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Summary of the Changes in the 8th Edition of the Tumor-Node-Metastasis Staging of Urological and Male Genital Organs Cancers

Erkek Genital Organ ve Ürolojik Kanserlerde 8. Tümör-Nodül-Metastaz Evrelemesindeki Değişikliklerin Özeti

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Introduction

Cancer staging has an important role in combating cancer. The American Joint Committee on Cancer (AJCC) has recently published the 8th edition of the AJCC Cancer Staging Manual (8E AJCC) (1). Contributions from genitourinary pathology are evident in the AJCC classification from many of the International Society of Urological Pathology (ISUP) consensus conferences on prostate, renal, testicular, and penile neoplasms that addressed staging issues and the 4th edition of the World Health Organization (WHO) classification of urinary and male genital organ tumors, which was published in early 2016 and was incorporated as the histologic classification system in the 8E AJCC, but the revised form of staging was not encompassed by the WHO classification totally (2). Actual grading systems were adopted for renal, prostate and penile cancers. In fact, major changes are fixed in testicular, penile, and prostate cancer.

This review summarizes the changes for renal, bladder, urinary tract, prostatic, testicular and penile cancers in the 8th tumor-node-metastasis (TNM) staging systems.

Changes in the 8th Tumor-Node-Metastasis Staging of Renal Cancers

Resection of the primary tumor along with the overlying Gerota's fascia and perinephric fat is recommended to interpret pathological staging of renal cancers (3,4). Changes in kidney cancer staging were minimal compared with other sites of the male genital and urinary tract. T3a criteria in the 7th edition are based on the pathologist's gross inspection of the hilar vessels. Sometimes tumor involvement of the renal vein and, its branches are unrecognized at the time of gross examination of the specimen. This problem is more common in partial nephrectomy specimens. Microscopic evaluation is much reliable to determine renal vein invasion. Therefore, clarifications were made in T3 category especially in T3a disease classification involving renal vein and its branches (Table 1). The wall of the renal vein and its branches may be thin with minimal muscular wall, and it may be so difficult to identify these structures (5). Tumor nodules and cords within the renal sinus mostly reveals intravascular tumor (5). Thus, the word "grossly" has been excluded in the current pathological T3a (pT3a) staging, and also invasion of the pelvicalyceal system is added in T3a category (Figure 1). Perinephric/sinus fat invasion should be confirmed microscopically. Invasion into fat by tumor cells with or without desmoplastic reaction, and vascular invasion in perinephric soft tissue are all evidence of perinephric invasion. Modifications in T3a may have impact on clinical trials for adjuvant chemotherapy when defining locally-invasive disease. Especially for clear cell and papillary renal cell carcinoma subtypes, the new four-tiered WHO/ISUP nucleolar grading is adopted instead of the traditional Fuhrman nuclear grading (2,4,6).

Changes in the 8th Tumor-Node-Metastasis Staging of Urinary Bladder Cancers

The AJCC provides a staging system for bladder cancer and the 8th edition was updated in 2017 (1).

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Most changes are in the N and M categories, but some clarifications and recommendations were made in the T categories (8). Although not formally included in the new staging system, several experts have recommended substaging of pT1 disease. Categorization of pT1 appears to have a prognostic value, with early invasion (microinvasive disease) into the lamina propria showing better outcomes than more advanced pT1 disease. The method of pT1 substaging has not been optimized, but microinvasive disease has been defined by different groups as invasive tumor of <1 high power field, greatest invasive tumor diameter of 1 mm, or invasive tumor above the muscularis mucosa extending to a depth of 2 mm or less. Categorizing pT1 disease is strongly recommended, by using one of the mentioned methods (9,10,11). There is limited data on the best methodology to stage urothelial carcinoma that concurrently involves the urinary bladder and the prostatic urethra (PU). It has been shown by several studies that bladder cancer with intraurethral prostatic stromal invasion has a better outcome than with transmural prostatic stromal invasion (12,13,14). In fact, in the 7th TNM edition, intraurethral spread to the prostate was excluded from pT4a, with the support of a number of studies (15,16). However, staging of intraurethral prostatic stromal invasion was not addressed properly. The 8E AJCC clarified that intraurethral prostatic stromal invasion should be categorized as T2 (per urethral staging and not bladder staging) and the bladder proper tumor be given a separate T category (per bladder staging). Still it is unclear how a concurrent urethral T2 tumor will impact a >T2 bladder proper cancer; emphasis in reporting should be given to the higher stage between the two (Table 1).

Most of the bladder diverticula are acquired and do not contain a muscularis propria layer (17). Therefore, tumor directly invades from the lamina propria into the perivesical soft tissue and diverticular invasive cancer has no T2 category (Figure 2). There are limited studies on diverticular tumor T categories and for this reason, it is not possible to make further comments on the prognosis (18,19,20).

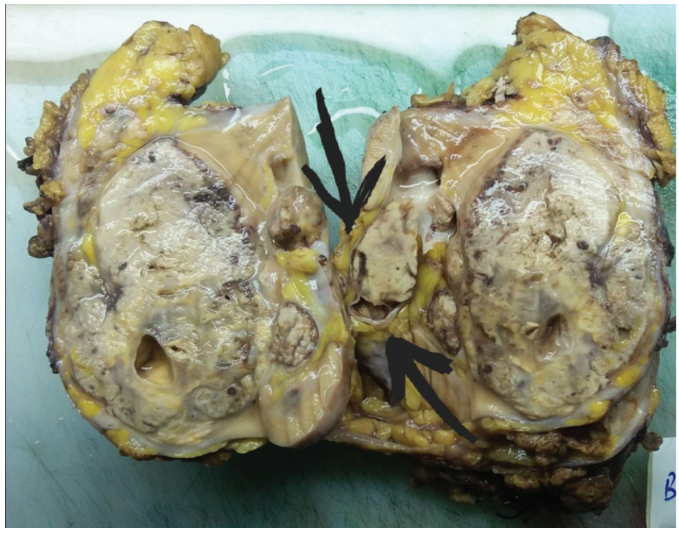

Figure 1. Renal vein invasion of the tumor

Based on contemporary mapping studies in which standard techniques were used to evaluate a pathologic specimen, excision of the primary nodal regions should result in an average of >12 lymph nodes (LNs) (21). Perivesical and non-perivesical LN involvements show no significant difference in survival (19). Therefore, in the revised form, perivesical LN among regional LNs is under the N category. By the way, 8E AJCC now classifies LN positivity beyond the common iliac as M1a and all other non-LN metastasis as M1b.

Changes in the 8th Tumor-Node-Metastasis Staging of Renal Pelvis and Ureteral Cancers

In fact, there is no obvious change in renal pelvis and ureteral tumors. In the 7th AJCC edition, metastatic LN greater than 5 cm was classified in the category of N3, however, in the revised form, it is now evaluated in N2 category (1).

Changes in the 8th Tumor-Node-Metastasis Staging of Urethral Cancers

Urethral staging criteria are used to classify carcinomas arising from the urothelial, glandular, or squamous lining of the PU, penile urethra or female urethra. Assignment of stage for urethral tumors is based on invasion into distinct regions, which is based on depth of invasion in the penile urethra and female urethra and into specified stromal elements in the PU. In the

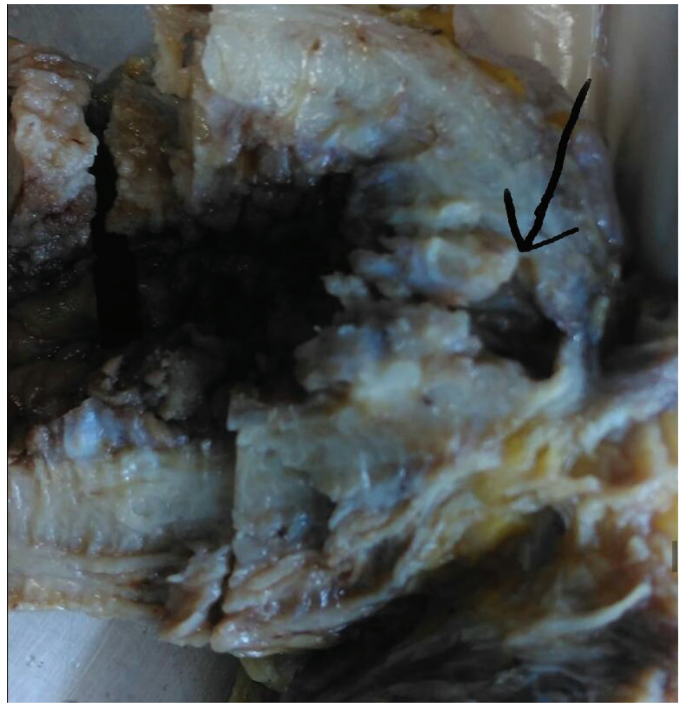

Figure 2. Invasive cancer with diverticulum in the urinary bladder

revised form, non-invasive papillary carcinomas of the urinary tract are subdivided into low-grade and high-grade disease. For prostatic urothelial carcinoma, carcinoma *in situ* in PU (Tis PU) and ducts (Tis PD) are now gathered in a single Tis category. Prostatic acinar involvement is also in the same Tis category. As in bladder cancer staging, extension to other organs, including extraprostatic extension of the bladder wall, should be categorized as T4 disease.

Perivesical LN involvement is added to N category in the 8E AJCC for urethral cancers. Besides, in the N category, 2 cm metastasis size cut-off is revised with the number of LN involvement (Table 1).

Changes in the 8th Tumor-Node-Metastasis Staging of Prostate Cancer

TNM staging is the most important parameter in determining the treatment modality in prostate cancer (22). Prostate-specific antigen levels and tumor grade were mentioned in staging prostate cancer in the AJCC Cancer Staging Manual, 7th edition, for the first time. This practice continues with revisions in the 8th edition (1). There is no pT1 category for radical prostatectomy specimens. According to tumor spread and localization, the 7th edition of the AJCC TNM staging system subdivides pT2 disease into three categories as pT2a, pT2b, and pT2c. Up to several retrospective outcome data analyses, this subdivision has no prognostic value. No data exist to allow correlation of pT2 stage subgroupings with survival in localized prostate cancer due to the indolent and prolonged clinical course of the disease.

The pT3 disease is subdivided into two categories as pT3a and pT3b, evaluating the presence of extraprostatic extension and the presence of seminal vesical invasion with or without extraprostatic extention, in the 8E AJCC TNM staging system. Tumor cells in periprostatic fat are the most easily recognizable sign of extraprostatic extension. Tumor detected in the apex/distal margin sections is not considered as extraprostatic extension. Assessing the extraprostatic extension, the terms "focally" (a few neoplastic glands just outside the prostate or extraprostatic tumor occupying less than one high-power field in no more than two sections) and "extensively" (more than focal) are recommended to be used. In the 8E AJCC, microscopic bladder neck invasion is considered as pT3a, similar to the old version.

Periseminal vesicle soft tissue invasion, staged as pT3a (extraprostatic extension), should be distinguished from seminal vesicle invasion (pT3b) that keeps the tumor cells in the muscular wall of the seminal vesicle. In the revised version, there is no change for staging (pN) LN metastasis in prostate cancer. The tumor that is fixed or invades adjacent structures other than seminal vesicles, such as rectum, bladder, levator muscles or pelvic wall, is categorized as pT4 (Table 1).

Changes in the 8th Tumor-Node-Metastasis Staging of Testicular Cancer

Histologic evaluation of the radical orchiectomy specimen must be used for the pT classification. The gross size of the tumor should be recorded. The size of the largest tumor should be used for determining pT category, in the presence of multiple separated tumor nodules. Careful gross examination should determine whether the tumor extends through the tunica albuginea and whether it invades the epididymis and/or hilar soft tissue and/or spermatic cord. Tumors measuring 2 cm or smaller should be submitted entirely. In addition, the ISUP testicular tumor panel recommended that if the tumor is >2 cm in greatest dimension, 10 blocks or a minimum of 1 to 2 additional blocks/cm, whichever is greater, should be submitted (23). The junction of tumor and non-neoplastic testis and at least one block remote from the tumor should be obtained to determine whether germ cell neoplasia in situ (GCNIS) is present. These sections will allow assessment of either the presence or absence of vascular invasion. The clinical serum markers are needed for comparison when assigning the pathological stage S category, but levels after orchiectomy are used to complete the status of the serum tumor markers (S) for pathological staging. Size is an important prognostic risk factor for seminoma. Determination of GCNIS is essential because of two important situation; one is new terminology GCNIS is adopted in staging in Tis category, and second, changes in nomenclature of germ cell tumors require this finding.

In the revised form, seminomas, limited in the testis and without lymphovascular invasion (LVI) will be subclassified as pT1a and pT1b according to greatest dimension whether the tumor is smaller than (pT1a) or ≥3 cm (pT1b) in (1,24,25). Also, this subclassification only applies to pure seminomas, and other germ cell tumors are excluded. Upon showing that, it is unrelated to the usual postpubertal germ cell tumors; spermatocytic seminoma has been renamed as spermatocytic tumor and is excluded from the TNM staging because of its excellent prognosis.

Although rete testis stromal invasion does not alter the TNM stage 8, in most centers, its presence or absence in germ cell tumors is reported since it has impact on adjuvant radiation or carboplatin chemotherapy decision for stage 1 disease.

The hilar soft tissue is composed of adipose and loose fibrous connective tissue and is adjacent to the head of the epididymis. Differentiation between spermatic cord invasion and hilar soft tissue invasion is important to be certain about the location of the origin of the spermatic cord at gross dissection (29). Invasion of either epididymis or hilar soft tissue is adopted in pT2 category in the absence of spermatic cord (pT3) or scrotal (pT4) invasion, respectively. Therefore, the hilar soft tissue and epididymis should be sampled macroscopically to confirm the

Table 1. Summary box for changes in the 8th tumor-node-metastasis staging of urological and male genital organs cancers

Specimen	Summary of the changes
Kidney	WHO\ISUP histologic grading adopted changes in T3a category; - The word "grossly" excluded - Muscle containing changed to segmental vein - Pelvicaliceal system invasion added
Urinary bladder	T1: subcategorization in TUR materials as "microinvasive" and "invasive"
	T2: diverticular invasive cancer has no T2 category
	T4: prostatic stromal invasion must be transmural from bladder, subepithelial stromal invasion staged as T2 (urethral)
	N1: perivesical lymph node added in N1 category
	M: divided into non-regional LN only (M1a) and non-LN distant metastases (M1b)
Urethra	Tis: Tis prostatic urethra and Tis prostatic ducts changed to a single Tis category prostatic acini involvement without stromal invasion added
	T2: clarified for urothelial carcinoma of the prostate as involving the prostatic urethral subepithelial connective tissue
	T4: clarified that direct bladder extension is included
	N1: perivesical LN added in N1 category
	N1 and N2: divided only by the number of LN involved (single versus multiple); size cut-off removed
Prostate	
	Gleason score adopted to ISUP 2014 criteria;
	Histologic grade: grade group added in addition to Gleason score pT2: no longer subcategorized based on bilaterality and extent of involvement pT3 divided into two categories; -pT3a: the presence of extraprostatic extension in any location -pT3b: presence of seminal vesical invasion with or without extraprostatic extension
Testis	Tis: new terminology germ cell neoplasia in situ adopted
	pT1: subcategorized pT1a and pT1b for pure seminoma using 3-cm tumor size cut-off
	pT2: epididymal invasion upstaged from T1 hilar soft tissue invasion added LVI only in spermatic cord without parenchymal invasion
	M1: discontinuous involvement of spermatic cord by LVI added
Penis	Histologic grade: the three-tiered (WHO/ISUP) grading adopted
	Ta broadened to non-invasive localized squamous cell carcinoma
	T1a and Tlb have been separated by LVI, PNI and high histologic grade T1a or T1b are described by the site where they occur on the penis and are designated glands, foreskin, or shaft T2: confined to tumor invasion into corpus spongiosum T3: tumor invasion into corpus cavernosum Urethral involvement no longer the determinant and can be T2 or T3 pN1: increased to up to two unilateral inguinal LN metastases without extranodal extension pN2: increased to >2 unilateral or bilateral inguinal LN metastases without extranodal extension

ISUP: International Society of Urological Pathology, LN: Lymph node, LVI: Lymphovascular invasion, PNI: Perineural invasion, WHO: World Health Organization, TUR: Transurethral resection

findings (Figures 3, 4). Macroscopically, it may not be possible to evaluate invasion of these structures, thus, the hilar region should be sampled and microscopically examined in all cases. Direct infiltration of the spermatic cord results in a pT3 category. A block should be taken where the spermatic cord emerges above the head of the epididymis. If there is direct invasion by the tumor in this block, pT3 can be assigned. Microscopically, if the tumor surrounds or involves the vas deferens, then this is considered spermatic cord involvement (pT3). Discontinuous involvement of the spermatic cord via a vascular thrombus is currently considered a metastatic deposit (pM1) in the revised AJCC system, and a tumor thrombus within a vessel without

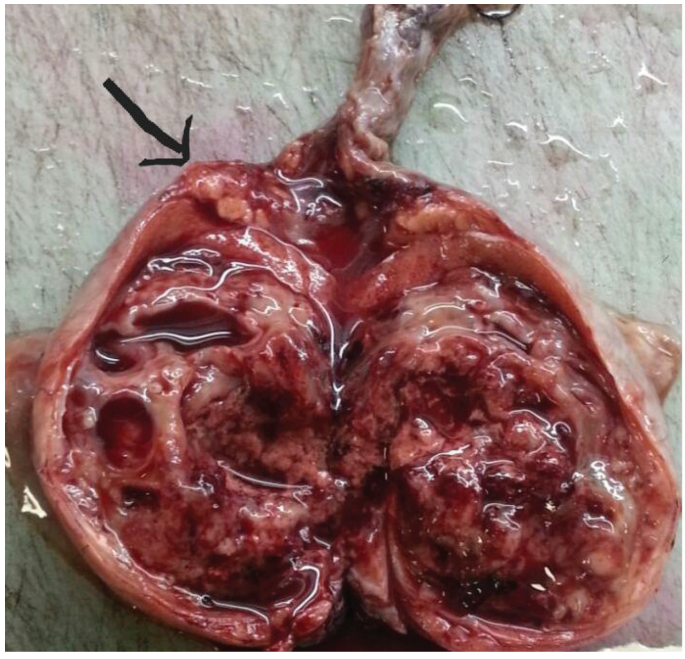

Figure 3. Mixed germ cell testis tumour with epididymis invasion

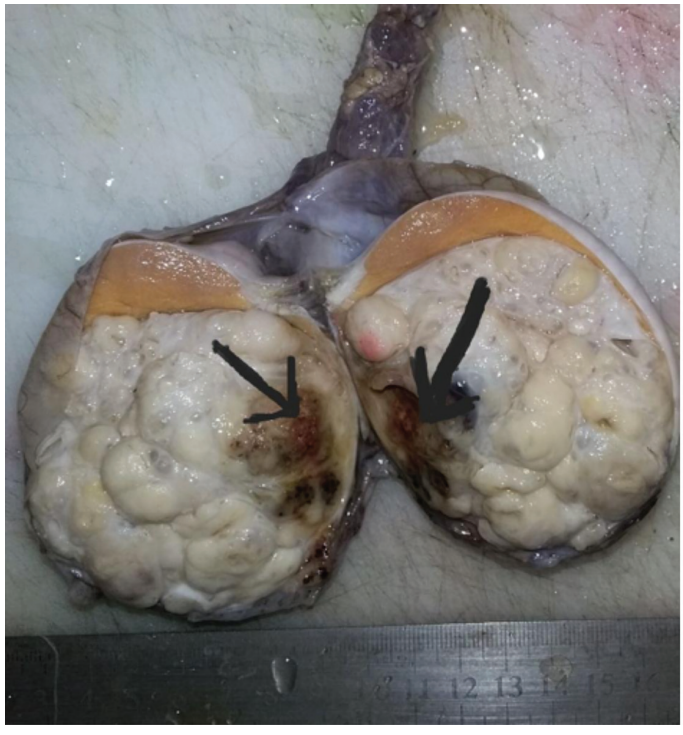

Figure 4. Seminoma with rete testis invasion

invasion is pT2. Epididymal invasion is now considered in pT2 category.

Changes in the 8th Tumor-Node-Metastasis Staging of Penile Cancer

The AJCC 7th edition referred to tissue layers between the skin and corpora as "subepithelial connective tissue". In the 8th edition, these areas are designated by their anatomical names to reflect the proper terminology and the levels of invasion prior to tumors reaching the corporal tissue (1). Complete resection of the primary lesion with tumor-free margins provides the greatest certainty that all histologic parameters in terms of grade, anatomic structures involved, and the presence or absence of prognostic factors important in assigning AJCC TNM stage are characterized subsequent to microscopic evaluation. In the current classification, in fact, the most changes are seen in penile cancer. The Ta category is expanded and applies to both pure verrucous carcinomas with no overt destructive invasion and non-invasive papillary, warty, basaloid, or mixed carcinomas (1).

In the previous editions, subepithelial tissue layer is used as a general definition, but the revised form includes precise definitions by glands, foreskin, or shaft regions allowing for more consistent categorization of T1 disease. T1 is also subcategorized into T1a and T1b as having different capacities for metastasis to inguinal nodes (10.5-18.1% vs 33.3-50%) (31,32). Some histomorphologic features such as perineural invasion, LVI and high-grade histology are used to differentiate T1a from T1b tumors (33,34). Invasion into corpus spongiosum is in T2 category while corpus cavernosum invasion is upstaged to T3. As accepted in the previous edition, pN1 and pN2 categories have been shown to have no significant difference in prognosis (35). In the light of some studies, it is determined that the laterality of LN metastasis is more important in predicting the outcome (36,37,38,39). Therefore, pN1 is now increased to up to two unilateral inguinal LN metastases, while pN2 is now modified as more than three unilateral or bilateral inguinal LN metastases. Tumor grading has traditionally been based on modifications of the Broder's grading system and consists of either a 3- or 4-grade system. The grade 3 category or presence of a sarcomatoid component is important in separating stage T1b from T1a primary tumors.

Conclusion

Staging is very valuable in the prognosis and treatment of cancer patients. Therefore, it should be revised at regular intervals so that new follow-up and treatment modalities can be identified. In this review, I tried to summarize the whole changes that were made in the 8th TNM staging. Although significant changes have been made in the T category, and there are new regulations in the N and M categories, still there are some points that have not yet been clarified and should be considered over time.

Keywords: Male genital cancers, Urological cancers, TNM, Staging

Anahtar Kelimeler: Erkek genital kanserler, Ürolojik kanserler, TNM, Evreleme

Ethics

Peer-review: Externally peer-reviewed.

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