Transitional Cell Carcinoma:

After studying the summary of TCC the student should be able to:

1. State two risk factors that predispose some people to TCC of the bladder.
2. State two indications for radical cystectomy.
3. State the TNM staging system for transitional cell carcinoma of the bladder.

Introduction:

1. Bladder cancer is the second most common cancer of the genitourinary tract with a mean age of diagnosis of 65 years.
2. Transitional cell carcinoma (TCC) is the most common type of urothelial malignancy (>90%) although squamous cell carcinoma (5-7%) and adenocarcinoma (1%) are other malignancies derived from the transitional epithelium of the urinary tract.
3. TCC occurs most commonly in the bladder (85%) however, since transitional epithelium extends from the fornix of the renal calyx to the proximal urethra, it may also arise in the kidney, ureter, prostate or urethra. Patients with TCC are said to have a "field change" disease where the entire transitional epithelium is susceptible to malignant transformation. In other words, whatever carcinogen or inciting event that led to the development of the original TCC has also affected the entire urothelium and multifocal tumours at different locations are expected in the future.

TCC of the renal pelvis

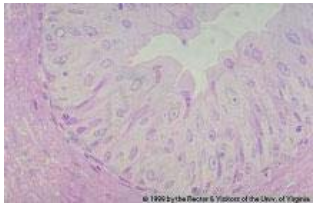
This section demonstrate some normal cortex, but the calyces show papillary tumor masses of transitional cell carcinoma that are invading the parenchyma.

Pathology:

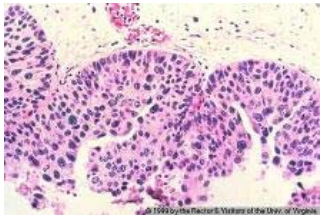
1. In general, TCC tends to behave in two distinct forms: low-grade, superficial tumours and high-grade, invasive tumours.
2. The male: female ratio is 3: 1 and the median age at diagnosis is 65 years for both sexes.
3. Risk factors:

A) Cigarette smoking (relative risk 4X that of non-smokers)
B) Occupational exposure to aniline dyes and aromatic amines (textile/apparel manufacturing, dry cleaning, painters, and leather tanning among a long list of "at-risk" -occupations).
C) Previous abdominal or pelvic irradiation (treatment of carcinoma of the cervix, for example)
D) Previous exposure to cyclophosphamide (particularly if cyclophosphamide-induced hemorrhagic cystitis developed).

Cystectomy section showing massive bladder tumour



Normal bladder urothelium



TCC -Microcopic pathology
Non-papillary carcinoma grade III. Note greater degree of nuclear

pleomorphism and presence of prominent nucleoli

Clinical Findings:

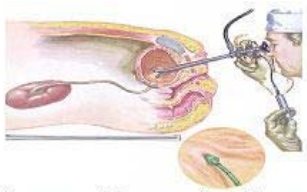
1. Bladder tumours are very unlikely to remain asymptomatic for long.
2. Gross, painless hematuria is the presenting symptom in 85% of cases. The bleeding is often intermittent therefore a thorough evaluation is mandatory even though the bleeding may have stopped by the time the patient seeks medical attention.
3. Occasionally, patients present with primarily irritative voiding symptoms (urgency, frequency, and dysuria) and these may be indicative of a diffuse carcinoma-in-situ or muscle invasive tumour.
4. Patients may present with hepatomegaly or lymphadenopathy if metastases are present.

Imaging and Investigations:

1. Initial evaluation follows the same investigations as outlined in the introduction for gross painless
hematuria:

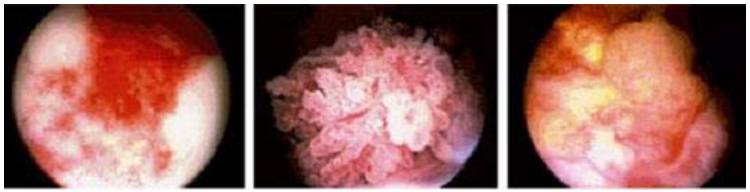
A) Urinalysis by microscopy including cytology and culture
B) Other laboratory tests include: WBC, hemoglobin, platelet count, creatinine, urea, INR, PTT.

2. Cystoscopy with bladder washings is the gold standard.



Cystoscopy with retrograde pyelogram

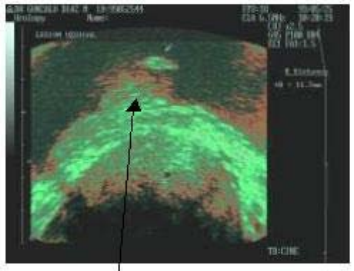
Cystoscopy showing papillary bladder tumour



Carcinoma in Situ, Ta Stage (grade 1-2) of Carcinoma of the Bladder, T1 Stage (grade 3) of Carcinoma of the Bladder

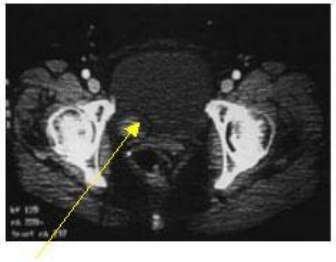
Three different stages of bladder carcinoma as seen by cystoscopy

3. If the abdominal ultrasound and cystoscopic examination are negative then an IVP, CT scan or, retrograde pyelogram are necessary to evaluate the ureters and renal pelvises.



US- TCC of the bladder

CT - TCC of the bladder



CT – Superficial TCC of the bladder

IVP – Superficial TCC of the bladder

4. If a bladder tumour is seen at the time of cystoscopy and bimanual examination of the pelvis suggests that it has not extended beyond the bladder then an attempt is made to completely resect the tumour transurethrally.

· The transurethral resection requires a general or spinal anaesthetic and the patient often spends at least one night in hospital. Very small tumours may be resected with IV sedation and the patient discharged the same day.
· The resection should include the tumour and a portion of the underlying detrusor muscle to allow for staging of the tumour.

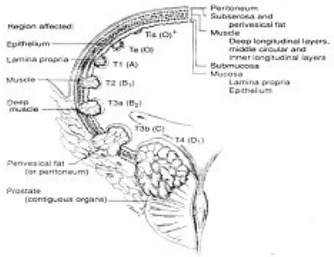
5. If the tumour has clearly extended beyond the bladder at the time of

cystoscopy, then the tumour is biopsied and a thorough metastatic evaluation is carried out before planning any further treatment.

TNM Staging of TCC of the Bladder
Tis carcinoma-in-situ; a flat, diffuse, high-grade malignancy confined to the epithelium (i.e.: non-invasive)
Ta non-invasive papillary tumour
T1 invasion into lamina propria
T2 invasion into superficial detrusor muscle
T3a invasion into deep detrusor muscle
T3b invasion into perivesical fat
T4 invasion into adjacent structures such as prostate, rectum, vagina or pelvic sidewall

N1 microscopic involvement of regional lymph node(s)
N2 gross involvement of regional lymph node(s)

M1 Distant metastases



Staging of bladder cancers

Treatment:

Cancer Stage	Initial Treatment Options
Superficial disease (Tis, Ta, T1)	TUR +/- intravesicle chemo- or immuno-therapy (eg. BCG, thiotepa, mitomycin C) adjuvantly to decrease recurrent rate
Invasive disease (T2a, T2b, T3)	Radical cystectomy + pelvic lymphadenectomy with urinary diversion and/or irradiation
Advanced/metastatic disease (T4a, T4b, N+, M+)	Initial systemic chemotherapy +/- selective surgery or irradiation

*TUR=Transurethral resec

Transurethral resection of t

1. Approximately 70% of all bladder tumours will be superficial at presentation, 2
cases will be muscle-invasive and 5% will be locally advanced or metastatic.
2. As mentioned previously, a "field change" disease is present and the tumours te
multifocal at presentation or recur at other sites after surgical excision. A thorougl
cystoscopic and radiologic examination of the entire urinary tract is required wher
bladder tumour is discovered to make sure there are no other tumours elsewhere.
3. After "curative" treatment for a bladder tumour, the patient must return for regular cy
and radiologic examinations to make sure no recurrence has developed. These regular
examinations should be performed for the rest of the patient's lifetime.

Additional Treatment Information

1. Treatment of superficial (stage Ta) tumours consists of transurethral resection of all v
tumours. If the histology shows a low-grade tumour then regular follow-up examination
is required. The patient is encouraged to stop smoking. Intravesical chemotherapy may l
considered for stage Ta tumours that are multifocal at presentation, recur rapidly or can
completely resected transurethrally. The chemotherapy is instilled via Foley catheter, all
remain in the bladder for a period of time then voided out. A variety of agents have bee
treat superficial bladder cancers; the most commonly used are BCG (Bacille Calmette-C
Thiotepa, mitomycin, doxorubicin and epirubicin. Carcinoma-in -situ (CIS) and stage T
are potentially aggressive malignancies and should be treated aggressively. Following
transurethral resection, intravesical treatments with BCG are started and continued wee
weeks. If any residual cancer remains then these patients should be treated with radical
cystectomy and urinary diversion. If the cancer is gone by 6 weeks but returns later, ano
course of BCG may be offered. Approximately 25% of patients with CIS will ultimately
cystectomy. BCG is the most effective of all the intravesical agents at preventing recurr
treating any residual cancer. BCG is a live, attenuated strain of mycobacterium bovis an

potentially cause a systemic mycobacterial infection if it enters the blood stream. The anti-tumour effect is thought to occur through a non-specific immune response to mycobacterium in the bladder that enhances the anti-tumour response of the immune system (local production of INF? enhancing NK cell mediated tumour cell killing).

2. Radical cystectomy is indicated in cases of muscle-invasive TCC or in refractory cases of CIS or superficial tumours. A careful metastatic evaluation is done before surgery to rule out patients with metastatic disease. In men, the operation is properly termed a radical cystoprostatectomy with pelvic lymph node dissection. The anterior urethra is also removed (leaving the penis and cavernosal bodies intact) in cases of CIS or TCC that involves the prostate. In women, the operation is usually an anterior exenteration (radical cystectomy with hysterectomy, bilateral salpingo-oophroectomy and resection of the anterior wall of the vagina. With cystectomy, the urine is diverted into an ileal conduit or a continent urinary reservoir constructed with a segment of bowel. The 5-year survival rates for stage T2, T3a and T3b are approximately 80%, 70% and 50% respectively.

3. TCC in the renal pelvis or ureter is rare compared to TCC in the bladder. The epidemiologic risk factors for upper tract TCC (primarily smoking and occupational exposures) are the same as TCC of the bladder with one notable exception. There is a strong association between Balkan nephropathy (interstitial nephritis endemic to certain Balkan regions in Eastern Europe). Individuals with Balkan nephropathy have a relative risk 100X greater than normal of forming upper tract TCC. Gross hematuria is the most common presenting symptom but upper tract TCC may also be discovered "incidentally" during evaluation of a patient with a bladder tumour. The diagnosis is strongly suspected when a "filling defect" is seen within the collecting system on an IVP or retrograde pyelogram. Aggressive, infiltrating TCC of the renal pelvis or calyx may resemble a renal cell carcinoma on ultrasound or CT scan. The operation for upper tract TCC with a normal contralateral kidney/ureter is a radical nephroureterectomy where the entire kidney, ureter and a small cuff of bladder (to include the ureteral orifice) are removed. Segmental resection of the ureter with reimplantaion may be considered for small, low-grade TCC of the distal ureter. The 5 year disease-specific survival for superficial upper tract TCC is over 90% following surgical excision. If the TCC has invaded into the peri-ureteral fat or renal parenchyma the 5 year disease-specific survival falls to 20% - 40%.

Retrograde pyelogram with TCC of the upper tracts

- If the opposite kidney is normal and there is no metastatic disease then treatment is a <u>radical nephrectomy</u>

4. Patients with metastatic TCC or locally-advanced unresectable TCC may receive chemotherapy however complete response rates are low. The chemotherapy most often used is M-VAC (methotrexate, vinblastine, adriamycin and cisplatin), which has objective partial response rates of approximately 50% - 70%. For patients with metastatic disease, M-VAC treatment has a 2 year survival of approximately 15% - 20%. This "complete response" of 15% - 20% is not always durable and there are few long-term survivors of metastatic TCC.

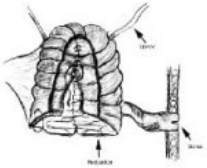
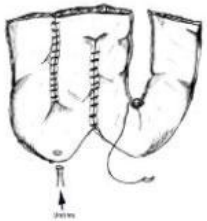
Urinary Diversion – Ileal conduit

<u>Pro</u>
- simplest to create
- lowest risk of metabolic complications
- lowest risk of surgical complications

<u>Con</u>
- abdominal stoma
- no continence (collection bag)

Urinary Diversion – Indiana pouch

- Continent but must use catheter
- Abdominal stoma but no collection bag
- Higher risk of metabolic complications



- Continent but must do self catherization
- No abdominal stoma
- Highest risk of metabolic and surgical complications
- Cannot be done if urethrectomy required