


**Testicular Cancer:
Management and Post-
Treatment Survivorship**


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Objectives

- Identify treatment options for testicular cancer depending on the subtype and stage
- Discuss common treatment-related side effects
- Describe three challenges that patients may face in the post-treatment survivorship phase




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Definition

Testicular cancer is a disease in which malignant cells arise in the testicle



More than 90% of cancers of the testicle develop in germ cells (cells that make up the sperm)



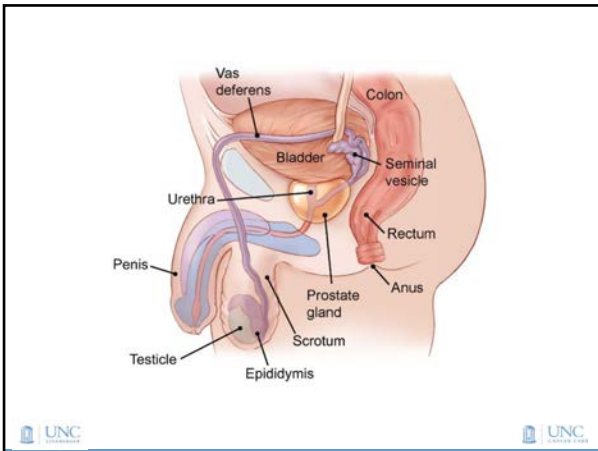
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Anatomy

- Testicles are part of the male reproductive system
 - Produce male hormones like testosterone
 - Produce sperm
 - Oval; 4-5 cm in length
- Multi-layered tunica cover the testes
- Seminiferous tubules are the site of spermatogenesis
- Epididymis: Coiled tube attached to the testis where sperm mature
- Vas Deferens: Sperm travel from epididymis via the vas



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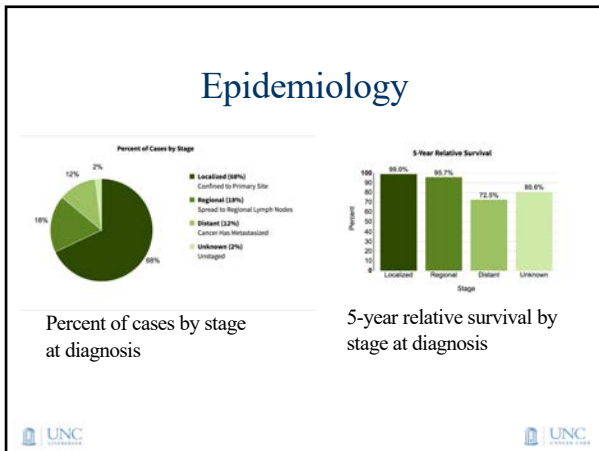
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Epidemiology

- 2021: 9,470 new cases
- 2021: 440 deaths
- Lifetime risk: 1 in 250
 - Risk of death: 1 in 5,000
- Average age at diagnosis: 33
 - 6% of cases occur in children and teens
 - 8% of cases occur in men over 55
- Accounts for about 0.5-1% of all male cancers
 - ~24th most common
- Most common cancer in boys/men ages 15-35

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- ### Risk factors
- ❖ Cryptorchidism (undescended testicle)
 - ❖ 7-10% of patients w/ testicular cancer have cryptorchidism
 - ❖ Family history
 - ❖ Father or brother
 - ❖ Only a small # occur in families
 - ❖ HIV
 - ❖ Personal history
 - ❖ 3-4% of men will develop bilateral tumors
 - ❖ Caucasian
 - ❖ Infertility
 - ❖ 2.8 x more likely than general population



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- ### Clinical Presentation
- **Most often, painless mass/lump in the testicle**
 - Heaviness, aching in lower abdomen or scrotum
 - Gynecomastia, breast tenderness
 - Caused by high levels of human chorionic gonadotropin (hcg)
 - Advanced disease
 - Low back pain (RPLN mass)
 - SOB, CP, cough (pulm mets)
 - Abdominal pain
 - 10-12% present w/ distant mets disease
 - 1-2% have bil disease at diagnosis

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Work-up & Diagnosis

- Physical exam
- Scrotal ultrasound
 - Sensitivity near 100% when combined with PE
 - Typically well defined and hypochoic
- Tumor markers
 - Pre-orchietomy
 - Post-orchietomy
 - Should be a predictable decline
 - Post-chemo/XRT
 - Therapeutic lag
 - CXR

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Serum Tumor Markers

Alpha-Fetoprotein



- Pure embryonal, yolk sac, mixed; not chorio or pure seminoma
- Half life 5-7 days

Beta-human chorionic gonadotropin

- All chorios, 40-60% embryonal, 5-10% seminoma
- Half life 24-36 hours

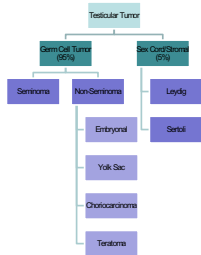
Lactate Dehydrogenase

- Low specificity for GCT; many false +
- Half life 4-5 days



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Histologic Variants



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    graph TD
      TT[Testicular Tumor] --> ST[Seminoma 95%]
      TT --> NST[Non-Seminoma 5%]
      ST --> S[Seminoma]
      NST --> E[Embryonal]
      NST --> YS[Yolk Sac]
      NST --> CC[Choriocarcinoma]
      NST --> T[Teratoma]
      ST --> SC[Sex Cord-Stromal 5%]
      SC --> L[Leydig]
      SC --> Sertoli
  
```

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NSGCT vs Seminoma

<ol style="list-style-type: none"> 1. Mixed Tumor <ol style="list-style-type: none"> 1. Mixture of seminoma and nonseminoma 2. Embryonal Carcinoma <ol style="list-style-type: none"> 1. Grey/white fleshy mass, papillary projections 2. AFP and HCG 3. Yolk sac Tumor <ol style="list-style-type: none"> 1. Yellow/pale grey, Schiller-Duval bodies 2. AFP and HCG 4. Choriocarcinoma <ol style="list-style-type: none"> 1. Grey/white, syncytiotrophoblasts and cytotrophoblasts 2. Never AFP, always HCG 3. Worst prognosis of all testis tumors 5. Teratoma <ol style="list-style-type: none"> 1. Cystic with multiple germ cell layers in different stages of maturation 2. No AFP or HCG 3. Chemo and radiation resistant 	<ol style="list-style-type: none"> 1. Classic <ol style="list-style-type: none"> 1. 95% of Seminomas 2. Large uniform cells with clear cytoplasm and distinct cell borders, lobulated and pale 2. Spermatocytic <ol style="list-style-type: none"> 1. 5% of Seminomas 2. Low metastatic potential
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Age/STMs/Treatment Response

Tumor	Age	AFP	HCG	XRT	Chemo
Yolk Sac	<10	Maybe	Maybe	Resistant	Sensitive
Chorio	20-30	Never	Always	Resistant	Sensitive
Embryonal	25-35	Maybe	Maybe	Resistant	Sensitive
Teratoma	25-35	Never	Never	Resistant	Resistant
Seminoma	30-40	Never	Maybe	Sensitive	Sensitive

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Radical Orchiectomy

- Inguinal approach
 - Testis removed with the surrounding tunica vaginalis, spermatic cord up to the level of the internal inguinal ring
- Avoid seeding the scrotum and disrupting the lymphatics
 - Trans-scrotal biopsy and trans-scrotal orchiectomy increase risk of local recurrence
- 1 hour operation
- Day op or overnight

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Post-orchietomy evaluation

- Post-orchietomy markers
 - It takes > 5 half-lives to eliminate circulating markers
 - 1-2 weeks for HCG; 3 weeks for LDH; 5 weeks for AFP
 - S stage is determined using the nadir value of post-orch markers
- CT abdomen and pelvis (chest if abnormal CXR or CT AP)
 - CT cannot differentiate between cancer, teratoma, necrosis, fibrosis
 - Abdominal CT has a 30% false negative rate

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Staging

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Risk categories

Risk Status	Nonseminoma	Seminoma
Good Risk	All of the following: -testicular or retroperitoneal primary tumor -M0 or M1a -S0 or S1	All of the following: -Any primary site -M0 or M1a -Normal AFP
Intermediate Risk	All of the following: -testicular or retroperitoneal primary tumor -M0 or M1a -S2	All of the following: -Any primary site -M1b -Normal AFP
Poor Risk	Any of the following: -Mediastinal primary tumor -M1b -S3	No patients are classified as poor risk

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Metastasis from Testis Tumors

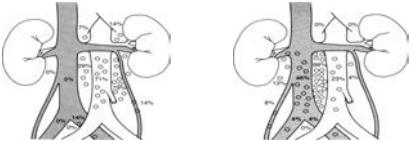

- Usually lymphatic spread
 - Chorio and yolk sac may metastasize hematogenously
- Retroperitoneal LN are the most common site of metastasis
- When normal lymphatic flow has not been altered, lymphatic spread occurs in a predictable and stepwise pattern
 - Right → interaortocaval RPLN
 - Left → left para-aortic RPLN
 - Often spread from right to left, and rarely left to right



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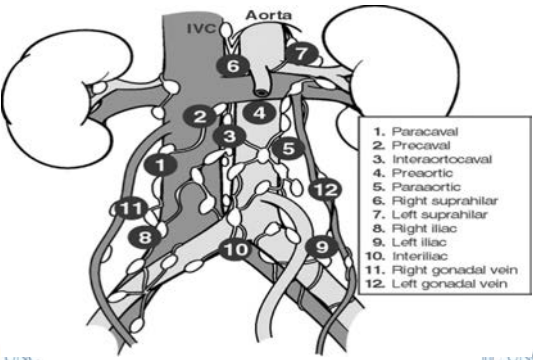
Metastasis from Testicular Tumors

- Inguinal nodes
 - If tumor invades through tunica vaginalis or into scrotum
 - Previous scrotal or inguinal surgery
- Pelvic nodes
 - If tumor invades into the epididymis or spermatic cord
- Distant non-node (most to least common)
 - Lung, liver, brain, bone, kidney, adrenal, GI tract, spleen





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Retroperitoneum



1. Paracaval
2. Precaval
3. Interaortocaval
4. Preaortic
5. Paraaortic
6. Right suprahilal
7. Left suprahilal
8. Right iliac
9. Left iliac
10. Interiliac
11. Right gonadal vein
12. Left gonadal vein



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Treatment after Orchiectomy






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Primary Chemotherapy

- ❖ Cisplatin is the most effective agent against GCT
- ❖ Bleomycin/Etoposide/Cisplatin (BEP) or Etoposide/Cisplatin (EP)
- ❖ Bleomycin: Antitumor antibiotic that binds to and breaks DNA
 - ❖ SE: Pneumonitis, pulmonary fibrosis, nail/skin change
- ❖ Etoposide: Alkylating agent
 - ❖ SE: Myelosuppression, mucositis, vomiting, alopecia
- ❖ Cisplatin: Cross links DNA
 - ❖ SE: Nephrotoxicity, neurotoxicity, ototoxicity, nausea, vomiting
- ❖ Carboplatin: Cross links DNA
 - ❖ SE: Myelosuppression, nausea, vomiting, neuropathy
 - ❖ One cycle is a tx option for stage IA or IB pure seminoma
 - ❖ Carbo should not be substituted for Cis in good risk patients because it results in a lower complete remission rate

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Other chemotherapy

- ❖ **Salvage Chemotherapy**
 - ❖ Indication: Progression on primary chemo or relapse after primary chemo
 - ❖ Regimens: Usually 4 cycles
 - ❖ Etoposide, Ifosfamide, Cisplatin (VIP)
 - ❖ Vinblastine, Ifosfamide, Cisplatin (VeIP)
 - ❖ Taxol, Ifosfamide, Cisplatin (TIP)
 - ❖ CR: 50%; sustainable DR: 25%
- ❖ **HD Chemotherapy and Auto Bone Marrow Transplant**
 - ❖ Indication: Extremely poor prognosis or poor response to standard chemo
 - ❖ Auto transplant after HDC because HDC kills marrow
 - ❖ 10-20% achieve durable remission
 - ❖ 5-10% mortality

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Radiation and RPLND



- ❖ External Beam Radiation Therapy (XRT)
 - ❖ Treatment for Stage I, IIA, or IIB pure seminoma
 - ❖ Toxicities = Nausea, vomiting, fatigue, bone marrow suppression, gastritis, peptic ulcer, secondary cancers
 - ❖ Prior abdominal XRT, IBS, should consider surveillance
- ❖ Retroperitoneal Lymph Node Dissection (RPLND)
 - ❖ Modified Template: Avoids RP dissection on contralateral side
 - ❖ Nerve sparing preserves nerves within the template
 - ❖ Right & left templates
 - ❖ If a palpable nodal met is discovered during a modified template, a full bilateral template should be performed
 - ❖ Margins of resection should not be compromised to maintain the template or preserve ejaculatory function
 - ❖ Morbidity is higher for post-chemo RPLND

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Pure Seminoma



- ❖ Stage IA or IB:
 - ❖ pT1-pT2: Observation, Carboplatin x 1 or XRT
 - ❖ pT3-pT4: Carboplatin x1 or XRT
 - ❖ XRT 20 Gy or 25.5 Gy
- ❖ Stage IIA, IIB
 - ❖ XRT or
 - ❖ BEP x 3 or EP x 4
- ❖ Stage IIC or III: Chemotherapy
 - ❖ Good risk: BEP x 3 or EP x 4
 - ❖ Intermediate risk: BEP x 4 or VIP x 4

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NSGCT



- ❖ Stage I (no risk factors)
 - ❖ Surveillance, NS-RPLND or BEP x 1
- ❖ Stage I (with risk factors; LVI, spermatic cord)
 - ❖ Surveillance or BEP x 1 or NS-RPLND
- ❖ After NS-RPLND
 - ❖ pN0: Observe
 - ❖ pN1 or pN2: Observe or EP x 2
 - ❖ pN3: EP x 4 or BEP x 3
- ❖ Stage IIC or III: Chemotherapy
 - ❖ Good Risk = BEP x3 or EP x 4
 - ❖ Intermediate and Poor Risk = BEP x 4
 - ❖ Complete Response= observe
 - ❖ Partial Response = NS-RPLND
 - ❖ Poor Response = Salvage therapy

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5-year Overall Survival

Stage	Risk Status	Seminoma	Nonseminoma
I	-	>98%	>98%
IIA or IIB	-	>95%	>95%
IIC or III	Good	86%	94%
	Intermediate	72%	83%
	Poor	-	71%






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Question 1

Which of the following is a treatment option for good risk stage IIC NSGCT?



1. Surveillance
2. Radiation plus 1 cycle of Carboplatin
3. Radiation only
4. BEP x 3 cycles

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Treatment Complications



- Hypogonadism
 - Usually not caused by unilateral orchiectomy alone
 - Bilateral orchiectomy
 - Cisplatin-based chemotherapy has severe dose-dependent effects on spermatogenesis
 - Complications related to hypogonadism: Osteoporosis, metabolic syndrome, type II diabetes, cardiovascular disease
 - Associated with diminished QOL
 - Screening
 - Treatment
- Infertility (SPERM BANK!)
 - Chemotherapy: Affect endocrine testicular function v direct impact on spermatogenesis
 - RPLND: Retrograde ejaculation resulting in infertility
 - Nerve sparing
 - Radiation therapy: Improper delivery
 - Spermatogenesis recovery: 50% in 2 years, 80% in 5 years
 - Fertility Preservation Programs
 - Psychosocial support

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Treatment Complications



- Neuropathy
 - Chemotherapy induced
 - Protect hands and feet
 - Medical management
 - Loose clothing, good shoes
- Fatigue
 - Treatment induced, hypogonadism, depression
 - Treat underlying cause(s)
 - Good sleep hygiene
 - Regular exercise
- Anxiety/Depression
 - Caused by cancer experience or pre existing
 - Mental health providers
 - Medical management
 - Encourage participation in support groups

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Treatment Complications

- Ototoxicity
 - Tinnitus/high frequency hearing loss, 4-8MHz (~20% of patients)
 - Assess noise exposure
 - Audiometry
- Nephrotoxicity
 - Decrease in GFR may not improve over time
 - Long-term renal function
- Pulmonary toxicity
 - Bleomycin toxicity
 - Smoking cessation
 - PFTs prior to bleomycin and as needed
- Pain
 - Chronic pain related to post-operative complications



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Treatment Complications

- Cardiovascular Toxicity
 - **Direct hypothesis:** Chemo causes diffuse endothelial damage, including coronary arteries, gradually leading to cardiovascular disease
 - Raynaud's phenomenon: 25-61% of survivors
 - Microalbuminuria: Present in 12% of patients treated with chemo and in <1% of those treated with orchiectomy or healthy age-matched controls.
 - Laboratory markers of inflammation: von Willebrand factor, fibrinogen, tissue-type plasminogen activator, CRP
 - Circulating endothelial cells
 - Platelet aggregation caused by Cisplatin thought to explain increased incidence of MI in young patients with no other risk factors.
 - **Indirect hypothesis:** Chemo leads to an increased incidence of cardiovascular disease risk factors including hypertension, hyperlipidemia, and the metabolic syndrome, which increase risk of cardiovascular disease.
 - Hyperlipidemia (32-82%)
 - Hypertension (50%)
 - Obesity (48%) BMI > 25

• Cardiac workup should be based on clinical presentation

• Evidenced-based screening guidelines do not exist

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Treatment Complications

- Second Malignant Neoplasms
 - Testicular Cancer survivors experience a 1.7-3.5 fold increased overall risk for Second Malignant Neoplasms compared to the general population
 - Risks After Radiotherapy
 - Leukemia: Absolute risk is low, ~9 cases per 10,000 patients per year followed for 15 years after 25Gy of a/p radiotherapy
 - Solid Cancers: Risks increase 5 years after treatment. Melanoma, lung*, thyroid, esophagus*, pleura*, stomach, pancreas, colon, rectum, kidney, bladder, connective tissue
 - *Supradiaphragmatic XRT rarely used anymore
 - Limit total amount of radiation without compromising cure rate
 - Risks After Chemotherapy
 - Leukemia: Absolute risk is low ~16 cases per 10,000 patients per year followed for 15 years
 - Solid Cancer: Related to prolonged accumulation on cisplatin?
 - Prior treatment may limit therapeutic options
 - Diagnostic radiation exposure
 - Conflicting results

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Question 2

You are counseling a patient about toxicity associated with Bleomycin. What side effect is unique to this chemotherapy agent used for testis cancer treatment?

1. Restless leg syndrome
2. Pulmonary toxicity (e.g., pneumonitis)
3. Dry mouth
4. Lower extremity edema

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Post-treatment

- ❖ After completion of treatment(s), patients transition into a surveillance program
- ❖ NCCN Guidelines
- ❖ "Usual practice" for all cancers
 - ❖ Most followed by primary oncology provider
 - ❖ Focus on monitoring for cancer recurrence and evaluating for persistent toxicity
- ❖ Challenges
 - ❖ Survivors can get lost in the shuffle in busy practice, where focus may be on patients who are undergoing active treatment
 - ❖ Underutilization of developing comprehensive follow-up plan that includes monitoring for late-term effects and optimizing use of specialty services
 - ❖ Ownership of care when patient has seen multiple oncology specialists

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Models of Survivorship Care



- ❖ Community-based, shared-care model
 - ❖ Most adult cancer survivors are treated in a community setting
 - ❖ Extensively studied in chronic diseases
 - ❖ E.g. Diabetes managed by both PCP and endocrinology
- ❖ Oncology provider
 - ❖ Delivers cancer therapy
 - ❖ Keeps PCP informed
 - ❖ Guidance in long-term survivorship care (including Survivorship Care Plan)
 - ❖ Transition care back to PCP at appropriate time
 - ❖ Available for questions, consults, referrals
- ❖ Primary care provider
 - ❖ Address physical and emotional needs
 - ❖ Assume care of aspects that are feasible in primary care setting
 - ❖ Refer for problems/periodic evaluations
 - ❖ Consult in areas of uncertainty

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Models of Survivorship Care



- ❖ Academic Medical Centers
 - ❖ Disease-specific cancer survivor programs
 - ❖ Earliest iteration of models for adult cancer survivorship care
- ❖ Comprehensive Survivor Programs
 - ❖ Consultative model
 - ❖ Primary oncologist refers patient for a one-time visit with the survivor-program staff
 - ❖ Oncology summary, surveillance plan, counseling re: late effects, psychological needs, risk reduction
 - ❖ Nurse practitioner-led survivor clinic
 - ❖ Embedded within the treatment team
 - ❖ Survivors are transitioned to the NP for formal follow up
 - ❖ Specialized multidisciplinary survivor clinic
 - ❖ MDs, APPs, SWs, RNs, psychologists, network of consultative specialists, all of whom specialize in the care of cancer survivors

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Models of Survivorship Care

- ❖ Unclear which models of survivorship care translate to improved patient outcomes
- ❖ Debate about who should be responsible for developing and providing a personalized plan for posttreatment care (even among groups in the same institution)
- ❖ Based on setting, resources, cancer diagnosis/treatment






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Components of Survivorship Care

- ❖ Coordination
 - ❖ Communication among patients, cancer team, PCP
 - ❖ Treatment summaries
 - ❖ Care Plans
- ❖ Prevention and Detection
 - ❖ Promoting healthy behaviors (physical activity, diet, substance use, sun protection)
 - ❖ Age appropriate screening procedures
- ❖ Surveillance
 - ❖ Assessment for recurrence
 - ❖ Late effects
- ❖ Intervention for consequences of cancer and treatment
 - ❖ Physical
 - ❖ Psychological
 - ❖ Social
 - ❖ Spiritual



❖ Based on IOM report

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Survivorship Care Plan (SCP)



- ❖ Incorporates treatment summary
- ❖ Oncology follow-up schedule
 - ❖ Based on NCCN Guidelines
 - ❖ Interval and what is being done at each visit
- ❖ Health maintenance and promotion
 - ❖ General
 - ❖ Exercise
 - ❖ Nutrition
 - ❖ Smoking
- ❖ Possible late effects of cancer and cancer treatment
- ❖ Support services
- ❖ Resources

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Testicular Cancer Treatment Summary



- ❖ Surgical procedures (date, surgeon)
 - ❖ Orchiectomy: Laterality, pathology
 - ❖ RPLND: Template, pathology
- ❖ Chemotherapy (end date, medical oncologist)
 - ❖ Name, dose, number of cycles
- ❖ Radiation (end date, radiation oncologist)
 - ❖ Fields, fractions

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Why does survivorship care matter for testis cancer patients?



- ❖ Immediate and long-term treatment-related toxicities
 - ❖ Sexual health
 - ❖ Infertility
 - ❖ Hypogonadism
 - ❖ Retrograde ejaculation
 - ❖ Chemotherapy-induced toxicity
 - ❖ Ototoxicity
 - ❖ Nephrotoxicity
 - ❖ Neuropathy
 - ❖ Fatigue
 - ❖ Cardiovascular toxicity
 - ❖ Mental health
 - ❖ Depression, anxiety
 - ❖ Body image
 - ❖ Secondary malignancies
 - ❖ Extensive follow up schedules

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Testicular Cancer Survivorship Clinic



- ❖ History
 - ❖ Established in 2008 as a vision of Liz Sherwood, NP and Paul Godley, MD
 - ❖ The LIVESTRONG Survivorship Center of Excellence at UNC Lineberger was formed with a \$1.5 million grant and charged with developing survivorship programs and services
 - ❖ Was one of seven National LIVESTRONG Centers of Excellence
 - ❖ Prior to this, patients followed with either urologist or medical oncologist, sometimes both.
 - ❖ Before revision of NCCN guidelines, could be seeing a patient upwards of every 2 months
- ❖ Current
 - ❖ Monthly, Nurse practitioner-led clinic
 - ❖ Transitioned to this model in ~2011

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Testicular Cancer Survivorship Clinic

- ❖ Transition into clinic following definitive treatment
 - ❖ Provider-dependent
 - ❖ Usually happens after first surveillance visit following chemo or surgery
- ❖ If patient has not received his SCP, I will review and provide with a copy
 - ❖ Used to be a Word document that I wrote for each patient!
- ❖ History, PE
- ❖ Review diagnostics
- ❖ Side effect management
- ❖ Discussion of health maintenance issues and priorities
 - ❖ Exercise, balanced diet, substance use, sexual practices, body image concerns
 - ❖ Referrals as needed
- ❖ Assessment of any issues relating to uncertainty
 - ❖ Fear, anxiety, worry

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- ### Benefits
- ❖ Consistent, high quality expert care
 - ❖ Provision of care plans
 - ❖ Management of late and long-term SE
 - ❖ Counseling on general health promotion strategies
 - ❖ Coordination/communication of care among members of the health-care team
 - ❖ Continuity
 - ❖ Frees up MD schedules to see new patients or patients in active treatment
 - ❖ Helps meet need since shortage of oncologists
 - ❖ Fosters communication between NP and PCP
 - ❖ Sustainable and cost-effective

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Question 3



Testicular cancer survivors may have unique needs as compared to pediatric patients and older adults. What are some challenges that they may face?

1. Long-term effects of treatment on fertility
2. Difficulty discussing emotional aspects of their cancer experience given societal standards
3. Barriers to adhering to surveillance schedule due to relocation due to college graduation, marriage, military deployment, career moves, etc.
4. All of the above

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Summary

- ❖ Testicular cancer has an overall low incidence, but most common in ages 15-40
- ❖ Highly treatable and curable; but delay in treatment can decrease overall survival
- ❖ Treatment options depend on subtype and stage
- ❖ Toxicities can be immediate or long-term
- ❖ Post-treatment surveillance care should include all aspects components of survivorship care

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Resources for Patients

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