Pathological staging (Required and Recommended)

Reason/Evidentiary Support

This dataset includes the American Joint Committee on Cancer (AJCC) TNM 8th edition[1] definitions. The implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. Union for International Cancer Control (UICC) 7th edition[2] or AJCC 7th edition[3] may be useful in the interim. If TNM 7th edition is used the following points should be noted:

1) Perineural invasion is now included as a stratifier between T1a and T1b tumours of the penis in addition to lymphovascular invasion and high grade in TNM8.

2) The division between T2 and T3 in TNM8 of the penis is entirely dependent on whether there corpus spongiosum or corpus cavernosum invasion irrespective of urethral involvement. This is the most significant change between TNM7 and TNM8.

3) The number of unilateral nodes to indicate N2 rather than N1 of the penis has increased to 3 from 2.

4) The size of metastasis is no longer used as a stratifier between N1 and N2 in unilateral regional nodes in urethral cancer.

5) The use of TX is to be avoided if at all possible and MX is not to be used.

6) Pathological staging should not be reported if the specimen submitted is insufficient for definitive staging. This may occur with biopsies or other specimens where depth of invasion or the required anatomical features cannot be discerned/assessed.

7) Staging in the presence of positive margins needs to be undertaken but made clear to clinicians. The term 'at least', as in pT2 at least, may be used to indicate a positive margin. It is not helpful to clinicians omit the stage if margins are positive.

By convention, the designation T refers to a primary tumour that has not been previously treated. The symbol p refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour or a biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesion. Pathologic staging is usually performed after surgical resection of the primary tumour.

Additional Descriptor

The m suffix indicates the presence of multiple primary tumours and is recorded in parentheses, e.g. pTa(m)N0.

Tumours of the Penis and Foreskin (TNM7 and TNM8)[2,4-7]

Primary Tumour (T)

Changes between TNM7 and TNM8 are indicated and/or highlighted in bold

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

Tis Carcinoma in situ (Penile intraepithelial neoplasia [PeIN]).

Ta TNM7* Non invasive verrucous carcinoma.

TNM8* Non invasive localised squamous cell carcinoma

T1 TNM7 Tumour invades subepithelial connective tissue

TNM8 Glans: Tumour invades lamina propria

Foreskin: Tumour invades dermis, lamina propria or dartos fascia

Shaft: Tumour invades connective tissue between epidermis and corpora regardless of location

All sites with or without LVI or perineural invasion and is or is not high grade

T1a **Tumour invades lamina propria or subepithelial connective tissue and is without lymphovascular or perineural invasion and is not high grade (i.e. grade 3 or sarcomatoid)

T1b ** Tumour invades lamina propria or subepithelial connective tissue and exhibits lymphovascular or perineural invasion and or is high grade (i.e. grade 3 or sarcomatoid)

T2 TNM7 Tumour invades corpus spongiosum or cavernosum.

TNM8 Tumour invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion

T3 TNM7 Tumour invades urethra.

TNM8 T3 Tumour invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion

T4 Tumour invades other adjacent structures.

*The dataset authors' view is that the category of non invasive verrucous carcinoma in TNM7 and non invasive localised squamous cell carcinoma in AJCC TNM8 is to be avoided as it is not evidence based.

** AJCC TNM8 introduces Perineural invasion into the pT1 category but UICC and AJCC TNM7 do not include perineural invasion as a stratifier in the pT1 category.

Regional Lymph Nodes (N)

pNX Lymph node metastasis cannot be established.

pN0 No lymph node metastasis.

pN1 TNM7 Metastasis in a single inguinal lymph node.

TNM8 Two or more inguinal metastases without extranodal extension (ENE)

pN2 TNM7 Metastases in multiple or bilateral inguinal lymph nodes.

TMN8 Three or more unilateral inguinal metastases or bilateral metastases

pN3 ENE of lymph node metastases or pelvic lymph node metastases.

Distant Metastasis (M)

M0 No distant metastasis (clinical category only).

M1 Distant metastasis present.

M1 includes lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.

Accurate staging and grading of tumours are used to determine subsequent clinical management and follow-up.

The anatomy of the penis is complex and difficulties often arise in distinguishing levels of invasion. The distinction between lamina propria and corpus spongiosum is made on the basis of vascularity. Vessels within erectile tissue are more angular and thin-walled with intervening fibromuscular tissue than those within the lamina propria which are more variably sized and separated by loose connective tissue.

Although there is a category of non-invasive verrucous carcinoma in the primary tumour classifications (Ta) in TNM7, the criteria for the diagnosis of this entity and its distinction from verrucous hyperplasia are unclear to the authors of this dataset and use of this category is not recommended. Although verrucous carcinomas have a pushing rather than infiltrative margin, they are nevertheless invasive. Invasion is often only superficial but more deeply invasive tumours may be observed. Non invasive localised tumours of the penis of any subtype are exceptionally rare in the authors experience.

Staging of pT1 is subdivided in TN 7 into pT1a for low-risk tumours and pT1b for high-risk tumours depending on the absence or presence of high-grade tumour and/or LVI. TNM8 also includes perineural invasion as a stratifier between T1a and T1b. The number of unilateral nodes needed upstage from pN1 to N2 has increased from two to three in TNM8. Metastatic tumour in regional lymph nodes with extranodal spread is categorised as pN3.

It was initially proposed that the pT2 primary tumour classification be subdivided to distinguish between invasion into the spongiosum and cavernosum, as some reports show that risk of metastases in increased in patients with invasion of the cavernosa. The Royal College of Pathologists (RCPath) dataset published in 2015 recommend substaging of T2 penile tumours into T2a (corpus spongiosum invasion) and T2b (corpus cavernosum invasion) as this is evidence based.[7] TNM8 now recommends that involvement of the corpus spongiosum is classified as T2 and involvement of corpora cavernosa is T3 irrespective of urethral involvement. The RCPath dataset is also being updated in 2017 to reflect TNM8.

In the case of multiple tumours, the tumour with the highest T category should be classified and the multiplicity or number of tumours should be indicated in parentheses, e.g. pT2 (m) or pT2.

Use of the category TX is to be avoided and the designation e.g. 'T (numerical value) at least' is preferable if full staging is not possible because of the nature of the specimen (e.g. small incision biopsies) or the presence of positive margins.

If deep structures are not sampled and/or the invasive tumour extends to the margins of excision staging should still be attempted but designated as 'pT1 at least'. The designation of pTX (unstageable) even in small biopsies should be avoided as far as possible as it is clinically unhelpful.

The category M0 should not be used in pathological staging. The term MX is no longer in use.

Tumours of the Distal Penile Urethra (TNM7 and TNM8)[2,8]

It should be noted that the N categories differ considerably between urethral and penile tumours and extranodal spread is not a feature of the urethral N staging (i.e. there is no N3 category). There are only minimal changes between TNM7 and TNM8.

Primary Tumour (T) of the Male Penile Urethra

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

Ta Non-invasive papillary carcinoma*.

Tis Carcinoma in situ**

T1 Tumour invades subepithelial connective tissue.

T2 Tumour invades any of the following: corpus spongiosum, periurethral muscle.

T3 Tumour invades any of the following: corpus cavernosum.

T4 Tumour invades other adjacent organs.

* The dataset authors' view is that the use of this category for non invasive squamous localised squamous cell carcinoma is to be avoided as it is not evidence based. This category includes non-invasive papillary urothelial carcinomas but these are very rare in the distal urethra.
** The dataset authors recommend the use of the same terminology (PeIN) for squamous precancerous lesions of the distal urethra as in the penis.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 TNM7 Metastasis measuring up to 2 cm or less in greatest dimension in a single lymph node.

TNM8 Single regional lymph node metastasis

N2 TNM7 Metastasis more than 2 cm in greatest dimension in a single node, or metastases of any size in multiple nodes.

TNM8 Multiple regional lymph node metastases

There are no different cN or pN categories in the Urethral tumour TNM which contrasts with the penile TNM.

Distant Metastasis (M)

M0 No distant metastasis*

M1 Distant metastasis.

* This is a clinical category, not to be used in pathological reporting.

References

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2 International Union against Cancer (UICC) (2009). *TNM Classification of Malignant Tumours (7th edition)*. Sobin L, Gospodarowicz M and Wittekind C (Eds). Wiley-Blackwell, Chichester, UK and Hoboken, New Jersey.

3 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.

4 Leijte JA, Gallee M, Antonini N and Horenblas S (2008). Evaluation of current TNM classification of penile carcinoma. *J Urol* 180(3):933-938; discussion 938.

5 Chaux A, Caballero C, Soares F, Guimaraes GC, Cunha IW, Reuter V, Barreto J, Rodriguez I and Cubilla AL (2009). The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. *Am J Surg Pathol* 33(7):1049-1057.

6 Chaux A and Cubilla AL (2012). Stratification systems as prognostic tools for defining risk of lymph node metastasis in penile squamous cell carcinomas. *Semin Diagn Pathol* 29(2):83-89.

7 RCPath (Royal College of Pathologists) (2015). Dataset for penile and distal urethral cancer histopathology reports. Available from: https://www.rcpath.org/resourceLibrary/dataset-for-penile-and-distal-urethral-cancer-histopathology-reports.html (Accessed 1st March 2016)

8 Corbishley CM, Rajab RM and Watkin NA (2015). Clinicopathological features of carcinoma of the distal penile urethra. *Semin Diagn Pathol* 32(3):238-244.