Radiation Therapy for Testicular Cancer

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Case

- 41 y.o. male presents with a 6 week history of painful right testicle
- Other sx's: decreased libido
- PMHx: Eczema, seasonal allergies
- PSHx: Vasectomy
- Medications: Rhinocort
- Allergies: NKDA

Case

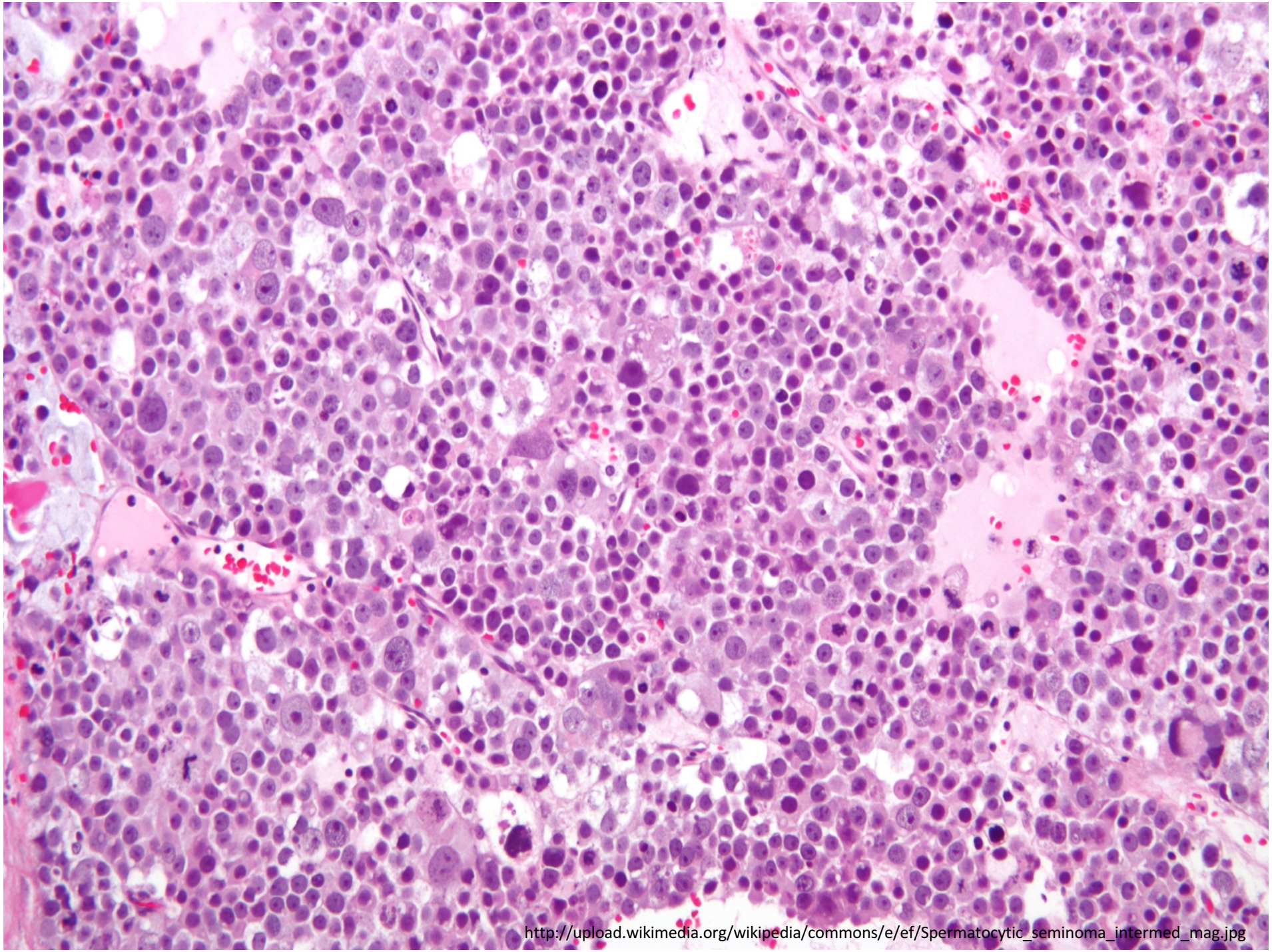
- Family Hx: No history of cancer
- Social Hx: Married with 3 children
- ROS: negative
- Exam: scrotum without lesion, TTP of right testicle but no palpable mass
- Labs: serum AFP, LDH, and HCG: WNL

Case

- Ultrasound Scrotum:
  - Multiple nodules in right testicle
  - Given multifocality, may represent non-seminomatous tumor
  - Right hydrocele
- CT: Abdomen/Pelvis
  - No evidence of metastatic disease
- CXR:
  - No evidence of disease

Case

- Right radical orchiectomy
- Pathology
  - Testicle, right, radical orchiectomy:
    - Spermatocytic seminoma
    - Multifocal, 1.0, 0.5 cm
    - Limited to testes, margins negative, no LVI
    - pT1 NX S0, Stage IA
    - IHC: -OCT3/4
- Referred to radiation oncology for evaluation for adjuvant therapy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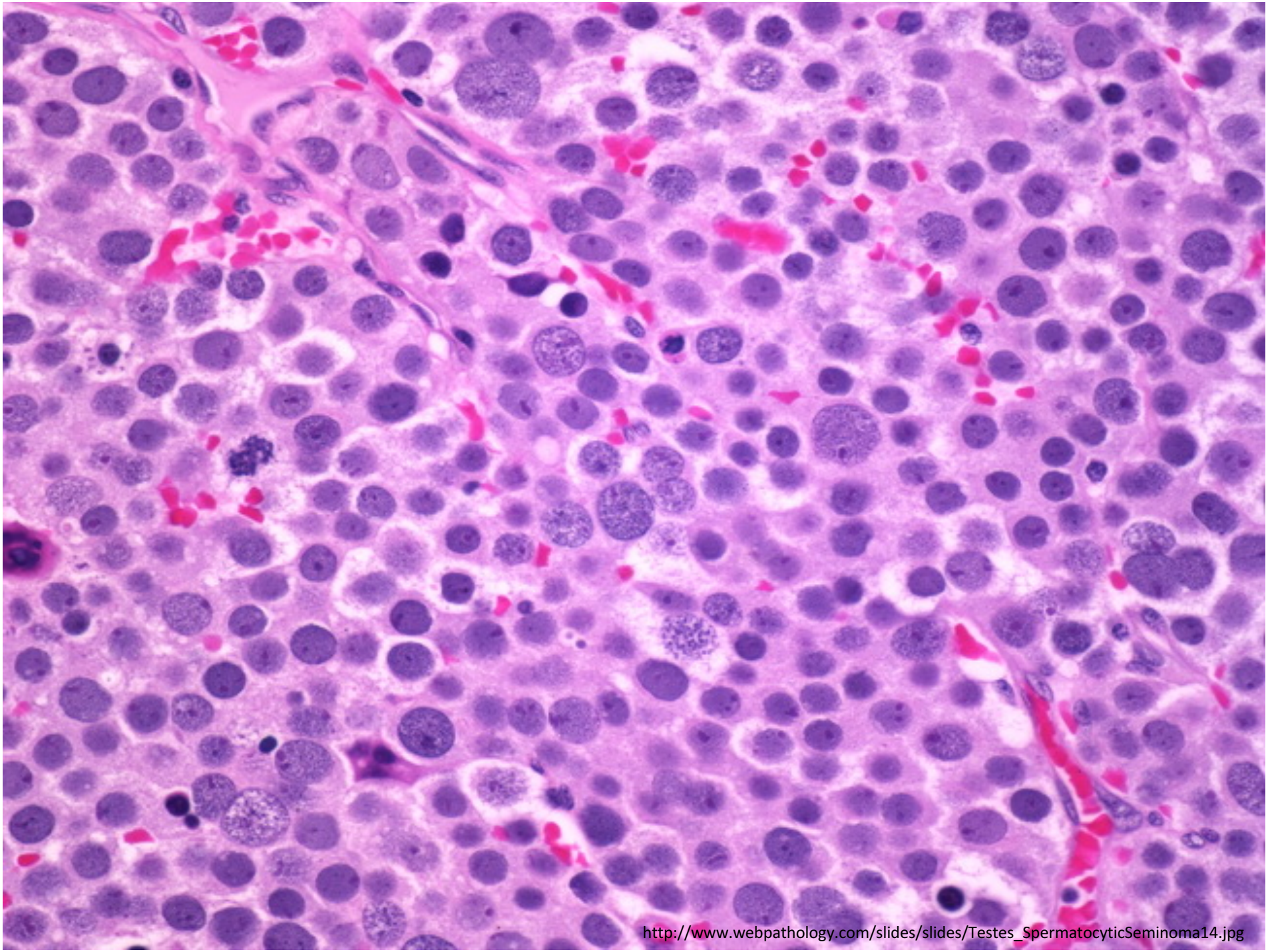
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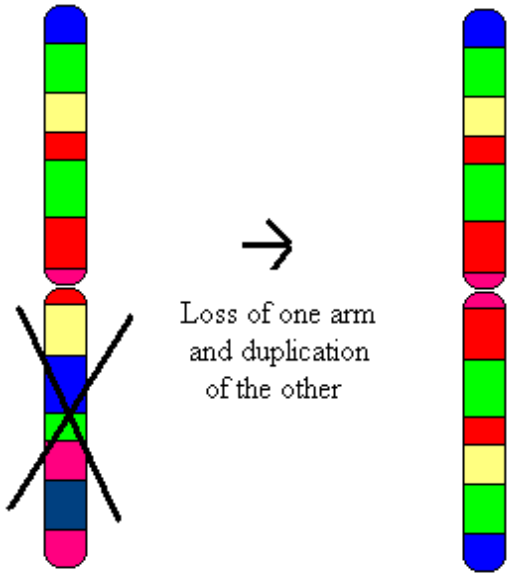
Testicular Cancer

- Only 1-2% of malignant tumors in men
- Most common malignant tumor in men ages 15-35
- World (2008): 52,000 cases with 9000 deaths
- US: 8480 cases with 350 deaths

- Isochrome 12p in 80% of germ cell tumors
  - DDX1, KRAS, c-KIT (ligand KITGL)
  - ITGCN and invasive tumors



Classification of Testicular Tumors

- Germ Cell Tumors (95%)
  - Seminomatous (35%)
    - Seminoma
    - Spermatocytic Seminoma
  - Non-seminomatous (5-10%)
    - Embryonal
    - Yolk Sac
    - Choriocarcinoma
    - Teratoma
  - Mixed (50-60%)

Classification of Testicular Tumors

- Sex Cord Stromal Tumors
  - Leydig Cell Tumors
  - Sertoli Cell Tumors
- Others
  - Lymphoma (most common in age >65)
  - Sarcomas

Germ Cell Tumors

- 10% occur outside of Testes
  - Most common locations: retroperitoneum and anterior mediastinum
  - Dysgerminoma of Ovary/mediastinum

- Seminomas: 4th Decade
- Non-seminomas: 3rd Decade

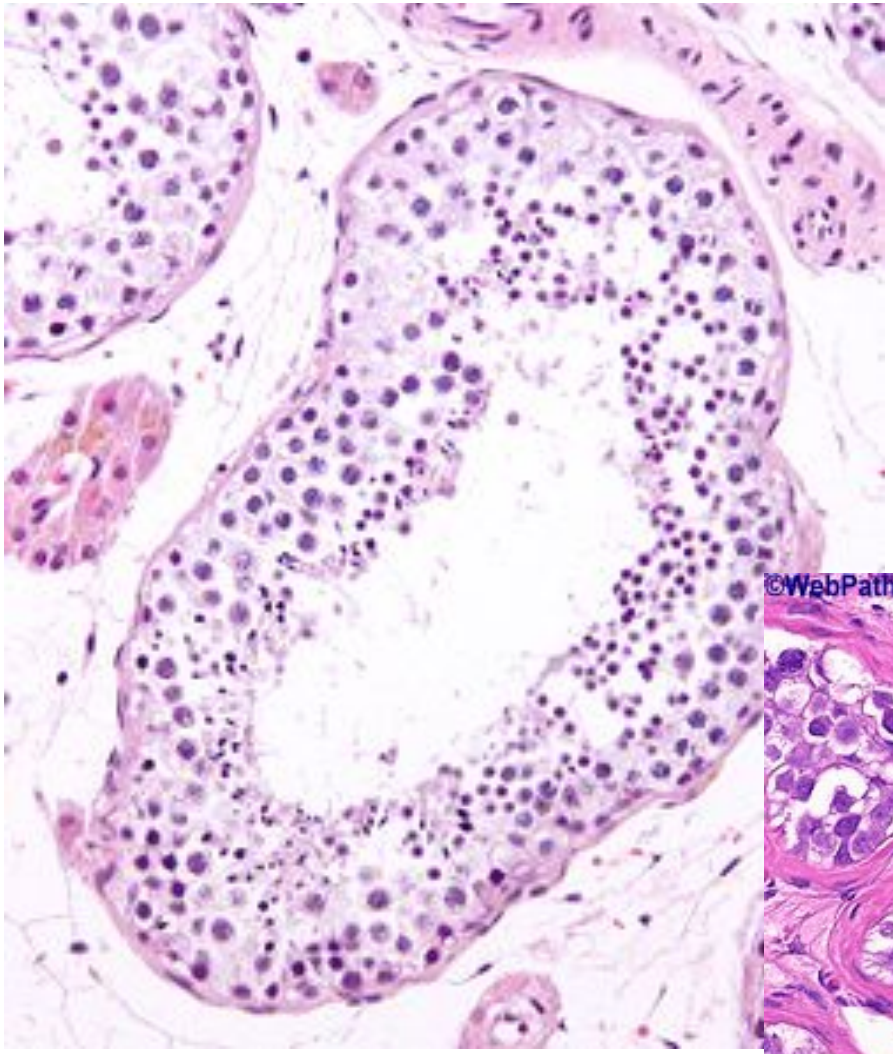
- European Decent: 6.36/100,000
- African Decent: 1.30/100,000

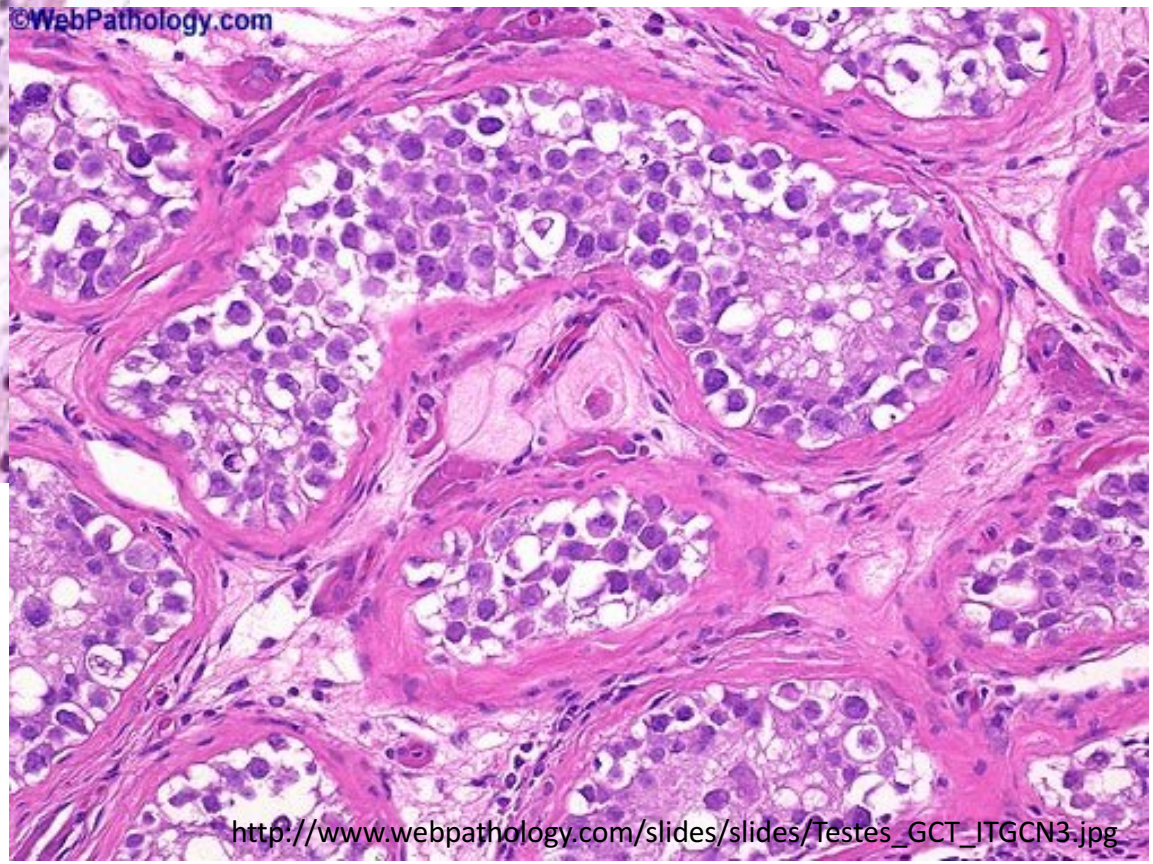
Seminoma

- Most common single tumor type (35%)
- 85% present in stage I
- Risk Factors
  - Cryptorchidism
  - Klinefelter's Syndrome
  - Diethylstibestrol (DES) exposure
  - Immunosuppression

Spermatocytic Seminoma

- Older age 50-60
- Rarely metastasize (1 of >200 cases in literature)
- More likely bilateral: 8-10% vs 2-4%
- Treatment:
  - Most urologists recommend orchiectomy with surveillance
  - No great data available





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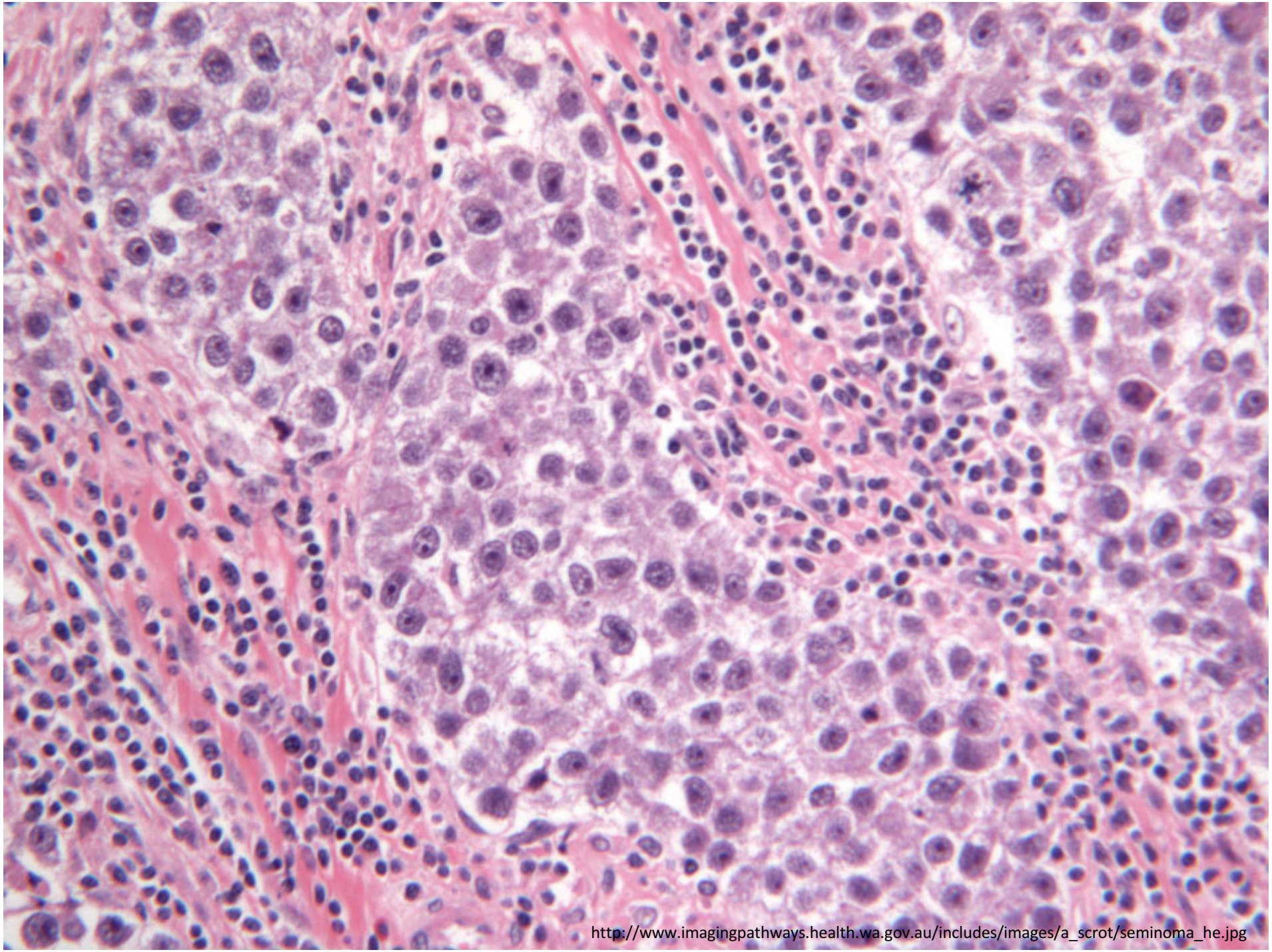

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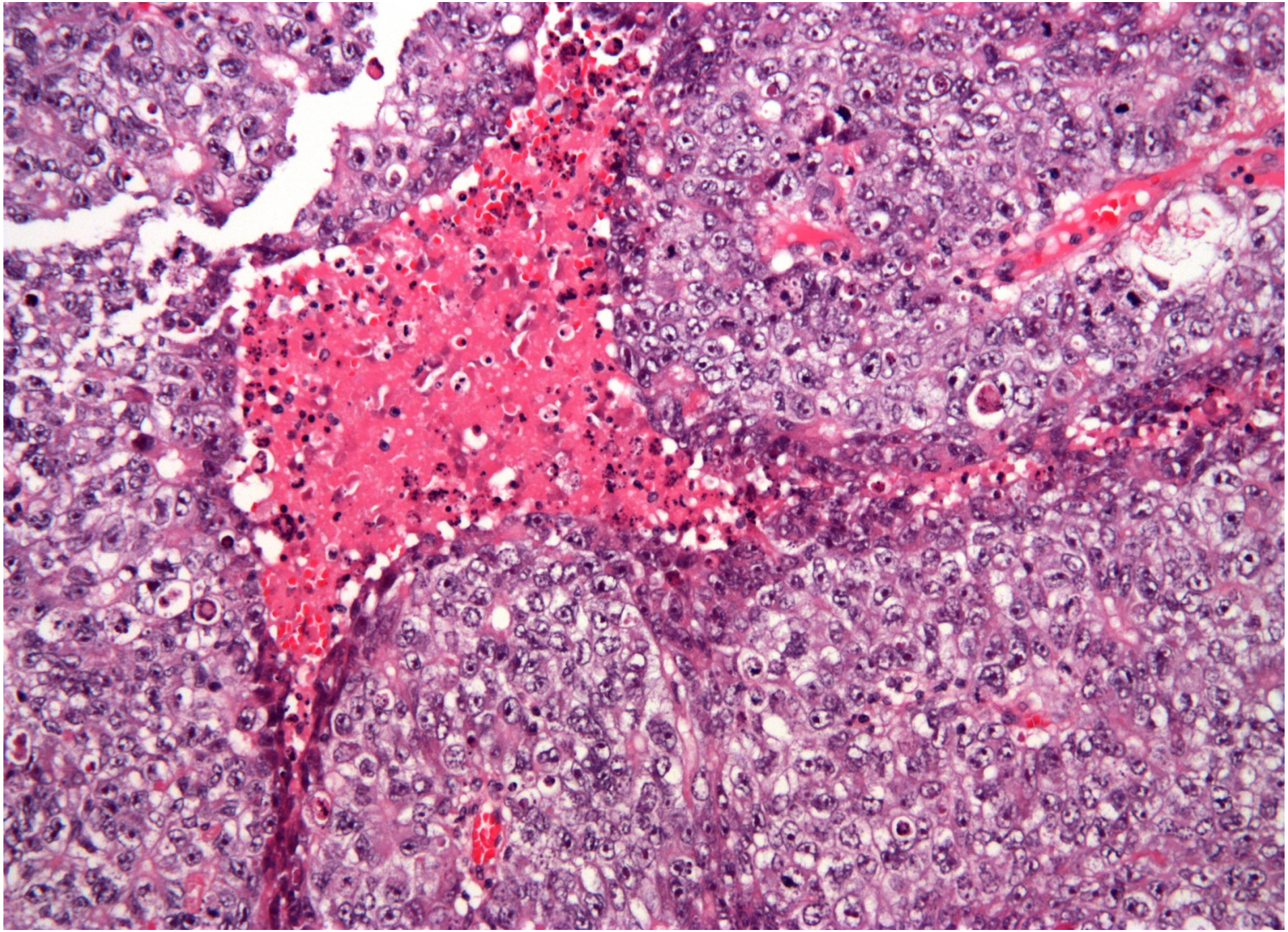

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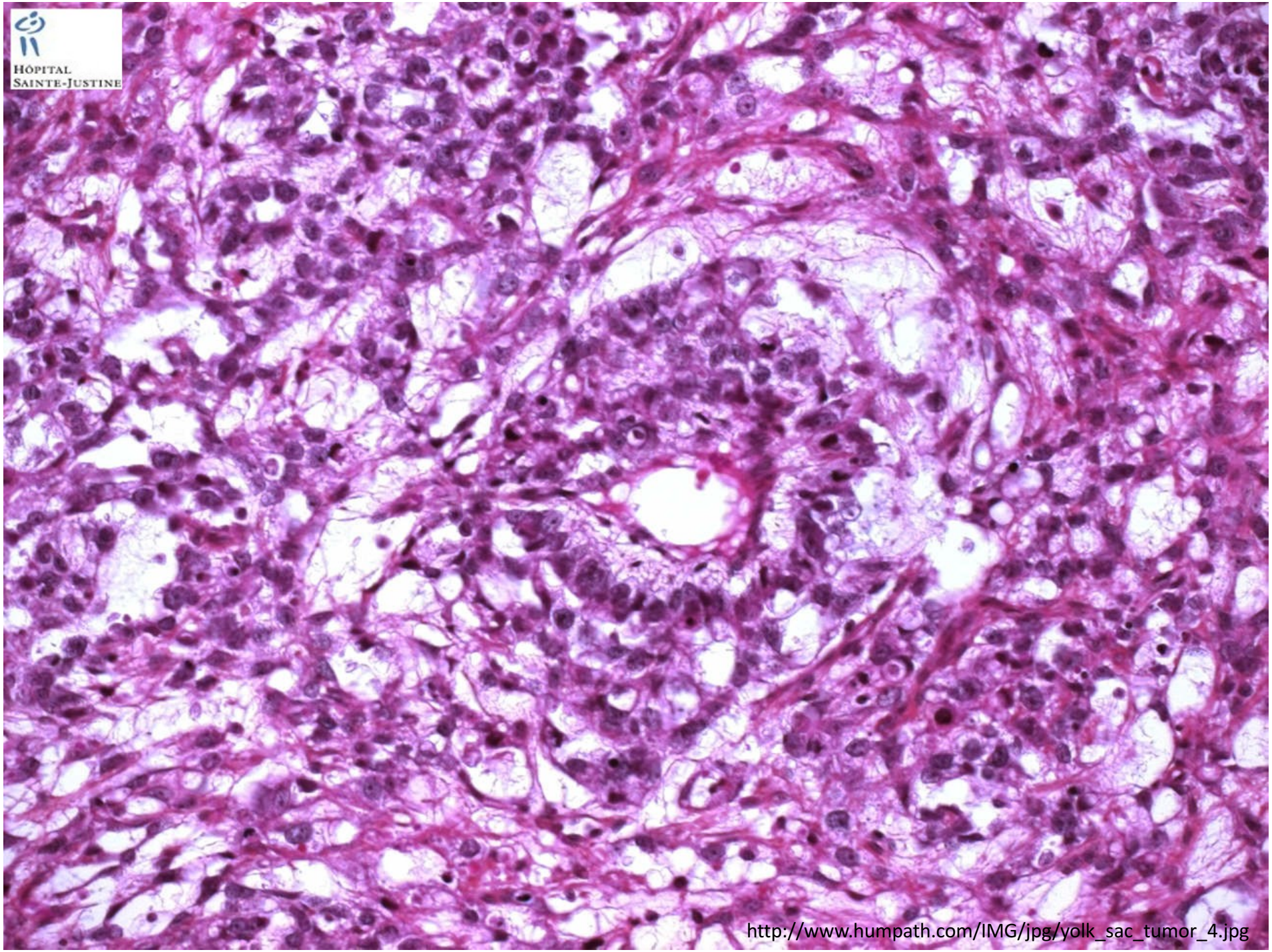
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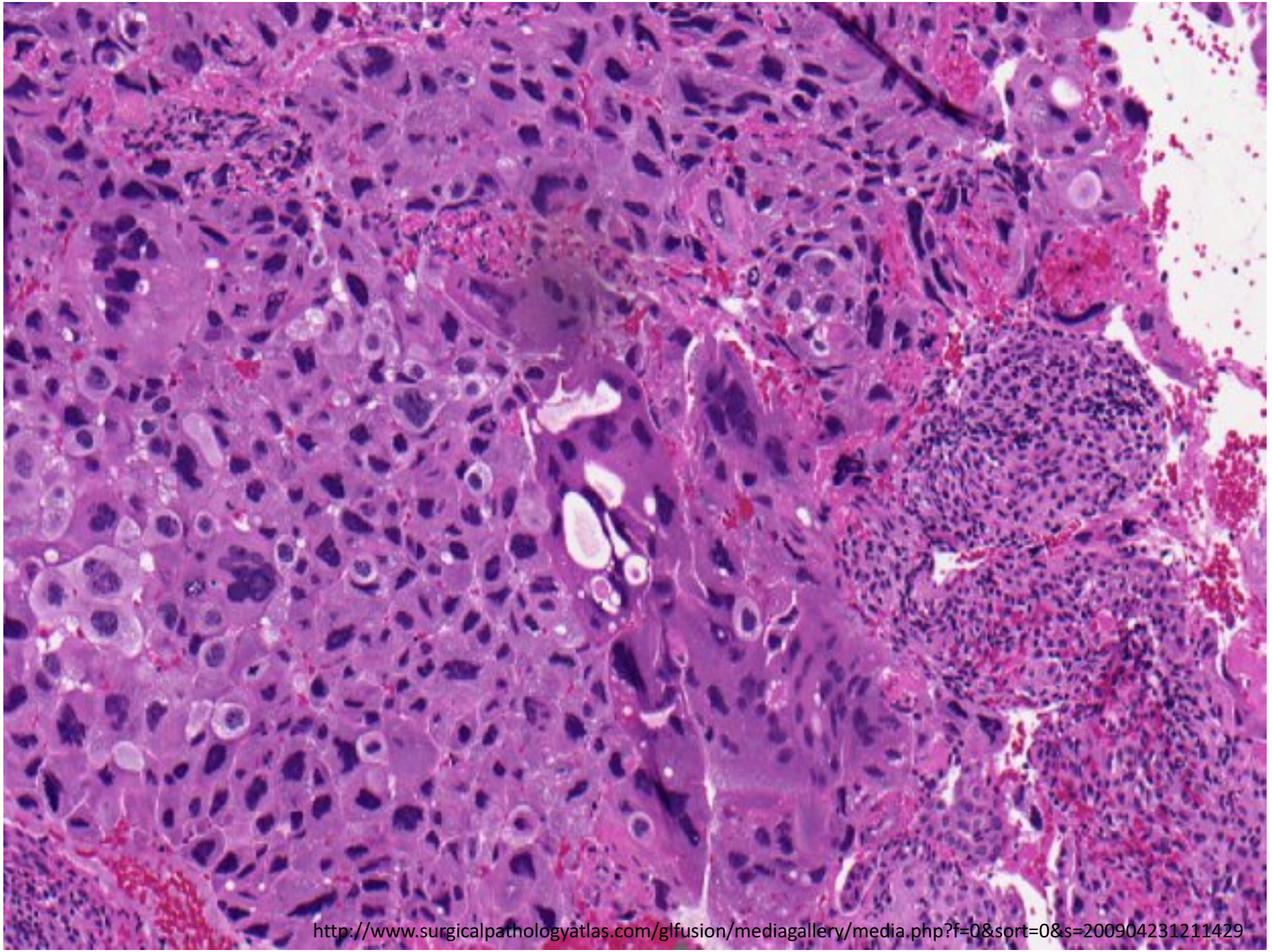
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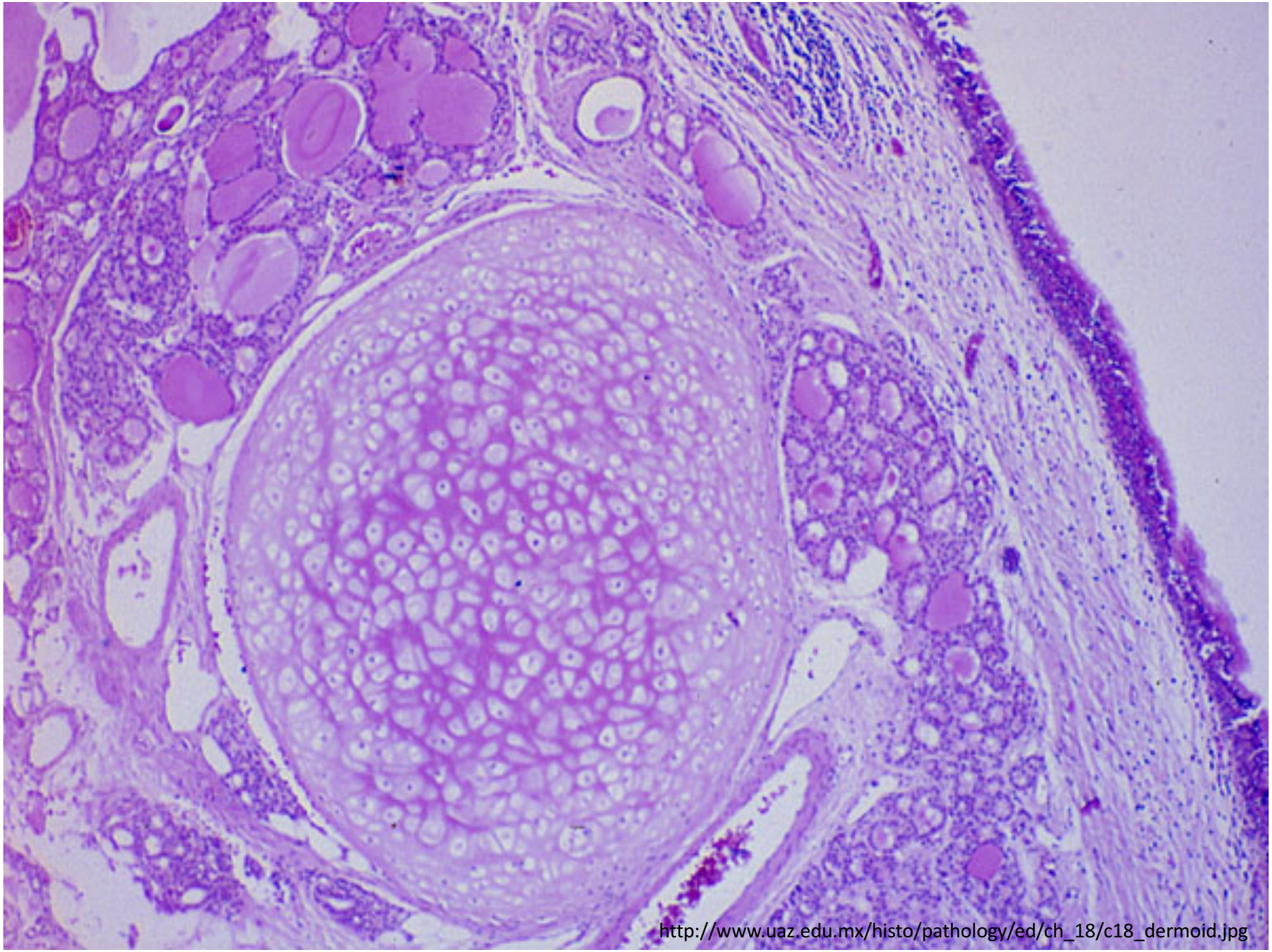
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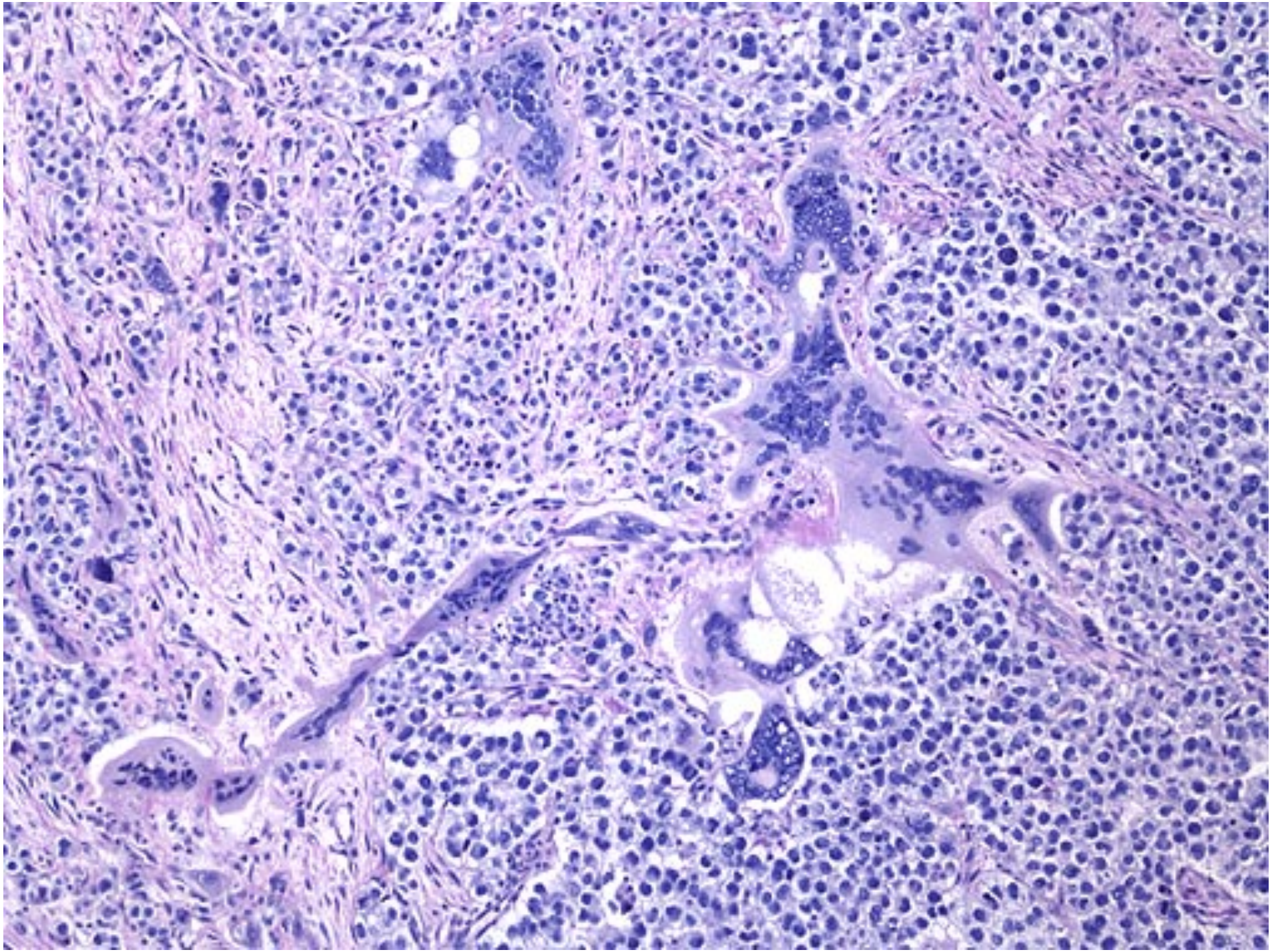

Stage TNM system

TX Unknown status of testis
T0 No apparent primary (includes scars)
Tis Intratubular tumor, no invasion
T1 Testis and epididymis only; no vascular invasion or penetration of tunica albuginea
T2 Testis and epididymis with vascular invasion or through tunica albuginea to involve tunica vaginalis
T3 Spermatic cord
T4 Scrotum

Grouping

Stage 0 – Tis, N0, M0, S0
Stage IA – T1, N0, M0, S0
Stage IB – T2-T4, N0, M0, S0
Stage IS – any T, N0, M0, S1-S3
Stage IIA – any T, N1, M0, S0-S1
Stage IIB – any T, N2, M0, S0-S1
Stage IIC – any T, N3, M0, S0-S1
Stage IIIA – any T, any N, M1a, S0-S1
Stage IIIB – any T, any N, M0-M1a, S2
Stage IIIC – any T, any N, M0-M1a, S3 any T, any N, M1b, any S

N0 No regional node involvement
N1 Node mass or single nodes ≤2 cm; ≤5 nodes involved; no node >2 cm
N2 Node mass >2 but ≤5 cm; or >5 nodes involved, none >5 cm; or extranodal tumor
N3 Node mass > 5 cm

MX Unknown status of distant metastases
M0 No distant metastases
M1a Non-regional nodal or lung metastases
M1b Distant metastasis other than non-regional nodal or lung
SX No marker studies available
S0 All marker studies normal

	LDH[*]	hCG (mIU/mL)	AFP(ng/mL)
S1	<1.5 × N &	<5000 &	<1000
S2	1.5–10 × N or	5000–50 000 or	1000–10 000
S3	>10 × N or	>50 000 or	>10 000

*LDH levels expressed as elevations above upper limit of normal (N).

Serum Tumor Markers

- HCG
  - Elevated in choriocarcinoma
  - 15% of seminoma patients
- AFP
  - Elevated in yolk sac tumor
  - If elevated, not pure seminoma
- LDH
  - Elevated in 60% of GCT
  - Acute phase reactant
- Measurement before/after orchiectomy can help monitor treatment response, disease remission

Survival

- Seminomas 5-yr OS
  - Stage I: virtually 100%
  - Stage II: 97%
  - Stage III: 85%
- Non-seminomatous Germ Cell Tumors 5-yr OS
  - Stage I: 99%
  - Stage II: 98%
  - Stage III: 86-50%

Stage III Risk Stratification

Table 1

IGCCCG Classification of Metastatic Disease

Classification	Seminoma	Nonseminoma
Good risk	Any primary site *and* No nonpulmonary visceral metastases *and* Normal AFP, any HCG, any LDH	Gonadal or retroperitoneal primary tumor No pulmonary or visceral metastases Good tumor markers (all): AFP <1,000 ng/mL, HCG <5,000 IU/L, LDH <1.5 × ULN
Intermediate risk	Any primary site *and* Nonpulmonary visceral metastases *and* Normal AFP, any HCG, any LDH	Gonadal or retroperitoneal primary tumor No pulmonary visceral metastases Intermediate tumor markers (any): AFP 1,000-10,000 ng/mL, HCG 5,000-50,000 IU/L, LDH 1.5 × ULN
Poor risk	NA	Mediastinal primary tumor *or* Nonpulmonary visceral metastases *or* Poor tumor markers (any): AFP >10,000 ng/mL, HCG >50,000 IU/L, LDH >10 × ULN

AFP: alpha-fetoprotein; HCG: human chorionic gonadotropin; IGCCCG: International Germ Cell Cancer Collaborative Group; LDH: lactic dehydrogenase; NA: not applicable; ULN: upper limit of normal.
Source: Reference 11.

Treatment Decisions

- Surgery: Radical inguinal orchiectomy with high ligation of spermatic cord
  - Only deferred for high-burden metastatic disease when chemotherapy may be offered first
- Seminoma vs. NSGCT/Mixed Tumor
- Stage at Presentation
  - Stage I, Stage II or Stage III

NSGCT Stage I

- Surveillance
  - 21% recurrence rate
  - Usually in first 12 months (after 24 months rare)
  - Usually to retroperitoneal LNs (60%)
  - Chemotherapy for salvage: >98% cure
- RPLND with nerve sparing
  - 10% recurrence rate
- Single cycle adjuvant BEP
  - Cisplatin, Etoposide, Bleomycin

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ORIGINAL REPORT

Randomized Phase III Trial Comparing Retroperitoneal Lymph Node Dissection With One Course of Bleomycin and Etoposide Plus Cisplatin Chemotherapy in the Adjuvant Treatment of Clinical Stage I Nonseminomatous Testicular Germ Cell Tumors: AUO Trial AH 01/94 by the German Testicular Cancer Study Group

Peter Albers, Roswitha Siener, Susanne Krege, Hans-Uwe Schmelz, Klaus-Peter Dieckmann, Axel Heidenreich, Peter Kwasny, Maik Pechoel, Jan Lehmann, Sabine Kliesch, Kai-Uwe Köhrmann, Rolf Fimmers, Lothar Weißbach, Volker Loy, Christian Wittekind, and Michael Hartmann

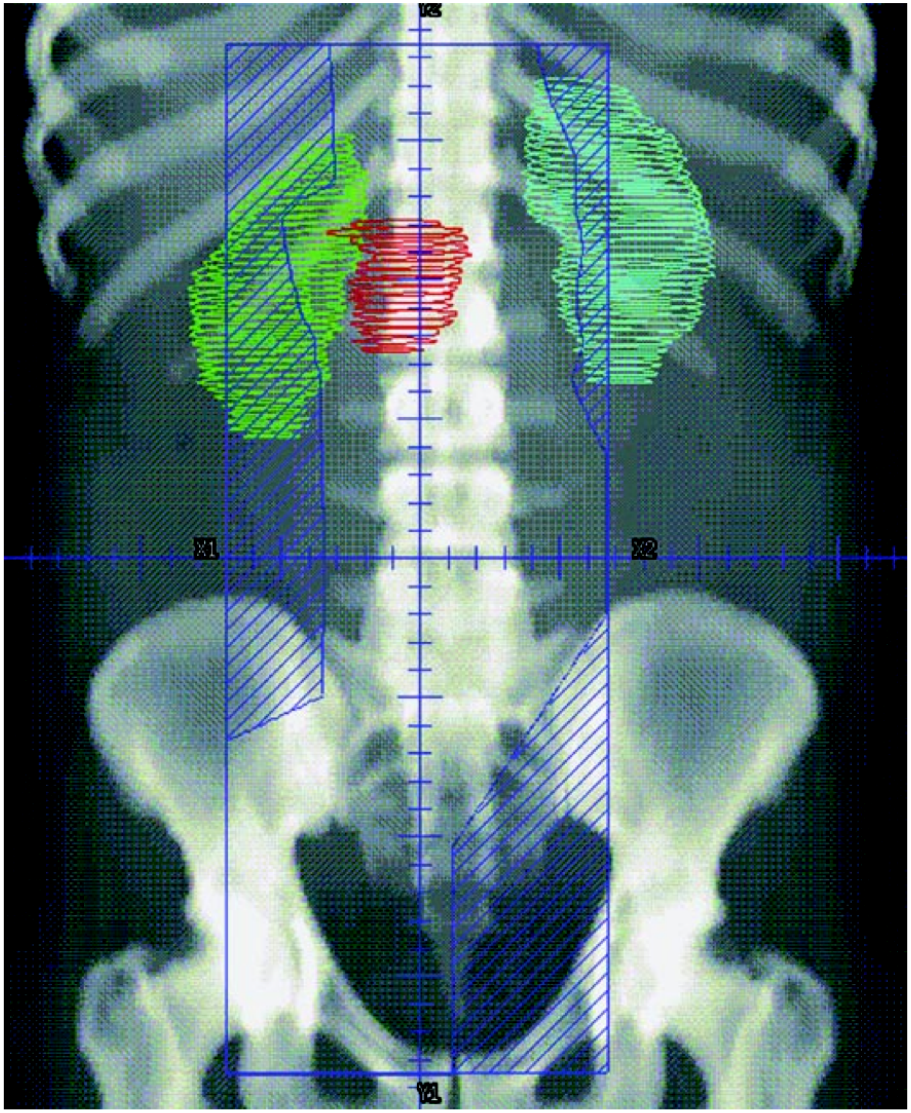
- 1996-2005: 286 patients randomized to RPLND or 1 Cycle of BEP
- Relapse rate of 10% vs 3% recurrence (HR 7.9 at 24 months)

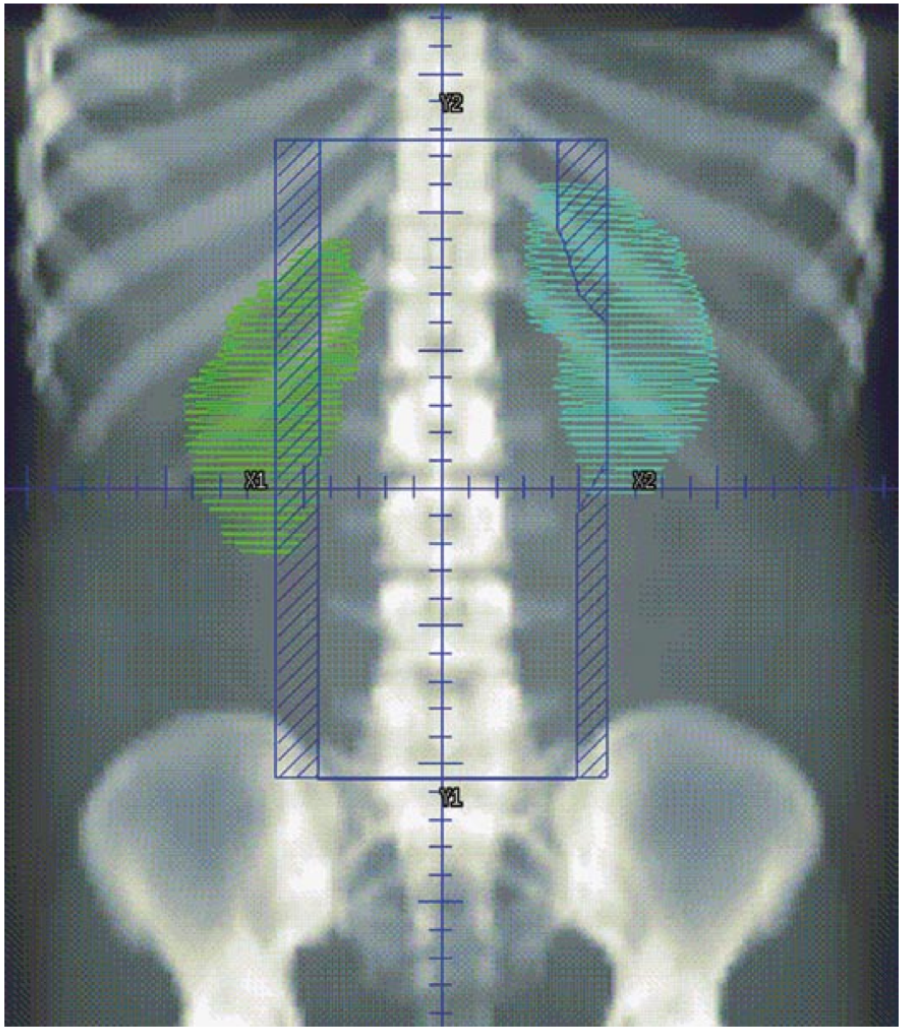
NSGCT Stage II and III

- Stage II
  - IIA – observation vs. RPLND vs. 2 cycles of BEP
    - Teratoma may favor surgery
  - IIB/C – chemotherapy BEP x2
- Stage III
  - Chemotherapy BEP x3 - 4
  - Good prognosis 5-yr OS 80%, Poor 50%
  - Increased survival at specialty centers

Seminoma Stage I

- Historically patients got radiation:
  - 30 Gy/15 fractions in “dog leg” configuration-paraaortics with ipsilateral inguinals
  - MRC trial TE 10, 1999, PA vs. “dog leg”
    - Fields: PA (sup T10/T11, inf L5/S1, lat inclusion of ipsilateral renal hilum); Dog-Leg (sup T10/T11; inf mid-obturator foramen; ipsilateral inclusion of renal hilum vertically down to L5/S1, then diagonal to lateral edge of acetabulum, then vertically down to mid-obturator foramen; contralateral transverse process vertically to L5/S1, then diagonal parallel with ipsilateral and vertically down to mid-obturator foramen)
    - 478 Men, same relapse rate, lower toxicity and better sperm counts with PA
  - MRC trial TE 18, 2005, 30 Gy/15 vs 20 Gy/10
    - 628 men, same relapse rate
    - return to work sooner (relatively similar toxicity at 12 wks, less lethargy at 4 weeks)


X1
X2
Y1


Y2
X1
X2
Y1

MRC trial TE 19/ EORTC 30982

- 1447 patients in 14 countries
  - 1 cycle carboplatin vs. radiation therapy (30/15 or 20/10)
  - 2005
    - 3-yr RFS carbo 95% vs RT 96%
    - Toxicity: reported less fatigue with carbo
    - Decreased 2nd testicular tumors with carbo 10 vs 2
  - 2011
    - 5-yr RFS carbo 94.7% vs RT 96%
    - Contralateral GCT carbo 2 RT 15 HR 0.22, P=0.03

Risk of Secondary Malignancy

- 2005, Scandanavian Study
- >40,000 testicular tumors
- Showed lifetime risk of 36% vs 23% for solid visceral cancers
  - Stomach, Bowel, Pancreas, and Liver

PREDICTED RATES OF SECONDARY MALIGNANCIES FROM PROTON VERSUS PHOTON RADIATION THERAPY FOR STAGE I SEMINOMA

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- 10 patients
- Planned with protons and traditional photons
- Predicted 6.94 excess bladder, large bowel, pancreas and stomach cancers with photons

Seminoma Stage IIA/IIB

- EBRT – 20 Gy/10 fractions to paraaortics and pelvic lymph nodes
- Boost dose (+10 Gy for IIA and +16 Gy for IIB) for gross lymph node disease
- Prior inguinal surgery disrupts lymphatics and may require contralateral node coverage

Seminoma IIC and III

- Chemotherapy
  - EP x4 vs BEP x3 (BEP x4 for intermediates)
  - Either good or intermediate IGCCCG prognostic group

Case

- Chose surveillance
- Follow-up
  - Follow up visit, CT abdomen and pelvis and Labs
    - every 3-4 months x 3 years
    - then q6 months x4 years
    - Then q 1year until 10 years

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