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The pathology of bladder cancer

Charles Jameson

Introduction

Carcinoma of the bladder is the seventh most common cancer worldwide [1]. It comprises 3.2% of all cancers, with an estimated 260 000 new cases each year in men and 76 000 in women. The highest incidence rates in males and females occur in Western Europe, North America and Australia. The UK annual incidence is over 10 000 new cases, with a male:female ratio of 5:2 [2–5].

Urothelial carcinoma is the most common type of bladder cancer. However, there is significant geographic variation, and in certain regions of the world, such as Egypt and parts of Africa, squamous cell carcinoma (SCC) of the bladder predominates.

Urothelial carcinomas of the renal pelvis, ureter and urethra are less common, accounting for approximately 10% of all urinary tract neoplasms.

It should be noted that the formerly used term "transitional cell carcinoma (TCC)" is now largely replaced by "urothelial carcinoma," although you will still hear urologists and pathologists use both interchangeably.

The WHO histological classification of tumors of the urinary tract (2004) is given in modified form in Table 1.1 [6].

The urothelium is the lining epithelium of the urinary collecting system and includes that of the renal pelvis, ureters, bladder and part of the urethra. Its thickness varies from three to seven cell layers, depending on the state of distension of the bladder. The turnover rate of those cells is low, of the order of three to six months. The cells desquamate but very few cells are seen in normal urine cytology specimens, i.e. normal urine is hypocellular. Very few mitotic figures are seen in normal urothelium. The presence of surface "umbrella cells" indicates normal maturation in the urothelium. These cells are large and elliptical and have abundant eosinophilic

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Table 1.1. WHO histological classification of tumors of the urinary tract [6] (modified)

Urothelial tumors
Infiltrating urothelial carcinoma with squamous differentiation with glandular differentiation micropapillary sarcomatoid
Non-invasive urothelial neoplasias urothelial carcinoma <i>in situ</i> (CIS) non-invasive papillary urothelial carcinoma, high grade non-invasive papillary urothelial carcinoma, low grade non-invasive papillary urothelial neoplasm of low malignant potential (PUNLMP) urothelial papilloma inverted urothelial papilloma
Squamous neoplasms Squamous cell carcinoma Verrucous carcinoma Squamous cell papilloma
Glandular neoplasms Adenocarcinoma enteric mucinous signet ring cell Villous adenoma
Neuroendocrine tumors Small cell carcinoma Carcinoid Paraganglioma
<i>Melanocytic tumors</i> Malignant melanoma Naevus
Mesenchymal tumors Rhabdomyosarcoma Leiomyosarcoma Angiosarcoma Other

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Table 1.1. (cont.)

Urothelial tumors

Hemopoietic and lymphoid tumors Lymphoma Plasmacytoma *Miscellaneous tumors* Carcinoma of Skene, Cowper and Littre glands Metastatic tumors and tumors extending from other organs



Figure 1.1 A section through normal bladder wall showing urothelium (arrows), lamina propria (LP), muscularis mucosae (white arrow), detrusor muscle (D) comprising inner longitudinal, circular, and outer longitudinal layers, and fat (F) distributed throughout wall. When tumor penetrates detrusor into perivesical fat (PVF) it becomes pT3 by TNM criteria (see also color plate section).

cytoplasm. The surface outline has a characteristic scalloped appearance. The umbrella cells have the unique property that they maintain the impermeability of the epithelium to urine, even when at full stretch. Figure 1.1 shows a section through a normal bladder wall and illustrates the urothelium, underlying lamina propria, muscularis mucosae, detrusor muscle and the perivesical fat. The thick muscle bundles of the detrusor may be difficult to distinguish and are distinct *only* in the region of the bladder neck. In addition, a thin, wispy, discontinuous layer of

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muscularis mucosae is present in about 5% of bladders and is located in the lamina propria. Fat can be present at all levels of the bladder wall.

Etiology

A number of risk factors are known for bladder cancer, of which smoking tobacco is the major one. Long-term use of analgesics containing phenacetin greatly increases the risk of developing urothelial cancer anywhere along the urinary collecting system. Occupational exposure to aniline dyes is also associated with bladder cancer. In particular, the aromatic amines benzidine and 2-naphthylamine and possibly 1-naphthylamine have been identified as bladder carcinogens. The drug cyclophosphamide has been reported to be associated with an increased risk of SCCs and sarcomas, particularly leiomyosarcomas. Chlornaphazine is also associated with bladder cancer development. In certain areas of the world schistosoma hematobium infections are associated with the development of SCCs of the bladder. Chronic infections and bladder calculi are also associated with these squamous tumors worldwide.

Genetics and multifocality of urothelial carcinomas

It is well known that urinary tract neoplasia is not necessarily limited to one single tumor. Frequent recurrence, multifocal tumors and the presence of "flat" lesions are characteristic of these tumors. Most multicentric bladder tumors are of monoclonal origin [6]. However, polyclonal cancers have also been reported [6], mainly in the early stages of tumors or in premalignant lesions. These observations have led to the hypothesis of "field defect," suggesting that environmental mutagens may cause fields of genetically altered cells that become the source of polyclonal, multifocal tumors [7].

Histopathological approach to bladder tumors

In histopathology practice, the types of specimens received from bladder cancers range from simple 3–4mm biopsies, to transurethral resection of (bladder) tumor (TURBT), to partial or radical cystectomy. In some cases cystoprostatectomy is performed and regional lymph node dissections may be performed for staging purposes.

There are a number of essential prognostic features to report in bladder tumor specimens, whether obtained as tumor biopsy samples (TURBT) or larger resection specimens (e.g. cystectomy), all of which have therapeutic import. These are as follows:

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- 1. *Type of cancer*. Urothelial, squamous, and small cell carcinomas, adenocarcinoma, and other rarer types are all well described. Any variants of predominant tumor types and evidence of divergent differentiation should be noted.
- 2. Grade. This is a histological estimation of the degree of differentiation, in other words, how much a tumor resembles the tissue of origin. There are two main grading systems in use most histopathologists and urologists still abide by the WHO 1973 grading system: grade 1 (well differentiated), grade 2 (moderately differentiated) and grade 3 (poorly differentiated). The future trend is to grade carcinomas as low grade or high grade, which is believed to be more relevant clinically. Grading is subjective by its nature and a more simple low/high grade approach reduces the interobserver variation considerably. The WHO 2004 grading system [6] incorporates the low/high grade approach.
- 3. *Stage*. The tumor, node, metastases (TNM) system (Table 1.2) is used in bladder cancer staging to describe pathological stage [8]. In TURBT specimens the pathologist is limited by the presence or absence of detrusor muscle tissue in the biopsy material. Often one can only say pT1b *at least*, e.g. if no muscle tissue is sampled in a carcinoma that invades the deep lamina propria. In biopsy samples where muscle is present, the stage could also be pT2a *at least*, as it is not possible to distinguish between the inner half of the muscularis (pT2a) and the outer half (pT2b).

If a radical cystectomy is performed with lymph node sampling or dissection it is possible to give a much more complete pathological stage, e.g. pT4 N2 MX.

Stage grouping is used by urologists, radiotherapists and oncologists once all the clinical, histopathological and radiological staging information is available [8]. Tumors of the renal pelvis, ureter and urethra have their own separate staging systems within the TNM system (Table 1.2).

- 4. *Diffuse or multifocal tumor*. It is important to describe the presence or absence of flat carcinoma *in situ* (CIS or pTis) in relation to the tumor itself or, more significantly, in random biopsy samples taken from the main tumor mass as the description has prognostic significance and impacts on management.
- 5. The presence or absence of detrusor muscle in the specimen.
- 6. *Lymphovascular (LVSI) space invasion*. This usually appears as small fragments of tumor in lymphatic spaces or blood vessels. It may also fill the vascular space completely as a so-called "tumor embolus." The significance of LVSI is in relation to possible tumor metastasis and is regarded by many oncologists as a poor prognostic factor.

The Royal College of Pathologists has produced a minimum dataset to incorporate all of the above features [9]. Tables 1.3, 1.4, and 1.5 illustrate the proformas for each specific urothelial tumor site.

Table 1.2. TNM pathological staging (6th edn, UICC)[8]

Renal pelvis and ureter

pT – Primary tumor

- pTX Primary tumor cannot be assessed
- pT0 No evidence of primary tumor
- pTa Non-invasive papillary carcinoma
- pTis Carcinoma in situ
- pT1 Tumor invades subepithelial connective tissue
- pT2 Tumor invades muscularis
- pT3 (Renal pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumor invades beyond muscularis into periureteric fat
- pT4 Tumor invades adjacent organs or through the kidney into perinephric fat

pN – Regional lymph nodes

- pNX Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastasis
- pN1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- pN2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- pN3 Metastasis in a lymph node more than 5 cm in greatest dimension

pM – Distant metastases

- pMX Distant metastases cannot be assessed
- pM0 No distant metastasis
- pM1 Distant metastases

Stage grouping

Stage 0a	Та	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	Τ2	N0	M0
Stage III	Т3	N0	M0
Stage IV	Τ4	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

Urinary bladder

- *pT Primary tumor*
- pTX Primary tumor cannot be assessed
- pT0 No evidence of primary tumor
- pTa Non-invasive papillary carcinoma
- pTis Carcinoma in situ

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Table 1.2. (cont.)

pT1	Tumor	invades	subepithelial	connective tissue	
-----	-------	---------	---------------	-------------------	--

- pT2 Tumor invades muscle:
- pT2a Tumor invades superficial muscle (inner half)
- pT2b Tumor invades deep muscle (outer half)
- pT3 Tumor invades perivesical tissue:
- pT3a microscopically
- pT3b macroscopically (extravesical mass)
- pT4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall:
- pT4a Tumor invades prostate, uterus or vagina
- pT4b Tumor invades pelvic wall or abdominal wall

pN – Regional lymph nodes

- pNX Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastasis
- pN1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- pN2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- pN3 Metastasis in a lymph node more than 5 cm in greatest dimension

pM – Distant metastases

- pMX Distant metastases cannot be assessed
- pM0 No distant metastasis
- pM1 Distant metastases

Stage grouping

Stage 0a	Та	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a,b	N0	M0
Stage III	T3a,b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

Urethra

- pTX Primary tumor cannot be assessed
- pT0 No evidence of primary tumor

Male and female

pTa Non-invasive papillary, polypoid or verrucous carcinoma

Table 1.2. (cont.)

pTis	Carcinoma in	situ								
pT1	Tumor invade	s subepithelial connecti	ve tissue							
pT2	Tumor invade muscle	s any of the following: o	corpus spongiosum, pro	state, periurethral						
pT3	Tumor invade anterior vag	s any of the following: o ina, bladder neck	corpus cavernosum, bey	ond prostatic capsule,						
pT4	Tumor invade	s other adjacent organs								
Transition	al cell carcinom	a of the prostate (prosta	tic urethra)							
pTis pu	Carcinoma in situ, involvement of prostatic urethra									
pTis pd	Carcinoma in	<i>situ</i> , involvement of pro	ostatic ducts							
pT1	Tumor invade	s subepithelial connecti	ve tissue							
pT2	Tumor invade periurethral	s any of the following: j muscle	prostatic stroma, corpus	spongiosum,						
pT3	Tumor invade bladder necl	s any of the following: c c (extraprostatic extensi	corpus cavernosum, bey ion)	ond prostatic capsule,						
pT4	Tumor invade	s other adjacent organs	(invasion of bladder)							
pN-	Regional lymp	h nodes								
pNx	Regional lymp	h nodes cannot be asses	ssed							
pN0	No regional ly	mph node metastasis								
pN1	Metastasis in a	single lymph node 2 cr	m or less in greatest dim	ension						
pN2	Metastasis in a	single lymph node mo	re than 2 cm or multipl	e lymph nodes						
рМ –	Distant metas	tases								
рМХ	Distant metast	ases cannot be assessed								
pM0	No distant me	tastasis								
pM1	Distant metast	ases								
Stage gro	uping									
Stage 0a		Та	N0	M0						
Stage 0is		Tis	N0	M0						
		Tis pu	N0	M0						
		Tis pd	N0	M0						
Stage I		T1	N0	M0						
Stage II	age II T2 N0 M0									
Stage III	Stage III T1, T2 N1 M0									
		Т3	N0, N1	M0						
Stage IV		T4	N0, N1	M0						
		Any T	N2	M0						
		Any T	Any N	M1						

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Table 1.3. Reporting proforma: urinary bladder

	Surname Date of birth Hospital NHS no Date of receipt Report no Pathologist		Forenames Sex Hospital no. Date of repo Surgeon	rting.		······							
	Nature of specimen/	procedure and c	ore macrosco	pic ite	ms							_	
	Biopsy 🛛 TUR Site(s) of biopsy or T	Partial cystectomy Radical cystectomy Tumor location											
	Weight of TURBT		(g)		Maxim	um tum	or size	e (n	nm)				
	Right obturator nodes Right pelvic nodes	Yes □ No Yes □ No	□ Left o □ Left p	bturato elvic n	or nodes	Yes Yes	יייסו ז ם ז ם	NO [NO []]				
	Invasion into perive	sical tissue (pT3I)Yes 🗆	No	D C	annot ass	sess						
	Margins N/A	D Negativ Distant	e 🗆 e to the near	est ma	rgin	(mn	n)	P Si	ositive ite(s)	····			
1	Core microscopic ite Tumor Uroth	ems nelial carcinoma			For u	urothelia	1		wно	1973		- 2004	
	subtype Squar (s) Aden	mous carcinoma ocarcinoma			carci	nomas:			Grade Grade		Low g	rade	
	(one or Small more) Sarco	cell carcinoma matoid carcinon	1a						Grade	•3 □	High g	rade	
	Other	e specify:			Asso Vasc	ciated Cl ular inva	IS Ision		Y Y	es □ es □	No No		
ļ	Carcinoma <i>in situ</i> or	ıly (pTis)				Yes		No		Cannot as	sess <u>(pTx)</u>		
ļ	Non-invasive papilla	ry tumor (pTa)				Yes		No		Cannot as	sess (pTx)		
i	Invasion into lamina	i propria (p I I) salf of muscle (n'	F 7 9)			Y es Ves		N0 No		Cannot as	sess (pTx)		
i	Invasion into outer l	nalf of muscle (p	Г2а) Г2b)			Yes		No		Cannot as	sess (pTx)		
i	Microscopic invasio	n into perivesica	tissue (pT3a)		Yes		No		Cannot as	sess (pTx)		
Ĺ	Invasion into perive	sical tissue confi	med (pT3b)			Yes		No		Cannot as	sess <u>(pTx)</u>		
L	Invasion into prosta	te, uterus, or vag	ina (pT4a)			Yes		No		Cannot as	sess <u>(pTx)</u>		
I	Invasion into pelvic	or abdominal wa	ll (pT4b)			Yes		No		Cannot as	sess <u>(pTx)</u>		
	Margins N/A	D Negativ Distant	e 🗆	est ma	rgin	(mn	a)	Po: Sit	sitive e(s)				
I	Right nodes To Obturator	tal No pos	<u>ECS</u>	N/A N/A N/A		Left no Obturat Pelvic Other: Please	des tor		otal	N <u>o</u> pos	ECS	N/A N/A N/A	
	pTNM stage: pT	pN	pM			SNON	AED o	odes					
	Signature of patholog	ist				Date	Т Т	·····	· · · · · · · · · · · · · · · · · · ·	M M		•	

Table 1.4. Reporting proforma: renal pelvis and ureter

Surname Date of birth Hospital NHS no Date of receipt Report no Pathologist					Forenames Sex Hospital no Date of reporting Surgeon									_
	Biopsy Site(s) of bi	Right ureter opsy		Left ureter		Right nephrouret Tumor lo Number Maximun	erectomy cation. of tumor n tumor	□ 's size	Lef	t neph (mm)	rouro	eterectom	y	
	Nodes Y Please speci	′es □ fv origin	No											
	Margins	N/A		Negative Distance	to the n	□ iearest ma	rgin	(mm)		Positi Site(s	ve)			
	Core micro	scopic iten	ns											
	Tumor subtype (s) (one or more)	Urothe Squam Adenoo Small o Sarcon Sarcon Other: Please	lial car ous car carcino cell car natoid o na specify	cinoma ·cinoma ma cinoma carcinoma :			Assoc	<u>cothelial</u> omas: iated CIS lar invasior	1	WH Gr: Gr: Gr:	IO 19 ade 1 ade 2 ade 3 Yes Yes	73	WHO Low g High g No No	2004 grade grade
1	Carcinoma	<i>in situ</i> onl	v (nTis	`			1	Ves	-	No		Cannot	assess (n]	
i	Non-invasiv	e papillar	y tumo	, r (рТа)				Yes		No		Cannot	assess (p	<u>[x]</u>
İ	Invasion in	to subepitl	nelial co	onnective	tissue (p	oTI)		Yes		No		Cannot	assess (p	<u>[x)</u>
ļ	Invasion in	to muscula	ris (pT	2)				Yes		No		Cannot	assess <u>(p</u> ´	<u>[x)</u>
I	(Renal pelvi parenchym	's) Invasio a (pT3)	n into r	enal perip	elvic fa	t or renal		Yes		No		Cannot	assess <u>(p</u> `	<u>[x)</u>
I	(Ureter) Inv	asion into	periur	eteric fat (pT3)			Yes		No		Cannot	assess <u>(p´</u>	<u>[x)</u>
l	Invasion in fat (pT4)	to adjacen	t organ	s or throu	gh kidn	iey to perii	rephric	Yes		No		Cannot	assess <u>(p</u>]	<u>[x)</u>
	Margins	N/A		Negative Distance	to the n	□ learest ma	rgin	(mm)		Positi Site(s	ve)			
ļ	Nodes Origin:	<u>N/A</u>		<u>Total</u>		<u>No posit</u>	ive	<u>ECS</u>	3	<u>Yes</u>		<u>No</u>		
pTNM stage: pT pN					М		SNOMED codes T M T M							
	Signature o Date	f patholog	ist	•••••		•••••	•••••							