CHAPTER
15 Tumors of the Urinary System

ADULT RENAL TUMORS

RENAL CARCINOMA

Incidence

Renal carcinoma accounts for about 1% of all cancers. The median age is 55 years and male predominance is 2:1.

Etiology

Renal cell carcinoma is related to chemical exposure, hereditary diseases or renal cysts. Carcinogenic exposure includes tobacco smoking and industrial chemicals. Hereditary predisposition includes Von-Hippel-Lindu syndrome (50%) and tuberous sclerosis. Both congenital polycystic kidney and dialysis acquired cysts are high-risk lesions.

The most common type (70%), or clear cell carcinoma, arises from proximal nephron (proximal convoluted tubules). This is associated with deletion of 3p 13 (VHL gene). Carcinomas which arise from the distal nephron have a different pattern of chromosomal abnormalities. Thus, papillary tumors exhibit trisomy of chromosomes 7 and 17 (MET gene); and chromophobe cell carcinoma shows, in addition, trisomy of chromosome 16 and loss of Y chromosome.

Molecular oncogenesis

The VHL protein normally binds with HIF-A (hypoxia-inducible factor-α subunit), resulting in degradation of the latter. With deletion of chromosome 3p, VHL protein is lost and HIF-A accumulates, resulting in activation of a variety of hypoxia-inducible genes and hence increased production of angiogenic and proliferative growth factors (e.g. VEGF, PDGF, TGF-α and EGFR). In addition, expression of metalloproteinases also occurs, resulting in matrix degradation and hence promoting metastasis. These molecular changes may be used in targeted therapy (e.g. tyrosine kinase inhibitors and monoclonal antibodies).

Macroscopy

The classic renal cell carcinoma (clear cell type) appears golden yellow in color, rounded, and cortical in location at one pole of the kidney (P 15-1, P 15-2). There is often focal hemorrhage and necrosis. Papillary carcinoma may be solid or cystic (P 15-3). Chromophobe cell type is characteristically brownish or grey-beige in color. Oncocytoma is typically mahogany brown in color with central stellate scar (P 15-4). Four gross types are recognized in renal carcinomas: solid, intracystic, multiple (5%) and bilateral (1%).

Histopathology

Renal cell carcinomas are classified according to their histogenetic origin into *proximal* nephron and *distal* nephron tumors (Table 15-1). The subgroups show significant prognostic and biologic differences. With the exception of Billini duct carcinoma, tumors of distal nephrons are associated with more favorable prognosis. Cytogenetically, clear cell carcinoma of the proximal nephron is characterized by deletion of 3p 13, whereas, tumors of distal nephron show different multiple chromosomal abnormalities (loss of Y chromosome and trisomy of 16, 17 and 7). The immunohistochemistry is also different. Thus, clear cell carcinoma is positive for both cytokeratin and vimentin, but, tumors of the distal nephron are positive for cytokeratin and negative for vimentin.

1. Clear cell carcinoma (70%) shows a trabecular or acinar pattern with intervening sinuses (P 15-5). The clear cytoplasm is due to fat and glycogen content. The nuclei are centrally located. Tumors

Table 15-1 Classification of Adult Renal Cell Carcinoma

Proximal Nephron		
Renal cell carcinoma		(82%)
Clear cell	70%	
Granular cell	10%	
Spindle cell	2%	
Distal Nephron		(18%)
Papillary carcinoma	10%	
Chromophobe cell type	5%	
Oncocytoma	2%	
Bellini duct carcinoma	1%	

are graded into 4 grades according to nuclear morphology (Fuhrman, 1982). In 10% of cases, the cytoplasm appears granular (P 15-6) and in 2% of tumors the cells appear spindle shaped or sarcomatoid (P 15-7). These two variants are more unfavorable than the clear cell type. Electron microscopy shows cytoplasmic inclusions (P 15-8).

2. Papillary carcinoma. (10%) most commonly complicates hemodialysis and exhibits a prominent papillary pattern (P15-9).

3. Chromophobe cell carcinoma (5%) is a special entity characterized by flocculent cytoplasm, perinuclear vacuoles, low cytoplasmic glycogen and high acid mucin content (positive Hale colloidal iron), cytokeratin positive and vimentin negative, and shows cell nesting or alveolar pattern (P 15-10). Electron microscopic studies (P 15-11) demonstrate microvesicles in the cytoplasm and cytogenetically, there are multiple chromosomal losses.

4. Oncocytomas (2%) are composed of cells with abundant eosinophilic granular cytoplasm. The nuclei are small rounded and regular (P 15-12). Electron-microscopy reveals abundant mitochondria in the cytoplasm (P 15-13). At present, oncocytoma is considered a benign tumor despite its local destructive effect to the kidney.

5. Collecting duct carcinoma of Bellini (1%) arises in the medulla and shows cuboidal cells with tubulopapillary pattern and desmoplastic stroma (P 15-14)

Immunohistochemistry

This is valuable in the differential diagnosis from other clear cell carcinomas. Characteristic of renal cell carcinoma is the coexpression of keratin 8 and 18, vimentin and CD10. Adrenal cell carcinoma is positive for inhibin and calretinin. Ovarian clear cell carcinoma is positive for cytokeratin 7 and CA-125.

Differential Diagnosis

1. Renal cell adenoma: strict criteria must be adhered to in the diagnosis of this rare tumor. A renal cell adenoma is of microscopic size (<5 mm), papillary pattern, nonclear scanty cytoplasm and noninvasive (P 15-15).

2. Juxtaglomerular cell tumor: This is also a rare benign renin-secreting tumor manifested by hypertension (P 15-16). Electron microscopy shows both rounded granules, as well as, rhomboid crystals of renin (P 15-17).

3. Xanthogranulomatous pyelonephritis which is rich in clear histiocytic cells may be misdiagnosed as clear cell renal cell carcinoma. However, the histiocytes are CD68 positive, associated with other inflammatory cells and lack the trabecular vascular pattern of renal cell carcinoma (P 15-18).

4. Renal cystic nephroma: this a duct tumor may be confused with cystic renal cell carcinoma, but, cystic nephroma cysts are lined by a single layer of hobnail epithelium (P 15-19).

5. Angiomyolipoma will appear by CT as a mass lesion in the kidney simulating renal cell carcinoma. Preoperative diagnosis is only possible if the renal tumor is associated with cutaneous lesions of tuberous sclerosis (only 25% of cases). Angiomyolipoma is a benign mesenchymal triphasic tumor composed of vascular, smooth muscle and fat cells (P 15-20).

Systemic Manifestations

Several paraneoplastic syndromes may be associated with renal cell carcinoma, including: anemia (21%), polycythemia, leukemoid reaction, fever, amyloidosis, hypercalcemia, hypertension, gynecomastia and Cushing's syndrome.

Spread

1. Local spread with invasion of perinephric fat (30%), Gerota's fascia, renal vein (10%) or adjacent organs, such as: adrenal, colon, pancreas, duodenum and retroperitoneum.

2. Lymph spread (30%) to hilar and periaortic lymph nodes.

3. Hematogenous spread to the lungs, bone and several unusual sites (often solitary).

4. Transperitoneal spread.

Prognosis

The prognostic factors of renal cancer, arranged in descending order of importance, are: tumor stage, nuclear grade, histologic type and aneuploidy (Thrasher, 1993). The histologic type and aneuploidy are dependent variables influenced by nuclear grade.

1.Tumor stage: The two most commonly used staging systems for renal cell carcinoma are the Robson classification (Fig 15-1) and the UICC (TNM) classification (Table 15-2). The former is more practical and the latter gives more details on lymph node status and tumor size. Stages I and II have a significantly better survival rate than those with locally invasive or metastatic tumors (Table 15-3). Renal vein invasion does not confer an additional adverse effect on survival provided it is

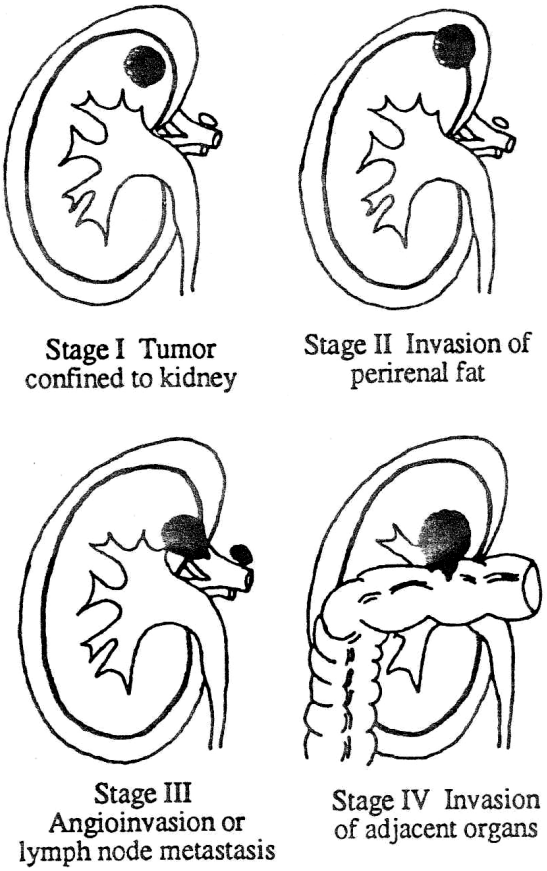

Fig 15-1 *Staging of renal carcinoma (Robson, 1969).*

Table 15-2 Staging of Renal Cell Carcinoma

	Stage	**5-year Survival %**
I	Confined to kidney	70
II	Spread to perinephric fat but within Gerota fascia	60
IIIa	Renal vein of vena cava invasion	40
IIIb	Lymph node metastasis	
IV	Extension to adjacent organs or distant metastases	10

(Robson, 1969)

Table 15-3 TNM Stages of Renal Carcinoma

Stage	
I	Confined to kidney (<7 cm), N0 M0
II	Confined to kidney (>7 cm), N0 M0
III	Single nodal metastases, or invasion of major veins, adrenal or perinephric fat but within Gerota fascia
IV	Tumors invading beyond Gerota fascia, and / or >1 lymph node metastases or distant metastases

associated with organ confined tumor and as long as the tumor thrombus can be removed completely. However, lymph node status has a significant unfavorable impact on prognosis; with 10-year survival of 62% in node negative patients, versus 8% in node positive patients.

2. Nuclear grade: This is a strong and independent predictor of survival. Fuhrman (1982) developed a grading system based on nuclear morphology, classifying renal tumors into four grades (Table 15-4). Three survival groups were identified, namely: those with a favorable prognosis (grade 1), those with dismal prognosis (grade 4), and a large group with an intermediate survival (grade 2 and 3).

3. Histologic type: The 5-year survival is 92% with chromophobe cell type, 62% with clear cell type and 46% with granular cell type. However, the relation of cell type to prognosis is determined largely by nuclear grade.

4. DNA ploidy: Univariate analysis revealed that DNA ploidy correlates with tumor progression and survival. Thus, patients with diploid tumors have a 10-year survival of 62%, versus, 37% for aneuploidy tumors.

Table 15-4 Nuclear Grade and Prognosis of Renal Cell Carcinoma

Grade		5-year Survival %
I	Small uniform nuclei	62
II	Intermediate-size nuclei with small nucleoli	32
III	Large nuclei, prominent nucleoli	30
IV	Large pleomorphic multilobed nuclei	10

RENAL PELVIS AND URETER CARCINOMAS

The majority of tumors are transitional cell carcinoma similar in etiology to bladder cancer (tobacco smoking, industrial exposure, phenacetin and calculi). Nearly 50% of patients have history of urothelial carcinomas of the urinary bladder or ureter, or later develop these additional tumors (P 15-21 to P 15-24). About 10% of cases are squamous cell carcinomas which are often associated with calculi or chronic infections. Approximately 75% of patients have tumors of low grade and stage. Overall, the 5-year survival rate is about 60%.

PEDIATRIC RENAL TUMORS

NEPHROBLASTOMA (WILMS TUMOR)

Incidence

Seven per million children under the age of 16 years are affected by Wilms tumor per year. It represents 8% of all childhood cancers (Children Cancer Registry UK) with a sex ratio of 1:1 and a median age of 2.5 years, but younger in bilateral cases. It is extremely rare in the first neonatal year. It ranks the fifth amongst all childhood cancers.

The clinical types are: sporadic (98.5%) and familial (1.5%). Bilaterality is 3% in sporadic cases and 20% in familial cases and occurs one year younger in the latter.

Pathogenesis

Ten percent of sporadic Wilms tumors are associated with deletion of WT1 tumor suppressor gene located at chromosome 11 p13. These cases are commonly associated with aniridia, hemihypertrophy and malformations of genitalia due to the presence of the closely linked genetic loci WAGR complex (W-Wilms, A-aniridia, G-genitourinary malformations, R-mental retardation) with variable expression depending on length of deleted segment.

Another deletion at 11pl5.5 (WT2 tumor suppressor gene) is associated with the Beckwith-Wiedemann syndrome (BWS) which presents with macroglosia, somatic gigantism, abdominal wall defects and hypoglycemia.

Recent molecular and cytogenetic findings lend support to a two stage mutational model (double-hit model of Knudson) for origin of Wilms tumor: the first is either a germ cell or somatic cell mutation (e.g. deletion of WT1 or WT2 tumor suppressor genes) and me second event is always postnatal (somatic).

Precursor lesions are metanephric embryonic cell remnants which are encountered in the renal parenchyma of about 30% of patients with Wilm's tumor.

Macroscopy

Although most Wilms tumors are unicentric tumors, yet a substantial number of cases arise multifocally in the kidney. Of 1905 cases of national study (NWTS) 103 (5.4%) involved both kidneys and an additional 133 cases (7%) were multicentric unilateral tumors. MRI may help differentiate nephrogenic rests from bilateral Wilms tumor. Extrarenal Wilms tumors are rare and occur mostly in retroperitoneal sites adjacent to kidney. It is also seen in the pelvis or inguinal region.

Most Wilms tumors have a uniform pale gray color (P 15-25). Hemorrhage and necrosis may impart a variegated appearance. Cysts are commonly encountered and the tumor usually appears as a sharply demarcated relatively spherical mass with pseudocapsule.

Histology

Classic triphasic pattern includes: neoplastic blastemal, epithelial (including tubular and glomeruloid structures) and stromal cells (Fig 15-2 and P 15-26). If the ratio of length to diameter of nuclei is over 3:1 the cells are classified as

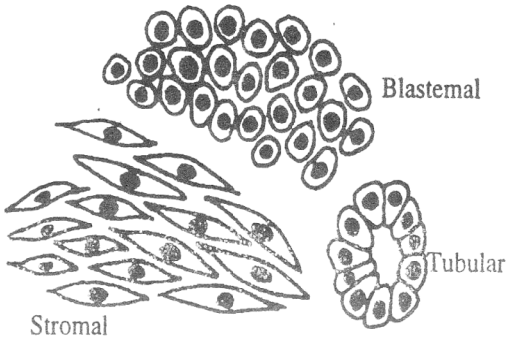

Fig 15-2 *The triphasic histologic structure of nephroblastoma*

Table 15-5 National Wilms Tumor Staging System (NWTS)

I	Tumor limited to kidney, completely excised
II	Tumor extends beyond Kidney, completely excised
III	Residual local tumor confined to abdomen
IV	Hematogenous metastases
V	Bilateral renal tumors at presentation

N.B. Stages are subclassified according to the presence or absence of anaplasia

stromal.

Usually these elements seem to recapitulate various stages of normal renal embryogenesis, but heterotopic cell types (e.g. muscle) are commonly observed. Biphasic patterns are common (e.g. blastemal and stromal cells) and some specimens consist predominantly or exclusively of one cell type.

Immunohistochemical studies

These are primarily of use in ruling out other primitive childhood tumors (e.g. neuroblastoma) especially in small biopsies or extremely undifferentiated tumors.

Spread and staging

The lungs are the most common site for metastasis. Wilms tumor is staged according to the NWTS system (Table 15-5) with indication of stage and histologic category.

Prognosis

About 90% of patients are now cured after recent combined modality therapy. The most important prognostic factors are tumor anaplasia and stage. Tumors with extreme nuclear atypia (anaplasia) are associated with a high rate of relapse and death in 57% of cases (Beckwith, 1978). Anaplasia is recognized by: (1) obvious hyperdiploid mitotic figures, (2) three- fold or greater nuclear enlargement, and (3) hyperchromasia (P 15-26). Anaplastic tumors constitute about 4.5% of cases and are rare below 2 years of age.

OTHER PEDIATRIC SARCOMAS

Three rare sarcomas may arise in the kidney during the first year of life, an age group not affected by Wilms tumor.

1. Mesoblastic nephroma (P 15-27) is a congenital tumor contributing 5% of pediatric renal tumors. It is composed of fibromatosis-like spindle cells, entrapping islands of dysplastic renal tissue. The majority have a favorable prognosis, but 7% metastasize.

2. Clear cell sarcoma (4%) is a malignant tumor composed of clear cells with alveolar pattern in a fibrotic stroma (P 15-28). It has a marked tendency to skeletal metastases.

3. Rhabdoid tumor (2%) is a malignant tumor of unknown histogenesis located in renal medulla. The cells are oval with eccentric nuclei, prominent nucleoli and hyaline cytoplasm rhabdomyoblast-like (P 15-29 and P 15-30). The one year survival is only 25%.

Differential Diagnosis

1. Metanephric adenoma is highly cellular epithelial tumor composed of small cells with tubular pattern (P15-31) which may show psammoma bodies. In adenofibroma a stromal component is evident (P 15 -32).

2. Nephorgenic rests are microscopic foci of persistent embryonic cells that are capable of developing into nephroblastoma (P 15-33). They may exist as multiple foci, termed nephroblastomatosis.

3. Renal dysplasia is a common cause of renal mass in the first year of lefe. Histologically, it is composed of a complex malformation of renal tissue (P 15-34).

4. Infantile polycystic kidney (P 15-35) presents as a renal mass which may be confused with nephroblastoma.

BLADDER CARCINOMA, WESTERN TYPE

THE GLOBAL EXPERIENCE

Incidence

Urinary bladder cancer ranks the ninth in world wide cancer incidence (Ploeget al, 2009). Incidence rates are highest in developed countries (3 to 4 times developing countries). The incidence rate in USA males is 20/100,000 and one in 25 men and one in 80 women will be diagnosed with bladder cancer some time in life. Moreover, the incidence is increasing due increase of cigarette smoking and aging of population. The relative frequency to other cancers is about 4%. The median age is 65 years and male predominance 3:1.

Etiology

The etiologic factors include exposure to bladder carcinogens or the presence of chronic bladder disease. (1) *Bladder carcinogens:* cigarette smoking is estimated to contribute about 60% of cases, whereas, industrial exposure is related to 30% of cases, mainly due to exposure to 2-naphthylamine in textile and rubber industries. Other chemical exposures include drugs (e.g. phenacetin and cyclophosphamide), and drinking water contaminated with arsenic or pesticides. (2) *Bladder disease* includes lithiasis, chronic cystitis and bilharziasis. Bladder cancer associated with bilharziasis will be separately discussed since it represents a distinct clinicopathologic entity.

Molecular Oncogenesis

There are two main pathways of bladder oncogenesis depending upon histologic type and grade (Fig 15-3):

1. The first pathway leads to a low grade transitional neoplasm, which is genomically stable and rarely metastasizing. There is activation mutation of FGFR-3 and deletions of chromosome 9p and 9q which contain genes that negatively regulate the cell cycle (CDKN2-A and CDKN2-B respectively).

2. The second pathway is operable in carcinoma in situ (C1S), high grade transitional carcinoma and squamous cell carcinoma. These are genomically unstable, muscle invasive and metastasizing tumors. Oncogenesis involves inactivation of several tumor suppressor genes, namely: TP53 (loss of chromosome 17), RB gene, PTEN and p16. There is more also frequent 9p chromosomal loss. In case of squamous cell carcinoma, the urothelial stem cell undergoes initial squamous metaplasia (transdifferentiation) to produce the squamous phenotype.

In this model, low-grade transitional tumors may undergo progression to high-grade types with rates of 3% in Ta and 10% in T1 tumors (Fig 15-3).

Macroscopy

Grossly, 67% of tumors arise from the upper bladder hemisphere (posterior and lateral walls) and 33% are basal in location. The carcinomas may be exophytic (projecting into the lumen), endophytic (invading bladder wall), or combined exo-endophytic. Exophytic tumors include three gross types: papillary, nodular and verrucous (P 15 -36 to P 15-38). Endophytic tumors may be ulcerative or diffuse (P 15-39). Gross multiple tumors are not uncommon (P 15-40).

Precursor lesions

These urothelial changes are classified by WHO and international Society of Urologic Pathologists (WHO/ISUR, 1998) into the following five groups:

1. Simple metaplasia (trans differentiation): This represents a change of the normal transitional urothelium to another mature type, squamous (P 15-41) or glandular type (P 15-42 and P 15-43).

2. Reactive atypia (hyperplasia): This describes an increase in epithelial cell layers beyond the normal 6 layers. It is usually a reversible reaction to injury, inflammation or irradiation.

3. Atypia of unknown significance: The term is applied when it a difficult to categorize the lesion as reactive or dysplastic.

4. Dysplasia: This includes moderate cellular atypia short of frank malignancy (P 15-44) and is associated with a progression rate of about 15%, Progression, as a urologic term, denotes the risk of a tumor to invade muscularis propria and hence develop metastases.

5. Carcinoma in situ, CIS (including marked dysplasia): This is a high-risk lesion, composed of anaplastic cells similar to those of invasive

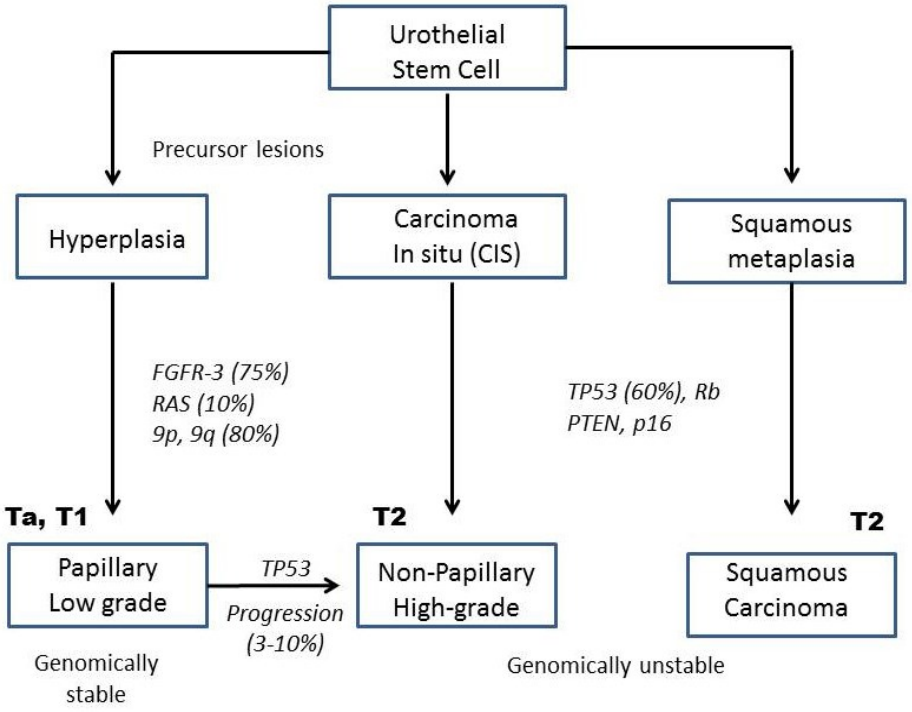

Fig 15-3 *Molecular oncogenesis model of bladder carcinomas and their precursor lesions. Two main pathways leads to either genomically stable tumors (papillary, low-grade) or genomically unstable tumors (non-papillary high grade and squamous carcinomas). Squamous carcinoma requires squamous transdifferentiation (metaplasia) of urothelial stem cells. Progression of papillary tumors to muscle invasive tumors occurs in 3% of Ta, 10% in TI (Adapted from Goebbels, 2010 and Metra et al, 2006).*

carcinoma, but, not invading the basement membrane. Carcinoma in situ may be composed of small or large cells, may affect urothelium focally or diffusely, and it may be primary (de novo) in 2% of cases, or arise in association with two thirds of invasive transitional carcinoma. Four histologic variants of CIS are described (Fig 15-4, P 15-45 to 15-48). The progression rate of CIS is about 50%.

Immunohistochemistry is useful in the differential diagnosis of CIS and reactive atypia. Thus, CIS is P53+, CK20+, high Ki-67 index and CD44-, whereas, reactive atypia is P53-, CK20-, has low Ki-67 index and CD44+.

Intravesical BCG immunotherapy is an effective treatment for CIS and will cure 50% of patients in 5 years and 30% in 10 years (Wein, 2012). The therapeutic effect requires several months to be completed. Any residual CIS after 6 months, detected by cytology or biopsy, is considered BCG failure and calls for a timely cystectomy.

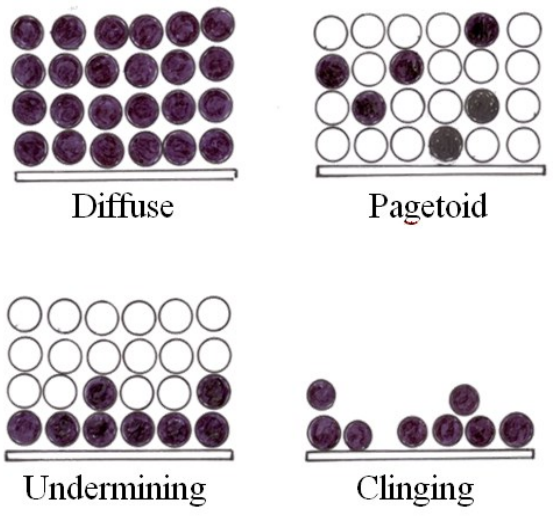

Fig 15-4 *The four main patterns of carcinoma in situ of urinary bladder. (A) Diffuse type, malignant cells (black circles) diffusely affects the entire thickness of urothelium, (B) Pagetoid pattern, malignant cells are randomly distributed among normal cells, (C) Undermining type, malignant cells are basal in location and (D) Clinging type, few remaining malignant cells attached to basement membrane.*

Histopathologic types

The relative frequency of bladder tumors, classified according to WHO, is presented in (Table 15-6). Papilloma, inverted papilloma (P 15-49) and villous adenoma are rare benign tumors which are recurrent but non-metastasizing. Four main malignant subtypes are recognized:

1. Transitional neoplasms: The term urothelial tumors is preferred by WHO. It includes several variants of different biologic potential: (a) *papillary transitional neoplasm of low malignant potential* is a solitary, well-differentiated, papillary non-invasive tumor (Ta). It resembles a papilloma, but the epithelial thickening exceeds the normal 6 layers (P 15-50). *Conventional transitional carcinoma* exhibits cellular anaplasia of variable degree (P 15-51 to P 15-53). They are best classified according to their growth patterns into papillary and nonpapillary (Fig 15-5 and Table 15-7). The latter is a more aggressive high-grade tumor with more tendency to muscle invasion (T2). *Unusual variants* of urothelial carcinomas are recognized. These include: urothelial carcinoma clear cell type, urothelial carcinoma with ectopic placental glycoprotein production, plasmacytoid variant, lipid cell variant, micropapillary variant, nested or deceptively benign variant, microcystic variant and osteoclastic variant. High grade transitional carcinoma may also show marked lymphatic permeation (P 15-55).

Table 15-6 Relative Frequency of Bladder Tumors (Western Series)

Benign	**2%**
Papilloma	
Inverted papilloma	
Villous adenoma	
Malignant	
Transitional carcinoma	90%
Papillary	
Non papillary	
Squamous carcinoma	5%
Conventional	
Verrucous	
Verrucoid	
Adenocarcinoma	2%
Gland forming	
Mucinous	
Signet-ring	
Clear cell (mesonephric)	
Urachal	
Undifferentiated	1%

(Eble, 2004; Wein, 2012 and Feig, 2012)

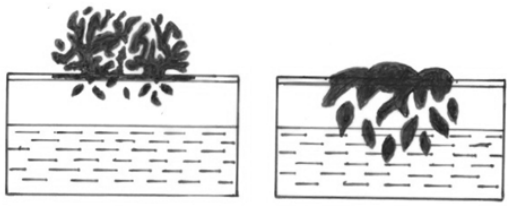

Fig 15-5 *Growth patterns of transitional cell carcinoma. The nonpapillary pattern in more aggressive*

2. Squamous cell carcinoma: Histologically, squamous cell carcinoma exhibits squamous differentiation throughout all parts of the tumor with obvious keratin formation. Three histologic variants are recognized, namely: (a) *conventional* squamous cell carcinoma, a potentially aggressive tumor capable of producing metastases (P 15-56 and P 15-57), (b) *verrucous* carcinoma, a favorable histologic subtype, recurrent but non-metastasizing with characteristic filamentous pattern (P 15-58) and (c) *verrucoid* carcinoma which combines the histology of both conventional and verrucous carcinoma, but exhibits the aggressive behavior of conventional squamous carcinoma.

3. Adenocarcinoma: The carcinoma exhibits glandular differentiation throughout its parts. Three main variants are recognized, namely: (a) gland-forming adenocarcinoma (b) signet-ring adenocarcinoma (P 15-59) and (c) mesonephric or clear cell adenocarcinoma (P 15-60).

4. Undifferentiated carcinoma: This highly-aggressive tumor lacks any definitive cell differentiation and, hence, subtyped according to cell morphology into small cell, spindle cell and

Table 15-7 Growth Patterns of Transitional Cell Carcinomas (299 TUR biopsies)

	Papillary	Nonpapillary
Relative frequency	41.5%	58.5%
High-grade (G3)	5.6%	67.4%
Muscle invasion (T2)	9.0%	72.0%

pleomorphic cell carcinoma (P 15-61).

Unusual tumors

1. Carcinosarcoma: this shows differentiation of both epithelial and mesenchymal elements (coexpression of CK and vimentin, as well as, desmin, P 15-62).

2. Mesenchymal tumors: such as leiomyosarcoma, rhabdomyosarcoma (P 15-63) and inflammatory myofibroblastic tumor.

3. Neuroectodermal tumors: such as pheochromocytoma, small cell undifferentiated carcinoma (P 15-64), carcinoid tumor and malignant melanoma (P 15-65).

4. Malignant lymphoma (MALT type NHL or plasmacytoma).

5. Germ cell tumors.

6. Metastatic tumors: (a) either local invasion from cervix, prostate or rectum. (b) hematogenous from breast or lung.

Tumor-like lesions

Pseudoneoplastic

1.Papillary and polypoid cystitis, follicular cystitis and bilharzial polyp (P 15-66).
2. Postoperative spindle cell nodule.
3. Condyloma accuminatum (HPV) (P 15-67).
4. Malakoplakia nodule.
5. Mesonephric and urachal remnants (P 15-68, P 15-69).
6. Hamartoma and fibroepithelial polyp.
7. Amyloid tumor.
8. Brunn's nest proliferations.
9. Endometriosis and ectopic decidual tissue.

Immunohistochemistry

The urothelium is characterized by coexpression of CK20 and CK7. Uroplakin III is a specific marker for transitional carcinoma, but, of moderate sensitivity. HER-2 is positive in high-grade transitional carcinoma and adenocarcinoma.

Grading

The WHO three tiered scheme (G1, G2 and G3) is generally adopted despite some inter-observer variation among pathologists. The two tiered system (low and high grade) is a more reproducible scheme, based on definite cytological criteria, but not in common use. In this system, low-grade carcinomas include G1 and G2, whereas, grade 3 tumors considered high-grade. The rate of progression is only 10% in low-grade carcinomas and 50% in high-grade tumors. Patients with high-grade tumors contribute about 25% of cases and are considered at high-risk.

Important histological criteria to identify high-grade transitional carcinomas are: (a) loss of normal vertical polarity of cells leading to disorganized pattern, (b) change of the oval uniform nuclei into rounded of pleomorphic shape, and (c) hypercellularity with crowded appearance resulting in nuclear contact and overlapping with decrease or loss of internuclear spaces. (d) prominent nucleoli, (e) active mitosis in all tumor layers and (f) solid pattern and infiltrative tumor margin.

Spread

1. Direct spread: intravesically to infiltrate bladder wall, or extravesical to involve contiguous structures (e.g. prostate, ureter, uterus or vagina) or non-contiguous structures (e.g. pelvic cellular tissue, pelvic bone, abdominal wall or intestine). The rectum is rarely infiltrated because in females it is separated from the bladder by the uterus, and in males it is separated by loops of intestine in Douglas pouch.

2. Lymph spread: the obturator and external iliac groups of pelvic nodes are the most common sites initially affected (Fig 15-6). Metastases in para-aortic lymph nodes may develop in advanced cases.

3. Blood spread to bones, lung and liver.

4. Peritoneal spread.

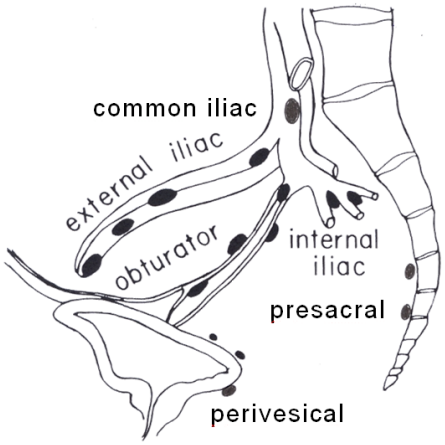

Fig 15-6 *The regional lymph nodes of urinary bladder. Metastases are most common in the obturator and internal iliac groups, bilateral involvement occurs in 40% of positive cases, spread to para-acrtic nodes is rare (1%) and represent distant metastases.*

Staging

The revised TNM staging system for bladder carcinoma is presented in (Tables 15-8 and 15-9, Fig 15-7). Urothelial carcinoma was formerly classified into superficial and deep according to invasiveness of muscularis propria. At present, these tumors are best classified at initial presentation (Wein, 2012) into: non-muscle invasive (70% of cases) and muscle invasive (30% of cases). Non muscle invasive tumors include Ta, Tis and T1, whereas, muscle invasive include T2 and more.

The relative frequency of non-muscle invasive categories and their risk of recurrence and progression are presented in (Table 15-10). Invasion of the main muscle layer of bladder (T2) is a serious phenomenon, because, once it happens, it is associated with a 50% risk of metastases. Categories T3 and T4 are considered locally advanced extravesical spread. It is noteworthy that invasion of contiguous structures such as prostate or ureter (T4a) is classified as stage 3 (P 15-70), whereas, invasion of non-contiguous structures such as intestine, anterior abdominal wall or pelvic bone (T4b) is classified as stage 4 (P 15-71).

TNM staging of bladder cancer has its own difficulties and limitations. Thus, in TUR specimens, in view of fragmentation of sample, crushing and cautery artifacts, it is rather difficult to distinguish Ta from T1, T1a from T1b, T2a from T2b. The overall agreement among pathologists in staging of TUR samples is about 60-68%. Moreover, there is a serious understaging of tumors, since patients classified as T1 in the initial TUR will show muscle invasion by repeat TUR (15%) or in the subsequent cystectomy specimen (30% of cases). Also, in cystectomy specimens it is difficult to differentiate invasion of perivesical fat (T3) from peritoneal invasion (T4). If this problem is suspected at operation, scrapping cytology smears from the peritoneum over the tumor, or cytology of ascetic fluid or peritoneal wash, may help to determine the exact stage.

Table 15-8 T Categories of Bladder Carcinoma

Ta	Papillary, noninvasive
TCIS	Flat, noninvasive
T1a	Lamina propria, superficial
T1b	Lamina propria, deep
T2a	Muscle invasion, Superficial
T2b	Muscle invasion, deep
T3a	Perivesical, microscopic
T3b	Perivesical, gross
T4a	Contiguous structures
T4b	Noncontignous structures

(Revised TNM classification, Eble, 2004)

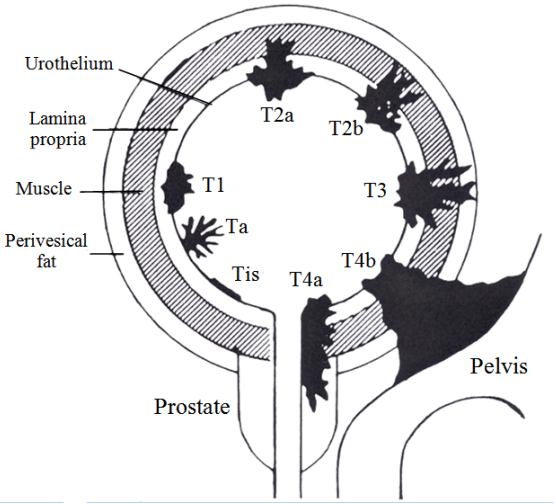

Fig 15-7 *The tumor (T) categories of bladder cancer (updated TNM classification, Eble, 2004).*

Risk-Adapted therapy

At present, both the stage and grade of tumors are used to guide therapy, but in the future a multiparameter prognostic index may be available for more precise patient stratification. In non-muscle invasive low-grade tumors, a conservative initial treatment policy is generally adopted (TUR, BCG) with preservation of bladder. Conversely, with invasion of muscularis propria (T2) or high-grade tumors (G3), cystectomy is the standard treatment. Adjuvant chemotherapy, neoadjuvant chemotherapy and bladder sparing options are still under investigation.

The Hazards of bladder conservation

There are three main challenges confronting the urologist whom treats non-muscle invasive carcinomas by TUR:

1. Multiplicity of tumors in the urinary bladder due to field cancerization of urothelium (up to 30% incidence if invasive and in situ tumors are considered). There is also the risk of associated

Table 15-9 TNM Stages of Bladder Carcinoma

Stage 0a	Papillary noninvasive neoplasm
Stage 0CIS	Flat noninvasive carcinoma
Stage I	Invasion of lamina propria (T1), N0, M0
Stage II	Invasion of muscularis propria (T2), N0, M0
Stage III	Invasion of perivesical fat (T3), prostate, uterus or vagina (T4a), N0, M0
Stage IV	Invasion of pelvic wall or abdominal wall (T4b), nodal or distant metastases

(Revised TNM classification, Eble, 2004)

tumors in upper urinary tract (6%) and lower urinary tract 40% with involvement of urethra and prostatic ducts by urothelial carcinoma.

2. Recurrence of tumor which may be due to a new primary tumor or residual neoplasm after the original resection. The recurrence rate varies between 25% and 90% depending upon tumor stage and grade (Table 15-10).

3. Progression of tumor which implies invasion of muscularis propria with subsequent risk of developing metastases in 50% of cases. The risk of progression varies between 3% to 50% according to tumor stage and grade (Table 15-10).

Risk factors

There is in no single factor which can determine precisely the risk of progression. However, several factors are associated with high tendency to progression, namely: (1) large tumors more than 5 cm in diameter (2) multiple tumors recurrent 3 months after TUR (3) high grade (G3), (4) carcinoma in situ not responding to BCG after 6 months (5) lymphangioinvasion in tumor stroma (40% risk of nodal metastases) (6) DNA aneuploidy (7) P53 mutation or over-accumulation.(8) multiple chromosomal abnormalities denoting genetic instability (9) gene expression profile by microarray analysis (future hope, but expensive technology).

High risk patients require very careful follow up (by urine cytology, biomarkers and cystoscopy), in order to detect muscle invasion easily and do a lifesaving timely cystectomy.

Prognosis After cystectomy

In western series, the 5-year overall a survival rate after cystectomy varied between 48% and 58% (Hantmann et al, 2006). By applying multivariate analysis, only tumor stage, lymph mode metastases and tumor grade are considered independent risk factors which affect prognosis. However, associated comorbidity also affect prognosis of patients subjected to radical cystectomy. Thus, the 5-years survival was 56% for patients younger than 70 years and 46% for patients older than 70 years (Bassin et al, 1999).

Prevention

1. Primary prevention involves eradication of etiologic factors or interfering with the carcinogenic process e.g. industrial safety, control of bilharziasis, control of smoking and chemoprevention by retinoids.

2. Secondary prevention implies early detection by (a) home-screening of high-risk indi-

Table 15-10 Recurrence and Progression Rates of Non-muscle-Invasive Urothelial Carcinomas

T category	Frequency %	Recurrence %	Progression %
Ta	60	25	3
Tis	10	90	50
T1	30		
T1 Low grade		50	10
T1 High grade		80	50

(Wein, 2012 and Feig, 2012)

viduals for microhematuria, or (b) urine cytology.

Although hematuria screening is highly sensitive, only 10% of those with positive tests had bladder cancer (poor specificity). Recently, some tumor markers: are promising for early detection of bladder cancer (Foresman, 1997). Examples are: Lewis X (Le X) blood-group-related antigen and the nuclear matrix protein 22 (NMP22-Matritech). Le X is expressed in malignant cells but not benign cells, has a reported sensitivity of 97% and a specificity of 85%. High levels of NMP22 protein in urine is observed in 70% of patients with recurrent tumors. These tests (combined with cystoscopy) appear promising for both detection of the disease, as well as, postresection follow up. Thus, bladder cancer can be detected at an early stage, prior to muscle invasion, leading to a much greater chance of saving both bladders and lives.

BILHARZIA-ASSOCIATED BLADDER CANCER

THE EGYPTIAN EXPERIENCE

Bladder carcinoma arising in association with bilharzial cystitis presents distinct clinicopathologic features quite different from that reported from Europe and North America (El-Bolkainy et al, 1981). Thus, it affects patients at a much younger age (mean: 46 years) who present by cystitis rather than hematuria. The tumors are commonly nodular and there is a high frequency of squamous cell carcinoma. Finally, the majority of tumors present at an advanced stage hence radical cystectomy is the main line of treatment. In this section we review this subject based on reports from NCI, Cairo and UNC, Mansura during the past 3 decades.

Bilharziasis

Bilharziasis (also known as schistosomiasis) is a parasitic disease that dates back to antiquity. The ancient Egyptians through settling and cultivating the Nile valley, were among the first to contract the disease. Thus, the main symptom hematuria was mentioned in Egyptian papyri (1500-1800 B.C.), and schistosome eggs were identified in Egyptian mummies through paleopathologic studies. In 1852, Theodor Bilharz, a German pathologist working in Cairo, discovered the worms of the disease. Ferguson in 1911 was the first to report on the high frequency of bladder cancer in Egypt and to suggest an etiologic relation with urinary bilharziasis, a fact which is now generally accepted.

Urinary bilharziasis is endemic throughout most of Africa, the Middle East, Madagascar, Reunion, Mauritius and India. In Africa, a high Frequency is reported in countries along river Nile such as Egypt and Sudan, as well as, countries around lake Victoria as Kenya and Uganda. The disease is also prevalent in the west of the continent (Gold Coast and Senegal) and the eastern side of the continent below the Equator (Mozambique, Zambia and New Guinea). In the Middle East, it occurs in Iraq, Iran, Syria, Saudi Arabia and Yemen.

Schistosomiasis tends to reach its highest prevalence and severity where agriculture depends on irrigation such as in Egypt (Fig 15-8). In this situation, the irrigation and drainage canals provide a favorable environment for the snail intermediate host and a large number of people are infected repeatedly through contact with water all the year around. The geographic coincidence of bladder cancer and endemic bilharziasis is remarkable, with reported high frequency of bladder cancer in the above mentioned countries.

The prevalence of urinary bilharziasis in rural Egyptian population was studied through different surveys to identify eggs in urine sample. The first country-wide survey, published by Scott in 1937, demonstrated high prevalence rates (60% in Nile Delta, 89% in Fayoum and 25% in Upper Egypt). Miller in 1976 reported a decrease in prevalence

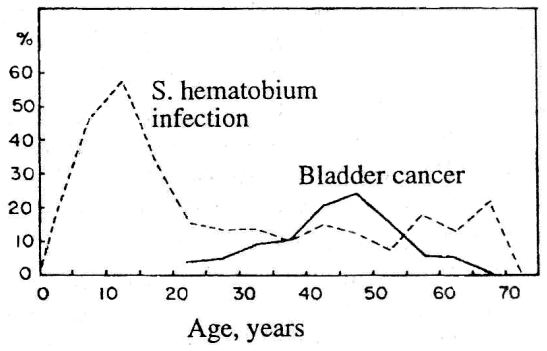

Fig 15-8 *The age distribution of Egyptian patients with S. hematobium infection and those with bladder cancer. The lag period between the two peaks of age in about 30 years.*

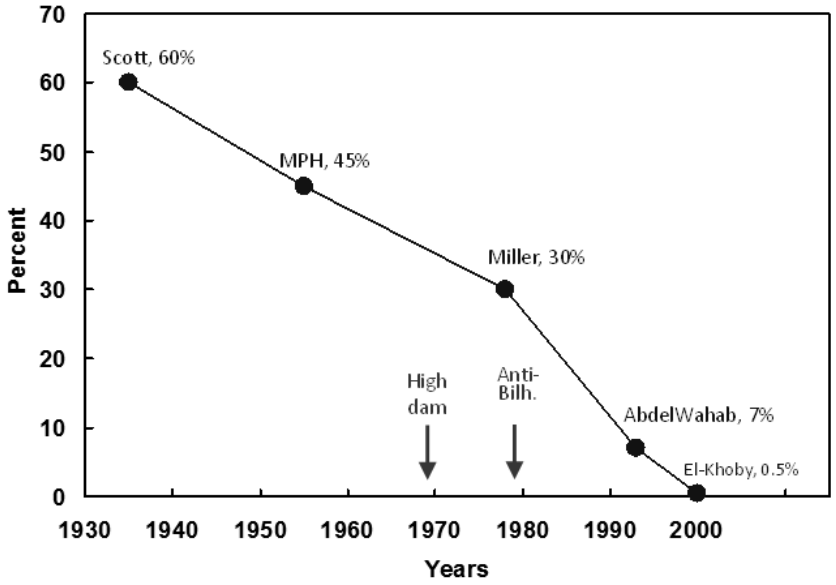

Fig 15-9 *The decline of prevalence of S. hematobium in Nile Delta in 70 years (Population survey by urine cytology). This decline is mainly due to oral antibilharzial therapy and ecological changes after the construction of High Dam.*

(30% in Nile Delta, 27% in Beni-Suef, and 6% in Upper Egypt). El-Khoby and associates in 2000 reported a significant reduction in prevalence (0.45% in Nile Delta, 13.7% in Fayoum and 7.8% in Upper Egypt).

The change in the prevalence of Schistosoma hematobium in rural population of Nile delta over 70 years is presented in (Fig 15-9). In early years (1930-1980). The decline in the prevalence was slight. At that time, the strategy to combat bilharziasis in Egypt involved treatment of patients by intravenous antimony compounds and control of snails by molluscicides. Both these efforts were of limited nature (both in time and place), hence, rather ineffective. However, a significant decline in the prevalence of S. hematobium infection was observed after 1980. This decline was mainly due to the widespread use of effective oral antibilharzial drugs (metrifonate in 1977 and praziquantel in 1985), but, ecologic changes, after construction of the high dam, unfavorable to the snail intermediate host may probably be another contributing factor.

Bladder cancer epidemiology

Three decades ago, bladder carcinoma was the foremost national oncologic problem in Egypt, but, in recent years a significant decline in its frequency was observed becoming second after breast and contributing only 11% of all cancers. Thus at NCI pathology registry (Mokhtar et al, 2007), bladder carcinoma represented 26% of all cancers during the time period (1985. to 1989), but, dropped to only 12% in recent years (2003-2004). The age standardized incidence rate (ASR) was estimated to be 16.2 per hundred thousand population in Gharbia population-based cancer Registry (Ibrahim et al, 2007).

The mean age was 46 years and male to female ration 4:1. This male predominance was most marked in squamous carcinoma (7:1) and least (2:1) in adenocarcinoma (Mokhtar et al, 2007).

Other countries in the Middle East with a high frequency of bladder cancer include: Iraq (10%), Jizan region in south of Saudi Arabia (6%), Yemen and Sudan. In Africa, a high frequency of bladder cancer was reported from the Gold Coast and South Africa in the Bantu. However, the reported frequency of bladder cancer in these countries is much less than that in Egypt due to the lower degrees of endemicity and severity of bilharziasis.

Etiology

The exact relation of bladder cancer in Egypt to bilharziasis has been a subject of long debate. Statistical association between two variables does not establish a cause and effect etiologic relation.

Strict logical criteria must be fulfilled to confirm causality, namely: strong association, site specificity, temporal relation and an available molecular model to explain carcinogenesis. The strong association is demonstrated several reports by the concomitant decline in the frequency of both bilharzia eggs and bladder carcinoma. Moreover, in a previous screening study in rural Egyptian population (El-Bolkainy et al, 1982), bladder carcinoma were only detected in farmers infested with bilharziasis. Site specificity of this relation is also evident, since patients infested with both urinary and intestinal bilharziasis only develop bladder and not colonic carcinoma. Temporal relation implies that the change in the cause must precede the change in the effect. This is also evident in the report of Gouda and associates (2007), since the decline of bilharzial prevalence in rural population occurred after 1990, whereas, the decline in the frequency of bladder cancer was observed after 2003.

Finally, two reasonable biological models are available to explain carcinogenesis, both involving the associated bacterial infection rather than the parasite. Thus, bacteria may produce carcinogenic *nitrosamines* from their precursors is urine (El-Aaser and El-Merzabani, 1981). The second model proposes that *free radicals* produced by inflammation will directly affect DNA causing gene mutation (Warren and Ghoneim, 1995). The above discussion, of our observations as well as others, supports an etiologic relation of bilharzial cystitis and bladder cancer.

Molecular Oncogenesis

The molecular mechanism is closely similar to the non-bilharzial carcinoma with only slight modification to explain the high frequency of squamous carcinoma. Two main pathways were proposed (Goeball and, Knowles, 2010), namely: (a) deletions of chromosome 9 leading to low-grade genomically stable tumors or (b) deletion of chromosome 9 and loss of TP53 gene function leading to high-grade genomically unstable tumor. It is noteworthy that chromosome 9 contains genes that control the cell cycle normally acting as negative regulators and TP53 gene is the master gene that keeps genomic stability. High-grade carcinomas always pass through a stage of carcinoma in situ (Fig 15-3).

The high frequency of squamous cell carcinoma in bilharzia-associated series is readily explained by the recent cancer stem cell theory. In the past, it was thought that squamous carcinoma arises from squamous metaplastic lesions. However, there is at present general agreement that cancer arises from the multipotential stem cells and not the mature terminally differentiated cells. Accordingly, squamous carcinoma arises from urothelial stem cells through a process of transdifferentiation (metaplasia) induced by the associated bilharzia cystitis.

The oncogenesis model, is supported by several reports of chromosomal changes (Aly et al, 2002, and Badawy 2010), as well as, molecular genetic studies. The latter revealed inactivation of tumor suppresser genes and overexpression of oncogenes.

1. Inactivation of tumor suppresser genes: TP53 gene alteration is the most common genetic change encountered, but, the frequency varied according to the method of study, as well as, tumor type and grade. Mutation of TP53 (detected by gene sequencing) varied between 33% and 40% (Warren et al, and Weintraub et al 1995). However, p53 overexpression (detected by immunohistochemistry) varied between 67% and 71% (Barsoum et al 2003, and Nouh, 1995). Human papilloma virus was detected in 46% of cases (Khaled et al, 2001), and the positivity was higher in squamous carcinoma (48%) than transitional carcinoma (36%). Human papilloma protein products (E6 and E7) are strong inhibiters of TP53. Another TP53 inhibitor, namely MDM2 is also overexpressed (Osman et al, 1997). Alterations in E cadherin adhesion molecules and apoptosis genes were also reported (Haitel et al, 2001).

2. Oncogene overexpression: various oncogenes were overexpressed including: Cyclin D1 and Ki-67 (Osman et al, 1997, and Barsoum 2003), telomerase (Abdesalam, 2001), but RAS mutation was not reported.

Precursor Urothelial Lesions

Bilharzia related bladder carcinoma is commonly associated with a variety of pathologic changes in bladder urothelium (Khafagy, et al 1972) including: squamous metaplasia (65.1%), columnar metaplasia (52.3%) and carcinoma in situ (40.7%). The high frequency of metaplastic changes (a result of chronic cystitis) explain the high frequency of squamous carcinoma and adenocarcinoma in bilharzial series. The high incidence of carcinoma in situ indicates a significant "field effect" of carcinogenesis and

explains the high frequency of multiple tumors (22%) and the high risk of local recurrence if conservation surgery is attempted.

Histopathology

The relative frequency of histologic types of bilharzia-associated bladder carcinoma in three Egyptian series is presented in (Table 15-11). The high frequency of squamous carcinoma (21% to 49%) is remarkable, as compared to a frequency of 6% in western series. Moreover, squamous carcinoma associated with bilharzia is commonly low grade (87%) compared to the high grade predominance in western reports. Verrucous carcinoma is a special variant (4%) of squamous carcinoma which is locally malignant and non-metastasizing. This unusual variant is only reported in association with bilharziasis.

Time Trend

A time trend retrospective analysis on 9843 patients treated by cystectomy at NCI, Cairo, during the years 1970-2007 was reported (Gouda et al, 2007). A significant decline of the relative frequency of bladder cancer was observed from 28% in the old series to 12% in the recent series. Bilharzia association dropped from 82% to 55% (Fig 15-10). There was a significant rise of transitional cell carcinomas from 16% to 66%, becoming at present the most common tumor type, with a significant decrease in squamous cell carcinomas from 76% to 28% (Fig 15-11) However, no significant change was observed in the advanced stage of the disease (Zaghloul et al, 2008). There was an increase in the median age of patients from 47.4 years to 60.5 years and a decrease of male: female (M/F) ratio from 5.4 to 3.3.

The decline in the relative frequency of bladder cancer is associated with a decline in bilharzia egg positivity in the specimen and is probably related to better control of bilharziasis in the rural population in Egypt. This was accompanied by a change in the histological profile of tumors, with significant predominance of transitional cell carcinoma and an increase in the age of patients, a pattern rather similar to that in western reports.

Stage

The grand majority of patients present at an advanced stage. Thus, muscle invasive (T2) and locally-advanced tumors (T3 and T4) contributed 98% at NCI Pathology Registry, Cairo (Zaghloul et al, 2008) and 89% in a report from UNC, Mansura (Ghoneim et al, 2008). Extravesical spread to involve other structures (T4) was noted in 13% of cases. The common structures involved in category T4 were: the

Table 15-11 Relative Frequency of Histologic Types of Bilharzia-associated Bladder Carcinoma in Egyptian Series

Source	NCI Registry [a]	Private series El-Bolkainy	UNC, Mansura [b] Ghoneim, 2008
No of cases	24017	3136	2720
Time interval	1985-2011	1991-2011	1970-2000
Nature of specimen	Cystectomy and biopsy	Cystectomy and biopsy	Cystectomy only
Histologic type			
Transitional	54.4%	69.7%	36.4%
Squamous	37.0%	21.1%	49.4%
Adenocarcinoma	4.5%	3.8%	9.6%
Undifferentiated	3.8%	5.4%	4.5%

a. NCI, National Cancer Institute, Cairo University
b. UNC, Urology and Nephrology Center, Mansura University

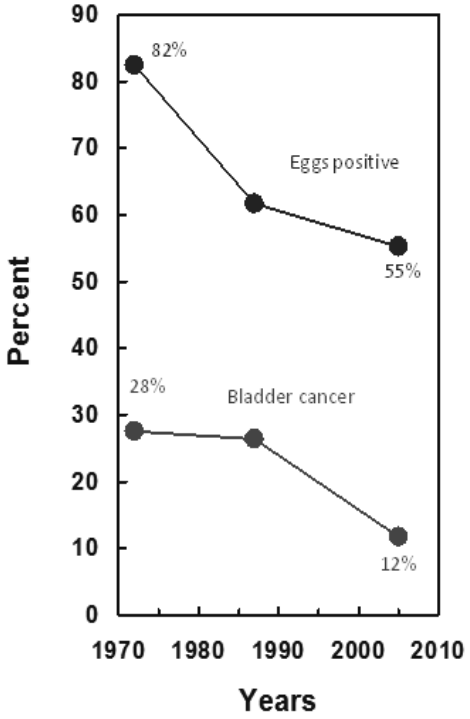

Fig 15-10 *The decline of frequency of bladder cancer in 37 years (NCI pathology Registry, time trend analysis on 3988 patients, Gouda et al, 2007). A drop in the frequency of bilharzia eggs in cystectomy specimen is also evident.*

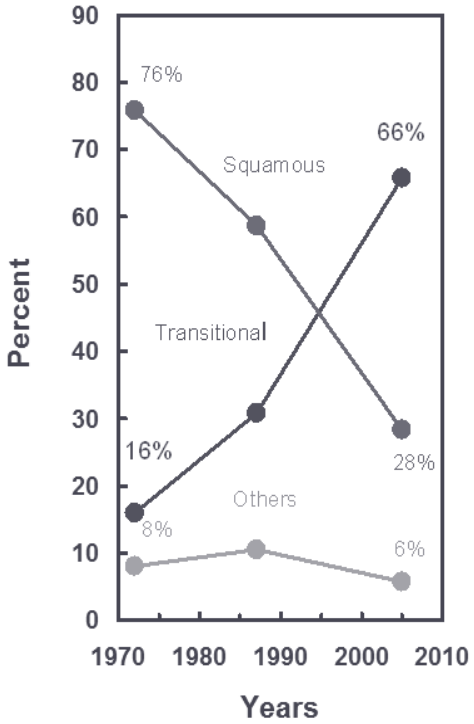

Fig 15-11 *The change of the histologic profile of bladder carcinoma in 37 years, a decline of squamous carcinoma and rise of transitional cell carcinoma (NCI Pathology Registry, 3988 patients, Gouda et al, 2007).*

prostate, uterus, vagina and peritoneum. The frequency of lymph node metastases was 20%. The total clinical error in staging was 33%, with a tendency to clinical understaging.

A detailed study of lymph node metastases in 200 radical cystectomy specimens (mean number 51 lymph node) was reported from UNC, Mansura (Abol-Enein et al, 2004). Bilateral nodal metastases was observed in 22 of the 38 positive nodes (58%), of which all except one were in the internal iliac and obturator nodes (the true endopelvic group). It was concluded that there is no sentinel node for bladder cancer (but rather a sentinel region of internal iliac and obturator groups) and there are no skipped metastases.

Prognosis

The largest series of survival analysis of 2720 patients treated by cystectomy was reported from UNC, Mansura (Ghoneim et al, 2008). The disease free survival was 56% at 5 years and 50% at 10 years. This survival is comparable to that reported from western series (Hautmann et al, 2006). Multivariate analysis revealed that only tumor stage, grade and lymph node metastases were the independent prognostic factors (Table 15-12). No significant difference was observed in survival of patients with different types of carcinomas. Thus, the 10-year survivals were: 53% for squamous, 48% for transitional and 51% for adenocarcinoma. In another series from NCI, Cairo, the 5-year disease free survival of adenocarcinoma was 46% (Zaghloul et al, 2006).

Prevention

Bilharzial bladder cancer is a good example of a preventable malignant disease. *Primary prevention* is possible if the parasite could be eliminated on a nation wide scale. The current strategy adopted in Egypt involves a combination of snail control and mass therapy of the infested rural population by oral antibilharzial drugs. These efforts have recently significantly reduced the prevalence of

Table 15-12 Significant Prognostic Factors of Bladder Carcinoma After Radical Cystectomy

Parameter	%5-yr survival	%10-yr survival
Stage		
T1	81.7	71.8
T2a	75.1	69.0
T2b	53.2	48.7
T3	39.8	35.7
T4	29.5	21.0
Grade		
I	68.4	62.9
II	54.2	48.0
III	39.5	34.4
Lymph nodes		
Negative	62.2	56.3
Positive	27.3	23.1
Overall disease free survival	55.5	50.0

(Multivariate analysis of 2720 cases, Ghoneim et al, 2008)

bilharziasis in Egypt. Chemoprevention is another feasible approach. Thus, it is possible by the admin -istration of retinoids to revert to normal the precancerous atypical squamous metaplastic lesions of the urinary bladder. *Secondary prevention* is also possible by early detection of the disease using urine cytology.

Urine Cytology

Value and Limitations

Malignant urothelial cells exfoliated in urine exhibit characteristic cytologic features diagnostic of malignancy, as well as, tumor type (P 15-72 to P 15-76). However, it is important to recognize that urine cytology is effective in some clinical settings, but, ineffective in another.

Effective use: (1) detection of high-grade transitional carcinoma and squamous cell carcinoma (sensitivity=95%), (2) follow up after intravesical BCG treatment (3) follow up after resection of low-grade transitional neoplasm to detect any progression to a high-grade transitional tumor (dedifferentiation), (4) screening of high risk individuals for early detection of bladder cancer (industrial or bilharzial).

Limitations and pitfalls: Cytology is ineffective in diagnosing low grade transitional neoplasms (sensitivity only 30%), as well as, in the follow up after intravesical chemotherapy. False positive cytology reports are rather common in patients with urinary calculi or those subjected to catheterization and instrumentation. The urologist must inform the pathologist of these conditions.

A screening project to detect bladder cancer by urine cytology was done during the period 1976-1981 on a rural population in the Nile Delta (EL-Bolkainy et al, 1982). That was a collaborative study between NCI, Cairo, NUC, Mansura and NIH, Bethesda USA. The target population was the inhabitants of 15 villages near Mansura (total 30614 subjects). Selective screening was done for the high risk group (19% of population), defined as farmers aged 20 years and above. Schistosoma hemaobium eggs were detected in urine in 24% of the high-risk individuals. The yield of screening was two bladder cancer cases per one thousand high-risk individuals screened (2/1000). Five of the 11 carcinomas detected were at an early stage (non-muscle invasive).

REFERENCES

Aly MS and Khaled HM: chromosomal aberrations in early stage bilharzial bladder Cancer Gen and Cytogenetic, 32:41-45, 2002.

Badawy O, Mostafa N, Fahmy A and Shoman S: Comparison of cytology and Multitarget fish in Urothelial carcinoma Egypt J Path, 30: 45-52, 2010.

Bassi PF, Draggo G and Piazza N: Pognostic factors after radical cystectomy Jural, 161: 1494 -1497, 1999 .

Abdel-Salam IM, Khalid HM and Gaballah HE: Telomerase activity in bilharzial bladder cancer, prognostic imply-cations. Urol Oncol, 6: 149-153, 2001.

Barsoum H, Abdel-Hameed and Nouh MA: The prognostic significance of p53, Bcl-2, cytokeratin 20 and ki-67 in primary superficial papillary transitional bladder carcinoma J Egypt Nat Cancer Inst, 15: 183-191, 2003.

EL-Aaser AA and EL-Merzabani MM: Biochemical detection of etiologic factors. In, Detection of Bladder Cancer, EL-Bolkainy and Chu Editors, NCI, AL-Ahram press, 1981.

El-Bolkainy MN, Mokhtar NM and Hussein MH: the impact of Schistosomiasis on the pathology of bladder carcinoma. Cancer, 48: 2643-2648, 1981.

El-Bolkainy MN, Chu EW, Ghoneim MA and Ibrahim AS: Cytologic detection of bladder cancer in rural Egyptian population infested with Schistosomiasis. Acta cytol 25: 303-310, 1982.

El-Bolkainy MN: in, Pathology and Genetics, tumors of the Urinary System and Male Genital Organs, who classification editor JN Eble, IARC Press, Lyon, page 124, 2004.

Feig BW and Ching CD: The MD Anderson Surgical Oncology. Wolters Kluwer Lippincott, Philadelphia, p

615-616, 2012.

Goebell PI and Knowles MA: Bladder cancer or bladder cancers ? Genetically distinct malignant conditions of the urothelium. Ural Oncol, 28: 409-428, 2010.

Ghoneim MA, EL-Mekresh MM, EL-Baz MA, EL-Attar IA and Ashamallah A: Radical cystectomy for carcinoma of the bladder, critical evaluation of the results in 1026 cases. J Urol, 158:393-399, 1997.

Ghoneim MA, Abdel-Latif M, El-Mekresh M, Abol-Enein H, Mosbah A, Ashamallah A and EL-Baz M: Radical cystectomy for carcinoma of the bladder, 2720 consecutive cases 5 years later. J Ural, 180:121-127, 2008.

Gouda I, Mokhtar N, Bilal D ,EL-Bolkainy T and El-Bolkainy MN: Bilharziasis and Bladder cancer, a time trend analysis of 9843 patients. J Egypt NCI, 19: 158-162, 2007.

Haitel A, Posch B and EL-Baz M: Bilharzial related, organ confined, muscle invasive bladder cancer, prognostic value of apoptosis markers proliferation markers, p53, E-Cadherim, EGFR and c-erb B-2. J Urol, 165: 1481-1487, 2001.

Hautmann RE, Gschwend JE and de petriconi RC: Cysectomy for transitional cell carcinoma of the bladder: results of surgery only series. J Urol, 176: 486, 2006.

Herrera GA and Silverberg SG: Renal tumors, lessons learned and what the future holds. Pathal Case RW, 11: 153-195, 2006.

Mitra AP, Datar RH and Cote RJ: Molecular pathways in invasive bladder cancer. J Clin Oncol, 24: 5553, 2006.

Nouh MA: Proliferative index and mutant p53 oncogene overexpression in bladder cancer, relation to survival. PhD thesis in cancer pathology, National Cancer Institute, Cairo University, 1995.

Osman I, Scher H, Zhang Z; Alternations affecting p53 control pathway in bilharzial-related bladder cancer. Clin Cancer Res, 3: 531-56,1997.

Perez-Montial D, Wakely PE and Hes O: High-grade urothelial carcinoma of the renal pelvis. Mod Pathol, 19: 494-503, 2006.

Ploeg M, and Aben KH: The present and future burden of urinary bladder cancer in the world. world J Urol, 27: 289 -293, 2009.

Shariat SF, Zlotta AR and Ashfaq R: Cooperative effect of cell-cycle regulators expression on bladder cancer development and biologic aggressiveness. Mod Pathol, 20: 445-459, 2007.

Warren W ,Biggs PJ, El-Baz M, Ghoneim MA, Stratton MR and Vemitt S: Mutations in p53 gene in schistosomal bladder cancer. Carcinogenesis, 16: 1181-1189, 1995.

Wein AJ: Editor-in-chief, Campbell-Walsh Urology, 10th edition, Elsevier-Saunders, philadelphia, 2012.

Weintraub M, Khaled H and Zekri A: p53 mutation in Egyptian patients with bladder cancer. Int J Oncol, 7: 1269-1274, 1995.

Zaghloul MS, Nouh MA, and Nasmy M: long-term results of primary adenocarcinoma of the urinary bladder, a report on 192 patients. Urol oncol. 24: 13-20, 2006.

Zaghloul MS, Nouh MA, and Moneer M: Time-trend in epidemiological and pathological features of Schistosoma -associated bladder cancer. J Egypt Nat Cancer Inst, 20: 168-174, 2008.