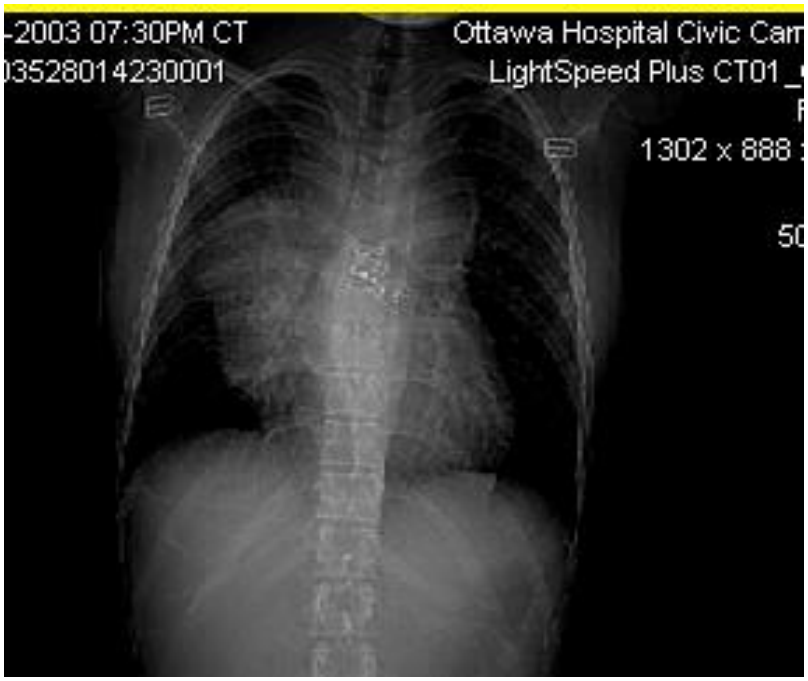
Biopsy: Nodular sclerosis type Hodgkin's disease

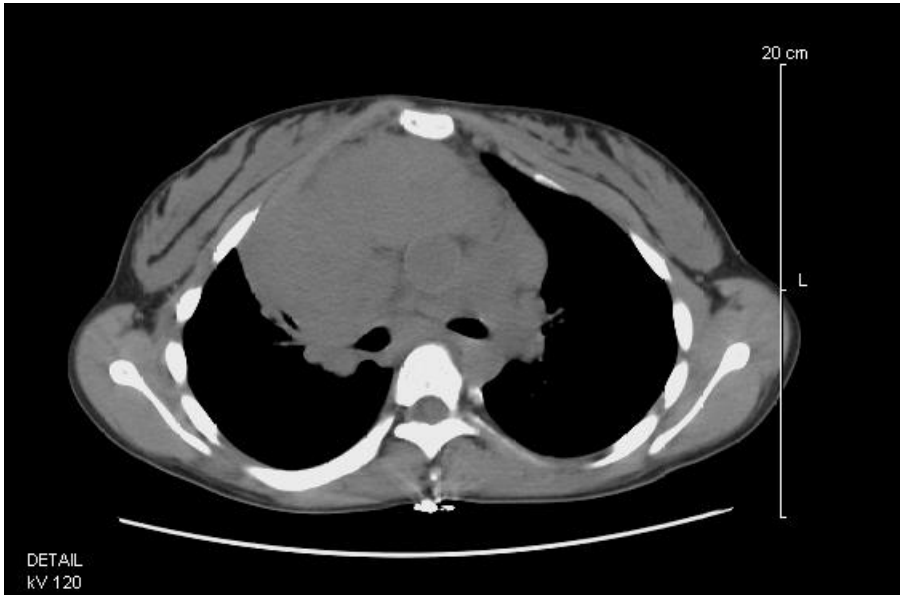
CT Chest: "Large, lobulated mass in anterior mediastinum extending from suprasternal notch to cardiophrenic angle…also an enlarged subcarinal node…"

Referral to Radiation Oncology

- History & Physical
- Pathology Review
- Discuss with Haematologist / Medical Oncologist
- CBC, ESR, creatinine, liver enzymes
- CT abdo-pelvis
- ^{67}Ga scan
- Bone marrow aspiration & biopsy

BW 037843

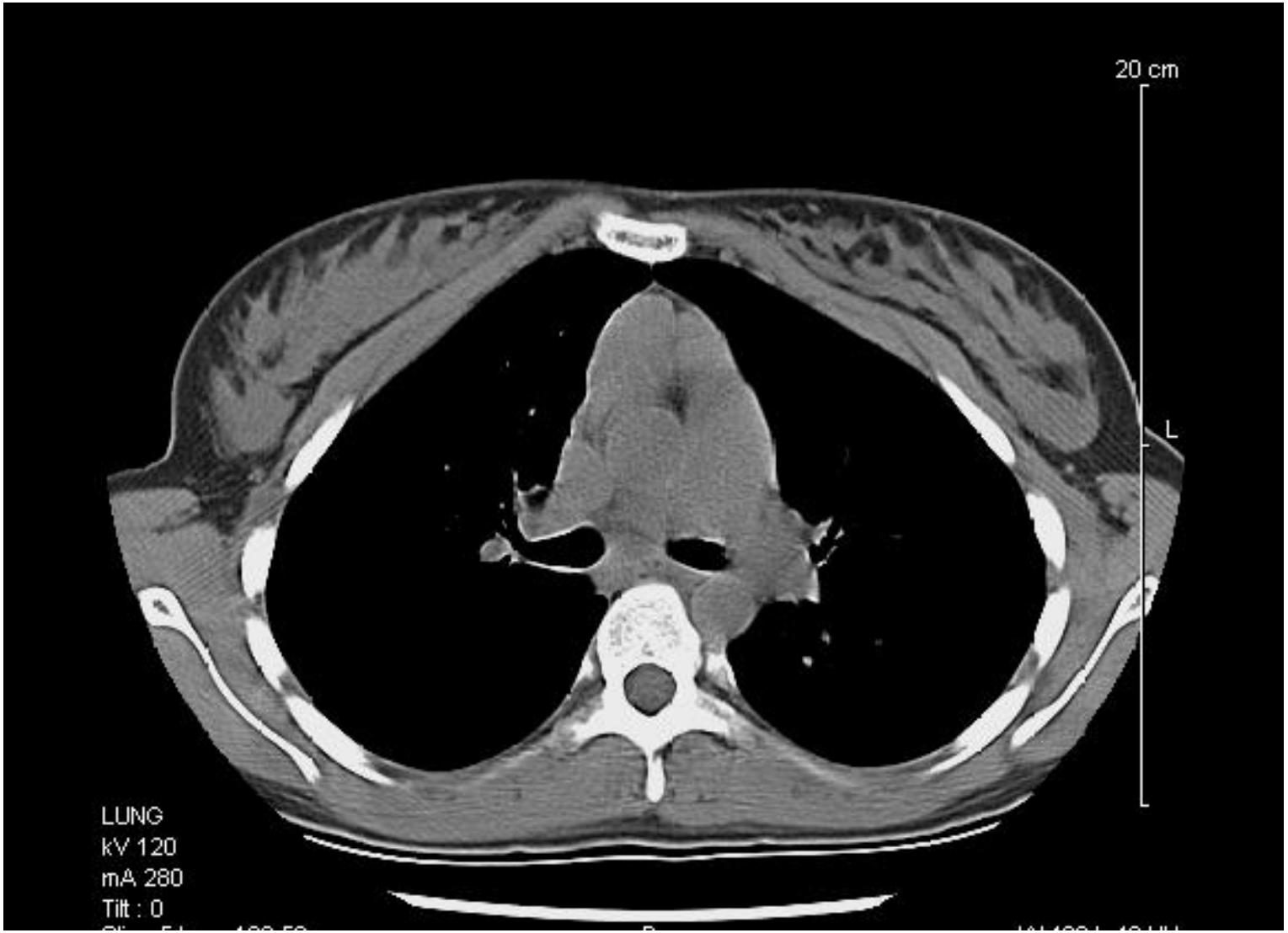


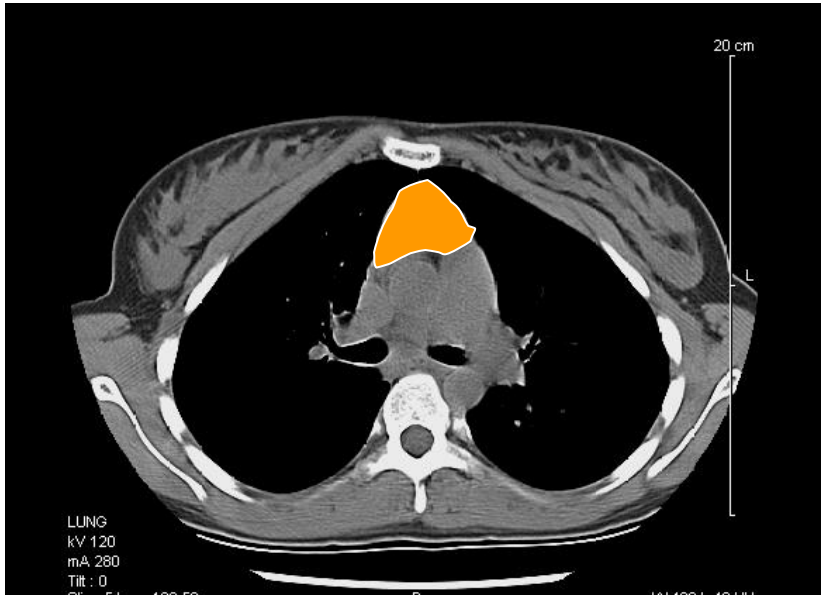


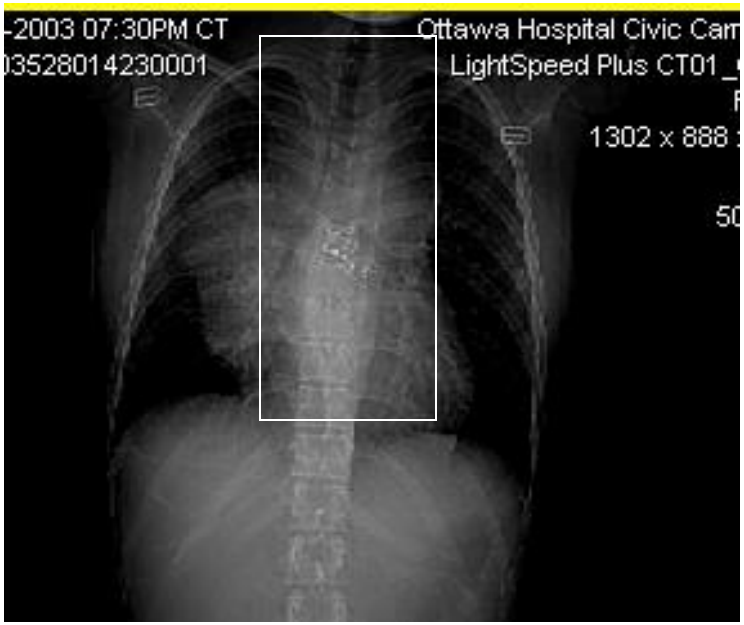
Hodgkin's Lymphoma, Nodular Sclerosis type

Stage I**XB**

ABVD x 8 cycles. Residual 4 x 6 cm ant. Mediastinal mass







CT simulation. GTV contoured. CTV = entire mediastinum with 2 cm lateral margin. Move breasts out of field. 6 MV photons. AP POP. 35 Gy / 20 / 4 weeks. Shielding after 25 Gy to protect heart.

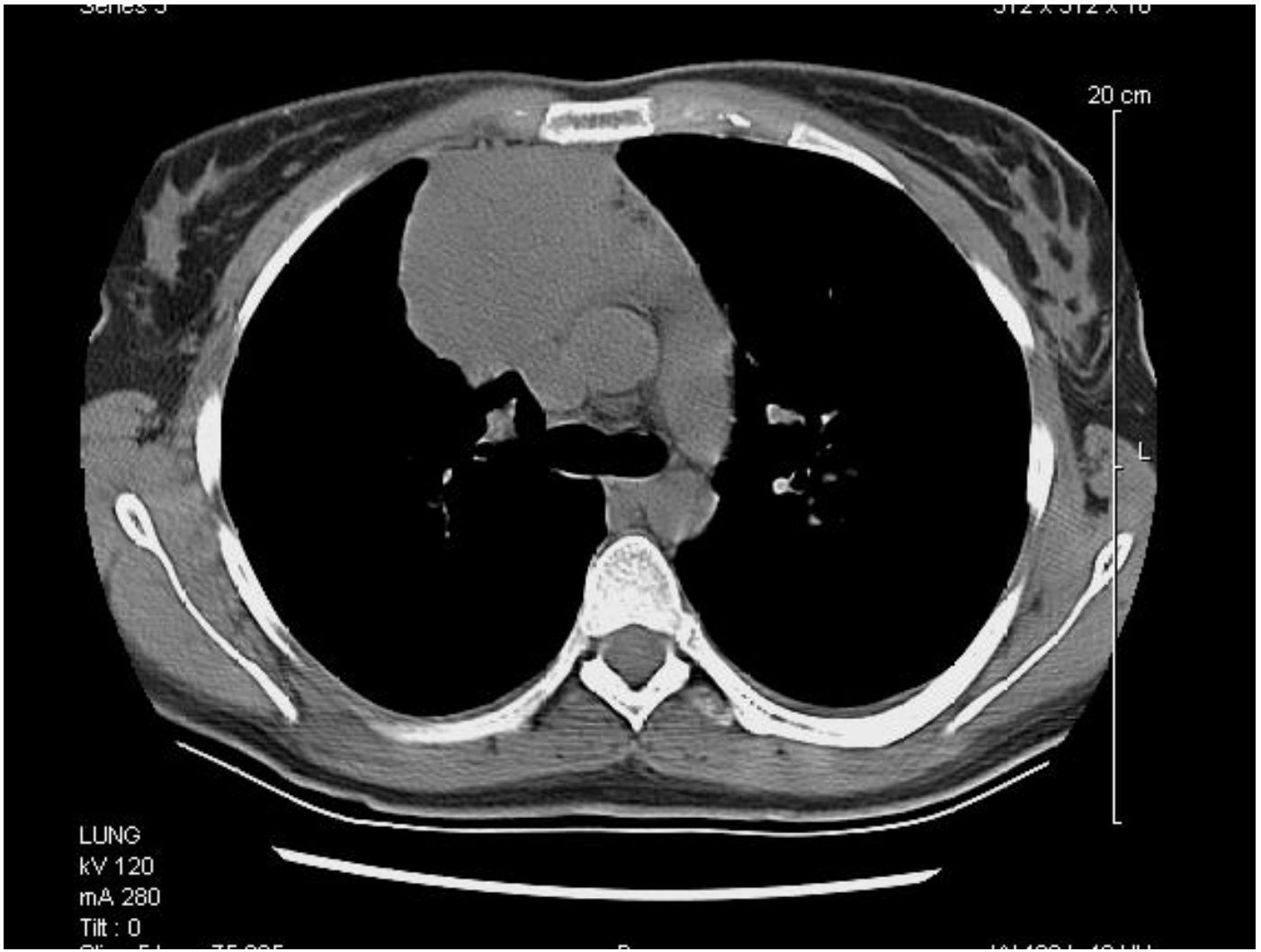
AD 036063

26 y.o. female with one year history of intermittent chest pain.

CXR: Anterior mediastinal mass

CT: 6 x 7.5 cm anterior mediastinal mass. No other lymphadenopathy seen.

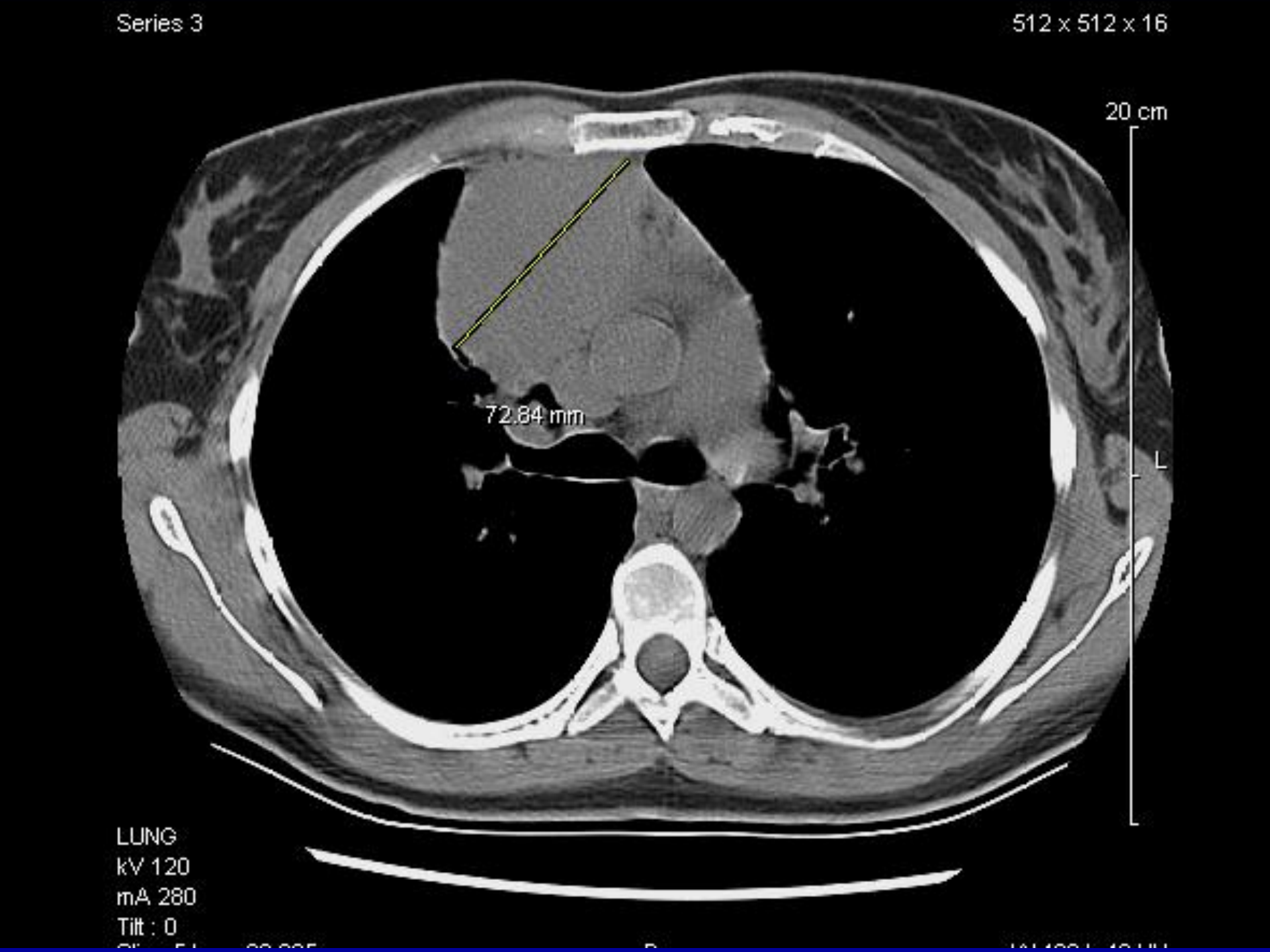
Biopsy: Non-Hodgkin's Lymphoma, large cell type. Probably mediastinal sclerosing type.

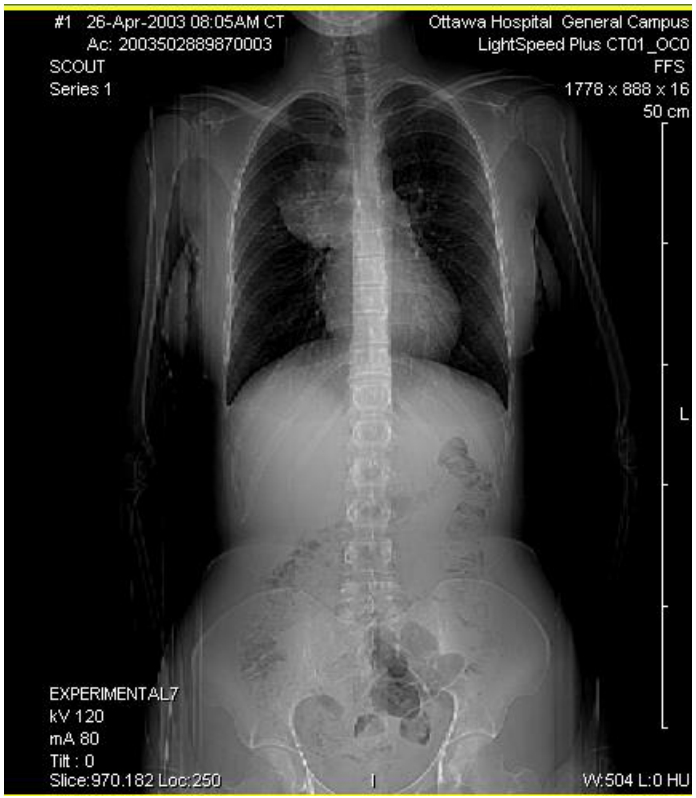

20 cm
L
LUNG
kV 120
mA 280
Tilt : 0

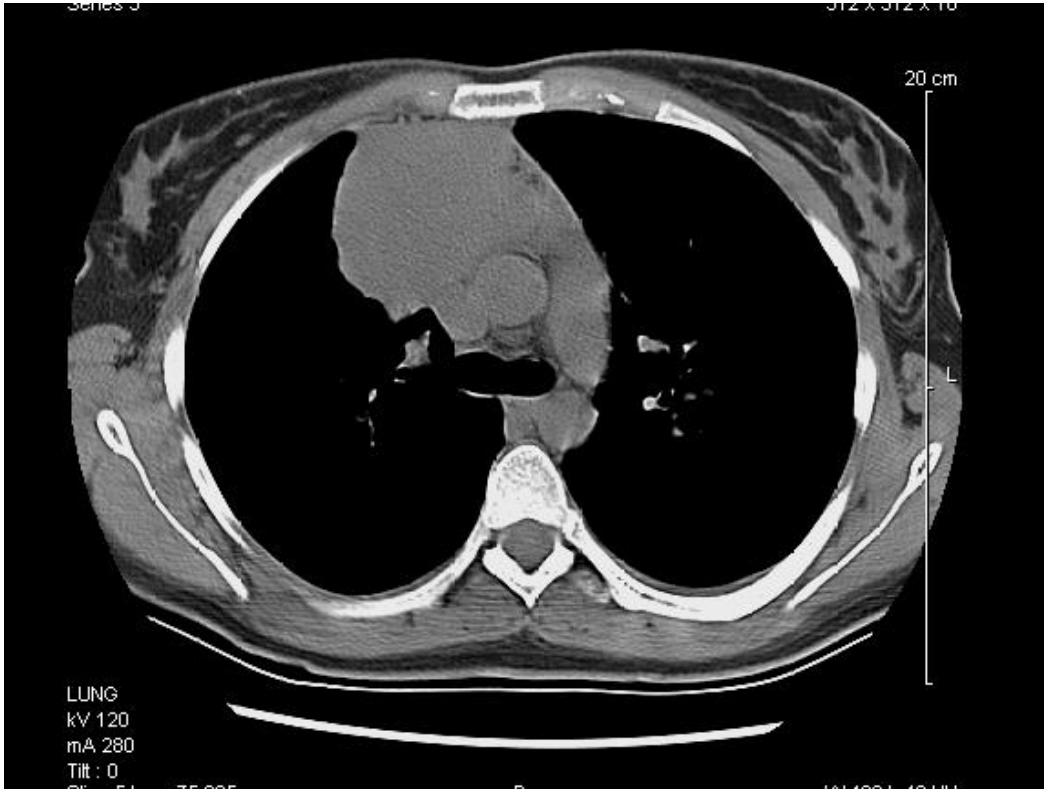
Referral to Radiation Oncology

- History & Physical
- Pathology Review
- Discuss with Haematologist / Medical Oncologist
- CBC, LDH, creatinine, liver enzymes
- CT abdo-pelvis
- ^{67}Ga scan
- Bone marrow aspiration & biopsy

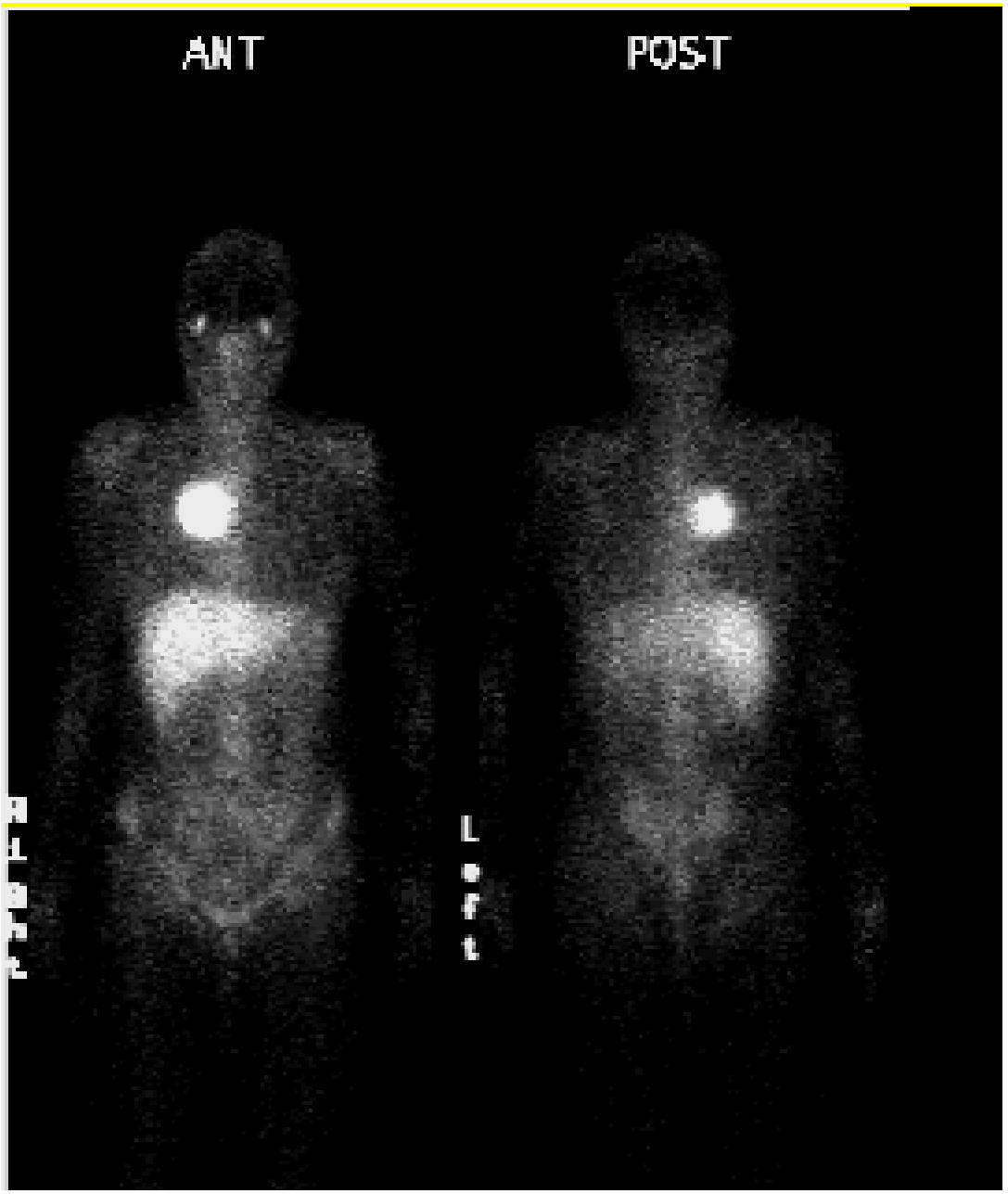
What Stage is this patient?


Series 3
512 x 512 x 16
20 cm
72.84 mm
L
LUNG
kV 120
mA 280
Tilt : 0

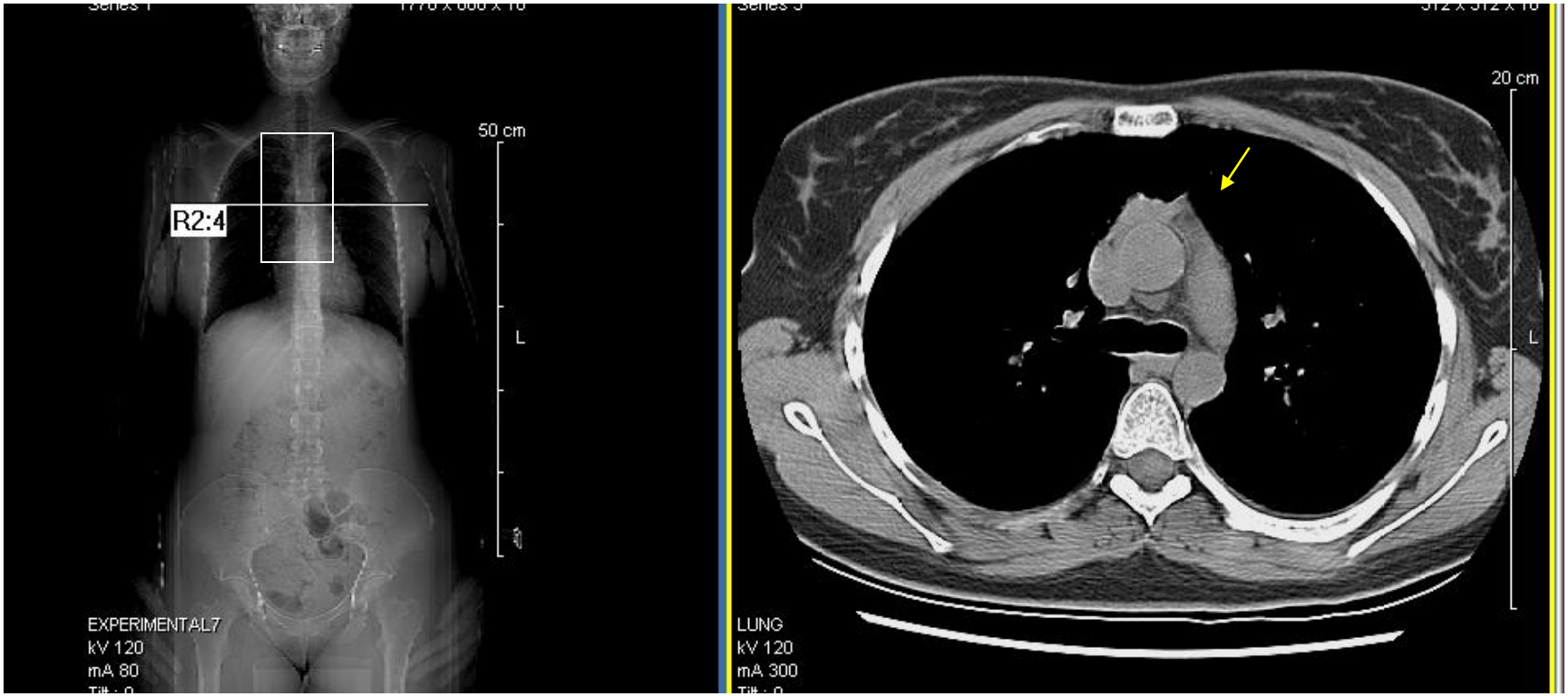




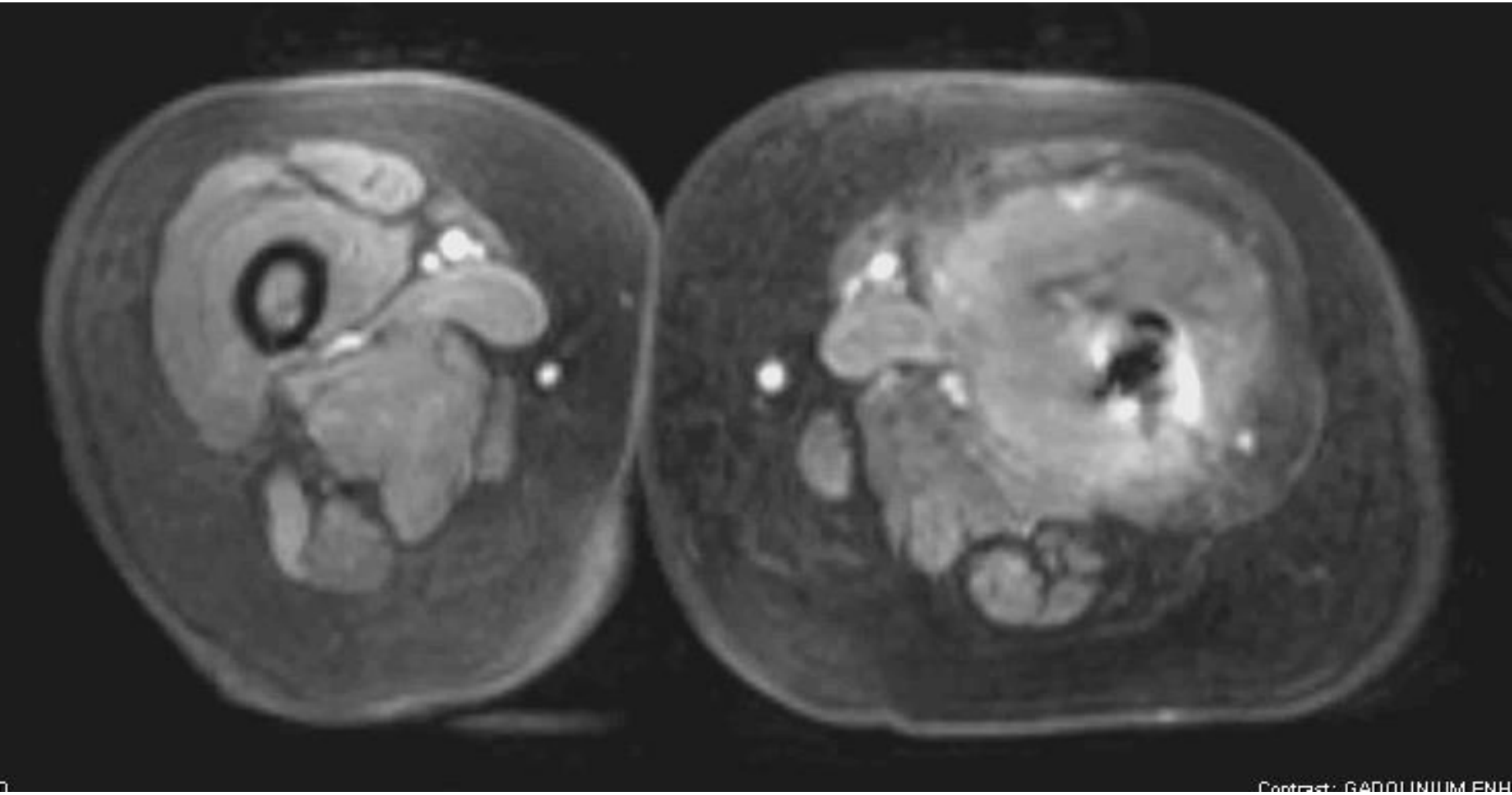
Bulky disease on CXR. Stage I**XA**

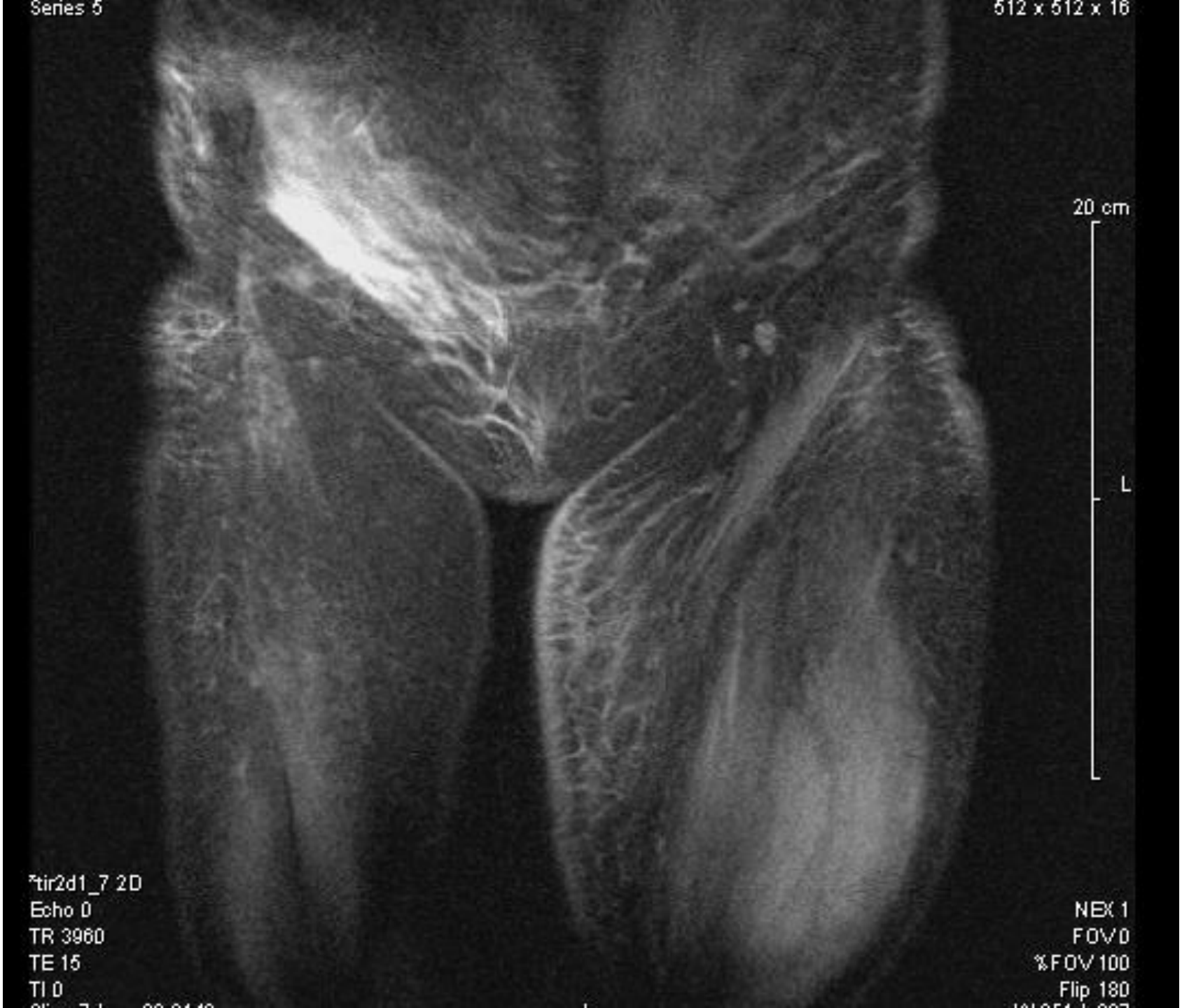

ANT
POST
L
e
f
t

CHOP x 6 cycles. 2 x 0.9 cm residual mass



RT to mediastinum: 40 Gy / 20


Contrast: GADOLINIUM ENH


Series 5
512 x 512 x 16
20 cm
L
*tir2d1_7 2D
Echo 0
TR 3960
TE 15
TI 0
NEX 1
FOV 0
%FOV 100
Flip 180