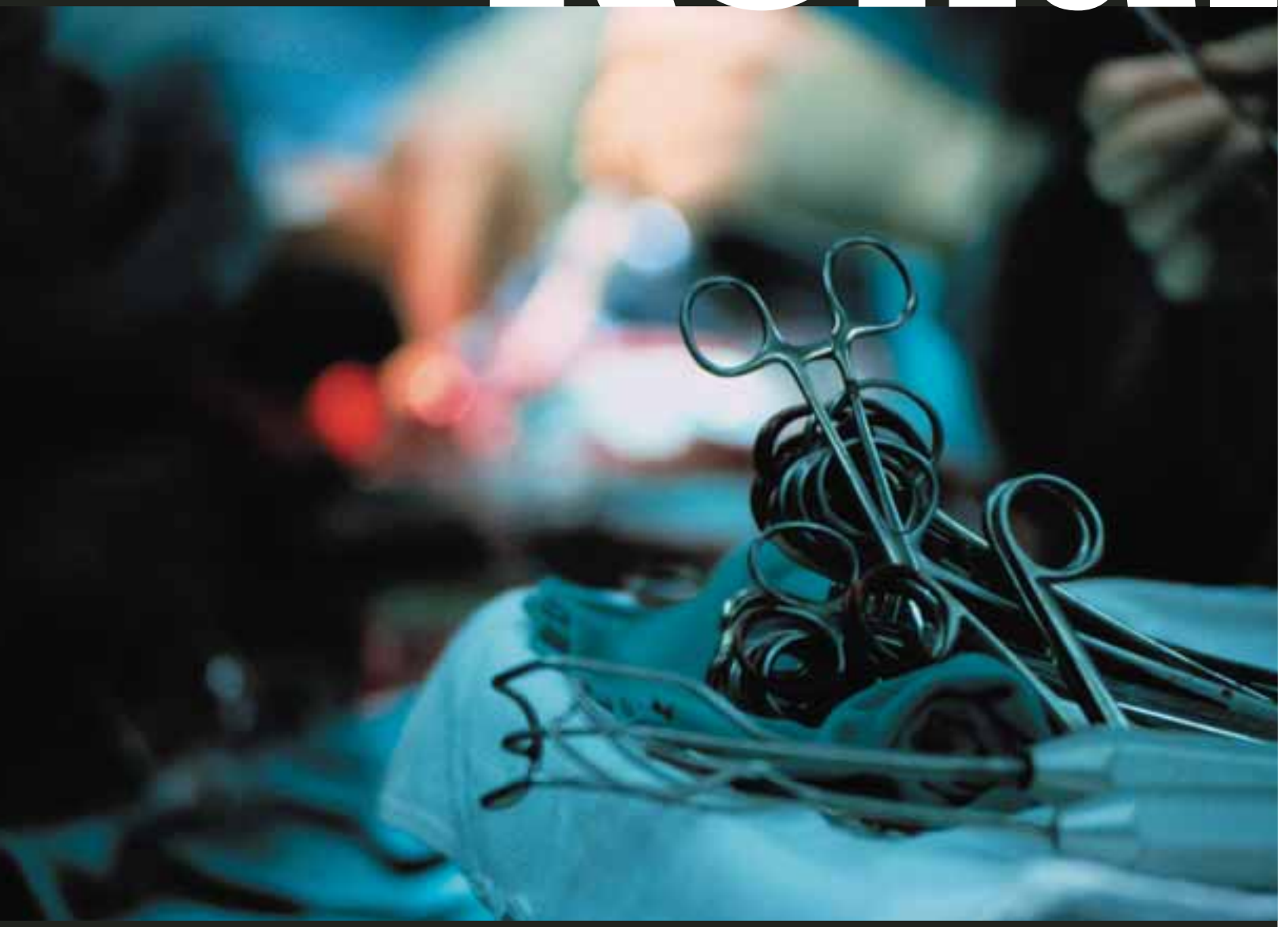
Renal



TRANSITIONAL CELL CANCER

RICHARD EVANS WILLS, MD, FACSM, FRSM, MBA
MICHAEL NORTON, DC
LARA CREASEY KETTEN, MA
JANE VINCENT YOUNG, MA

Transitional cell carcinoma of the renal pelvis accounts for 7% of all kidney tumors. It is curable in more than 90% of patients, if it is superficial and is confined to the renal pelvis.[1,2,3,13] Deep invasive tumors that are still confined to the renal pelvis have a 10-15% likelihood of cure. Tumors with penetration through the urothelial wall or with distant metastasis are usually not curable with currently available forms of treatment.[1,3,13]

Anatomy and physiology

The kidneys are positioned behind the peritoneum in the abdominal cavity, against the back muscles of the upper abdomen,[15,17] and are protected by the lower ribs. As the main functional organs of the urinary system, the kidneys utilize three processes to produce urine: glomerular filtration, tubular reabsorption, and tubular secretion.[15,17,18]

The kidneys are embedded in adipose tissue that acts as a cushion and is, in turn, covered by a fibrous connective tissue membrane called renal fascia. Renal fascia (called Gerota's fascia) helps hold the kidneys in place. Each kidney has an indentation called the hilus on its medial side. At the hilus, the renal artery enters the kidney, and the renal vein and ureter emerge. The renal artery is the branch of the abdominal aorta, and the renal vein returns blood to the inferior vena cava.[17] The ureter carries urine from the kidney to the urinary bladder (Figures 1-2).

The internal structure of the kidney from a coronal or frontal section contains three areas: the renal pelvis, the renal medulla and the renal cortex.

Renal pelvis

The first area is the renal pelvis; this is not a layer of tissues, but instead a cavity formed by the expansion of the ureter within the kidney at the hilus.[17] Funnel shaped extensions of the renal pelvis, called calyces or calyx, enclose the papillae of the renal pyramids.

Renal medulla

The middle section is the renal medulla, which is made of loops of Henle and collection tubules. The renal medulla consists of wedge-shaped pieces called renal pyramids. The tip of each renal pyramid is its apex or papilla.[17] The urine flows from the renal pyramids into the calyces, then into the renal pelvis and out the ureter.

Renal cortex

The outer most area is called the renal cortex and consists of nephrons. The nephron is the structural and functional unit of the kidney. Each nephron has two major parts: a renal corpuscle and renal tubule.[17,18] Figure 1b shows the parts of the nephron with their blood vessels.

Blood flow

The pathway of blood flow through the kidney is an essential part of the process of urine formation. Blood from the abdominal aorta enters the renal artery and then branches extensively within the kidney into small arteries. The smallest arteries give rise to afferent arterioles in the renal cortex. From the afferent arterioles, to peritubular capillaries, to veins within the kidney, to the renal vein, and finally to the inferior vena cava.[17,18] In this pathway there are two sets of capillaries, and in those capillaries metabolic exchanges take place between the blood and tissues.[15,17,18] The next exchanges are in the capillaries that form blood in plasma.

Functions of the kidneys

The kidneys perform the following additional functions that are not directly related to the formation of urine: secretion of renin, production of erythropoietin, and activation of vitamin D. When blood pressure decreases, the juxtaglomerular cells in the walls of the afferent arterioles secrete the enzyme renin.[18] Renin then initiates the renin-angiotensin mechanism to raise blood pressure. The end product of the mechanism is angiotensin II, which causes vasoconstriction and increases the secretion of aldosterone, both of which cause vasoconstriction and increase the secretion of aldosterone, which help raise blood pressure[11,14,18] (Figure 3).

A normal blood pressure is essential to normal body functioning. One of the most serious changes is a sudden, drastic decrease in blood pressure, as would follow severe trauma/hemorrhage and will initiate the formation of angiotensin II. In these ways, the kidneys help ensure that the heart has enough blood to pump to maintain cardiac output and blood pressure.[18,19]

Erythropoietin is secreted whenever the blood oxygen level decreases (a state of hypoxia) (Figure 4). Erythropoietin stimulates the red bone marrow to increase the rate of RBC production (erythropoiesis). With more RBCs in

circulation, the oxygen-carrying capacity of the blood is greater, and the hypoxic state may be corrected.[18,19]

Vitamin D exists in several forms which are converted to calciferol (D2) by the kidneys (Figure 5). Calciferol is the most active form of Vitamin D, which increases the absorption of calcium and phosphorus in the small intestine.[18,19]

The kidneys are the principal regulators of the internal environment of the body. The kidneys either directly or indirectly regulate the composition of all body fluids as they form urine from blood plasma.[11,12,18,19] The kidneys are also of great importance in regulation of the pH of the body fluids.

Humans are able to live with just one kidney; however, if both fail or become diseased, transplants are possible. The first kidney transplant was performed in 1953. Since the donor and recipient were identical twins, rejection was not a problem. Thousands of kidney transplants have been performed since that time, and the development of immunosuppressive medications has permitted many people to live a normal life with a donated kidney.[3,4]

Transitional cell cancer of the renal pelvis

The major prognostic factor at the time of diagnosis of upper tract transitional cell cancer is the depth of infiltration into or through the

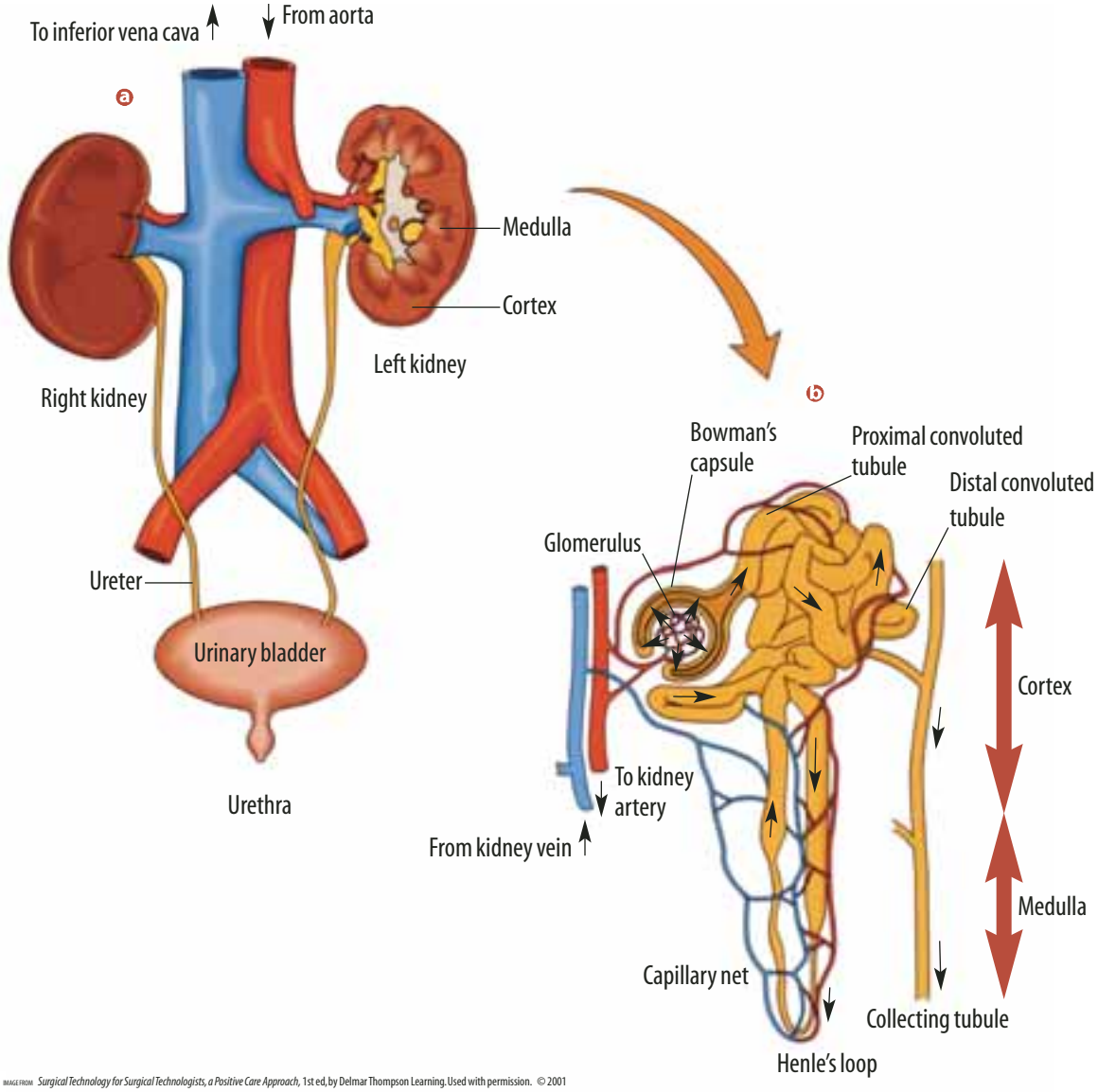


IMAGE FROM *Surgical Technology for Surgical Technologists, a Positive Care Approach*, 1st ed, by Delmar Thompson Learning. Used with permission. © 2001

FIGURE 1

a View of the kidneys, ureters and bladder

b A nephron unit and related structures. Arrows indicate blood flow.

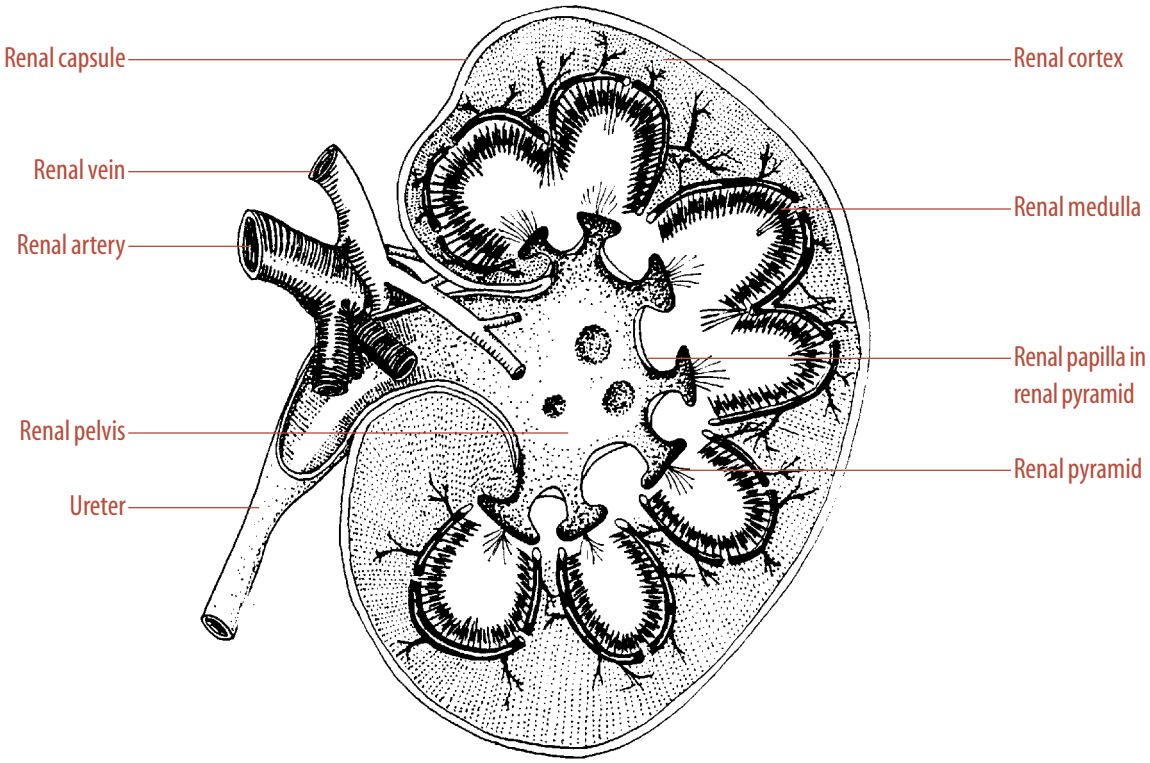


IMAGE Courtesy of Richard Wills, MD

FIGURE 2

Cross section of the human kidney

uroepithelial wall.[11,12,13] However, even if cystoscopy and pyeloscopy are successfully implemented, accurate assessment of depth of invasion is difficult. Therefore, total excision of the ureter with a bladder cuff, renal pelvis, and kidney is recommended in an attempt to provide the greatest likelihood of cure.[1,4,13]

Most superficial tumors are likely to be well differentiated, and those tumors that are infiltrative are likely to be poorly differentiated.[1,3] The incidence of synchronous or metachronous contralateral upper-tract cancer ranges from 2-4%; the incidence of subsequent bladder cancer in the setting of prior upper-tract transitional cell cancer ranges from 30-50%.[1,3,4,13] When involvement of the upper tract is diffusing, the likelihood of subsequent development of bladder cancer increases to 75%. DNA ploidy has not added significant prognostic information beyond that provided by stage and grade.[1,3,4]

The majority of upper-tract uroepithelial tumors are of transitional cell histology.[1] Squamous cell cancer of the urinary tract constitutes less than 15% of the tumors of the renal pelvis and a smaller percentage of ureteral tumors and is often associated with chronic calculus disease and infection.[1,4,11,13]

Grade of transitional cell cancer of the upper tract has generally been found to correlate with stage. Superficial tumors are generally graded I

or II, whereas the majority of infiltrative tumors are grades III and IV. Prognosis is worse for high-grade (III and IV) than for low-grade (I and II) tumors.[1,4,11,13]

Though comparable in many respects to staging systems described for bladder cancer, unique structural aspects of the renal pelvis and ureter have led to several differences in the classification schema of tumors that involve the upper tracts.[1,4,11,13] Clinical staging is based on a combination of radiographic procedures (intravenous pyelogram, computed tomographic scans) and more recently, ureteroscopy and biopsy.[4]

The advent of rigid and flexible ureteroscopic techniques has permitted endoscopic access to the ureter and pelvis.[4,5] This may permit greater accuracy in preoperative definition of the stage and grade of an upper-tract neoplasm. In addition, fulguration and endourological access permits resection or laser coagulation of highly selected low-stage, low-grade lesions of the ureters.[3,4,5,14] However, this approach is still within the realm of investigation since there is the possibility of inaccurate assessment of the stage and extent of disease, and the adequacy and risks of such treatment have not yet been defined.[1,3,4,12] Because of the inaccessibility of ureteral and pelvic anatomy, accurate staging requires pathologic analysis of the surgically excised specimen.[1,3,4,12,14]

Table 1 **TNM definitions[4]**

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(For renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
T4	Tumor invades adjacent organs or through the kidney into perinephric fat

Regional lymph nodes (N)[4]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but no more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

Note: Laterality does not affect the N classification.

Distant metastasis (M)[4]

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

The American Joint Committee of Cancer (AJCC) has designated staging by TNM classification (Table 1) to define carcinoma of renal pelvis and ureter.[4] Table 2 shows the AJCC stage groupings. Patients may also be designated as having localized, regional or metastatic disease as follows:

Localized

Patients with localized disease may be classified into three groups.

Group 1: Low-grade tumor confined to the urothelium without lamina propria invasion (Papilloma Grade I transitional cell cancer).[1,4,11,12,13]

Group 2: Grade I-III carcinomas without demonstrable subepithelial invasion or focal microscopic invasion or papillary carcinomas with carcinoma in situ and/or carcinoma in situ elsewhere in the urothelium.[1,4,11,12,13]

Group 3: High-grade tumors that have infiltrated the renal pelvic wall or renal parenchyma or both, but are still confined to the kidney. Infiltration of muscles in the upper tract may not be associated with as much potential for distant dissemination as appears to be the case for bladder cancer.[1,4,11,12,13]

Regional

Group 4: Extension of tumors beyond the renal pelvis or parenchyma and invasion of peripelvic

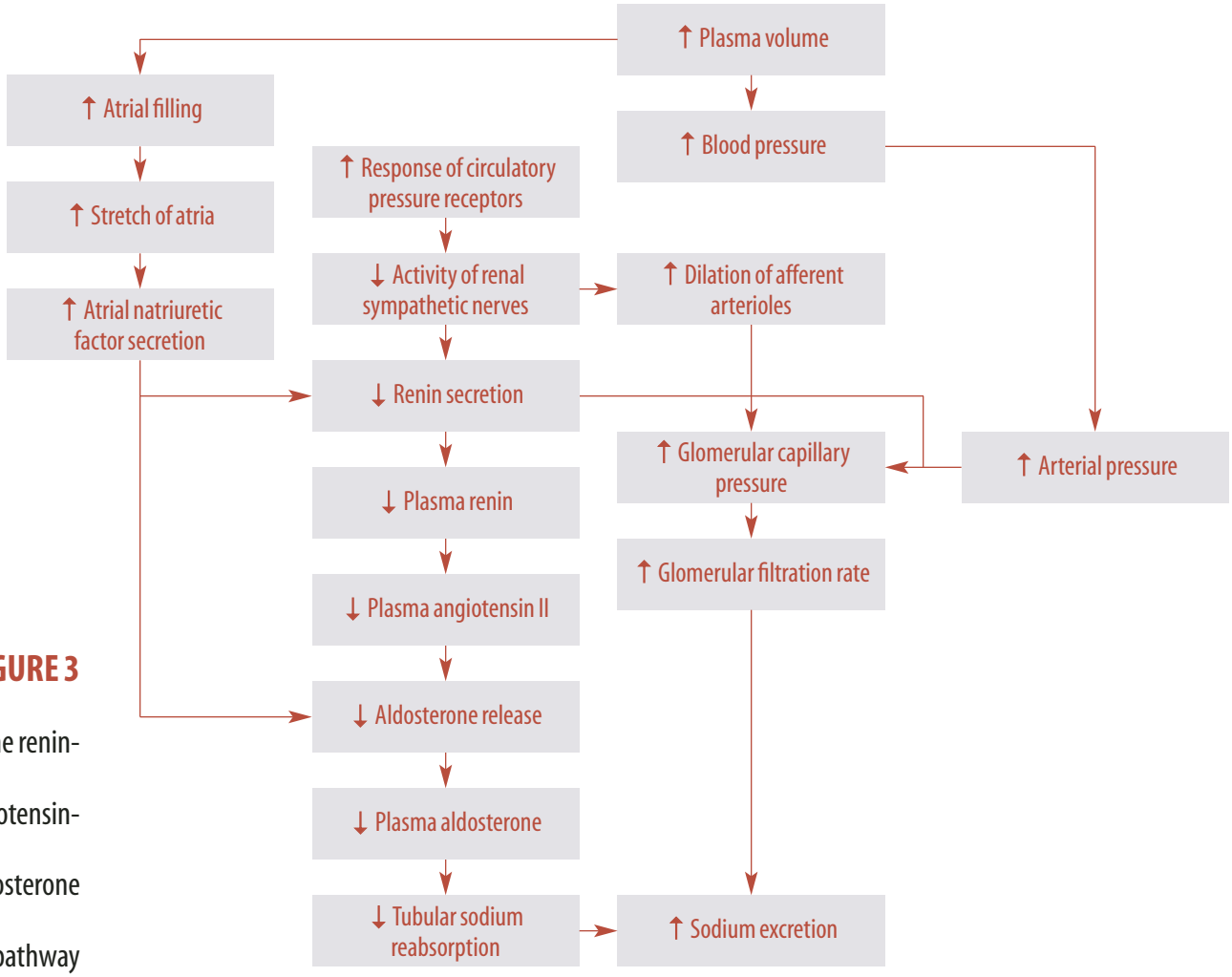


FIGURE 3

The renin-angiotensin-aldosterone pathway

and perirenal fat, lymph nodes, hilar vessels, and adjacent tissues.[1,4,11,12,13]

Metastatic
Spread of the tumor to distant tissues.

Each of these classifications has been subclassified into categories of unicentricity or multicentricity, the latter being an indication of a more pervasive tumor diathesis and generally a more ominous course.

Although the classifications listed above have prognostic significance, they can only be determined at the time of nephroureterectomy, which is the treatment of choice for patients with this disease.[1,4,5] Because of the high incidence of tumor recurrence within the intramural ureter among patients who have had incomplete excisions of this area, nephroureterectomy should include the entire ureter and a margin of periureteral orifice mucosa (bladder cuff).[1,3,4,5]

A TNM system for staging has been established and has demonstrated accurate predictions of survival. The TNM staging system may be a better predictor of prognosis than tumor grade, although both are strongly predictive of survival.[4] In one report, median survival for patients with tumors confined to subepithelial connective tissue was 91.1 months compared to 12.9 months for patients with tumors invading the muscularis and beyond.[2,3,4] Cytologic analysis promises to identify low-stage, low-grade tumors at high risk of recurrence by virtue of their aneuploid histograms.

The rarity of synchronous bilateral renal pelvic neoplasia, the low incidence of a synchronous development of contralateral upper-tract tumors, and the increased risk of tumor recurrence in the ipsilateral ureter distal to the original pelvic tumor are the rationale for total nephroureterectomy with bladder cuff in the setting of most renal pelvic transitional cell cancers and ureteral cancers.[1,2,3,4]

Contemplation of anything less than total excision must take into account the potential risk for tumor recurrence anywhere in the upper-tract unit. In other than univocal, low-grade, low-stage renal pelvic tumors, the probable extensive involvement of both contiguous and noncontiguous sites would appear to make segmental excision an unnecessary portion with a potentially serious risk. However, an operative possibility includes segmental excision of a particular lesion.[1,2,4] If the extent of a tumor can be determined by intraoperative assessment, and frozen section histologic diagnosis confirms low-grade, univocal tumor of limited size, then segmental excision is possible. This approach should be reserved for highly selected patients, including those who have solitary kidney or decreased renal function and who require maximal preservation of renal tissues.[1] The likelihood of tumor recurrence in this setting and of extension of disease outside the renal pelvis once the pelvis has been violated, is a serious risk that must be heavily considered when offering a patient this therapeutic option.[3,4]

Table 2 **AJCC stage groupings[4]**

Stage 0a	Ta, N0, M0
Stage 0is	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0
Stage IV	T4, N0, M0
	Any T, N1, M0
	Any T, N2, M0
	Any T, N3, M0
	Ant T, Any N, M1

Ureteral transitional cell cancer may readily offer the possibility of segmental excision if the absence of proximal disease can be documented.[1,4] In this setting, attention is focused on the ease of reconstruction of the ureter and restoration of ureterovesical continuity. This is most feasible if the cancer is in the distal ureter. If partial ureterectomy is possible and proximal

disease has been excluded, then segmental excision and ureteral reimplantation can be performed.[3,4]

Systematic, regional lymph-node dissection in conjunction with nephroureterectomy or segmental excision has not been found to enhance the effectiveness of surgery if tumors are of high-grade or high-stage, since in these instances the overall results are so poor.[1] Correspondingly, lymph node involvement is uncommon in low-stage disease, and lymphadenectomy is therefore unlikely to affect spread of the tumor. Thus lymph node dissection at the time of nephrectomy may offer prognostic information, but little, if any, therapeutic benefits.[1,2,4]

ly or percutaneously may permit destruction of a primary cancer.[4,5] Introduction of cytotoxic agents has also been employed. Although a biopsy can be taken for staging purposes, the accuracy of this still remains to be determined. The efficacy of treatment by these maneuvers has not been established.

1. Electroresection and fulguration or laser fulguration (if superficial).[3,4,5]
2. Any parenchyma sparing procedure (segmental resection; ureteroscopic or percutaneous resection/fulguration/laser destruction) if renal unit is solitary or renal function is depressed.[3,4,5]

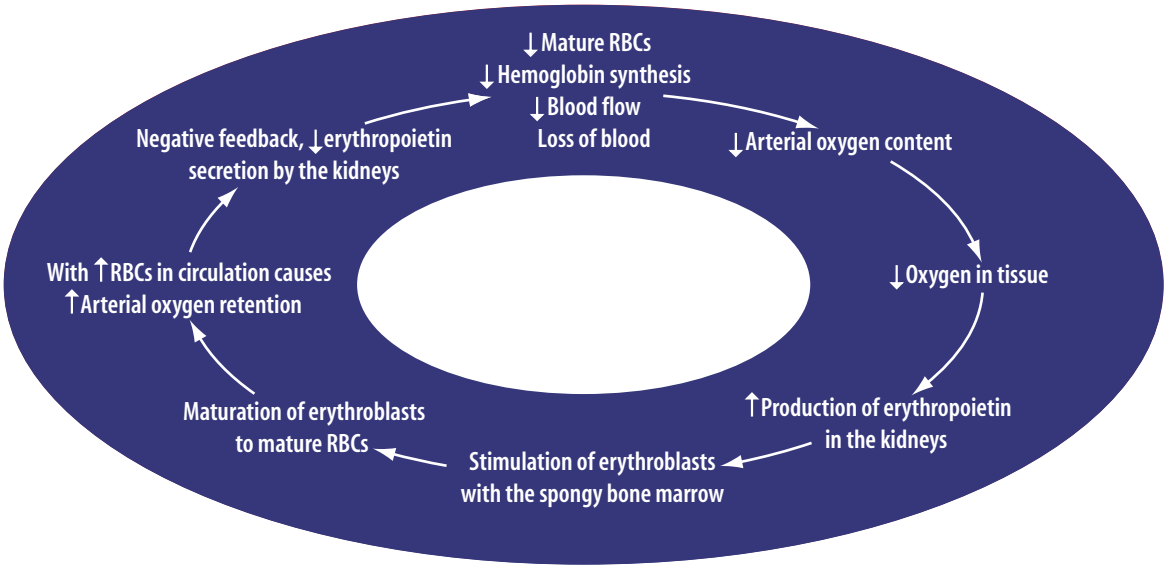


FIGURE 4
Erythropoietin regulation of erythropoiesis

Treatment options

Standard

1. Nephroureterectomy with cuff of bladder.
2. Segmental resection of ureter—only if tumor is superficial and located in the distal one-third of ureter.

Under clinical evaluation

The development of new instrumentation for endourological treatment of upper-tract transitional cell cancer has provided new options for regional management of these cancers.[1,3,4] Introduction of electrofulguration and resection instruments or laser probes either transureteral-

3. Intrapelvic or intraureteral cytotoxic (tholepin, misogynic, doxorubicin) or immunologic/inflammatory (BCG, interferon) therapy for superficial transitional cell cancers in the bladder have led to the occasional use of these agents in the treatment of upper-tract cancers. The use of this approach will be limited by: the extent of disease in the renal pelvis; access of agents to the area of disease; the sensitivity of the cancer being treated; and the adequacy and accuracy of initial tumor staging and continuing monitoring. Long-term follow-up of the results of such treatments has generally not been reported, and the efficiency of this approach cannot be

assessed, largely because experience has been limited to those patients whose compromised clinical status (solitary kidney, renal failure, medical risks for surgery) may have influenced clinical outcome.[2,3,4,5]

4. Laser vaporization/coagulation. Transurethral and percutaneous access to the upper-tract has permitted the use of laser therapy in the control of superficial upper-tract transitional cell cancer. This approach is dependent on accurate staging and adequate visualization of the lesions that need to be coagulated. Results of this approach are, at present, too preliminary to assess. Therapeutic efficiency, however, will depend on staging accuracy of initial treatment and ease of monitoring such patients for disease recurrence and possible progression.[4,5]

Treatment of extensive regional disease has not had well-documented success thus far by either radiation or systemic chemotherapy. Patients with extensive regional disease should be considered for clinical trials.[4,5]

Conclusion

The prognosis for any patient with metastatic or recurrent transitional cell cancer is poor. The proper management of recurrence depends on the sites of recurrence, extent of prior therapy, and individual patient considerations. Chemotherapy regimens that have been shown effective for metastatic bladder cancer have generally been applied to transitional cell cancer arising from other sites. Patients with distant metastases have a poor prognosis, and can be appropriately offered investigational treatment on a clinical trial.[4,5]

In patients with metastatic or recurrent transitional cell carcinoma of the bladder, combination chemotherapy has produced high response rates and occasional complete responses.[2,3,4,12] Results from a randomized trial that compared M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) to single-agent cisplatin in advanced bladder cancer show a significant advantage with M-VAC showing a positive advantage at 39%. Other chemotherapy agents that have shown activity in metastatic transitional cell cancer include the following: palliate, ifosfamide, gallium nitrate, and gemcitabine. Ifosfamide and gallium have shown limited activity in patients previously treated with cisplatin.[7,11,12,13,14]

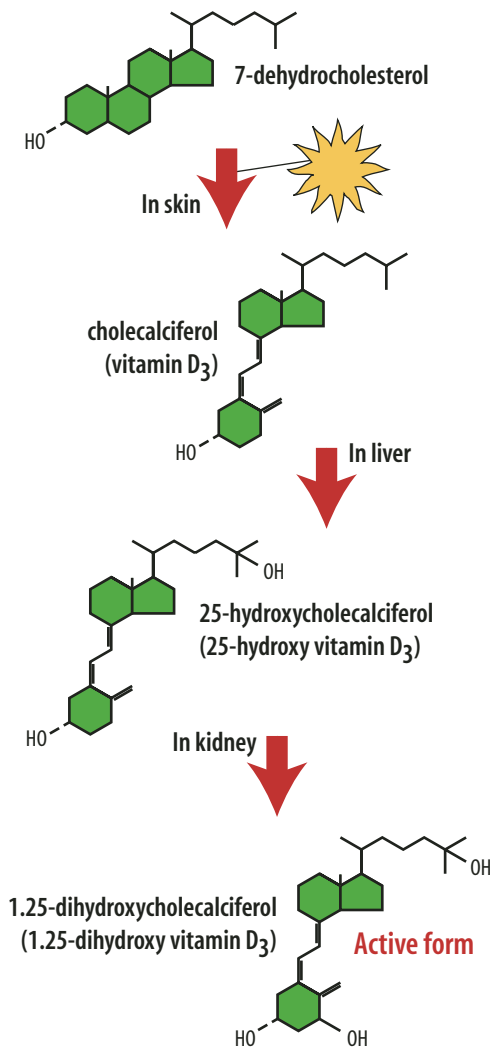


FIGURE 5

Synthesis of Vitamin D

About the authors

Richard Evans Wills, MD, FACSM, FRSM, MBA, is professor of clinical medicine, at Stevens-Henager College in Salt Lake City, Utah, and owner of Intermountain Medical Research and Development.

Michael Norton, DC, is an adjunct professor at Stevens-Henager College and owner of Chiropractic Health and Fitness.

Lara Creasey Ketten, MA, is an adjunct professor at Stevens-Henager College.

Jane Vincent Young, MA, is a teaching assistant and adjunct professor at Stevens-Henager College.

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