Utilizing the Tumor-Node-Metastasis Staging for Prostate Cancer: The Sixth Edition, 2002

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ABSTRACT The Sixth Edition of the tumor-node-metastasis staging system for prostate cancer attempts to provide a helpful staging paradigm for clinicians. Accurate staging is critical not only for managing individual patients, but also for ascertaining trends in disease pattern in a large population of patients with prostate cancer. Several modifications have been made in an attempt to improve the cohesiveness and uniformity of patient evaluation and to aid in future meaningful clinical research. As data are accumulated and analysis continues, ongoing critical evaluation of this staging system will undoubtedly incorporate new evidence-based factors and bring about future refinements to prostate cancer staging. (CA Cancer J Clin 2008;58:54–59.) © American Cancer Society, Inc., 2008.

INTRODUCTION

Since the 1940s, the tumor-node-metastasis anatomic-based system of staging has been utilized, with the American Joint Committee on Cancer (AJCC) providing important leadership in its formulation. Revisions have occurred periodically throughout this time period, resulting in the current version published in 2002. Each iteration of the classification scheme attempts to further improve the clinician’s ability to assess malignancies (see Table 1).

Among men, prostate cancer continues to be the most common (excluding skin cancer) cancer and is the second leading malignant cause of death. With its widespread impact, prostate cancer continues to receive much scrutiny and research. The Sixth Edition guidelines attempt to present a practical, reproducible, and population-based staging scheme in this continually evolving field.

DIFFERENCES BETWEEN THE FIFTH (1997) AND SIXTH (2002) EDITIONS OF THE AJCC STAGING SYSTEM

There are 2 primary alterations between the Fifth Edition (1997) and the Sixth Edition (2002). First, once again, primary T2 lesions have been divided to include T2a, T2b, and T2c as opposed to T2a and T2b. In continually evaluating data, deficiencies in the system are not always resolved with new criteria. Data published in clinical series since publication of the Fifth Edition have demonstrated that recurrence-free survival following treatment was different if the primary clinical tumor stage (T stage) utilized in the Fourth Edition (1992) system was employed.

A large series of more than 2,000 patients who underwent radical prostatectomy for organ-confined disease revealed significant differences in outcomes for patients with a differentiation of disease within a single lobe. The single classification of single lobe disease of T2a in the 1997 classification combined the 1992 classification of T2a and T2b. When examining outcomes, this combining did obscure differences in the cancer recurrence rates elicited by the former 1992 classification of T2a and T2b ($P < .0001$).

Thus, the attempt to simplify the classification scheme to clinical T2a and T2b tumors did not stratify as well as the T2a, T2b, and T2c classification. As a result, the staging with T2a, tumor involving one-half of a lobe or less; T2b, tumor involving more than one-half of a lobe but not both lobes; and T2c, tumor involving both lobes, was readopted in the Sixth Edition. These are the same subcategories found previously in 1992. There is continuing accumulation of data...
**TABLE 1  Definition of TNM**

| Primary Tumor (T)                      |
|---------------------------------------|
| **Clinical**                          |
| TX | Primary tumor cannot be assessed     |
| T0 | No evidence of primary tumor         |
| T1 | Clinically apparent tumor neither palpable nor visible by imaging |
| T1a| Tumor incidental histologic finding in 5% or less of tissue resected |
| T1b| Tumor incidental histologic finding in more than 5% of tissue resected |
| T1c| Tumor identified by needle biopsy (e.g., because of elevated PSA) |
| T2 | Tumor confined within prostate*      |
| T2a| Tumor involves one-half of one lobe or less |
| T2b| Tumor involves more than one-half of one lobe but not both lobes |
| T2c| Tumor involves both lobes            |
| T3 | Tumor extends through the prostate capsule** |
| T3a| Extracapsular extension (unilateral or bilateral) |
| T3b| Tumor invades seminal vesicle(s)     |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall |

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.**

| Pathologic (pT)                       |
|---------------------------------------|
| pT2* | Organ confined             |
| pT2a | Unilateral, involving one-half of one lobe or less |
| pT2b | Unilateral involving more than one-half of one lobe but not both lobes |
| pT2c | Bilateral disease          |
| pT3 | Extracapsular extension     |
| pT3a | Extracapsular extension**  |
| pT3b | Seminal vesicle invasion    |
| pT4 | Invasion of bladder, rectum |

*Note: There is no pathologic T1 classification.**

| Regional Lymph Nodes (N)              |
|---------------------------------------|
| **Clinical**                          |
| NX | Regional lymph nodes were not assessed |
| N0 | No regional lymph node metastasis    |
| N1 | Metastasis in regional lymph node(s) |
| **Pathologic**                        |
| pNX | Regional nodes not sampled |
| pN0 | No positive regional nodes |
| pN1 | Metastases in regional node(s)      |

| Distant Metastasis (M)*               |
|---------------------------------------|
| MX | Distant metastasis cannot be assessed (not evaluated by any modality) |
| M0 | No distant metastasis               |
| M1 | Distant metastasis                  |
| M1a| Non-regional lymph node(s)          |
| M1b| Bone(s)                              |
| M1c| Other site(s) with or without bone disease |

*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

Abbreviations: TNM, tumor-node-metastasis; PSA, prostate-specific antigen. Reprinted from Greene FL, Page DL, Fleming ID, et al1 with permission from Springer-Verlag.
arteries. They include the following groups: pelvic, not otherwise specified (NOS); hypogastric; obturator; iliac (internal, external, or NOS); and sacral (lateral, presacral, promontory, or NOS). The side or bilateral nature of disease does not affect the node classification. The significance of regional lymph node metastasis (pN) in staging prostate cancer lies in the presence of metastatic foci present within the lymph nodes.

Distant lymph nodes lie outside the confines of the true pelvis. They can be imaged using ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine-based studies, or lymphangiography. The most common form of evaluation for soft tissue evaluation remains the CT scan; however, its yield remains low (approximately 5% to 10%) for men with PSA <20 ng/ml and Gleason score <8.\footnote{In a prospective evaluation of more than 3,600 patients, CT evaluation with positive results occurred 20% of the time for men with PSA >50 ng/ml or for men with PSA >20 ng/ml and whose tumor was Gleason score 8 to 10.\footnote{Even with values of PSA >25 ng/ml, the sensitivity of CT scan is approximately 35%.\footnote{Involvement of distant lymph nodes, although lymphatic in nature, is classified as M1a. The distant lymph nodes include aortic (para-aortic lumbar); common iliac; inguinal, deep; superficial inguinal (femoral); supraclavicular; cervical; scalene; and retroperitoneal, NOS.}

Metastatic Sites

Osteoblastic metastases are the most common nonnodal site of prostate cancer metastasis and are designated as M1b. Although not common, metastatic prostate cancer can involve nonbony anatomic locations. Sites would include lung, liver, adrenal gland, and other soft tissue, including peritoneum or visceral sites; these would be examples of the M1c category.

CLASSIFICATION

Clinical

Clinical staging parameters are determined prior to therapy and remain unchanged even if pathological findings differ. It is these important pretreatment parameters that help determine therapy. Initial assessment involves DRE of the prostate and histological confirmation of prostate carcinoma, usually by transrectal ultrasound and biopsy. Although its usefulness is somewhat limited with nonpalpable tumors, for more advanced disease, DRE remains an important staging component. In the majority of patients, radiographic imaging studies, including ultrasound, CT scans, and MRI scans, are not yet accurate enough to be helpful in staging.\footnote{This is especially true in patients with Gleason scores less than 7 and PSA values <20 ng/ml. In fact, today the majority of patients are at a relatively low risk of positive nodes or metastases, and the risk of false-positive imaging studies in asymptomatic patients has exceeded the frequency of true-positive or true-negative studies in several reports.\footnote{In general, surgical removal of the prostate, including regional node specimen, and histological confirmation are required for pathological T-stage classification. A biopsy, however, under certain, less common circumstances can provide pathological T-stage classification. An example would include locally advanced disease where biopsy of the rectum reveals prostate cancer resulting in pT4 classification without removal of the prostate. Similarly, histological identification of prostatic adenocarcinoma in the bladder would indicate pT4 disease. Another example would be a biopsy revealing carcinoma involving extraprostatic soft tissue, which would result in a pT3 classification. Similarly, a biopsy of the seminal vesicle that revealed adenocarcinoma infiltrating the seminal vesicles would also indicate a pT3 classification. Macroscopic bladder involvement warrants a pT4 stage. There is controversy in assigning advanced stage (pT4) disease when there is microscopic involvement of the bladder neck, as data suggest that this does not portend an adverse prognosis.\footnote{It has been suggested that extraprostatic extension may be further classified as focal (few neoplastic glands outside the confines of the prostate) versus established or nonfocal\footnote{Firm criteria for designation of focal pT3 classification.}}}}
versus established extraprostatic disease are not established.

Margin positivity, potentially influenced by surgical technique as well as anatomic extent of disease, should be specified along with pathological stage. Positive surgical margin status is not classified specifically in the T stage because at the time of formulation, the data were inconclusive regarding impact on disease outcomes based on a consequence of surgical technique and/or anatomic extent of disease. However, the R1 descriptor (residual microscopic disease) within the staging criteria evaluation form does take into account residual microscopic disease. It is important that the staging clinician note this information when available for each patient. Pathologists, on the other hand, have adopted the terms pT2x or pT2+ to incorporate the margin positivity status into the pathological stage designation.

The Gleason grading system is recommended for use in determining tumor grade as its prognostic importance has been verified in many large clinical cohorts of prostate cancer patients. A primary and a secondary grade or pattern (range 1 to 5 each) are assigned and then summed to yield a total score. Scores of 2 to 10 are thus possible. If a single focus of disease is seen, it should be reported as both grades and doubled. For example, if a single focus of Gleason Grade 3 disease is seen, it is reported as 3+3. Recent refinements by pathologists in the application of Gleason grade to pathological specimens have been made. In addition to Gleason score, other prognostic factors for survival have been identified for prostate cancer. These include age of patient, comorbid diseases, histological type, PSA and percent free-PSA level, surgical margin status, and ploidy. These parameters are all captured in the staging evaluation forms. The currently useful and validated prognostic factors in prostate cancer need to be consistently reported by pathologists using elements included in the College of American Pathologists prostate protocols.

The vast majority of prostate carcinomas are adenocarcinomas referred to as conventional, usual, or microacinar. Certain special subtypes, including mucinous, small cell, ductal, signet ring cell, and sarcomatoid, exist. Adenosquamous and squamous cell carcinomas also are classified within this scheme. This classification, however, does not apply to sarcoma or transitional cell carcinoma of the prostate, the latter being classified as a urethral tumor.

As with other staging systems, the AJCC has received questions from staging clinicians regarding correct implementation of the guidelines. In reviewing the submitted questions, several themes were recurrent. A common question involved pathological staging for patients who do not undergo radical prostatectomy, but instead undergo some other localized therapy or who are incidentally found to have cancer during another procedure. A clinical stage can be determined by the biopsy that has diagnosed the cancer, but in many cases there is insufficient tissue to assess the highest pathological stage, and thus these patients have a pTx designation. For instance, a patient with a Gleason 6 prostate cancer diagnosed at biopsy performed due to a PSA elevation with a normal exam would be a cT1c. If he undergoes radiation therapy, his primary tumor pathological staging would have a pTx designation.

Another common question involves clinical staging of a tumor that is found in one or both lobes by needle biopsy, but is not palpable or visible by imaging. There is no laterality specification for T1 tumors, and regardless of side or bilateral involvement, this situation is classified as cT1c. If the patient undergoes prostatectomy and pathological data is gained, the pathological stage will take into account more factors. For instance, if a cT1c primary tumor is found to have extraprostatic extension to seminal vesicles in a pathological specimen, it would have a pT3b stage; the clinical stage would not change. Importantly, to continue to gain further insight into this disease process, investigators should specify whether clinical staging into the T1c category is based on DRE only or on DRE plus transrectal ultrasound. This collected information continues to be reviewed to help in adapting further possible modifications to the staging scheme.

Another common question involves the extension of disease beyond the apex of the prostate as implied by a positive surgical margin. If fat is not present in the apical section, but tumor is present...
at the surgical margins, the appropriate staging would be pT2x or pT2+. Some uropathology experts designate such cases as pT3, the rationale being that if the urologist has gone as far wide and distal as possible and only malignant glands are seen at the margins, then the tumor should be considered extraprostatic. Rarely, fat may be present at the apex of the prostatectomy specimen, and the presence of tumor in adipose tissue at this site indicates pT3 disease.

FUTURE REVISIONS TO PROSTATE CANCER STAGING

As with other malignancies, the staging of prostate cancer will continue to evolve, and controversial issues will continue to arise. Even a simple and innocent-enough appearing question such as the primary outcome endpoint is problematic in prostate cancer; the multitude of opinions and reported outcomes makes unanimity of opinion difficult. Nevertheless, it is difficult issues like this that are addressed and continually evaluated.

Recent data may prompt changes in certain anatomic categories that may need further stratification. One potential change utilizes data involving the impact of seminal vesicle involvement on cancer recurrence and expands again the T3 category to T3a, T3b, and T3c. In addition, currently the majority of patients are clinically diagnosed with a cT1c primary tumor based on a normal DRE, but a biopsy based on an elevated PSA. With the diversity of possible pathological stages and outcomes for these patients, the clinical T1c staging may need to be further enumerated. The staging for these patients and others may be influenced by newer and more accurate radiographic imaging techniques such as MRI-spect imaging.

Another critical clinical data point for evaluation involves biopsy core results, specifically the amount of cancer within the biopsy specimens as determined by length or percentage of cancer in the cores. These biopsy results may be influential enough to alter clinical staging. Similarly, recent data suggest that the regional site evaluation of lymph node involvement should include a thorough inspection of pelvic sites with a complete resection as opposed to a node sampling that may underestimate pathological stage and adversely affect survival. However, more research is needed to demonstrate a definitive impact on staging requirements and outcomes.

With evolving treatment algorithms, the impact of certain factors and previous treatments have affected not only future therapeutic choices, but also outcomes for patients. Recent data on adjuvant and salvage therapies such as radiation therapy following radical prostatectomy have demonstrated again the heterogeneous nature of this disease process. Advanced cancer in the form of hormone-refractory prostate cancer is not currently formally staged, but may deserve more attention and a separate focus in the future.

The utilization of clinical and pathological predictive assessment tools should not replace but, instead, should enhance the current system. A number of algorithms have been published that utilize the impact of many factors to predict local stage, risk of positive nodes, or risk of treatment failure. While predictive nomograms are useful to assign individual risk, the AJCC staging system, in addition to its role in guiding treatment and determining prognosis, is used for grouping patients for comparison of the end results for cancer management. Nonanatomic prognostic factors will likely be further incorporated as a continued evolution of collaborative staging takes place. Examples include the incorporation of Gleason score and PSA as a serum marker. It is important for the clinician to realize the impact of the acquisition of data such as PSA, margin status, tumor ploidy, and others that are captured with the AJCC staging forms. The impact of these factors is being assessed continuously by the staging committee, and their true impact may be learned by the data collection that comes with careful staging.

CONCLUSION

Clinical and pathological staging based on the tumor-node-metastasis system remains critical in the evaluation and treatment of prostate cancer patients. This field, however, is constantly changing, and as new findings influence practice patterns, these discoveries must be critically analyzed and considered for inclusion in this staging scheme.
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