Cancer in Men

Bladder Cancer (because we had to put it in somewhere!), Prostate Cancer, Testicular Cancer

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Bladder Cancer

- Most frequent uroepithelial tumor
- About 75,000 cases per year and 15,000 deaths
- Male:Female ratio=3:1
- Most occur in patients between 50 and 80 years of age

Introduction

- Most common focus is on the posterior and lateral walls
- Field cancerization—the entire bladder is susceptible to toxin exposure and second primaries are frequent
- Risk of bladder cancer is 2-3 times as high in urbanites

Carcinogens and Bladder Cancer

- Increased incidence in smokers—most important risk factor in westernized countries; secondhand smoke implicated in women with bladder cancer as well
- Workers in rubber, leather, chemical materials, painters, textile workers, metal workers, and laboratory industries are at increased risk
- Chinese herbs—aristocholic acid causes urothelial cancers (component of Balkan nephropathy)
- *Schistosoma hematobium*—causes squamous carcinomas of the bladder

Pathology of Bladder Cancers

- Transitional cell carcinomas account for 90-95% of all bladder cancers diagnosed in North America
- Squamous carcinomas and adenocarcinomas account for the bulk of the remainder
- Leiomyosarcoma is rare, but does occur

Pathology of Bladder Cancers

- Low-grade: recurs after treatment, but rarely invades. Recurrence is common, but metastasis and death are rare
- High-grade: recurs after treatment and has a strong tendency to invade the muscular layer of the bladder and metastasize. Most deaths due to bladder cancer are of this type

Clinical Presentation

- Hematuria (often painless) is the presenting symptom in 70% of patients with bladder cancer
- Bladder irritability occurs in 25% of patients
- At the time they are diagnosed 70% are confined to the bladder and only 7% have clinical evidence of metastases
- Urinary obstructive symptoms may occur when tumors occur near the urethral ostium

Diagnosis

- Most often established by cystoscopic biopsy
- In high risk patients, urinary cytology may be an effective screening tool and is helpful for evaluating high grade in situ lesions
- Due to the high incidence of second primaries, visualization of the upper urothelial tract (by contrast urography) is REQUIRED

Staging

- Appropriate studies…
  - Cystoscopic examination of the bladder and biopsy with rectal (vaginal) exam under anesthesia
  - Contrast urography of the upper urinary tract
  - CXR
  - Baseline biochemical and hematologic studies
  - CT of abdomen/pelvis (to exclude local spread and nodal metastases)

Treatment of Carcinoma *In Situ*

- Frequently a multifocal disease
- Treatment is tailored to the individual
- Initially, many lesions may be managed by intravesical chemotherapy
- If voiding symptoms occur or invasiveness occurs (adverse prognostic signs) the patient is urged to undergo total cystectomy (almost 100% cure rate)
- Close follow-up is required

Treatment of Superficial Low Grade Lesions

- Best managed by transurethral surgery
- Tumor recurrence is the rule and multiple surgeries are the norm
- Total cystectomy for these lesions is rarely required
- Intravesical chemotherapy (thioTEPA, Adriamycin, mitomycin-C, bcg) is of value for patients with frequent recurrences and noninvasive disease

Treatment of High Grade High Stage (II or higher) Tumors

- Simple TURB is seldom adequate
- Resection of the involved bladder (segmental cystectomy) is an option to total cystectomy
- 5 year survival rate (Stage II,III) of about 25% with surgery alone
- Radiation not of benefit
- Some recommend adjuvant chemotherapy as for advanced disease

Treatment of Advanced Disease

- Surgical fulgration and resection for palliative benefit
- Radiation may be of use for local control and relief of urinary irritability in patients who are poor candidates for surgery
- Most patients are managed by combination chemotherapy for palliative intent

Chemotherapy for Bladder Cancer

- Single agents

Cisplatin/Carboplatin

Methotrexate

Adriamycin

Cyclophosphamide

Ifosfamide

Gemcitabine

Pemetrexed

Paclitaxel

Docetaxel

Mitomycin C

Vinca alkaloids

Ixabepilone

Chemotherapy for Bladder Cancer

- Combinations
  - Cisplatin combinations generally favored
  - GC (Gemcitabine, Cisplatin)
    - Less toxic than MVAC though equivalence to MVAC not established
  - MVAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin)
    - Given on a 28 day cycle
    - Response rate is 65% and duration of response averages 8 months
    - Reasonably toxic

Prostate Cancer

- Introduction
- Clinical Presentation
- Diagnosis
- Management of Disease by Stage

Introduction

- The most common cancer in men
  - Over 180,000 cases and 26,000 deaths per year
- Median age at onset—66 years, incidence increases exponentially after age 40
- 98% of all prostate cancers are adenocarcinomas, the remainder are sarcomas, transitional carcinomas, and small cell carcinomas
- Prostatic Intraepithelial Neoplasia (PIN)—the high grade form may be a precursor for adenocarcinoma

Etiology

- Cause is unknown
- Environmental factors appear to play a role (higher in Westernized society)
- Some familial clustering is found
- Autopsy studies have found occult prostate cancer in as much as 40% of males over 75 years of age

Clinical Presentation

- Most often asymptomatic, with a mass found on routine rectal exam
- Many present with obstructive uropathy, with carcinoma found on TURP specimen
- If widespread, many men complain of leg edema, leg pain and pelvic fullness from metastases to presacral and iliac lymph nodes
- Additionally, metastases to bone and lung may occur. Liver metastases are infrequent

Diagnosis of Prostate Cancer

- A biopsy of every suspicious prostate mass is essential
- Most biopsies are done as a transrectal approach with either direct palpation or guidance by ultrasound
  - 80-90% success rate
  - Complications (bleeding, abscess formation) are rare
- Limited role for tumor markers in diagnosis of cancer

Tumor Markers and Prostate Cancer

- Prostate specific antigen (PSA)—may be elevated in BPH and prostate cancer
  - Level may be increased slightly with manipulation of prostate
  - Progressive increases in serum levels of prostatectomized males appear to correlate with amount of tumor present
  - Free/Bound PSA and PSA velocity
    - Additional strategies to assist detection of disease at early stage

Staging of Prostate Cancer

- The standard evaluation for prostate carcinoma includes…
  - Physical/rectal exam
  - PSA
  - Chest x-ray
  - Prostate nodule biopsy
  - Bone scan
  - CT of pelvis helpful to assess nodal status

Tumor Grade and Staging

- The most favored histologic grading is Gleason score
  - Tumors are graded 1 (most like normal tissue) to 5 (anaplastic) in each of two features—nuclear differentiation and cellular composition
  - The two scores are added together to arrive at a final score

Tumor Grade and Staging

- The most favored histologic grading is Gleason score
  - Basically…
    - 2-4—well differentiated, closely resemble normal glands
    - 5-6—moderately well differentiated, some glandular appearance
    - 7—moderately poorly differentiated
    - 8-10—poorly differentiated

Treatment of Prostate Cancer

- General Principles
  - The roles of surgery and radiation are still not clearly defined
  - Significant overlap in treatment exists, and treatment for most men can be tailored to meet the needs of the individual
  - Treatment to maintain urinary patency is required
  - With current surgical practice, urinary continence is

Treatment of Stage I Disease

- Older patients may be managed by watchful waiting
- Patients over age 70 with histologically aggressive disease can be managed conservatively
  - Radiotherapy, brachytherapy (radioactive seed implantation)
- Younger patients usually considered for either RT or radical prostatectomy

Treatment of Stage II Disease

- Tailor treatment to the age and overall performance status of patient (watchful waiting is appropriate for older men with indolent tumor)
- Standard therapy is radical prostatectomy
- Patients with palpable (T_2) disease or with microscopically diffuse disease are at increased risk for metastases and lymphadenectomy is considered
- External beam XRT and brachytherapy effective and many studies show equivalent results to radical prostatectomy

Treatment of Stage III Disease

- Radical prostatectomy with lymphadenectomy and XRT are virtually identical
- Relapse rate is high in this group, but adjuvant chemotherapy not of proven value
- In some studies, hormonal therapy for 1-2 years may improve disease free interval

Treatment of Stage IV Disease

- Prostate tissue is hormonally receptive and therefore hormonal manipulation is recommended
- The use of LHRH agonists (leuprolide, goserelin) will reduce testosterone to near-castrate levels within 3 weeks of administration
- The addition of a testosterone-receptor blocking agent (flutamide, bicalutamide) further increases the efficacy of LHRH-A
- Surgery or XRT may still be needed for obstructive symptoms
- Bisphosphonates can minimize skeletal-related complications

Chemotherapy in Prostate Cancer

- Not used for patients other than Stage IV
- No standard therapy
- Active agents include…

Docetaxel	Paclitaxel	Vinca alkaloids
Abiraterone	Mitoxantrone	Estramustine
Cabazitaxel	Etoposide	Adriamycin
Gemicitabine	Cyclophosphamide	Sipuleucel-T

Germ Cell Tumors

- Introduction
- Clinical Presentation
- Pathology
- Diagnosis/Staging
- Treatment of Disease by Stage

Introduction

- Represent only about 1% of all male cancers (about 8700 per year)
- Most common solid tumor in males between ages 29 and 35
- Three peak age groups…
  - Infants—embryonal carcinoma and yolk sack tumors most common
  - Young adults—all types
  - Older adults—seminoma
- Strong association with cryptorchidism and testicular tumors
  Cause of germ cell tumors unknown

Clinical Presentation

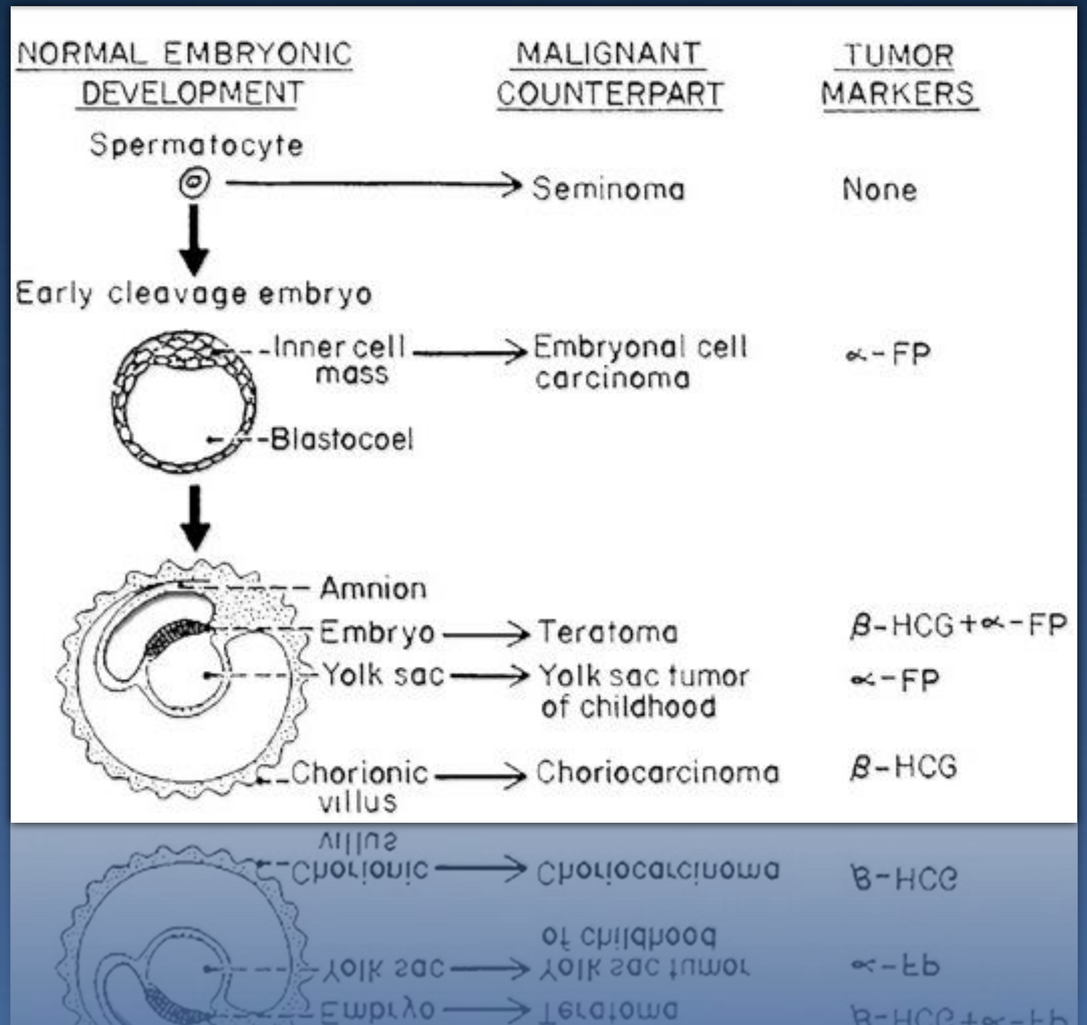
- Most complain of scrotal swelling, discomfort, or heaviness
- Pain reported <20% of the time—usually in the scrotum, but back pain from paraaortic node metastases can occur
- Gynecomastia—occurs 10-15% of the time
- Constitutional symptoms…
  - Fatigue, malaise
  - Weight loss
  - Fever

Pathology of Germ Cell Tumors

- For general purposes, germ cell tumors can be divided into two broad categories
  - Seminomas
  - Nonseminomatous germ cell tumors (NGCT)
- Additionally, germ cell tumors can occur in the testis (over 90%) or in primordial germ cell nests in the mediastinum or retroperitoneum which fail to regress in embryonic life (about 5%)

Pathology of Germ Cell Tumors

- Related to respective layers in embryo
- In nonseminomas, tumor marker can be somewhat specific



Seminoma Subtypes

- Classic—most common
- Anaplastic—present with a higher stage when diagnosed
  - 3 mitoses per high power field, very aggressive
  - Treat just like classic seminoma
- Spermatocytic—occurs universally in elderly men
  - Slow growing with excellent prognosis
  - Tends not to metastasize

Nonseminoma Subtypes

- Embryonal carcinoma—highly malignant, anaplastic tumor
- Teratoma
  - Mature—slow growing, least aggressive
  - Immature—more aggressive than the mature type
- Choriocarcinoma—rare, must have both cytotrophoblastic and syncytiotrophoblastic tissue for diagnosis, fairly aggressive
- Yolk sac tumor—very rare but very aggressive tumor

Clinical Course

- The natural history of germ cell tumors is metastases via the retroperitoneal lymph nodes
- Occasionally, hematogenous spread can occur
- These are highly treatable, mostly curable tumors!

Diagnosis and Staging

- Diagnosis depends on biopsy of suspicious testicular mass
- The correct procedure for testicular biopsy is delivery of the testis out of the scrotum—DO NOT DO A TRANSSCROTAL BIOPSY!
- Tumor markers (AFP, βHCG)
  - Often elevated in NGCT but NORMAL in seminoma
  - Levels directly reflect tumor bulk and are valuable in detecting disease recurrence
  - LDH
    - LDH-1 may be elevated in seminomas

Diagnosis and Staging

- Required procedures
  - Biopsy and histopathologic review
  - Chest x-ray
  - Tumor markers (βHCG, AFP)
  - CT of abdomen/pelvis for adenopathy
  - US of both testes (risk of contralateral disease is ~2%/year for the 15 years post-diagnosis)

Surgery for Germ Cell Tumors

- Radical orchiectomy—removal of affected testis and cord
  - Allows for determination of adverse prognostic factors (capsule invasion, direct extension to spermatic cord or vascular structures) and precise pathologic diagnosis
- Retroperitoneal lymph node dissection—gross exoneration of all paraaortic, iliac, and presacral lymph nodes
  - Morbidity—lymphedema, ileus, postoperative recovery

Radiation for Germ Cell Tumors

- Usually to the retroperitoneum
- Given for these reasons…
  - Retroperitoneal treatment in patients who are not surgical candidates
  - Residual masses after treatment for seminoma
  - As part of multimodal therapy

Chemotherapy for Germ Cell Tumors

- Cornerstone is a platinum-containing combination regimen
- Both seminomas and NGCT are responsive, usually curable diseases
- Treatment is aggressive and some morbidity occurs in about 75% of cases, mortality from treatment is rare
- Complications
  - Alopecia
  - Pancytopenia—fever, bleeding, anemia (RBC transfusions)
  - Nausea/vomiting—minimal to absent
  - Pulmonary fibrosis (bleomycin) or cardiomyopathy (Adriamycin)

Treatment of Seminomas

- Stage I—radical orchiectomy followed by active surveillance (preferred) or retroperitoneal radiation
- Stage II_A and II_B—radical orchiectomy followed by radiation; chemotherapy can be used if radiation inappropriate
- Stage II_C and C—radical orchiectomy followed by chemotherapy

Treatment of NGCT

- Stage I—radical orchiectomy followed by retroperitoneal node dissection, active surveillance of conscientious patients an option (no difference in survival)
- Stage II_A and II_B—radical orchiectomy with either retroperitoneal lymph node dissection and/or chemotherapy
- Stage II_C and III—radical orchiectomy and chemotherapy, surgery for debulking of residual tumor