BLADDER CANCER

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Disclosures

Nothing to disclose

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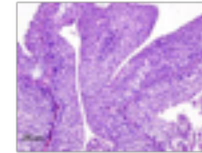
-Most common urinary malignancy
-Urothelial (previously transitional cell) most common histology



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Non urothelial bladder cancers <5%
-Squamous cell (Schistosomiasis - East Africa and Middle East)
-Adenocarcinoma
-Metastatic cancers

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Incidence and prevalence of urothelial carcinoma

-9th most common cancer in the world
-77,000 new cases, 16,000 deaths each year in US

-1985-2005 # of bladder cancers diagnosed in US increased 50%, while 5 year survival rate increased 75 to 81% 1975-1996

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-Median age of diagnosis 69 yo in men and 71 yo in women
-White males have highest risk
-Women and African American men present with more advanced disease

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Risk Factors

Environmental exposures
-Smoking
-Occupational
-Water contamination
-Water intake inversely proportionate to risk

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Smoking

-responsible for ~1/2 of urothelial carcinomas in men and women
->60 known carcinogens in cigarette smoke
-current smokers ~ 4 x more likely to have bladder cancer
-risk decreased to ~ 2 x in former smokers
-less risk with pipe or cigar smoking
->30 pk yr smoking higher risk of aggressive disease

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Risk Factors

-Chronic cystitis (increased squamous cell carcinoma)
-Upper tract cancers
-HPV
-Radiation
-Cyclophosphamide
-Aristocholic acid (Chinese herb)
-Phenacetin

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Risk Factors

TZD's (Thiazolidinediones)
-Pioglitazone (Actos) and rosiglitazone shown to increase risk of bladder cancer in a large UK cohort study
-More recent international study on exposure analysis of >1 million patients showed no increased risk

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Risk factors

Air pollution - conflicting results

Artificial sweeteners - large doses of saccharin induced bladder tumors in rats - extremely high level exposure in perinatal period

Hair dyes - exposure in hair stylists linked to increased risk - no increased risk seen in personal use

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Genetics

Carcinogenesis in urothelium - complex interaction of oncogenes, tumor suppressor genes, and over expression of normal growth factors

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Heredity

-Most studies show a small increased risk in relatives of those with bladder cancer - highest if affected relatives diagnosed < 60 yo

-Multiple genes thought to play a role - p53, RB

-Evidence that there are inherited differences in metabolism of toxins which increases bladder cancer risk

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Clinical presentation

Painless hematuria
-Microscopic 5% risk
-Gross 20% risk

Pain
-Either due to obstruction, locally advanced tumor, or metastases

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Clinical presentation

Irritative voiding symptoms ~1/3 of patients, especially CIS (carcinoma in-situ)

Obstructive voiding symptoms - less common, tumor location near bladder neck

Constitutional symptoms - weight loss, fatigue, anorexia signs of advanced disease

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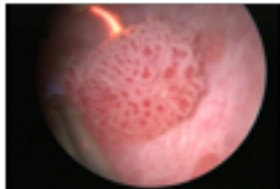
Work-up

UA, cytology, upper tract study, office cystoscopy



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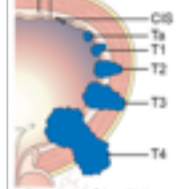

- Stage at initial presentation
- 75 % → Superficial or non muscle invasive
- 20 % → Invasive
- 5 % → Distant disease

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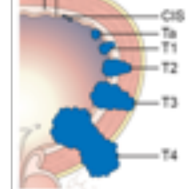

Non muscle invasive vs muscle invasive

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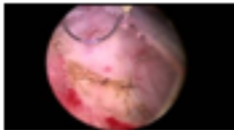
Initial treatment transurethral resection

-Need to ensure complete resection and muscular propria in specimen

-Repeat TUR in 6 weeks if high grade T1 (invading lamina propria) - ~30% initially under-staged



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Non muscle invasive

Prognostic factors

-Most important factors are histologic stage and grade

-40-80% non-muscle invasive bladder cancers recur

-25% progress to muscle invasive

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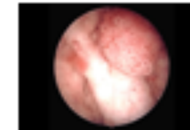
Non muscle invasive

Stage

Ta - confined to mucosa - often low grade and frequently recur multiple times prior to invasion - 6-28% risk of progression



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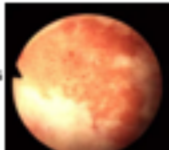
Non muscle invasive

Stage

T1 - invades into lamina propria - almost always high grade - 20-25% progress to muscle invasive

Tis - carcinoma in situ - high risk of progression - nearly 45% in some studies



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Non muscle invasive

Histologic grade

Low grade vs. High grade

Any high grade tumor at much higher risk for progression

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Non muscle invasive

Treatment

TUR + post operative instillation of mitomycin C

-allowed to dwell for 1 hour, may cause irritative symptoms

-nearly 20% decrease recurrence risk

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Non muscle invasive

High risk - CIS, high grade disease, T1, multiple, large > 3 cm low grade tumors

After TURBT and mitomycin C - treatment is intravesical BCG (Bacillus Calmette-Guerin)

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Intravesical BCG therapy

Live attenuated Mycobacterium bovis
-consistently decreases risk of recurrence and progression compared with chemotherapy when used for at least 1 year

Mechanism - triggers immune response which correlate with anti tumor activity

-most effective agent for non-muscle invasive bladder cancer

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BCG Schedule

-6 week induction cycle
-3 week maintenance cycles at 3, 6, 12, 18, 24, 30, 36 months for high risk disease

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BCG Complications

Large review of 585 patients toxicities included urinary frequency (71%), cystitis (67%), fever (25%), hematuria (23%)

-should not be given after traumatic cath, active cystitis, persistent gross hematuria after TURBT

-prosthetic devices not at increased risk

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BCG Complications

<5% serious complications but may include
-severe hematuria, granulomatous prostatitis, epididymitis, contracted bladder, and sepsis

-sepsis occurs now ~1 in 15,000 patients treated with BCG

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BCG Complications

-mild symptoms usually resolve in 48 hrs - if fever (esp >102.5) - initially treat with fluoroquinolone - if > 48 hrs, then worry for BCG sepsis

BCG sepsis - hospitalize with ID consult
-if disseminated infection outside of the bladder, need multi drug therapy 3-6 months (INH, rifampin, ethambutol)

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BCG Complications

Prevention - avoid with active UTI, traumatic cath, or persistent gross hematuria after TURBT - BCG should be delayed

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Other intravesical agents for non muscle invasive bladder cancer

-mitomycin C
-epirubicin
-gemcitabine
-interferon alpha
-thiotepa

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Experimental intravesical therapies

-Adenoviral interferon alpha-2b recombinant adenovirus vector

-Oportuzumab monitor -recombinant fusion protein

-BC-819 - DNA plasmid

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Non muscle invasive

Early cystectomy

-T1 with high risk features
-Large tumors unable to be completely resected with TUR
-Recurrent or persistent T1 tumors
-BCG refractory high grade disease

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Non muscle invasive bladder cancer

Post treatment surveillance cystoscopy

-Q3-6 mo for 1-2 yrs, and then annually
-Low risk tumors - may decrease frequency of surveillance

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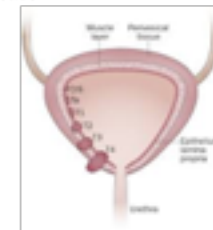
Muscle invasive bladder cancer
-T2, T3, T4 disease



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Muscle invasive bladder cancer

~~1/2 will develop metastatic disease in 2 years despite radical cystectomy (16,000 people die in US each year)

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Radical cystectomy gold standard treatment

-High morbidity (up to 60%) and mortality (up to 3%)

-Removal of the bladder, adjacent organs, regional lymph nodes

Involves urinary diversion

-ileal conduit

-orthotopic neobladder

-Continent catheterizable reservoir (Indiana pouch)

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Muscle invasive bladder cancer

Neoadjuvant chemotherapy results in lower risk of recurrence and improvement in survival

-Cisplatin based combination regimens

-Consistently demonstrates increased survival

-2009 study showed only ~ 20% patients received neoadjuvant chemotherapy

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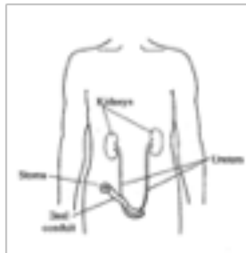
Ileal conduit



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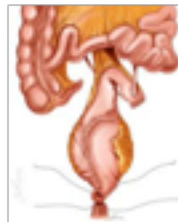
Orthotopic neobladder



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Continent catheterizable reservoir (Indiana pouch)

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Muscle invasive bladder cancer

Radiation therapy

-Lower survival rates than cystectomy - typically only used in poor surgical candidates

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Take home points

-Despite increased survival rates, 16,000 people still die in US each year

-Quit smoking

-High recurrence rates

-BCG effective

-Early cystectomy can save lives

-Vigilant surveillance

-Quit smoking

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Questions?