

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

Sam S. Chang, MD; Mahul B. Amin, MD

Dr. Chang is Associate Professor of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN.

Dr. Amin is Chairman, Department of Pathology & Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA.

Published online through *CA First Look* at <http://CAonline.AmCancerSoc.org>.

DOI: 10.3322/CA.2007.0002

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.



To earn free CME credit for successfully completing the online quiz based on this article, go to <http://CME.AmCancerSoc.org>.

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 2002.¹ 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.² 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.^{3,4}

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 ($P < .0001$).³

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)	
<i>Clinical</i>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent 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.	
**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.	
<i>Pathologic (pT)</i>	
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	Extraprostatic extension
pT3a	Extraprostatic extension**
pT3b	Seminal vesicle invasion
pT4	Invasion of bladder, rectum
*Note: There is no pathologic T1 classification.	
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).	
Regional Lymph Nodes (N)	
<i>Clinical</i>	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
<i>Pathologic</i>	
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.

assessing the prognostic significance of whether substratification into pT2a, b, and c; pT2a and b; or a single category of pT2 without substratification is clinically valuable. There is opportunity in future revisions of the AJCC staging to refine pT2 disease based on such information.

Second, Gleason score is emphasized as the grading system of choice. No longer are the terms “well differentiated,” “moderately differentiated,” and “poorly differentiated” recommended for grading. Numerous studies have verified the importance of Gleason Grade 3 to 5 (scores 6 to 10) in assessing tumor risk and outcomes.⁵⁻¹⁰

ANATOMIC EVALUATION

Primary Site

Adenocarcinoma of the prostate most frequently arises within the peripheral zone of the gland. The transition and central zones are less often involved. The majority of times the cancer is multifocal. Although digital rectal examination (DRE) is normal in the majority of patients with prostate cancer (cT1),^{11,12} clinical data regarding usefulness of DRE in more advanced disease exists, and it remains the most common modality to stage clinically the primary tumor.¹³ The diverse nature of the clinical T1c category emphasizes the need for the treating clinician to include other prognostic factors, such as Gleason histological grade and prostate-specific antigen (PSA) level, when describing the clinical and pathological extent of the tumor.⁴

Diagnosis of clinically suspicious areas of the prostate can be confirmed histologically by needle biopsy. Less commonly, prostate cancer may be diagnosed by microscopic examination of the resected tissue from a transurethral resection of the prostate for obstructive voiding symptoms. The histological grade of the prostate cancer is important for prognosis. The Gleason score for assessing the histological pattern of prostate cancer is preferred and further described later.

Regional and Distant Lymph Nodes

The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac

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 <8.¹⁴ 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 10.¹⁴ Even with values of PSA >25 ng/ml, the sensitivity of CT scan is approximately 35%.¹⁵

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.¹⁶ 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.^{14,15,17,18}

Pathological

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.^{19,20} 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 nonfocal²¹ for more extensive involvement, implying a worse prognosis.²² Firm criteria for designation of focal

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.²³ 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.^{5,24-26} 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.²⁷ 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.²²

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.²⁸ 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.

COMMON QUESTIONS

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+.²¹ 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.²⁹

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.³⁰⁻³³ 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.^{34,35} The staging for these patients and others may be influenced by newer and more accurate radiographic imaging techniques such as MRI-spect imaging.³⁶

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.^{9,37} 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.^{21,38,39} 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.^{40,41} Recent data on adjuvant and salvage therapies such as radiation therapy following radical prostatectomy have demonstrated again the heterogeneous nature of this disease process.⁴² 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.⁴³

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.^{40,44} 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.⁴⁵⁻⁴⁷ 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.

REFERENCES

- Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer-Verlag; 2002.
- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
- Han M, Walsh PC, Partin AW, Rodriguez R. Ability of the 1992 and 1997 American Joint Committee on Cancer staging systems for prostate cancer to predict progression-free survival after radical prostatectomy for stage T2 disease. *J Urol* 2000;164:89-92.
- Ramos CG, Carvalho GF, Smith DS, et al. Clinical and pathological characteristics, and recurrence rates of stage T1c versus T2a or T2b prostate cancer. *J Urol* 1999;161:1525-1529.
- Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 1993;71:3582-3593.
- Epstein JI. Pathology of prostatic intraepithelial neoplasia and adenocarcinoma of the prostate: prognostic influences of stage, tumor volume, grade, and margins of resection. *Semin Oncol* 1994;21:527-541.
- Miller GJ. New developments in grading prostate cancer. *Semin Urol* 1990;8:9-18.
- Aihara M, Wheeler TM, Ohori M, Scardino PT. Heterogeneity of prostate cancer in radical prostatectomy specimens. *Urology* 1994;43:60-66.
- Freedland SJ, Terris MK, Csathy GS, et al. Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. *J Urol* 2004;171:2215-2220.
- McNeal JE, Villers AA, Redwine EA, et al. Histologic differentiation, cancer volume, and pelvic lymph node metastasis in adenocarcinoma of the prostate. *Cancer* 1990;66:1225-1233.
- Veltri RW, Miller MC, Mangold LA, et al. Prediction of pathological stage in patients with clinical stage T1c prostate cancer: the new challenge. *J Urol* 2002;168:100-104.
- Smith JA Jr. Stage T1c prostate cancer: perspectives on clinical management. *Semin Oncol* 1995;13:238-244.
- Carvalho GF, Smith DS, Mager DE, et al. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng/ml or less. *J Urol* 1999;161:835-839.
- Albertsen PC, Hanley JA, Harlan LC, et al. The positive yield of imaging studies in the evaluation of men with newly diagnosed prostate cancer: a population based analysis. *J Urol* 2000;163:1138-1143.
- Flanigan RC, McKay TC, Olson M, et al. Limited efficacy of preoperative computed tomographic scanning for the evaluation of lymph node metastasis in patients before radical prostatectomy. *Urology* 1996;48:428-432.
- Ferguson JK, Bostwick DG, Suman V, et al. Prostate-specific antigen detected prostate cancer: pathological characteristics of ultrasound visible versus ultrasound invisible tumors. *Eur Urol* 1995;27:8-12.
- Carroll P, Coley C, McLeod D, et al. Prostate-specific antigen best practice policy—part II: prostate cancer staging and post-treatment follow-up. *Urology* 2001;57:225-229.
- Scardino P. Update: NCCN prostate cancer Clinical Practice Guidelines. *J Natl Compr Canc Netw* 2005;3(suppl):S29-S33.
- Yossepowitch O, Sircar K, Scardino PT, et al. Bladder neck involvement in pathological stage pT4 radical prostatectomy specimens is not an independent prognostic factor. *J Urol* 2002;168:2011-2015.
- Dash A, Sanda MG, Yu M, et al. Prostate cancer involving the bladder neck: recurrence-free survival and implications for AJCC staging modification. *American Joint Committee on Cancer. Urology* 2002;60:276-280.
- Epstein JI, Amin M, Boccon-Gibod L, et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol Suppl* 2005;216:34-63.
- Srigley JR, Amin MB, Epstein JI, et al. Updated protocol for the examination of specimens from patients with carcinomas of the prostate gland. *Arch Pathol Lab Med* 2006;130:936-946.
- Ohori M, Wheeler TM, Kattan MW, et al. Prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 1995;154:1818-1824.
- Roehl KA, Han M, Ramos CG, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol* 2004;172:910-914.
- Blute ML, Bergstralh EJ, Iocca A, et al. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status to predict biochemical failure after radical prostatectomy. *J Urol* 2001;165:119-125.
- D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol* 2005;23:4975-4979.
- Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2005;29:1228-1242.
- Randolph TL, Amin MB, Ro JY, Ayala AG. Histologic variants of adenocarcinoma and other carcinomas of prostate: pathologic criteria and clinical significance. *Mod Pathol* 1997;10:612-629.
- Sirintrapun SJ, Tomaszewski J, Narula N, et al. Histologic landmarks that define extraprostatic extension (EPE) at the prostatic apex: characteristics of extraprostatic tissue at the apex as dissected by robotic radical prostatectomy (RP). *Mod Pathol* 2007;20(suppl):177A.
- Ravery V, Boccon-Gibod L. T3 prostate cancer: how reliable is clinical staging? *Semin Oncol* 1997;15:202-206.
- Secin FP, Bianco FJ Jr, Vickers AJ, et al. Cancer-specific survival and predictors of prostate-specific antigen recurrence and survival in patients with seminal vesicle invasion after radical prostatectomy. *Cancer* 2006;106:2369-2375.
- Masterson TA, Pettus JA, Middleton RG, Stephenson RA. Isolated seminal vesicle invasion imparts better outcomes after radical retropubic prostatectomy for clinically localized prostate cancer: prognostic stratification of pt3b disease by nodal and margin status. *Urology* 2005;66:152-155.
- Tefilli MV, Gheiler EL, Tiguert R, et al. Prognostic indicators in patients with seminal vesicle involvement following radical prostatectomy for clinically localized prostate cancer. *J Urol* 1998;160:802-806.
- Gretzer MB, Epstein JI, Pound CR, et al. Substratification of stage T1C prostate cancer based on the probability of biochemical recurrence. *Urology* 2002;60:1034-1039.
- Hung AY, Levy L, Kuban DA. Stage T1c prostate cancer: a heterogeneous category with widely varying prognosis. *Cancer J* 2002;8:440-444.
- Wang L, Hricak H, Kattan MW, et al. Prediction of organ-confined prostate cancer: incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. *Radiology* 2006;238:597-603.
- Sanwick JM, Dalkin BL, Nagle RB. Accuracy of prostate needle biopsy in predicting extracapsular tumor extension at radical retropubic prostatectomy: application in selecting patients for nerve-sparing surgery. *Urology* 1998;52:814-818.
- Bader P, Burkhard FC, Markwalder R, Studer UE. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? *J Urol* 2002;168:514-518.
- Clark T, Parekh DJ, Cookson MS, et al. Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. *J Urol* 2003;169:145-147.
- Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2005;23:7005-7012.
- D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.
- Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291:1325-1332.
- Chang SS, Benson MC, Campbell SC, et al. Society of Urologic Oncology position statement: redefining the management of hormone-refractory prostate carcinoma. *Cancer* 2005;103:11-21.
- Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433-439.
- Lee AK, Levy LB, Cheung R, Kuban D. Prostate-specific antigen doubling time predicts clinical outcome and survival in prostate cancer patients treated with combined radiation and hormone therapy. *Int J Radiat Oncol Biol Phys* 2005;63:456-462.
- Zhou P, Chen MH, McLeod D, et al. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol* 2005;23:6992-6998.
- Roach M 3rd, Weinberg V, Sandler H, Thompson I. Staging for prostate cancer: time to incorporate pretreatment prostate-specific antigen and Gleason score? *Cancer* 2007;109:213-220.