Staging of Genitourinary Malignancies: Updates and Challenging Areas

Jeff Simko, Ph.D., M.D.
UCSF Departments of Anatomic Pathology and Urology

The goals of this presentation are to provide an update of recent changes to the tumor staging rules used in the United States and around the world (i.e. the TNM system), and to illustrate and highlight challenging areas in the determination of tumor stage for genitourinary malignancies.

The most important issue that all surgical pathologists must be certain that they are aware of at this immediate time point is that the AJCC/UICC staging rules have been changed and updated from the AJCC sixth edition staging rules, to the seventh edition effective January 1, 2010. ALL resected malignant tumors should now be staged using the rules in this new 7th edition staging manual; this became available in late 2009 and is a requisite tool for all pathologists diagnosing carcinomas. It can be purchased through a number of vendors, although explanations of the staging rules, and recent changes are also available at the websites of both world bodies that are charged with maintaining the integrity of the TNM system; the AJCC (American Joint Committee on Cancer, http://www.cancerstaging.org) and UICC (International Union Against Cancer, http://www.uicc.org/resources/tnm).

Some general changes that apply to nomenclature and reporting of TNM for all tumors have occurred, and I strongly suggest review of these, which are presented in great detail in chapter 1 of the 7th Edition. I highlight some of the more important ones here. Most importantly, for surgical (p) staging, the pMX category has been dropped, so if a surgical resection does not contain distant metastasis, the tumor would be staged with pTN, rather than pTNMX (i.e. no more stage pMX); a pM1 can be used if tissue diagnosis of distant metastasis is obtained at surgical resection. For lymph nodes, discrimination between direct extension into a lymph node is not considered different from metastatic spread; both are considered lymph node metastasis for staging. Similar to the sixth edition for colorectal tumors, the approach to round collections/deposits of tumor within adipose tissue in the lymph drainage area of a nearby primary tumor is to diagnose them as positive lymph nodes for staging purposes for all tumor types. The additional classifiers added to TNM (e.g. “y” for neoadjuvant therapy, “r” for recurrence after a disease-free interval, “m” for multiple simultaneous tumors in the same organ) have been clarified and examples of their use presented in tabular form. Additionally, while the 6th edition seemed to highlight extension of the TNM system to include G (grade), L (lymphatic involvement), V (vein involvement), and R (margin status), the 7th edition seems to backpedal from the use of these additional staging categories with only the R category seriously discussed; R0 = margins free of tumor, R1, microscopic tumor at resection margin, and R2 gross tumor at resection margin. Lastly, the 7th edition is ~50% thicker than the 6th edition. It has a substantially increased number of diagrammatic explanations of staging scenarios, more survival and outcome curves (Kaplan-Meier or KM curves), and for the most common tumors (e.g. colon, lung, breast, prostate) sections describing so called “prognostic features.” These are features, that while not necessarily anatomic, or even part of TNM staging, have been shown at various levels of evidence, to have either prognostic and/or predictive value, and are recommended to be included in pathology reporting if at all possible. Some of these are well
known and have been common in oncologic practice for a number of years (e.g. ER, PR, Her2 for breast cancers, serum PSA level for prostate cancer), while others are relatively new and require molecular testing (e.g. KRAS mutation status for colorectal cancer; expression array analysis for breast cancer). In a sense, I find these sections extremely interesting and give a nice view of where tumor pathology is currently headed, and also what the future might look like (although if the costs of sequencing continue to decline at current rates, we likely will just be sequencing every patient's tumor that comes into the lab; stay tuned).

While this new 7th edition manual is rather comprehensive, there will always be some rare situation where a tumor presents in a manner that does not fit neatly into any particularly-recognized staging scenario. Fortunately, there is aid available for such cases, either at the TNM helpdesk of the UICC (http://www.uicc.org/tnm-help-desk) or the Inquiry and Response System at the American College of Surgeons Committee on Cancer website (http://web.facs.org/coc/). I've used the TNM helpdesk in the past and had rapid response times with excellent explanations, but according to others, recent attempts have taken up to a full week for a response. This website recently was shut down as well, but I just noticed that it is back up for the time being. For this lecture, I reviewed the ACSCOC website and found the database of previous questions not all that useful, however you can still submit your own questions.

Changes to the staging rules for all tumors, including genitourinary malignancies are presented in the 7th edition manual; the rest of this discussion will focus on areas recognized as challenging for the determination of accurate staging.

Renal tumors:
To start, I find that the gross location, and gross pattern of tumor growth can be great aids in getting an excellent idea as to the type of tumor you might be dealing with right from the start, which can aid in taking appropriate sections for staging. The most common primary renal tumors (e.g. clear cell, papillary, chromophobe and unclassified) seem to more commonly grow in expansile rather than infiltrative fashion (pushing tissue out of their way, rather than infiltrating around innate structures) thereby forming masses, seem more commonly located in the cortex rather than medulla and also appear more encapsulated / pseudoencapsulated. Tumors like urothelial carcinomas (transitional cell carcinoma), collecting duct carcinomas and medullary carcinomas, while they certainly can form mass lesions, certainly have a more infiltrative pattern of growth and sinuate around and surround native structures rather than push them out of the way. They also appear more likely to be centered in the medullary region rather than cortex, although when they get very large this can become difficult to recognize. Not always, but the vast majority of times, urothelial carcinoma involves the renal pelvis or more distal structures, and likely never starts as a primary tumor in the kidney (one might debate this, but I would guess that there have been rare instances that it has; I would still stage such tumor, if it is truly invasive, as renal pelvis tumor involving kidney with a pT3 stage). With their penchant for infiltrative growth, these tumors do not appear encapsulated, and they also have the potential to involve kidney tubules as purely in situ tumors without invasion in some instances (urothelial carcinoma in situ; technically pTis).
Renal vein invasion: Gross invasion of the renal vein or its smooth muscle-walled branches is now staged as pT3a (pT3b in the 6th edition). From the definition, this determination is supposedly made by gross examination. However, most times, the walls of these veins are very thin, and determination as to whether they contain smooth muscle or not really requires histologic confirmation. This can be difficult to recognize when the vessel is stretched and dilated by the tumor, however I find the use of trichrome stains extremely useful for highlighting smooth muscle of vessel walls, as opposed to the fibrosis seen due to tumor capsule formation. Elastin stain may also be helpful, but I find that sometimes the vessel is so stretched by tumor, that the elastin fibres appear fragmented, making it much more difficult to interpret. One could also use immunohistochemistry for smooth muscle, but that seems a bit overkill to me. Still, whenever faced with a suspected primary malignancy of the kidney, one should open the hilar vessels from the renal vein and artery just as one does in autopsy evaluations, but only after taking and submitting the vessel margins first. Such an approach will allow one to see if any large vascular structures are involved by tumor, and help guide sampling for accurate tumor staging (see references for details). Clear cell renal cell carcinoma clearly has an affinity for vascular spaces, and these tumors are commonly hemorrhagic and within vessels. Some believe that whenever such tumors form nodules in the renal hilum, that it is due to vein invasion at these locations, so such nodules really need to be sampled to evaluate for either blood vessel or renal sinus fat invasion in these areas.

Extension of tumor from the renal vein into the vena cava below or above the diaphragm is considered pT3b and pT3c respectively. In such cases, the surgeon will extract this tumor from the vena cava, so one must correlate with operative findings for determining the extent of the thrombus. This also requires histologic confirmation, as sometimes such thrombi are not carcinoma, but rather fibrin and/or a xanthomatous reaction that can mimic the histology of carcinoma. Sometimes immunohistochemical studies are needed to discriminate between these possibilities and /or rule out partial tumor involvement of an otherwise fibrin-inflammatory thrombus.

Related to this, tumor thrombus in renal vein may appear to extend beyond the vein margin in the resected specimen received in pathology, and can lead to erroneous diagnosis of a positive surgical margin at the renal vein. However, careful inspection of this thrombus usually shows round contours with no transections or crush defects that one would expect from cross-clamping. Via imaging techniques, the surgeon should know the extent of the thrombus before clamping and incising the renal vein, in order to avoid creation of tumor embolus. After such is done, the vein commonly retracts to expose the thrombus and can create an artificial positive margin. For this reason, I do not report such a finding as a positive margin, but rather leave margin status indefinite in the report and describe the possibilities in the comment. I reserve reporting of tumor present at this margin to cases where I actually see tumor infiltrating into the renal vein wall of the margin section. Such is most certainly an indication that microscopic tumor is in the residual of this vessel wall left in the patient. This discussion is not unimportant; I have seen the reporting of artificially exposed thrombus as “positive” margins in the past, which was leading to disqualifying these patients from clinical trials that they may otherwise have benefited from. Therefore, care should be taken in the reporting of these margins.
Penetration of renal capsule (pT3a): Many times, renal cortical tumors extend a significant
distance beyond the natural contour of a normal kidney to a degree that one would think that
there is no possible way that such tumors cannot be infiltrating the perirenal fat. However, after
taking many sections that all show a fibrous capsule without tumor cells actually adjacent to
adipose tissue, one still might be tempted to stage such a tumor pT3a. Many times, very careful
microscopic inspection of the capsule, even for very large tumors, will allow one to recognize
crushed and attenuated benign renal tubules within the capsule; such is indicative of crushed
kidney between the tumor and the fat, and clearly allows one to avoid overstaging. Another aid
to avoiding this pitfall is the consideration that if tumor were truly infiltrating fat, such fat would
be adherent to the tumor. If the fat falls from the capsule during an incision during grossing, or
is highly mobile, it most certainly is not infiltrated by tumor. One should focus the sampling to
areas where fat is adherent to the tumor capsule, and/or where the tumor contours are irregular.
I believe that these approaches can streamline sampling, as well as increase detection of tumor
infiltration of perirenal fat in these instances. Unfortunately, renal sinus fat is naturally adherent
and immobile, thus preventing one from taking advantage of these approaches, so such
requires ample sampling as described in the vein section above (references).

Tumor beyond Gerota's fascia is pT4: Gerota's fascia is a thin transparent membrane that
separates perirenal fat adherent to the kidney from the pararenal fat of the retroperitoneum, and
creates a plane that allows for these structures to be easily separated. Pathologists usually only
get to appreciate this anatomical structure when they remove kidneys at necropsy, and this
sometimes leaves one wondering where this structure is in their radical nephrectomy specimen.
When one receives a nephrectomy specimen that is covered by fat, the margin of the specimen
most likely represents the limit of Gerota's fascia. If tumor is present at this margin, I do not
report the tumor as pT4 but rather just report the size and location of the positive margin, and
leave it to the surgeon to determine if this represents a Gerota's violation or not. The only time
that I report on the Gerota's fascia status, is if I have portions of other organs in the specimen,
such as liver, colon, pancreas or spleen, and I have tumor adjacent to them or into them.
Almost certainly the tumor has gone beyond Gerota's fascia if the surgeon is forced to excise
these other structures.

Adrenal Gland and Renal Tumors: The 7th edition staging manual clarifies that if tumor directly
infiltrates the adrenal gland from a primary renal tumor, it is staged pT4, and if deposits of renal
tumor separate from the primary mass are identified in the adrenal gland, it is staged pM1. This
issue is rather straightforward, except that sometimes it is difficult to discriminate a well
differentiated clear cell renal cell carcinoma from adrenal cortical tissue. Even with substantial
experience, this sometimes requires immunohistochemical study to better clarify, and use of
melan-A, inhibin and synaptophysin markers can aid in recognizing the innate adrenal tissue
from any metastatic tumor. Keep in mind that there are reports that adrenal cortical carcinomas
are commonly positive with markers thought to be specific for renal tumors, such as RCC
antigen and PAX-2 (references). While I have yet to see this phenomenon in native benign
adrenal cortical tissue, such is enough to make me proceed with caution when using such
immunohistochemical stains for this purpose. Lastly, one must also be cognizant of the
possibility that benign adrenal cortical rests may be present within the kidney. While this
phenomenon is rare, it can be mistaken for a renal cortical tumor on imaging, and possibly lead to a resection and diagnosis as clear cell renal cell carcinoma if one is not familiar with this possibility.

Urothelial-lined structures; the renal pelvis, ureter, urinary bladder and urethra:
Staging rules for all of these structures are almost the same, and are actually very similar to those of the tubular viscera of the gastrointestinal tract. These rules are easily illustrated in diagrams (including those in the staging manual), however a number of challenges exist in actually recognizing tumor at these various stages.

Lamina Propria Invasion (pT1): In biopsies, whether dealing with a flat urothelial carcinoma in situ (pTis) or a non-invasive papillary urothelial carcinoma (pTa), it can be challenging to recognize the earliest manifestations of invasion (pT1). This is especially true for papillary tumors with an inverted growth pattern, where large bulbous masses can appear to extend to great depths of the lamina propria, tempting one to interpret as invasion. If one recognizes that these masses have smooth contours along the interface with the basement membrane, this is a sign that the tumor is still in situ (pTa for papillary tumors). When such tumors become infiltrative, they almost always display some key characteristics that I like to use to recognize them; 1) Individual cells or very small nests or clusters with irregular contours, 2) a retraction artifact around invasive tumor cell clusters (in fact it gives the false impression of lymphatic invasion, which almost is never the case with these small clusters of cells), and 3) so called “paradoxical maturation” which is actually a relative decrease in the nuclear-to-cytoplasmic ratio of the tumor cells once they are invasive, as compared to any overlying in situ component.

One must always consider a couple of exceptions to the generalizations made above. First, sometimes rare single stromal cells with bizarre-appearing atypical nuclei are seen in lamina propria of the urinary bladder. However, if one looks closely, this atypia is more of the degenerative type, and these cells never form masses indicative of proliferation or tumor, and they do not have retraction artifact around them. Second, rare small clusters of benign epithelial cells are sometimes present in the lamina propria, and sometimes these clusters have irregular contours and even satellites of individual cells, but again, these cells lack retraction artifact around them and also lack any cytologic atypia. Related to this, and probably the greatest pitfall, is when one is dealing with the rare tumor called the nested variant of urothelial carcinoma. These tumors are challenging to recognize because they characteristically do not have retraction artifact, do not have obvious irregular contours of the infiltrating nests (although these irregularities are there if one looks closely, but they are deceptively subtle), and while they actually do have diagnostic nuclear atypia, it appears deceptively bland because nuclear membrane irregularities are minimal and rather uniform (all nuclei look similar, but the nuclei are mildly enlarged and the chromatin is abnormal). Unfortunately, usually the biggest tipoff that one is dealing with this tumor, is the huge number of small nests that are present.

Smooth muscle in biopsies of urothelial tract: The staging manual makes the point of discriminating between superficial lamina propria (superficial to muscularis mucosa; pT1a) and deep lamina propria (deep to muscularis mucosa; pT1b) invasion. In practice, this is only possible with well-oriented specimens, such as cystectomy specimens, because the muscularis
mucosa can be of variable thickness and completeness (even can be absent) in these structures. If one does see INVASIVE tumor around both sides of scant smooth muscle bundles, I myself feel confident that the tumor is at least stage pT1b. Keep in mind that von Brunn’s nests and/or cystitis cystica can appear to present around muscularis mucosa bundles due to tangential sectioning of such, and this could give the appearance of “invasion” if seen on both sides of smooth muscle bundles, so one should make certain that the cells appear invasive.

More challenging, and of much more importance clinically, is recognizing muscularis mucosa involvement (pT1b) from that of muscularis propria (pT2), as this is a point where therapeutic choices are radically different. Unfortunately this is many times impossible, because the specimens are commonly crushed, cauterized and/or poorly oriented, and the smooth muscle present is scant. I only feel confident of it being muscularis propria when I have at least a few large bundles of dense smooth muscle in the biopsy, and/or it happens to be extremely well-oriented tissue (yes, I know, not very objective criteria here). The presence of fat is also unreliable, as it can be present in lamina propria. Recently, a new antibody called smoothelin has been described that is supposed to be helpful in discriminating between these muscle types, with muscularis propria staining more strongly than muscularis mucosa. As this is a relative difference in staining intensity, I personally find the interpretation of these stains to be extremely challenging. The presence of cautery always makes me uncomfortable with the interpretation of immunohistochemical reactions and I have also had cases where vessel wall smooth muscle was the strongest staining smooth muscle in the biopsy. There is a clear need to have additional aids to perform this important discrimination, and if one is able to comfortably apply and interpret the staining pattern of something like smoothelin to make this discrimination, it is a very good thing for their patients. In all of these cases, the presence or absence (or inability to determine with confidence) of muscularis propria in the specimen should appear in the pathology report of transurethral resections.

Invasion beyond the viscus (pT3): Attempts have been made to clarify the definition of extension of tumor beyond the urinary bladder wall into the pericystic fat (pT3a). It has been stressed that fat can be present within the urinary bladder wall, so one really must see tumor extend beyond the limits of the smooth muscle contours of the urinary bladder to recognize stage pT3a from that of tumor confined to outer portions of bladder (pT2b). I sometimes find this to be very challenging, as the limits of the detrusor muscle (muscularis propria of the bladder) can be very irregular in some cases, and drawing an imaginary line along the outer limit of the muscularis propria is open to various interpretations in such cases. If a strict definition is used that requires that tumor extend into fat beyond the most outer limits of the smooth muscle wall contour, we most certainly will see a stage migration downward, and a subsequent poorer prognosis for T2b-staged patients. Such may not be a bad thing, as in general, it is always better to lean towards understaging and “do no harm” than to overstage and “overtreat” when not necessary.

Prostate involvement (pT4): One of the most common, and significant mistakes that I see in staging urinary bladder tumors is in recognizing invasion of the tumor into the prostate gland, which is pT4. This corresponds to direct extension of the invasive portion of a primary tumor of
the bladder through the bladder wall and into the prostate gland, and is best recognized by taking longitudinal sections parallel with the course of the urethra that also include the tumor, and junction of the urinary bladder wall and the prostate gland. A very common occurrence is the extension of urothelial carcinoma in situ along the urethra into the prostate gland, with subsequent focal invasion of the prostate gland at this additional location. Such a scenario is not uncommon, but it does not correspond to pT4 disease. This really needs to be considered a different primary invasive tumor in a different organ (the prostate gland), and therefore should be staged separately from any other bladder or urethral tumors that are present.

Prostate gland staging:
Urinary bladder invasion (microscopic -> pT3a; gross involvement -> pT4): The most significant change in prostate tumor staging is in the clarification of urinary bladder invasion by primary prostate adenocarcinoma. Such has always been staged as pT4 in the past, but microscopic invasion of detrusor muscle by prostate tumors has outcomes more in line with those of extraprostatic spread of tumor through the capsule (pT3a). This is now reflected in the staging changes of the 7th edition. Prostate tumor that grossly extends into the bladder from the prostate is still staged T4 (either pT4 or hopefully more commonly as cT4, as surgery for such patients is rarely indicated). With practice, this is actually easy to recognize. The smooth muscle of the prostate is very compact, and is not separated into separate fascicles the way that detrusor muscle is. By sectioning the bladder margin of the prostatectomy and submitting perpendicular sections of the margin, either radially (similar to what is commonly done for cervix) or preferably in a sagittal manner perpendicular to the bladder margin, and putting on edge so that approach of tumor to the margin can be recognized, the difference between detrusor and prostate smooth muscle easily can be appreciated, and determination of both bladder margin status and bladder muscle involvement can be performed easily and accurately.

Extraprostatic extension (pT3a): This has always been a controversial area because the prostate capsule is not a well-defined anatomic structure. Firstly, the capsule blends imperceptibly with fibrous tissue and the skeletal muscle of the urethra sphincter at the prostatic apex. For this reason, extraprostatic extension (EPE) is difficult to define at this location, and it is best to consider as pT2, even if tumor is seen microscopically into adjacent skeletal muscle bundles that commonly are scattered through the apical portions of the prostate (obviously if there is nothing but large fascicles of skeletal muscle in a specimen taken away from the apex, one should consider any tumor in such to be extraprostatic). Secondly, the anterior of the prostate is another location where the capsule is absent, but I will consider EPE whenever the tumor is infiltrating the loose fascicular bundles of smooth muscle that have the appearance of bladder wall muscle (as described above), and/or skeletal muscle, fibrous tissue or fat in this area. Fortunately, the majority of prostate tumors are located in the posterior portion of the gland where a “capsule” is more recognizable.

The Baylor group wrote an excellent report on the significance of various “levels” of “capsule” penetration and how they correlate with outcome a number of years ago now. These results showed a significant difference in PSA recurrence between tumors with clear infiltration of fat versus those that were not, and therefore a definition was established. However, this definition does not take into account the fact that prostate tumors can generate a fibrotic
desmoplastic response that can mask EPE if one applies this strict definition. This is also highlighted by a recent study performed by these groups to evaluate interobserver variability for diagnosing EPE and positive margins. In the study, a group of urologic pathologists met and came to consensus on a set of slides representing the spectrum of what did, did not and was equivocal for EPE, with 10 examples in each of these three categories. They then sent them to a set of volunteer or “test” pathologists also recognized as experts in the field. These volunteers were instructed to only diagnose these cases as positive or negative only (no equivocal). The results actually showed excellent agreement between all of the pathologists for both the positive and negative cases (and actually there was agreement for four of the 10 “equivocal cases as well), but interestingly there was one negative case that 10 of the 12 volunteers called positive, and it was an example where the tumor was expanding the capsule out into fat, but without any tumor actually in the fat itself. If one looks closely at this case, it is clear that the “test” pathologists were using different criteria for defining EPE relative to the consensus group.

In drawing an analogy from what one sees with renal tumors in the kidney, I do not feel comfortable diagnosing EPE just because the prostate gland has a tumor bulging from it. Tumors can stretch tissue and organ capsules without perforating them. For this reason, as well as it being clear that tumor into fat is too strict a definition, I have developed the habit of using trichrome stains to highlight both the intrinsic smooth muscle of the prostate stroma, as well as this fibrotic reaction to tumor. Essentially, if I see any prostate smooth muscle between the tumor and the nearest fat, I will not diagnose EPE, and conversely, if I see tumor within fibrosis that is between fat and the last fascicle of intrinsic prostate smooth muscle, I will diagnose EPE. Keep in mind that sometimes, “loose” smooth muscle bundles are seen separated from the prostate by fat. I rarely consider these bundles when evaluating EPE.

Sometimes one can see tumor in the fat at the ends of prostate needle core biopsies. If I see tumor within this adipose tissue, or within nerves within this fat, and it clearly cannot be due to artifactual displacement of either fat against tumor, or vice versa, I will diagnose this in the biopsy report, which is treated as pT3a. If either is immediately adjacent to each other, but tumor is not actually seen within (intermixed with) the fat, there is a possibility that each has been pressed up against each other during processing (artifact). In such case, it still is likely to be tumor in fat and pT3a. However, I describe this in the report stating that this likely represents EPE, but an artifact cannot be entirely excluded. While a recent study quantified the probability identifying intraprostatic fat in a radical prostatectomy specimen at ~4%, tumor was never seen in this fat, the collections of fat were all microscopic, the deposits were not near the edge of the prostate, and the images presented showed the fat to have extreme variability in size, raising the question as to whether any of these collections were gas mimicking fat. For these reasons, I still feel confident with the diagnosis of extraprostatic extension if I am certain that I am seeing this at the end of a biopsy core. This same approach can be taken for whether tumor is within seminal vesicle in a biopsy specimen.

Prostate resection margins positive for tumor (R1 or R2): A number of recent reports have indicated that positive resection margins are a significant risk factor for PSA recurrence after radical prostatectomy, and for this reason, some centers are more often offering adjuvant therapy when such is reported. While the presence of tumor at the margin is rather straightforward (tumor cells at the inked surface of the specimen), there are differences as to
whether the positive margin is due to surgical disruption of the capsule exposing the tumor (intraprostatic) versus a complete prostate resection with extraprostatic tumor spread present at the inked margin. Whichever of these two situations that happens to be responsible for the formation of positive margin (type of positive margin) should be reported. There also seems to be a relationship to the size and location of this positive margin as well, and as suggested by the recent CAP guidelines for reporting prostatectomy specimens, we are reporting the type, location, length and also Gleason pattern present at all positive resection margins identified.

References:
General:


Kidney:


Urothelial-lined structures (renal pelvis, ureters, urethra and urinary bladder):


Prostate Gland:


