Testicular Seminoma

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Case Presentation

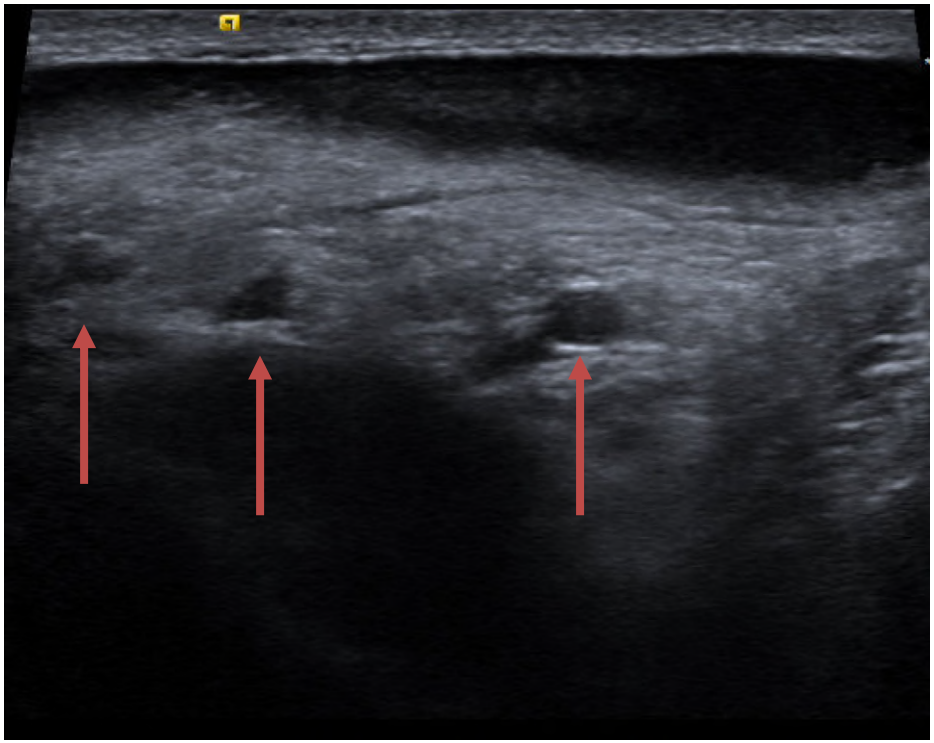
- **HPI:** 44-year-old man with mildly painful right testicular mass noted 1 week prior
- **PMHx:** Left varicocele, hyperlipidemia
- **PSHx:** None
- **FHx:** No first-degree relatives with cancer
- **Social Hx**: Nonsmoker, no illicit drug use
- **ROS:** No other pertinent symptoms
- **Physical exam:** Firm mass, superior aspect of right testicle; no tenderness, erythema, warmth
- **Labs:** B-hCG, AFP and LDH within normal limits

Pre-Treatment Imaging

- Right testicular ultrasound (US) showed at least 3 hypoechoic, hypervascular lesions with the largest measuring 1.5 cm

- CT A/P without evidence of retroperitoneal lymphadenopathy

US scrotum and testes at diagnosis: color flow and spectral Doppler



Clinical Course

- Patient underwent right radical inguinal orchiectomy, June 2019
- Pathology from surgery demonstrated multiple nodules (largest lesion measuring 1.5 cm) of seminoma, classic type, AJCC 8th edition stage pT1a with invasion of the rete testis but confined within the tunica vaginalis, with negative margins

Testicular Mass: Differential Diagnoses[1]

- **Non-neoplastic**
  - Segmental infarction
  - Testicular hematoma
  - Testicular infection (orchitis)
  - Epidermoid cyst
  - Adrenal rests
  - Sarcoidosis
  - Splenogonadal fusion
- **Neoplastic**
  - Germ cell tumor (GCT)
    - Seminoma
    - Non-seminomatous GCT
      - Embryonal carcinoma
      - Yolk sac tumor
      - Choriocarcinoma
      - Teratoma
    - Mixed seminoma and NSGCT
  - Sex cord-stromal tumors
    - Leydig cell tumor
    - Sertoli cell tumor
    - Granulosa cell tumor
    - Thecoma-fibroma
  - Miscellaneous, ie:
    - Lymphoma
    - Sarcoma
    - Metastasis

Background

- Germ cell tumor = 95% of all testicular cancers[2]
  - Seminoma (~40%[3])
  - Non-seminomatous germ cell tumor (NSGCT)
    - More likely to metastasize, worse prognosis, less radiosensitive[4]
  - Mixed seminoma and NSGCT

Testicular Seminomas

- Incidence of seminoma has been steadily rising[5,6]
- Most common solid malignancy in males ages 15-44 years[7]
- Main categories[8]:
  - Classical
  - Spermatocytic
  - Seminoma with syncytiocytotrophoblastic cells

Risk Factors

Cryptorchidism[9]
Disorders of sexual development[10]
Hypo/infertility[11,12]
Contralateral germ cell tumors (GCTs)[13]
Fetal exposure to endocrine disruptors[14]
Family history (5-19x increased risk if brother, 2-4x increased risk if father)[15]
Marijuana use – inconclusive[16]
Highest incidence in Northern European countries, lowest incidence in African and Asian countries[17]

Diagnosis: Presentation

- Painless lump in testicle *(most common)*[18]
- Uncomfortable testicular mass, enlargement or induration[18]
- Acute pain due to concurrent orchitis or epididymitis[18]
- New onset infertility[19]
- Rarely can be extragonadal, typically along the midline (ex: mediastinum)

Diagnostic Work-Up: History and Physical Exam[2]

- Examine bilateral testicles
  - 1.8% of seminomas are bilateral, though more often metachronous than synchronous[20]
- Transillumination
  - Light will not transmit through a solid tumor, while a hydrocele would glow a soft red color[21]

Diagnostic Work-Up: Labs[22]

- Laboratory evaluation: serum tumor markers
  - ***B-hCG***: elevated in 10-15% of seminomas
  - ***AFP***: if elevated, *not* a pure seminoma
  - ***LDH***: marker of tumor burden
- Serum tumor markers should be measured before orchiectomy and repeated after orchiectomy for staging and risk stratification[2]

Diagnostic Work-Up: Imaging

- Scrotal ultrasound with Doppler bilaterally
  - Homogeneously hypoechoic mass, rare calcifications/cysts[1]
  - If testicular microlithiases are noted without a solid mass or GCT risk factors, there is no increased risk of malignancy, and no further evaluation is needed[1]
- MRI
  - Not used in initial evaluation of a testicular mass unless there are equivocal US findings or location of mass is uncertain[23]
  - Multinodular, sharply defined, homogeneous mass of low signal intensity on T2[1]

Fertility Considerations

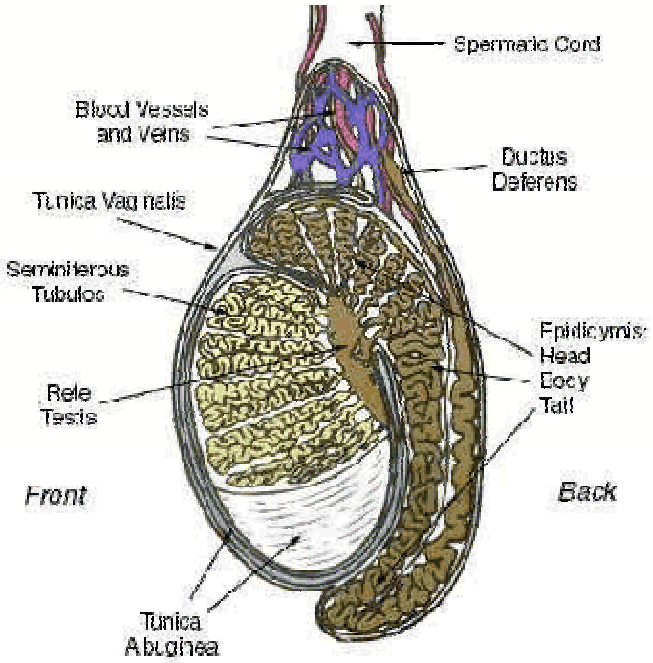
- >50% of men with testicular cancer have oligospermia *prior to receiving any treatment*[24]
  - 48% post cisplatin-based chemo successfully father a child[25]
  - >90% post-orchiectomy surveillance successfully father a child[25]
  - >3 Gy to remaining testicle can cause permanent infertility[26]
  - 22% will need assisted reproductive technology (ART)[25]
- <50% of oncology providers regularly counsel men on fertility preservation prior to initiating treatment[27]
  - Fertility assessment, semen analysis and offer of sperm banking should be part of every work-up

Seminoma: Classic & Unique Features

- Histology[1]: sheets of monotonous cells, pale cytoplasm, large nuclei, intervening thin fibrous septa
- Clinical features[28]:
  - Metastasis: retroperitoneal lymph nodes, lungs, liver, bones
  - Unlike non-seminomatous germ cell tumors, no retroperitoneal lymph node dissection for seminomas

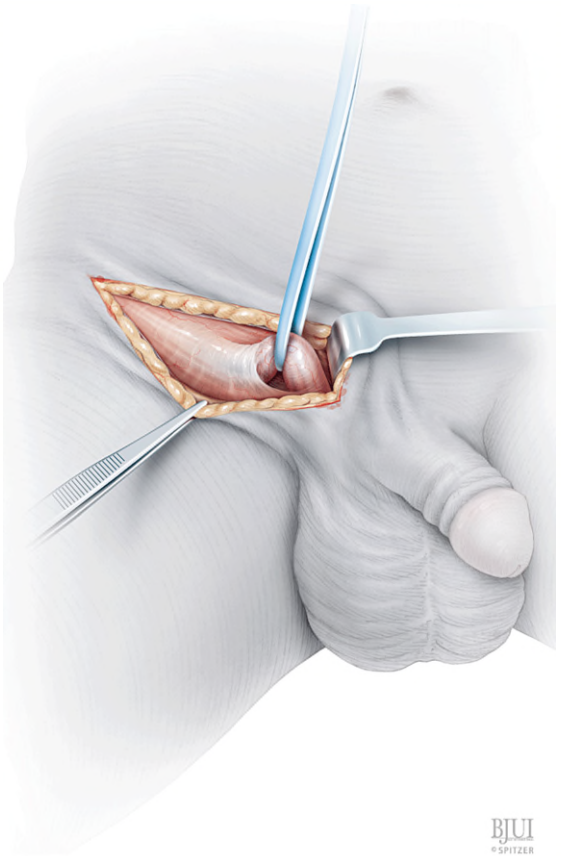
Testicular Anatomy Review

- Nodal drainage of testicles is primary to retroperitoneal region
  - Left testicle→ left paraaortic lymph node[29]
  - Right testicle→ right paracaval, precaval, and retrocaval nodes[29]
- Right testicular vein drains directly into inferior vena cava (IVC)
- Left testicular vein drains into the left renal vein before the IVC



Orchiectomy Approach

- Radical inguinal orchiectomy with high ligation of the spermatic cord is standard of care; minimizes disruption of lymphatics and lymphatic spread to the inguinal and pelvic nodes[2]
- Avoid scrotal incisions; they can alter lymphatic drainage, with increase in locoregional recurrence[2]



Pathologic Staging – AJCC 8th Edition[30]

Pathological T	Primary Tumor
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia in situ
pT1	Tumor limited to testis [including rete testis invasion without lymphovascular invasion (LVI)]
- pT1a	Tumor smaller than 3 cm in size
- pT1b	Tumor 3 cm or larger in size
pT2	Tumor limited to testis (including rete testis invasion with LVI) OR tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial later covering the external surface of tunica albuginea with or without LVI
pT3	Tumor directly invades spermatic cord soft tissue with or without LVI
pT4	Tumor invades scrotum with or without LVI

Pathological N	Regional Lymph Nodes
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node (LN) mass 2 cm or smaller in greatest dimension and less than or equal to 5 nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a LN mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than 5 nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a LN mass larger than 5 cm in greatest dimension

Tables adapted from the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Testis Cancer 8th edition, 2017

Pathologic Staging – AJCC 8th Edition[30]

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
- M1a	Non-retroperitoneal nodal or pulmonary metastases
- M1b	Non-pulmonary visceral metastases

S	Serum Markers
S X	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5x upper limit (UL) of normal and hCG (mIU/mL) <5,000 and AFP (ng/mL) <1,000
S2	LDH 1.5-10x UL of normal or hCG (mIU/mL) 5,000-50,000 or AFP (ng/mL) 1,000-10,000
S3	LDH> 10x UL of normal or hCG (mIU/mL) > 50,000 or AFP (ng/mL) > 10,000

Tables adapted from the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Testis Cancer 8th edition, 2017

Prognostic Stage Groups – AJCC 8th Edition[30]

- No histologic grading
- At time of diagnosis, 75-80% of patients are clinical stage I[31]

	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	Sx
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	Sx
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Stage I

Stage II

Stage III

Table adapted from the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Testis Cancer 8th edition, 2017

National Comprehensive Cancer Network (NCCN) Guidelines[32] – Stage 1 Primary Treatment Options

- Radical inguinal orchiectomy followed by one of the following:
  1. Active surveillance *(strongly preferred)*

Surveillance for pT1-pT3 tumors

	Year 1	Year 2	Year 3	Year 4	Year 5
H&P (serum tumor markers optional; testicular US for equivocal exam)	Every 3-6 mo	Every 6 mo	Every 6-12 mo	Annually	Annually
Abdominal +/- Pelvic CT wwo contrast (consider replacing with MRI**)	At 4-6, and 12 mo	Every 6 mo	Every 6-12 mo	Every 12-24 mo	Every 12-24 mo (unless clinical indicated, no CT past 5y)
CXR	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated

  2. Single-agent carboplatin
  3. Radiotherapy (RT): 20 Gy - 25.5 Gy

**__TRISST MRC TE24__[33] randomized, prospective trial from 2021: early results demonstrate that MRI is non-inferior to CT and 3-scan schedule is non-inferior to 7-scan schedule

Table adapted from the National Comprehensive Cancer Network Guidelines Version 1.2022

Localized Seminoma – Active Surveillance

- Orchiectomy + adjuvant RT or adjuvant chemo have cure rates approaching 100%, but *active surveillance is gaining popularity:*
  - Avoids overtreating 80-85% of patients cured by orchiectomy alone[34]
  - If needed, salvage therapies are very effective given seminoma's high radio/chemosensitivity[35]
  - A retrospective study[36] from 2018 found active surveillance to have equivalent survival compared to adjuvant therapy in the rare case of clinical stage IS
- Active surveillance is appropriate for low-risk stage I seminoma[37]

Localized Seminoma – Adjuvant Treatment

- Possible cases in which active surveillance may be inferior:
  - A retrospective analysis[38] from 2015 found primary tumor size (continuous) and primary tumor size > 3 cm both prognosticate increased relapse risk
    - *May support adjuvant therapy rather than surveillance in setting of larger primary tumor size*
  - A retrospective analysis[39] from 2017 found that primary tumors > 3 cm have both increased early relapse risk and increased recurrence risk after 5 years
    - *May support adjuvant therapy rather than surveillance in setting of larger primary tumor size*

Localized Seminoma – RT vs Chemo

- **MRC TE19**[40] (2011): *should chemo or RT be used in the adjuvant setting for stage I disease?*
  - Randomized, prospective trial that compared carboplatin (AUC 7) x1 to RT (20-30 Gy, PA or dog-leg fields)
  - Carboplatin is non-inferior to RT in 2-year relapse-free rate
  - Second primary germ-cell tumor rate lower with carboplatin than RT
  - *The bottom line: increasing popularity of **adjuvant carboplatin** over RT*

Localized Seminoma – RT vs Chemo

- A retrospective study[41] (2005) found:
  - 2.0x increased relative risk (RR) of solid cancer with RT
  - 2.7x increased RR for in-field solid cancers with RT
  - 1.8x increased RR for solid cancers with chemo
- While the increased relative risk of solid cancers (excluding hematologic) with chemo is not zero, this still led to a *further decrease in popularity of adjuvant RT compared to chemo*
  - Adjuvant RT no longer recommended in European Association of Urology (EAU) guidelines

Evolution of Adjuvant Seminoma RT

- **MRC TE10 trial**[42] (1999) – *can we have favorable outcomes using smaller fields?*
  - 478 patients randomized to para-aortic (PA) strip vs dog-leg (para-aortic nodes, external iliac nodes, orchiectomy scar) RT field at 30 Gy/15 fx
    - Excluded patients with prior ipsilateral inguinal or scrotal operations
  - Similar 3-year recurrence-free survival and overall survival, but less nausea, vomiting, diarrhea and better sperm recovery in PA group
  - *The bottom line: preference for **para-aortic node** field over dog-leg in adjuvant setting (unless previous ipsilateral scrotal/inguinal surgery)*

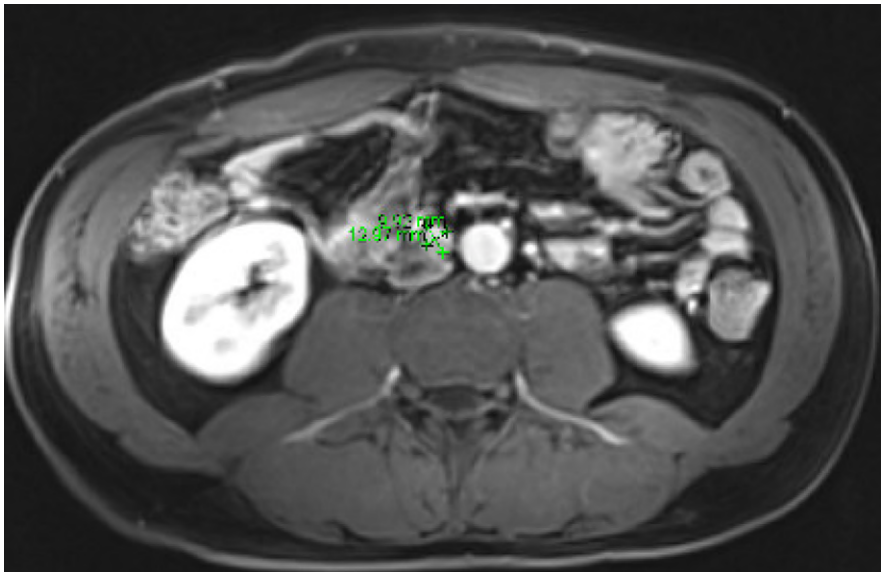
Evolution of Adjuvant Seminoma RT

- **MRC TE18 trial**[43] (2005) – *can we have favorable outcomes using lower total dose?*
  - 625 patients randomized to 20 Gy/10 fx vs 30 Gy/15 fx
  - Less moderate-severe lethargy, less inability to carry out normal work in 20 Gy/10 fx group
  - *The bottom line: preference for **20 Gy/10 fx** rather than 30 Gy/15 fx in the adjuvant setting*

Back to Our Patient…

- Patient elected to pursue active surveillance, no adjuvant therapy
- March 2020, (9 months post orchiectomy), MRI pelvis demonstrated new enlarged right para-aortic/aortocaval lymph node measuring up to 1.0 cm
- Patient asymptomatic, B-hCG undetectable, LDH and AFP within normal limits
- Initial consultation in radiation oncology clinic: recommended salvage radiotherapy with conventional fractionation

Surveillance MRI pelvis wwo contrast



Treatment Paradigm for Recurrent Seminoma[32]

- **Stage IIA:**
  - 20-25.5 Gy to modified dog-leg field*, boost to positive nodes (30 Gy) in 1.8-2.0 Gy per fx *(**preferred**) –OR–*
  - Chemo: BEP# x 3c *–or–* EP& x 4c
- **Stage IIB:**
  - 20-25.5 Gy to modified dog-leg field*, boost to positive nodes (36 Gy) in 1.8-2.0 Gy per fx *–OR–*
  - Chemo: BEP# x 3c *–or–* EP& x 4c *(**preferred if >3cm**)*
- **Stage IIC, III:** BEP# x 4c *–or–* VIP† x 4c

*Dog-leg field: retroperitoneal + proximal ipsilateral iliac lymph nodes- shown to have high rates of 6-year disease-free survival, 100% disease-specific survival for relapsed seminoma, in a 2003 prospective trial[44]

#BEP =bleomycin, etoposide, cisplatin
&EP = etoposide, cisplatin
†VIP = etoposide, ifosfamide, cisplatin

Shifts in Recurrent Seminoma Treatment

- Prophylactic mediastinal or supraclavicular node RT is not recommended – there is increased risk of cardiac death with elective mediastinal RT[45]
- Adjuvant RT is standard treatment for stage IIA, if no contraindications – there is improved 5-year overall survival with adjuvant RT over adjuvant chemo in stage IIA[46]
- Chemo is preferred for stage IIB with mass >3 cm – there is lower incidence of side-effects and regional recurrence in stage IIB "bulky" disease (>3 cm) when using chemo over RT[47]
- Chemo is standard of care for stage IIC – the 5-year relapse-free rate is 44% with salvage RT and >90% with salvage chemo in stage IIC[48]

Treatments Under Investigation for Recurrent Seminoma

- **SAKK 01/10 phase II trial**[49] (2021): *Does combination de-escalated chemo + RT control stage II disease with reduced toxicity compared to salvage chemo or salvage RT alone?*
  - 116 patients with seminoma stage IIA/IIB; de novo or relapse on active surveillance
  - Chemotherapy: 1c carboplatin AUC7
  - Involved node RT:
    - Stage IIA= 30 Gy; stage IIB= 36 Gy
    - Median planning target volume (PTV) = ~25% of standard of care dog-leg PTV
  - Median follow-up 4.5 years→ 3-year progression-free survival (PFS): stage IIA = 95.2%, stage IIB = 92.6%
  - *The bottom line:* ***favorable 3-year PFS using combination deescalated carboplatin + involved node RT****, with* ***less toxicity*** *than standard chemo or RT alone*

Treatments Under Investigation for Recurrent Seminoma

- **SEMS phase II trial**[50] (2021): *Can surgery be considered as salvage therapy for recurrent seminoma?*
  - 55 patients with isolated retroperitoneal (RP) node relapse between 1-3 cm in size, treated with retroperitoneal lymph node dissection (RPLND)
  - Median follow-up 24 months; 10 recurrences post RPLND = 18% recurrence rate, median time to recurrence = 8 months
  - *The bottom line: awaiting full data set, although preliminary results suggest **RPLND is not as effective** as RT or chemo*

Treatments Under Investigation for Recurrent Seminoma

- **PRIMETEST phase II trial**[51] (2019): *Can surgery (RPLND) be used in stage IIA/B seminoma without adjuvant treatment?*
  - Two-part study:
    - Feasibility pilot (n=9)
      - Stage IIA/B/C
      - 3 patients developed recurrences
    - Phase II study (n=14), interim results:
      - Stage IIA/B
      - Mean follow-up = 12.5 months (range 3-25 months)
      - 10/14 patients (71%) free of recurrence, 4/14 (29%) developed a recurrence
      - Mean time to recurrence = 6.8 months
  - *The bottom line: awaiting study completion,* ***primary RPLND not as effective*** *for stage IIA/B as RT or chemo*

Patient Simulation[2,32]

- CT planning: supine to block out kidneys
  - May use IV contrast to delineate vessels
- Clamshell on contralateral testicle to reduce risk of infertility from scattered irradiation
- Position penis out of field

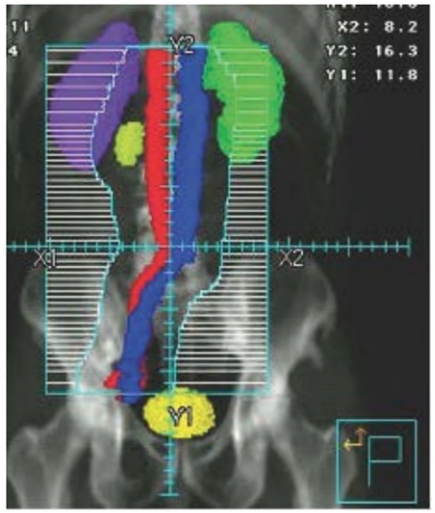
Patient Simulation[32]

- **Stage I (para-aortic strip)**
  - Superior border: T11/T12 interspace
  - Inferior border: L5/S1 interspace
  - Lateral borders: 10 cm wide, make sure to block majority of kidneys
- **Stage II (dog-leg)**
  - Superior border: T11/T12 interspace
  - Inferior border: top of acetabulum
  - Lateral border: tip of ipsilateral L5 transverse process to superolateral border of ipsilateral acetabulum
  - Medial border: tip of contralateral L5 transverse process to medial border of ipsilateral obturator foramen

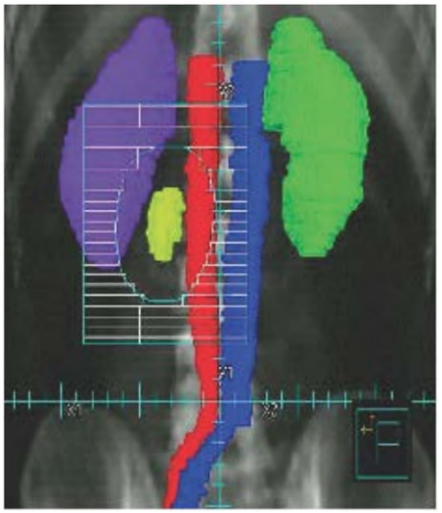
Target Volumes[52] (Conventional Fractionation) – Stage II

- ***Gross tumor volume (GTV)***
  - Paraaortic + proximal ipsilateral iliac lymph nodes
- ***Clinical target volume (CTV)***
  - CTV1 = GTV + 0.5 cm margin
  - CTV2 = GTV + lymphatic risk areas *(below)*
    - If right: right paracaval, precaval and inter aortocaval nodes
    - If left: left paracaval, precaval, inter aortocaval, latero-aortic, pre-aortic and renal hilar nodes
- ***Planning target volume (PTV)***
  - CTV1 + CTV2 + 0.5 cm margin to account for treatment set-up errors

Stage II RT Large Field



Stage II Cone-down Field



Images adapted from National Comprehensive Cancer Network Testicular Cancer Guidelines, Version 1.2022

Pre-Treatment Consideration

- Our patient completed his prescribed course of treatment and tolerated it well overall with minimal fatigue
- Most common acute side effects are nausea and emesis[53]
- Patients should receive a pre-treatment anti-emetic, such as ondansetron[54], 1 hour before treatment

Toxicity

- Anticipated side effects[55] (using conventional fractions, depending on treatment fields):
  - Acute: nausea, vomiting, diarrhea, dysuria, fatigue, dermatitis
  - Late: nephrotoxicity, CV disease, secondary solid tumor malignancies (stomach, bowel, bladder, etc.)

Dose Constraints[32]

- Organs at risk (OAR): stomach, colon, kidneys, pancreas, liver
- No more than 50% of the volume of each kidney (D50) may receive ≥8 Gy
- In patients with one kidney, no more than 15% of the kidney (D15) may receive ≥20 Gy

Treatment Plan

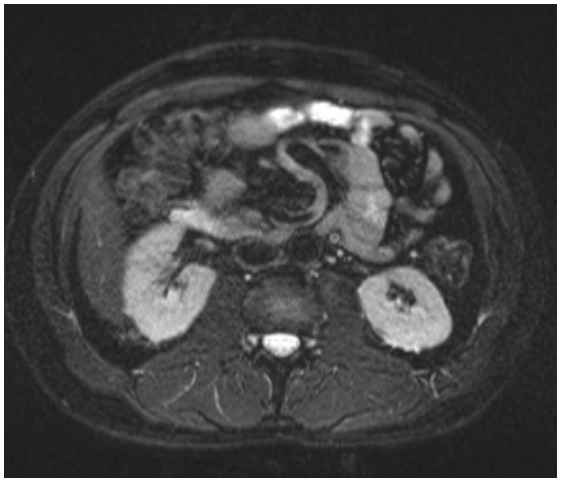
- April 2020: Patient received salvage radiotherapy with 20 Gy in 10 fractions with 3D conformal radiotherapy (3D-CRT) using AP/PA fields to the right para-aortic LN and ipsilateral pelvis
  - IMRT has increased low dose spray which incurs a higher risk of secondary malignancies, thus use 3D-CRT due to decreased D50 to OAR[32]
- Boost to gross disease: 10 Gy in 5 fractions
- Cumulative dose: 30 Gy in 15 fractions

Our Patient: Surveillance, Response

- NCCN surveillance recommendations for stage IIA or non-bulky stage IIB post-RT or post-chemo[32]:

	Year 1	Year 2	Year 3	Year 4	Year 5
H&P (serum tumor markers optional; testicular US for equivocal exam)	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal +/- pelvic CT with contrast (consider replace with MRI)	At 3 mo, then at 9 or 12 mo	Annually	Annually	As clinically indicated	As clinically indicated
CXR	Every 6 mo	Every 6 mo	-	-	-

MRI abdomen wwo contrast



- April 2020-Dec 2021: patient doing well without clinical or radiographic evidence of progression, as pictured

Table adapted from the National Comprehensive Cancer Network Guidelines Version 1.2022

Summary

- Seminomas are the most common solid malignancy in young men and carry an excellent prognosis
- They are unlikely to recur following inguinal orchiectomy, and active surveillance is recommended for patients who are able to pursue recommended routine surveillance
- If seminoma recurs, either chemo or RT are appropriate for stages IIA and IIB, though chemo is preferred for bulky stage IIB, stage IIC and stage III; new studies suggest potential for a combination of both modalities

References

1. Marko J, Wolfman D, Aubin A, Sesterhenn I. Testicular Seminoma and Its Mimics:From the Radiologic Pathology Archives. *RadioGraphics*. 2017;37(4):1085-1098. doi:10.1148/rg.2017160164
2. Stephenson A, Eggener SE, Bass EB et al: Diagnosis and treatment of early stage testicular cancer: AUA guideline. J Urol 2019; 202: 272.
3. Types of Testicular Cancer | SEER Training. Training.seer.cancer.gov. https://training.seer.cancer.gov/testicular/intro/types.html. Published 2022. Accessed January 18, 2022.
4. Nauman M, Leslie SW. Nonseminomatous Testicular Tumors. [Updated 2021 Aug 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK568754/
5. The American Cancer Society medical and editorial content team. "Facts about Testicular Cancer: Testicular Cancer Statistics." *American Cancer Society*, https://www.cancer.org/cancer/testicular-cancer/about/key-statistics.html.
6. Ghazarian AA, Trabert B, Graubard BI, Schwartz SM, Altekruse SF, McGlynn KA. Incidence of testicular germ cell tumors among US men by census region. *Cancer*. 2015;121(23):4181-4189. doi:10.1002/cncr.29643
7. Batool, A., Karimi, N., Wu, XN. *et al.* Testicular germ cell tumor: a comprehensive review. *Cell. Mol. Life Sci.* 76, 1713–1727 (2019). https://doi.org/10.1007/s00018-019-03022-7
8. Cedeno JD, Light DE, Leslie SW. Testicular Seminoma. [Updated 2021 Aug 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448137/
9. Seetharam V, Hameed Z, Talengala S, Thomas J. Bilateral cryptorchidism with bilateral synchronous abdominal testicular germ cell tumour. *Case Reports*. 2014;2014(feb12 1):bcr2013203085-bcr2013203085. doi:10.1136/bcr-2013-203085
10. Chemes H, Venara M, del Rey G et al. Is a CIS phenotype apparent in children with Disorders of Sex Development? Milder testicular dysgenesis is associated with a higher risk of malignancy. *Andrology*. 2015;3(1):59-69. doi:10.1111/andr.301
11. Walsh TJ, Croughan MS, Schembri M, Chan JM, Turek PJ. Increased risk of testicular germ cell cancer among infertile men. *Arch Intern Med*. 2009;169(4):351-356. doi:10.1001/archinternmed.2008.562
12. Machiela M, Dagnall C, Pathak A et al. Mosaic chromosome Y loss and testicular germ cell tumor risk. *J Hum Genet*. 2017;62(6):637-640. doi:10.1038/jhg.2017.20
13. Fosså S, Chen J, Schonfeld S et al. Risk of Contralateral Testicular Cancer: A Population-based Study of 29 515 U.S. Men. *JNCI: Journal of the National Cancer Institute*. 2005;97(14):1056-1066. doi:10.1093/jnci/dji185
14. Fénichel P, Chevalier N. Is Testicular Germ Cell Cancer Estrogen Dependent? The Role of Endocrine Disrupting Chemicals. Endocrinology. 2019;160(12):2981-2989. doi:10.1210/en.2019-00486
15. Chia VM, Li Y, Goldin LR *et al*. Risk of cancer in first- and second-degree relatives of testicular germ cell tumor cases and controls. *Int. J. Cancer* 2009; 124: 952–7.
16. Gurney J, Shaw C, Stanley J, Signal V, Sarfati D. Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. *BMC Cancer*. 2015;15(1). doi:10.1186/s12885-015-1905-6
17. Ferlay J, Soerjomataram I, Dikshit R *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 2015; 136: E359–86.
18. Pasqualotto FF, Pasqualotto EB, Agarwal A, Thomas AJ Jr. Detection of testicular cancer in men presenting with infertility. Rev Hosp Clin Fac Med Sao Paulo. 2003 Mar-Apr;58(2):75-80. doi: 10.1590/s0041-87812003000200004. Epub 2003 Jun 25. PMID: 12845359.

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References

19. Cancer Statistics Factsheets SEER. *Testicular Cancer*. National Cancer Institute, Bethesda, MD. 2019. Available at:https://seer.cancer.gov/statfacts/html/testis.html. Accessed September 5, 2019.
20. Che M, Tamboli P, Ro JY, Park DS, Ro JS, Amato RJ, Ayala AG. Bilateral testicular germ cell tumors: twenty-year experience at M. D. Anderson Cancer Center. Cancer. 2002 Sep 15;95(6):1228-33. doi: 10.1002/cncr.10804. PMID: 12216089.
21. Junnila J, Lassen P. Testicular Masses. Aafp.org. https://www.aafp.org/afp/1998/0215/p685.html. Published 2022. Accessed January 18, 2022.
22. Gilligan TD, Seidenfeld J, Basch EM, Einhorn LH, Fancher T, Smith DC, Stephenson AJ, Vaughn DJ, Cosby R, Hayes DF; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol. 2010 Jul 10;28(20):3388-404. doi: 10.1200/JCO.2009.26.4481. Epub 2010 Jun 7. PMID: 20530278.
23. Thomas K, Jeong D, Montilla-Soler J, Feuerlein S. The role of diagnostic imaging in the primary testicular cancer: initial staging, response assessment and surveillance. *Transl Androl Urol*. 2020;9(S1):S3-S13. doi:10.21037/tau.2019.07.01
24. Williams D, Karpman E, Sander J, Spiess P, Pisters L, Lipshultz L. Pretreatment Semen Parameters in Men With Cancer. *Journal of Urology*. 2009;181(2):736-740. doi:10.1016/j.juro.2008.10.023
25. Brydøy M, Fosså S, Klepp O et al. Paternity Following Treatment for Testicular Cancer. *JNCI: Journal of the National Cancer Institute*. 2005;97(21):1580-1588. doi:10.1093/jnci/dji339
26. De Felice F, Marchetti C, Marampon F, Cascialli G, Muzii L, Tombolini V. Radiation effects on male fertility. *Andrology*. 2018;7(1):2-7. doi:10.1111/andr.12562
27. Schover L, Brey K, Lichtin A, Lipshultz L, Jeha S. Oncologists' Attitudes and Practices Regarding Banking Sperm Before Cancer Treatment. *Journal of Clinical Oncology*. 2002;20(7):1890-1897. doi:10.1200/jco.2002.07.174
28. Cedeno JD, Light DE, Leslie SW. Testicular Seminoma. [Updated 2021 Aug 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448137/
29. Coursey Moreno C, Small W, Camacho J et al. Testicular Tumors: What Radiologists Need to Know—Differential Diagnosis, Staging, and Management. *RadioGraphics*. 2015;35(2):400-415. doi:10.1148/rg.352140097
30. Amin MB, Edge SB, Greene FL, et al., editors. AJCC Cancer staging manual. 8th ed. New York: Springer International Publishing; 2017.
31. Sokoloff MH, Joyce GF, Wise M; Urologic Diseases in America Project: Testis cancer. J Urol 2007;177:2030-2041.
32. National Comprehensive Cancer Network. Testicular Cancer (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf. Dec 10, 2021.
33. Joffe J, Cafferty F, Murphy L et al. Imaging modality and frequency in surveillance of stage I seminoma testicular cancer: Results from a randomized, phase III, factorial trial (TRISST). *Journal of Clinical Oncology*. 2021;39(6_suppl):374-374. doi:10.1200/jco.2021.39.6_suppl.374
34. Vaz R, Bordenali G, Bibancos M. Testicular Cancer—Surgical Treatment. *Front Endocrinol (Lausanne)*. 2019;10. doi:10.3389/fendo.2019.00308
35. Jones G, Arthurs B, Kaya H et al. Overall Survival Analysis of Adjuvant Radiation Versus Observation in Stage I Testicular Seminoma. *Am J Clin Oncol*. 2013;36(5):500-504. doi:10.1097/coc.0b013e318254950a
36. Kamran S, Seisen T, Markt S et al. Contemporary Treatment Patterns and Outcomes for Clinical Stage IS Testicular Cancer. *Eur Urol*. 2018;73(2):262-270. doi:10.1016/j.eururo.2017.06.013

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References

37. Nichols C, Roth B, Albers P et al. Active Surveillance Is the Preferred Approach to Clinical Stage I Testicular Cancer. *Journal of Clinical Oncology*. 2013;31(28):3490-3493. doi:10.1200/jco.2012.47.6010

38. Chung P, Daugaard G, Tyldesley S, et al. Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. *Cancer Med*. 2015;4(1):155-160. doi:10.1002/cam4.324

39. Nayan M, Jewett MA, Hosni A, Anson-Cartwright L, Bedard PL, Moore M, Hansen AR, Chung P, Warde P, Sweet J, O'Malley M, Atenafu EG, Hamilton RJ. Conditional Risk of Relapse in Surveillance for Clinical Stage I Testicular Cancer. Eur Urol. 2017 Jan;71(1):120-127. doi: 10.1016/j.eururo.2016.07.013. Epub 2016 Aug 12. PMID: 27527805.

40. Oliver RT, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, Gabe R, Pollock P, Stenning SP. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol. 2011 Mar 10;29(8):957-62. doi: 10.1200/JCO.2009.26.4655. Epub 2011 Jan 31. PMID: 21282539.

41. Travis L, Fosså S, Schonfeld S et al. Second Cancers Among 40 576 Testicular Cancer Patients: Focus on Long-term Survivors. *JNCI: Journal of the National Cancer Institute*. 2005;97(18):1354-1365. doi:10.1093/jnci/dji278

42. Fosså S, Horwich A, Russell J et al. Optimal Planning Target Volume for Stage I Testicular Seminoma: A Medical Research Council Randomized Trial. *Journal of Clinical Oncology*. 1999;17(4):1146-1146. doi:10.1200/jco.1999.17.4.1146

43. Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, Stenning SP. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol. 2005 Feb 20;23(6):1200-8. doi: 10.1200/JCO.2005.08.003. PMID: 15718317.

44. Classen J, Schmidberger H, Meisner C, Souchon R, Sautter-Bihl ML, Sauer R, Weinknecht S, Köhrmann KU, Bamberg M. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol. 2003 Mar 15;21(6):1101-6. doi: 10.1200/JCO.2003.06.065. PMID: 12637477.

45. Hanks G, Peters T, Owen J. Seminoma of the testis: long term beneficial and deleterious results of radiation. *International Journal of Radiation Oncology*Biology*Physics*. 1992;24(5):913-919. doi:10.1016/0360-3016(92)90475-w

46. Paly JJ, Lin CC, Gray PJ, Hallemeier CL, Beard C, Sineshaw H, Jemal A, Efstathiou JA. Management and outcomes of clinical stage IIA/B seminoma: Results from the National Cancer Data Base 1998-2012. Pract Radiat Oncol. 2016 Nov-Dec;6(6):e249-e258. doi: 10.1016/j.prro.2016.05.002. Epub 2016 May 8. PMID: 27345128.

47. Giannatempo P, Greco T, Tana S et al. Radiotherapy or Chemotherapy for Clinical Stage Iia and Iib Seminoma: a Systematic Review and Meta-Analysis of Patient Outcomes. *Annals of Oncology*. 2014;25:iv298. doi:10.1093/annonc/mdu337.48

48. Chung PW, Gospodarowicz MK, Panzarella T, Jewett MA, Sturgeon JF, Tew-George B, Bayley AJ, Catton CN, Milosevic MF, Moore M, Warde PR. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol. 2004 Jun;45(6):754-59; discussion 759-60. doi: 10.1016/j.eururo.2004.01.020. PMID: 15149748.

49. Papachristofilou A, Bedke J, Hayoz S et al. Treatment compliance and early toxicity in SAKK 01/10: Single-dose carboplatin and involved-node radiotherapy for treatment of stage IIA/B seminoma. *Journal of Clinical Oncology*. 2020;38(6_suppl):405-405. doi:10.1200/jco.2020.38.6_suppl.405

50. Daneshmand S, Cary C, Masterson T et al. SEMS trial: Result of a prospective, multi-institutional phase II clinical trial of surgery in early metastatic seminoma. *Journal of Clinical Oncology*. 2021;39(6_suppl):375-375. doi:10.1200/jco.2021.39.6_suppl.375

51. Albers P, Hiester A, Grosse Siemer R, Lusch A. The PRIMETEST trial: Interim analysis of a phase II trial for primary retroperitoneal lymph node dissection (RPLND) in stage II A/B seminoma patients without adjuvant treatment. *Journal of Clinical Oncology*. 2019;37(7_suppl):507-507. doi:10.1200/jco.2019.37.7_suppl.507

52. Boujelbene N, Cosinschi A, Boujelbene N *et al.* Pure seminoma: A review and update. *Radiat Oncol* 6, 90 (2011). https://doi.org/10.1186/1748-717X-6-90

53. Khoo V, Rainford K, Horwich A, Dearnaley D. The effect of antiemetics and reduced radiation fields on acute gastrointestinal morbidity of adjuvant radiotherapy in stage I seminoma of the testis: A randomized pilot study. *Clin Oncol*. 1997;9(4):252-257. doi:10.1016/s0936-6555(97)80011-8

54. Ruhlmann C, Jahn F, Jordan K et al. 2016 updated MASCC/ESMO consensus recommendations: prevention of radiotherapy-induced nausea and vomiting. *Supportive Care in Cancer*. 2016;25(1):309-316. doi:10.1007/s00520-016-3407-8

55. Zagars G, Ballo M, Lee A, Strom S. Mortality After Cure of Testicular Seminoma. *Journal of Clinical Oncology*. 2004;22(4):640-647. doi:10.1200/jco.2004.05.205

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