Chapter 28
Testicular Cancer

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PEARLS

- Spermatogenesis: spermatogonia → spermatocytes → spermatids → spermatozoa. Takes ~2 months in adult men.
- LN drainage.
  - L testicle: testicular vein → L renal vein → paraaortic LN.
  - R testicle: testicular vein → IVC below level of renal vein → paracaval and aortocaval nodes.
  - Prior inguinal surgery may disrupt drainage and redirect through iliac nodes.
- *Pathology*: >95% are germ cell tumors (GCTs) = seminomas and nonseminomatous germ cell tumors (NSGCTs).
- Sixty percent of tumors are mixed and 40% are pure (seminoma most common pure).
- Seminoma is the most common single histology, but together NSGCTs are more common.
- Seminoma subtypes: classic (>90% of cases, stains + for PLAP) and spermatocytic (older age, cured by orchiectomy, rarely metastasizes, stains negative for PLAP). Anaplastic no longer considered a subtype.
- NSGCTs subtypes: embryonal carcinoma (most common NSGCT), yolk sac tumor (elevated AFP, Schiller Duval bodies), choriocarcinoma (elevated β-hCG, rarest pure GCT), teratoma, and mixed GCTs.
- Other tumors: Sertoli cell tumors (produce estrogen, present with gynecomastia); Leydig cell tumors (produce androgens and estrogen, present with early puberty, gynecomastia); lymphoma; embryonal rhabdomyosarcoma.
- Risk factors: undescended testicle, first-born, pre/perinatal estrogen exposure, polyvinyl chloride exposure, advanced maternal age, Down's syndrome, Klinefelter's syndrome (47XXY), CIS, HIV/AIDS.

WORKUP

- H&P, bilateral testicular ultrasound, β-hCG, AFP, LDH, CBC, chemistries, fertility assessment ± sperm banking, CXR, CT abdomen and pelvis, CT chest if ≥ stage II
- Repeat tumor markers if elevated preoperatively
  - β-hCG half-life is 24–36 h; AFP half-life is 3.5–6 days
  - β-hCG is rarely elevated in seminoma. If AFP elevated, not pure seminoma
- Bone scan and/or MRI brain if clinically indicated

STAGING (AJCC 7TH ED., 2010):TESTICULAR CANCER

- The definition of TNM and the stage grouping for this chapter have not changed from the AJCC 6th Ed., 2002.

Primary tumor (T)*

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a pathologic stage is assigned

pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor (e.g., histologic scar in testis)
pTis: Intratubular germ cell neoplasia (carcinoma in situ)
pT1: Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea, but not the tunica vaginalis
pT2: Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3: Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4: Tumor invades the scrotum with or without vascular/lymphatic invasion

**Note*: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Regional lymph nodes (N)

Clinical

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, not more than 2 cm in greatest dimension
N2: Metastasis with a lymph node mass more than 2 cm, but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm, but not more than 5 cm in greatest dimension
N3: Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

pNX: Regional lymph nodes cannot be assessed
pN0: No regional lymph node metastasis
pN1: Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, not more than 2 cm in greatest dimension
pN2: Metastasis with a lymph node mass more than 2 cm, but not more than 5 cm in greatest dimension; or more than five nodes positive, not more than 5 cm; or evidence of extranodal extension of tumor
pN3: Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant metastasis (M)

M0: No distant metastasis
M1: Distant metastasis
  M1a: Nonregional nodal or pulmonary metastasis
  M1b: Distant metastasis other than nonregional lymph nodes and lung

continued

Anatomic stage/prognostic groups

Group	T	N	M	S (serum tumor markers)
0:	pTis	N0	M0	S0
I:	pT1–4	N0	M0	SX
IA:	pT1	N0	M0	S0
IB:	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS:	Any pT/Tx	N0	M0	S1–3 (measured post orchiectomy)
II:	Any pT/Tx	N1–3	M0	SX
IIA:	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
IIB:	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
IIC:	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
III:	Any pT/Tx	Any N	M1	SX
IIIA:	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
IIIB:	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC:	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

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Royal Marsden staging

System

I: Limited to testis
IIA: Nodes <2 cm
IIB: Nodes 2–5 cm
IIC: Nodes 5–10 cm
IID: Nodes >10 cm
III = Nodes above and below diaphragm
IV = Extralymphatic mets

~10-Year survival (seminoma)

I: RFS 96–98%, CSS 99–100%
IIA: RFS 92%, CSS 96–100%
IIB: RFS 86%, CSS 96–100%
IIC: RFS 70%, OS 90% (RT alone)
IID: RFS 50% (RT alone), 90% (chemo)
IIIA/B: OS 90%
IIIC: OS 80%

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TREATMENT RECOMMENDATIONS FOR SEMINOMA

Stage	Recommended treatment
All patients	■ Radical inguinal orchiectomy with high ligation of spermatic cord
I Seminoma	■ Post resection: surveillance (relapse rate 16%) or RT (20 Gy to paraaortic ± pelvic LN), or carboplatinum × 1–2 cycles
IIA/IIB Seminoma	■ RT 20 Gy to pelvic and paraaortic LN with boost to gross disease (30 Gy for IIA, 36 Gy for IIB). Consider etoposide, cisplatin (EP) chemo × 4c for select IIB patients

continued

IIC/D and III Seminoma	■ Chemo (etoposide, cisplatinum, ± bleomycin): EP × 4c or BEP × 3c
NSGCT	■ IA: open nerve-sparing retroperitoneal LN dissection (nsRPLND) or surveillance in compliant patients ■ IB: open nsRPLND or BEP chemo × 2c or surveillance if T2 and compliant pt ■ IS: EP chemo × 4c or BEP chemo × 3c ■ IIA: if markers negative, open nsRPLND or EP chemo × 4c or BEP chemo × 3c. If persistent tumor marker elevation, chemo ■ IIB: if markers negative, open nsRPLND or EP chemo × 4c or BEP chemo × 3c. If persistent tumor marker elevation or multifocal LN mets with aberrant drainage, chemo ■ IIC/IIIA: primary chemo. RT for brain metastases

STUDIES

SURVEILLANCE

- Warde et al. (2002): 638 patients with stage I seminoma followed with surveillance with 7-year follow-up. Increased relapse with tumors >4 cm, LVSI, and rete testis involvement. Relapses: 0 risk factors = 12%, 1 risk factor = 16%, 2 risk factors = 30%. Prior study showed age <34 years also increased risk of failure

RT FIELD AND DOSE FOR STAGE I

- MRC (Fossa et al. 1999): 478 patients with stage I seminoma randomized to dogleg vs. paraaortic RT. No difference in 3-year RFS/OS with dogleg (97/96%) vs. paraaortic (99/100%). Three-year pelvic RFS was 100% with dogleg vs. 98% with paraaortic. Paraaortic had decreased nausea and vomiting, lower azospermia (11 vs. 35%), and more rapid recovery of sperm count. Two percent pelvic relapse in PA-only arm.
- MRC (Jones et al. 2005): 625 patients with stage I seminoma randomized to 20 vs. 30 Gy RT in 2 Gy fx. RT was paraaortic (with dogleg for patients with prior inguinal surgery). Five-year RFS was not different (97% 30 Gy, 96.4% 20 Gy). 20 Gy arm had decreased lethargy and inability to carry out normal work 1 month after treatment.

CHEMO FOR STAGE I

- MRC/EORTC (Oliver et al. 2005): 1,447 patients with stage I seminoma randomized to carboplatin × 1c vs. RT. RT was 20–30 Gy (87% PA, 13% dogleg). Median follow-up 4 years. 3-year RFS = RT 95.9%, carboplatin 94.8%. Relapse sites: carboplatin = 74% PA, 0% pelvic vs. RT = 9% PA, 28% pelvic. Carboplatin patients took less time off from work compared to RT. Update (Oliver et al. 2008): no difference in 5-year RFS (95% chemo, 96% RT), fewer new GCTs with chemo (2 patients vs. 15 with RT).

SECOND CANCER RISK

- Travis et al. (2005): review of >40,000 men with testicular cancer in 14 population registries in Europe and North America. For patients diagnosed by age 35 years, cumulative risk of second solid cancer 40 years later (i.e., to age 75 years) was 36% for seminoma and 31% for nonseminoma compared with 23% for the general population. Increased relative risk of solid cancers was noted for RT (RR = 2.0), chemotherapy alone (RR = 1.8), and both (RR = 2.9).

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RESIDUAL MASS

- Puc et al. (1996): 104 patients with stage IIC, III, or extragonadal primary who underwent surgery and had CR or PR of tumor markers. If a radiographic mass was <3 cm, only 3% of patients had pathologic evidence of failures. For masses >3 cm, 27% of patients had evidence of failure.
- De Santis et al. (2004): 51 patients with seminoma treated with chemo with residual masses. Compared pathologic predictive value of PET and CT. PET PPV 100% and NPV 96% for viable tumor. CT (≤3 vs. >3 cm) PPV 37% and NPV 97%.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Prior to simulation, fertility assessment ± sperm bank
- Simulate supine
- Need IVP or CT to block out kidneys and rule out horseshoe kidney
- Place clamshell on uninvolved testicle. Position penis out of field
- Borders: PA = T10/T11 superiorly to L5/S1 inferiorly. Dogleg,

inferior border is top of obturator foramen. Lateral = tips of transverse processes of lumbar vertebra or 2 cm margin on all nodes (about 10–12 cm wide). For left-sided tumors, widen field to include left renal hilar nodes

- If prior inguinal surgery, treat contralateral inguinal and iliac regions (Figs. 28.1 and 28.2)

DOSE PRESCRIPTIONS

- 20 Gy at 2.0 Gy/fx. Alternatively, 25.5 Gy at 1.5 Gy/fx
- Boost IIA nodes to 30 Gy and IIB nodes to 36 Gy

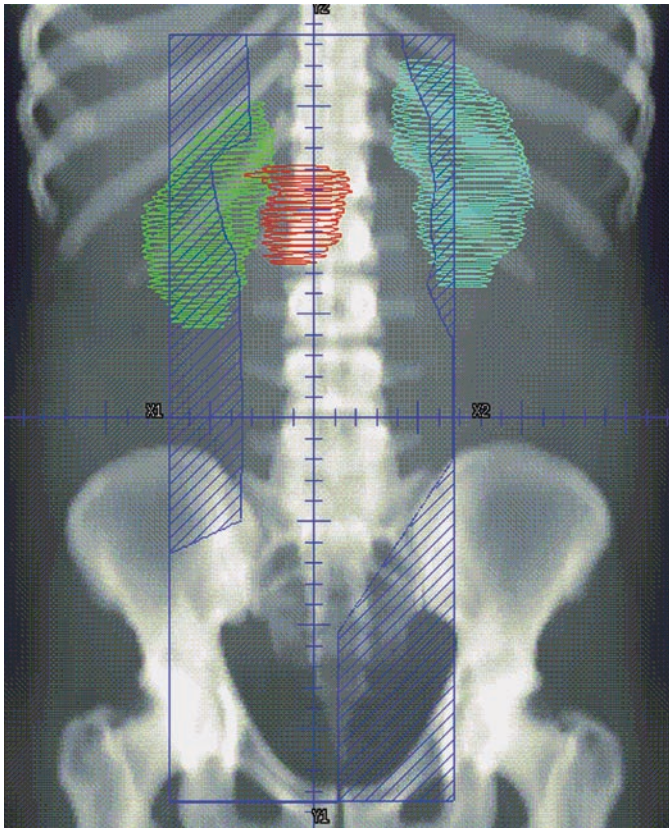

Fig. 28.1 DRR of a dogleg field used to treat a stage IIB seminoma

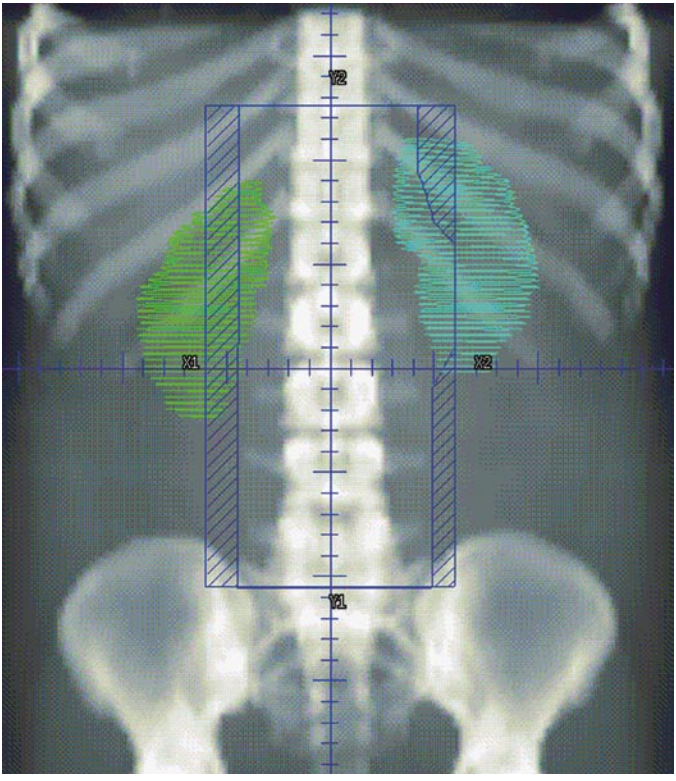

Fig. 28.2 DRR of a paraaortic field used to treat a stage I seminoma

DOSE LIMITATIONS

- 50 cGy causes transient azospermia with recovery at 1 year, but only 50% of patients reach their baseline
- 80–100 cGy causes total azospermia with recovery 1–2 years later for some patients
- 200 cGy causes sterilization
- Clamshell reduces testicle dose by 2–3× (dogleg without shield ~4 cGy/fx, with shield ~1.5 cGy/fx; paraaortic without shield ~2 cGy/fx, with shield ~0.7 cGy/fx)
- Kidneys: limit at least 70% <20 Gy

COMPLICATIONS

- Acute nausea, vomiting, diarrhea
- Late small bowel obstruction, chronic diarrhea, peptic ulcer disease (<2% with <35 Gy)
- With testicular shielding, most patients will have oligospermia by 4 months that lasts ~1 year
- Infertility: 50% of patients have subfertile counts on presentation or after surgery. After RT, 30% able to have children
- BEP causes immediate azospermia, but >50% recover sperm count
- Chemo side effects = alopecia, nausea, myelosuppression, pulmonary fibrosis, ototoxicity
- Second cancers: 5–10% increased risk vs. general population after RT

FOLLOW-UP

- See NCCN Guidelines (www.nccn.org)
- After RT for stage I seminoma
  - H&P, labs (AFP, β-HCG, LDH), and CXR every 3–4 months for year 1, every 6 months for year 2, then annually. Pelvic CT annually for 3 years for patients treated with PA-only RT (not needed if PA and pelvic RT)
- Stage I surveillance
  - H&P, labs every 3–4 months for years 1–3, every 6 months for years 4–7, then annually. CT abdomen and pelvis at each visit. CXR at alternate visits up to 10 years
- PET/CT can predict viable tumor in postchemotherapy residual disease.

REFERENCES

De Santis M, Becherer A, Bokemeyer C, et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol 2004;22:1034-1039.

Fossa SD, Horwich A, Russell JM, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol 1999;17:1146.

Jones WG, Fossa SD, Mead GM, et al. 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;23:1200-1208.

Morton G, Thomas G. Testis. In: Halperin EC, Perez CA, Brady LW, et al., editors. Principles and practice of radiation oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. pp. 1503-1518.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Testicular Cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/testicular.pdf. Accessed on June 1, 2009.

Oliver RTD, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomized trial. Lancet 2005;266:293-300.
Oliver RT, Mead GM, Fogarty PJ, et al. Radiotherapy vs carboplatin for stage I seminoma: updated analysis of the MRC/EORTC randomized trial. J Clin Oncol 2008;26:abstr 1.
Puc HS, Heelan R, Mazumdar M, et al. Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. J Clin Oncol 1996;14:454-460.
Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005;97:1354-1365.
Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002;20:4448-4452.

FURTHER READING

Becherer A, De Santis M, Karanikas G, et al. FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. Eur J Radiol 2005;54(2): 284-248.
Garwood D. Cancer of the Testis. In: Leibel SA, Phillips TL, editors. Textbook of radiation oncology. 2nd ed. Philadelphia: Saunders; 2004. pp. 1031-1046.
Hussey D, Meistrich M. The Testicle. In: Cox JD, Ang KK, editors. Radiation oncology: rationale, technique, results. 8th ed. St. Louis: Mosby; 2003. pp. 605-628.