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Mario C. Beduschi · Ricardo Beduschi
Joseph E. Oesterling

Stage T1c prostate cancer: defining the appropriate staging evaluation and the role for pelvic lymphadenectomy

Abstract A good staging system should be able to accurately reflect the natural history of a malignant disease, to express the extent of the disease at the time of diagnosis, and stratify patients in prognostically distinctive groups. The staging system for prostate cancer, as it is today, fails to fulfill these requirements. Approximately one third of the patients who undergo surgery for complete excision of prostate cancer in fact do not have a localize disease. The incidence of tumor at the inked margin may reach 30% for T1 stage and up to 60% for clinical T2b prostate cancer according to comparision with pathologic examination of resected specimen. Several concepts have been recently proposed as a means of improving the accuracy of the available staging system. In this paper, we review current aspects of clinical and pathological staging of prostate cancer, and the importance of these new concepts on the early stages of prostate cancer.

Prostate cancer (PCa) is a frequent and deadly malignancy that has become a major health concern for society, physicians, and health organizations worldwide. In the United States an estimated 334,500 new cases of prostate cancer (PCa) will be diagnosed and 41,800 men are expected to perish from this disease in 1997 [68]. For this reason, clinicians and researchers have joined efforts to improve our understanding of this disease process. As a result, the diagnosis and staging of PCa has been in a state of evolution over the past two decades. In addition, recent changes in practice patterns have compelled urologists not only to provide high quality medical care but to do so in a cost-effective manner. Without question, staging is one of the many areas of PCa management that has been modified considerably in recent years.

Clinical staging attempts to reflect the natural history of PCa, establish the correct anatomic extension and burden of the disease, and stratify patients into distinct prognostic groups. An accurate clinical staging, in combination with other relevant clinical information at diagnosis, allows the urologist to estimate the prognosis and develop the best treatment strategy possible. This paper discusses the accuracy and usefulness of various staging modalities that either have been or are currently being used to determine the extension of PCa at the time of diagnosis. A review of these staging procedures is timely, especially considering that such issues as stage migration have resulted from the institution of early detection programs [1, 12, 16, 17]. The discussion that follows attempts to provide the foundations for the development of a standardized approach to the clinical staging of T1c PCa, which will hopefully lead to the elimination of unnecessary or ineffective procedures. We believe that the application of a rationalized, consensual algorithm for T1c PCa staging not only is clinically desirable but should also result in considerable savings for the health-care economic resources worldwide.

T1c prostate cancer

In 1992, following a consensus conference, an updated TNM staging system was published that is now considered the international standard for PCa staging [86]. This revision of the previous TNM system introduced a new PCa category – stage T1c – with the purpose of recognizing nonpalpable, nonvisible cancers that were identified by prostate biopsy (needle biopsy or transurethral resection of the prostate, TURP) as a result of an elevated serum prostate-specific antigen (PSA) level.

M. C. Beduschi · R. Beduschi
The University of Michigan,
1500 East Medical Center Drive, Ann Arbor,
MI 48109-0330, USA

J. E. Oesterling (✉)
5410 Meadowcrest Dr.
Ann Arbor, MI 48105, USA

Table 1. Comparison of staging systems for prostate cancer

	American	TNM[b]
Nonpalpable cancer:		
≤ 5% of TURP tissue[a]	A1	T1a
≥ 5% of TURP tissue[a]	A1	T1b
Cancer detected by biopsy (e.g., elevated PSA)	B0	T1c
Palpable or visible cancer clinically confined within the capsule:		
≤ Half of one lobe	B1	T2a
≥ Half of one lobe, but not both lobes	B1	T2b
Both lobes	B2	T2c
Cancer with local extracapsular extension:		
Unilateral	C1	T3a
Bilateral	C1	T3b
Seminal vesicle invasion	C2	T3c
Invasion of bladder neck, rectum, external sphincter	C2	T4a
Invasion of levator muscle or pelvic wall	C2	T4b
Metastatic cancer:		
Single regional lymph node, ≤2 cm in greatest dimension	D1	N1[c]
Single regional lymph node, 2–5 cm, or multiple regional lymph nodes ≤5 cm	D1	N2
Single regional lymph node, > 5 cm	D1	N3
Distant metastasis	D2	M1
Nonregional lymph node(s):	D2	M1a
Bones	D2	M1b
Other sites	D2	M1c

Stage groupings for TNM staging systems (*G* Grade on 1–4 scale)

Stage 0		T1a	N0	M0	G1	
Stage I		T1a	N0	M0	G2, 3, 4	
	T1b	N0	M0	Any G		
	T1c	N0	M0	Any G		
	T1	N0	M0	Any G		
Stage II		T2	N0	M0	Any G	
Stage III		T3	N0	M0	Any G	
Stage IV		T4	N0	M0	Any G	
	Any T		N 1, 2, 3		M0	Any G
	Any T		Any M		M1	Any G

[a] Different definitions exist for substaging of A1 and A2 cancers
[b] N0 or NxM0 for T1–T4 (see above for stage groupings)
[c] *Nx* regional lymph nodes are not assessable, *Mx* distant metastasis is not assessable

There is no equivalent pathologic stage for clinical stage T1c PCa, and such tumors are invariably up-staged after surgery, usually to stage T2 or T3. Today, at least 25% of the PCa diagnosed in the United States are clinically staged as T1c, and most of these patients undergo an extensive, often unnecessary preoperative and intraoperative staging evaluation [e.g., computerized tomography (CT) scan, bone scan, magnetic resonance imaging (MRI) scan, bilateral pelvic lymphadenectomy].

The American staging system for PCa was introduced in 1956 by Whitmore [104]. It makes use of the letters A through D to denote stages and was modified by Jewett [44] to allow substaging of group B. Recently, similarly to the TNM system, the American system has been updated to accommodate PSA-detected cancers – stage B0 (Table 1) [62].

Clinical staging modalities

The most commonly used clinical parameters for determining the preoperative extent of PCa are digital rectal examination (DRE), PSA concentration, Gleason score from the biopsy specimen, and radionuclide bone scan. Other staging tests that can yield useful information about the extent of disease in select patients include reverse transcriptase-polymerase chain reaction (RT-PCR) assay (molecular staging), seminal vesicle biopsy, imaging studies (CT scan and MRI scan), and bilateral pelvic lymphadenectomy.

Digital rectal examination

First introduced by Whitmore [104] and later popularized by Jewett [44], DRE has become the classic method for assessing the local extent of prostate malignancy. Although essential, DRE lacks sensitivity and specificity in predicting organ-confined (OC) or non-organ-confined (NOC) disease. If compared with the final pathologic evaluation of the surgical specimen, DRE findings present a false-negative rate for NOC disease of approximately 48%, according to several reports [1, 4, 15, 20, 28, 37, 51, 53, 55, 65, 74, 76, 77, 80, 97, 103, 108].

Partin et al. [74] evaluated 1058 patients, whereby both the DRE and radical prostatectomies were performed by a single urologist and a single pathologist evaluated the surgical specimens. The overall specificity, sensitivity, and accuracy of DRE in predicting OC disease was 9%, 98%, and 57.7%, respectively. Conversely, the negative predictive value of DRE for OC disease was in the range of 80–93%, meaning that when DRE indicates an NOC cancer it is frequently correct. Similar results were reported by Ohori et al. [66].

Epstein et al. [29] examined the preoperative clinical and histopathologic characteristics of 157 men with clinical stage T1c disease, eventually treated with radical prostatectomy, and compared these findings with those obtained in 439 patients who had their prostates removed due to a clinical T2 PCa. In all, 16% of the T1c tumors were found to be insignificant tumors confined to the prostate gland (volume $< 0.2\ cm^3$, Gleason score < 7); 10% had OC tumors with volumes of between 0.2 and 0.5 cm^3 , 37% had larger but favorable tumors (volume > 0.5 cm or capsular penetration; only Gleason score < 7), whereas 37% of the patients had either locally or regionally advanced disease (capsular penetration, Gleason score ≥ 7 or positive surgical margins, seminal vesicle, and/or lymph node involvement) [29]. Oesterling et al. [62] and Noldus and Stamey [57] conducted two independent investigations evaluating men with T1c PCa (PSA > 4.0 ng/ml and normal DRE). Histopathology study of the specimens revealed that the majority of these patients (85% and 87.7% respectively) had OC disease.

In summary, DRE displays a poor performance in terms of specificity for OC PCa and sensitivity for NOC disease. DRE frequently underestimates the extent of disease for PCa, and it is especially inaccurate in the staging of T1c and T2 PCa, many of which are found to be T3c on final pathology reports [17, 58, 66, 69]. However, in patients with a PSA value of < 4.0 ng/ml and a Gleason score of < 7 the presence of a nonsuspicious DRE defines a patient population with a high probability of having localized disease. The positive predictive value of DRE for NOC PCa is good; in other words, when the DRE indicates a T3a or higher PCa, it is most likely an NOC tumor. Despite its limitations, the clinical staging of all newly diagnosed PCa starts with a carefully performed DRE.

Prostatic acid phosphatase

The relationship between PCa and prostatic acid phosphatase (PAP) was first demonstrated more than 50 years ago [34, 41]. PAP is not prostate-specific, since the enzymatic activity of this phosphatase has been identified in many body fluids and tissues. The clinical utility of PAP is controversial, since a normal PAP serum concentration does not guarantee the absence of extraprostatic disease [2, 59, 83]. Stamey et al. [90] analyzed 378 patients with PCa in an early study designed to compare the clinical usefulness of PAP and PSA. They found that the serum PSA concentration was elevated in 122 of 127 men with newly diagnosed, untreated PCa, including 7 of 12 patients with unsuspected early disease and all of 115 men with more advanced disease. The PSA concentration increased with advancing clinical stage and was proportional to the estimated volume of the tumor. On the other hand, the PAP concentration was elevated in only 57 of the patients with PCa and did not correlate with tumor volume or with the stage of PCa [90]. Burnett et al. [13] found that only 4.6% (21 of 460) of men with PCa had an elevation in PAP levels, and only 1 of 460 patients (0.2%) with a PSA value of < 20 ng/ml had an abnormal and uniquely useful PAP finding. Considering that an elevated PAP level adds little, if any, extra clinical information beyond that of total serum PSA concentration, measurement of serum PAP (enzyme or immunology assay) has no practical role in the staging of T1c or any other newly diagnosed PCa and, therefore, should not be utilized.

Prostate-specific antigen

PSA is a chymotrypsin-like serine protease that ultimately enhances sperm motility by liquefying the semen. As its synthesis occurs almost exclusively at the prostate gland level, for all practical purposes, PSA is prostate gland-specific but not PCa-specific [17, 58, 69]. Once in the blood circulation, this protease's function is inhibited by its binding with alpha-1 antichymotrypsin (ACT), resulting in the formation of the PSA-ACT complex [58]. Total PSA refers to the sum of all immunodetectable species of PSA (free plus complexed forms). The predominant bound form of PSA is PSA-ACT, which accounts for approximately 90% of all complexed forms of PSA [50, 92]. Free PSA possesses at least one antigenic epitope that becomes unavailable once binding with ACT has occurred. Antibodies targeted against this free epitope represent the basis for the development of immunohistochemistry assays that distinguish free from total PSA.

Lilja et al. [50] and Stenman et al. [92] observed that through the quantification of free and complexed forms of PSA, they could enhance the specificity of PSA for detecting PCa. Following several investigations, it now appears that percentage of free PSA values (free PSA/total PSA) are most useful in the range where the total PSA concentration is high-normal or only moderately elevated (3.0–10.0 ng/ml) [58, 63]. However, to date the reported investigations addressing the application of percentage of free PSA with the intent of determining the clinical stage of PCa have shown that this variable does not improve our accuracy in staging PCa [38, 75]. Several patient population-based studies have been reported, demonstrating that the total serum PSA concentration correlates directly with both the clinical and the pathologic stage of PCa. In most cases, however, a single total serum PSA measurement does not provide

Table 2. Nomogram for prediction of final pathologic stage for T1c prostate cancer[a]

Gleason score	PSA (ng/ml)			
	0.0–4.0	4.1–10.0	10.1–20.0	>20.0
	Prediction of organ-confined disease (%)			
2–4	92	82	–	33
5	81	71	55	24
6	69	59	41	22
7	55	43	24	7
8–10	–	31	–	3
	Prediction of established capsular penetration (%)			
2–4	22	29	–	50
5	30	34	40	54
6	34	38	45	53
7	40	44	52	67
8–10	–	48	–	74
	Prediction of seminal vesicle involvement (%)			
2–4	<1	<1	<1	<1
5	<1	<1	<1	<1
6	1	1	1	2
7	4	5	6	9
8–10	–	23	–	31
	Prediction of lymph nodal involvement (%)			
2–4	<1	1	–	6
5	1	1	3	9
6	2	2	4	8
7	2	3	7	24
8–10	–	5	–	41

[a]Adapted from Partin et al. [74]

accurate staging information for the individual patient [16, 30, 35, 40, 60, 70, 74, 79, 84, 90]. Partin and Oesterling [58, 69] have reported data that describe the application and limitations of total serum PSA for screening and detection of PCa as well as its correlation with stage, tumor volume, and local or distant metastases. Efforts are being directed toward establishing clinically relevant cutoff points for total serum PSA that, by correlating with the above-cited variables, would allow a more accurate prediction of pathologic staging of newly diagnosed PCa.

More recently, Partin and Oesterling [69] described total serum PSA staging guidelines for PCa. In all, 70–80% of men with PSA concentrations of <4.0 ng/ml have pathologically OC PCa, and 50% of men with PSA levels of >10 ng/ml have extension into the pericapsular adipose tissue [70, 74]. PSA concentration is directly related to the volume and stage of the PCa, but exact interpretation of the PSA level is impaired by confounding factors that interfere with PSA measurements (benign prostatic hyperplasia [BPH], prostatitis, prostate epithelial component of the gland) [17, 58, 69, 92]. Partin et al. [70] have also observed that men with more advanced disease have a higher Gleason score and tumor volume and produce less PSA per gram of tumor tissue. Kleer et al. [47] and Partin et al. [74] used a logistic regression modeling approach and demonstrated that the combination of total serum PSA, Gleason score, and DRE provides the best results in terms of predicting pathologic stage. From these findings, Partin et al. [74] constructed predictive probability plots and nomograms to help the urologist in the preoperative prediction of final pathologic stage for patients with clinically localized PCa (Table 2). Logistic regression formulas using PSA as an independent variable are common in the urology literature. Such models are most accurate in predicting capsular penetration and are less precise in predicting more advanced disease. In summary, total serum PSA makes a significant contribution to the staging of newly diagnosed PCa, especially when used in combination with Gleason scores and DRE findings.

Molecular staging

Molecular staging of PCa correlates the pathologic stage of a localized PCa with RT-PCR (reverse transcription-polymerase chain reaction) assay results. The RT-PCR technology was first used for PCa detection in 1990 and has since provided substantial information for the understanding of prostate cancer [101]. The RT-PCR method has the ability to detect the presence of a minute number of prostate cells in any sample of body tissue. As a result, the presence of prostate cancer metastases could be detected theoretically at an earlier time, providing the basis for a more adequate treatment strategy. The presence of distant prostate disease is being investigated in the most common sites for metastatic spread (lymph nodes and bone marrow) and also in the bloodstream. Regardless of the tissue source, intact RNA is isolated from the specimen, and reverse transcription (RT) of RNA to cDNA is conducted. Once it has been obtained,

the PCR is then used to amplify selected sequences in the cDNA. The RT-PCR assay is capable only of identifying a prostate cell that has migrated into the vascular system (lymphatic or venous) and has survived, because the RNA quickly degrades once the cell has died. It also should be mentioned that a positive RT-PCR reaction, while indicating the presence of prostate cells in the blood, does not indicate whether these cells are cancerous or possess the required ability to establish a metastatic site. This phenomenon is a potential shortcoming of the RT-PCR technology.

A recent investigation at Columbia University, using RT-PCR for PSA performed on peripheral blood samples, has provided data that show potential in helping the preoperative staging of patients with PCa [45]. It appears that increased assay positivity correlates directly with increasing tumor stage. As based on this experience, a negative RT-PCR assay ensures OC disease in 88% of cases [45]. When combined with other clinically relevant parameters (e.g., PSA, DRE, Gleason score), the RT-PCR assay has an even better predictive ability. With serum PSA levels of < 10 ng/ml and a negative RT-PCR index, 81% of cases revealed an OC cancer. Conversely, if the serum PSA values is > 10 ng/ml and the RT-PCR index is positive, the patient has a 90% chance of having positive surgical margins, seminal vesicle involvement, or lymph node dissemination of cancer. The difference between these two groups analyzed by follow-up data demonstrates PSA failure rates of 7% for the first group and 43% for the latter cohort. A recent pathology review, conducted at the same institution, demonstrated that a positive RE-PCR result combined with a preoperative needle biopsy showing perineural invasion was highly predictive of nonlocalized disease. As an isolated variable, RT-PCR reached 91% specificity and 51% sensitivity in predicting extraprostatic disease [67].

In summary, these data suggest that RT-PCR, when targeted against a prostate-specific marker (e.g., PSA), may be useful in differentiating patients with metastatic disease from those who do not have advanced PCa. The concept of molecular staging is a promising technology for early prostate cancer staging, but there is no consensus regarding its clinical value at present. For this reason, the use of RT-PCR should be restricted to the field of scientific research and should not yet be used routinely in the management of patients with clinically localized PCa.

Biopsy pathology for clinical staging

Systematic biopsy of the prostate

A systematic sextant biopsy of the prostate increases the detection rate of PCa, regardless of DRE or ultrasound abnormalities, and data obtained from the biopsy can also be used to predict the tumor volume and pathologic stage of the PCa [8, 23, 36, 39]. Obtained through a sextant biopsy, parameters such as the number of positive cores, the tumor location and bilaterality, estimation of percentages of Gleason grades 4 and 5, and perineural and capsular invasion, among others, have been evaluated for their contribution to the accurate prediction of PCa stage [27, 88].

Peller et al. [77] have reported that patients with four or more positive cores have a sensitivity of 50%, a specificity of 93.2%, and an accuracy of 79% for extracapsular penetration. Hammerer et al. [37] evaluated a group of 103 men prior to radical prostatectomy; they determined the sensitivity and specificity of the number of positive sextant cores and the percentage of linear involvement in these cores with regard to predicting lymph node metastases. Five or more positive cores reveal a sensitivity of 66% and a specificity of 94% in predicting lymph node involvement. In all, 53 patients had fewer than 5 positive cores, and only 3 of them (5.6%) had positive lymph nodes. Bostwick et al. [11] evaluated 314 men who underwent prostate biopsy and, through the use of PSA, biopsy Gleason score, and percentage of cancer in the biopsy specimen, were capable of reliably predicting capsular penetration and final pathologic stage. These findings have been confirmed by other authors as well. Pericapsular fibroadipose tissue involvement, perineural invasion, and tumor in the apex on biopsy are also highly predictive of capsular penetration and indicate to the surgeon the need to sacrifice the ipsilateral neurovascular bundle [1, 7, 42, 80, 97, 102].

Investigations are currently under way, focusing on the number of prostate cores per biopsy to be performed as a function of the patient's age, prostate volume, and critical life-threatening tumor volume [56, 100], i.e., the most appropriate number of cores that should be obtained from a given patient in terms of not only identifying a significant yet curable PCa but also providing sufficient information about the stage of disease. However, this must be accomplished in such a manner that very small tumors that are not clinically significant are not detected. In 1997, all patients should undergo at least a systematic sextant biopsy of the prostate due to the great amount of information this procedure provides for staging and subsequent management.

Histologic grade

The Gleason system is the most commonly used grading system in PCa, and it has been shown to correlate with the extent of disease and the patient's prognosis [6, 31, 32]. The presence of a Gleason score of ≥ 7 or of a Gleason grade of 4 or 5 is associated with a less favorable prognosis [26, 27, 65, 93, 108]. The importance of the Gleason system as a predictor of stage is supported by several multivariate analyses of prognostic criteria of disease extent [4, 9, 14, 26, 27, 43, 54, 62, 71, 72, 85, 96, 106]. A Gleason score of ≥ 7 has an accuracy of 58% in predicting

OC disease (sextant biopsy) [5]. Nevertheless, the Gleason system has limitations, including the following

1. The Gleason system is accurate in predicting prognosis only on the extreme ends of its scoring spectrum, and the majority of men with PCa (75–80%) have intermediate scores (5–7).
2. The infrequent finding of Gleason scores of between 2 and 4 (well-differentiated) or between 8 and 10 (poorly differentiated).
3. Gleason scores of 6 and 7 may have quite a different staging status for the individual patient, depending on the presence and percentage of the Gleason 4 component.
4. The biopsy Gleason score is usually lower than the final postoperative Gleason score (undersampling) [25, 52, 71, 74].

The biopsy Gleason grading system is a useful tool for predicting the stage of disease, but it has limitations in terms of accuracy. For this reason it should be combined with other relevant parameters (PSA and local clinical stage) so as to maximize its performance in predicting the final pathologic staging.

Seminal vesicle biopsy

Seminal vesicle biopsy is recommended for patients with a PSA value of >10 ng/ml, a Gleason score of >4, and a positive DRE (T2b), who are being considered for radical prostatectomy to reduce preoperative understaging. Consequently, this approach should not be performed on a regular basis for patients with a stage T1c PCa [3, 22, 93, 95, 98].

Imaging evaluation

A series of imaging techniques have been evaluated as methods for staging PCa, including intravenous excretory urography (IVU), transrectal ultrasound (TRUS), computerized tomography (CT), magnetic resonance imaging (MRI), and radionuclide bone scan.

Intravenous urography

Excretory urography is neither useful nor recommended for the staging of patients with clinically localized PCa, particularly for men with PSA-detected prostate cancer (stage T1c)

Transrectal ultrasound

Rifkin et al. [82] conducted a multicenter study to evaluate the ability of TRUS to predict capsular penetration in surgical specimens of patients subjected to radical prostatectomy for clinical stage T2 PCa. The data collected from 219 patients revealed a specificity of 46% and a sensitivity of 66%, with an overall accuracy of 46% being obtained for the prediction of OC PCa (126 of 219 cases). A comparison of TRUS with other modalities commonly used to predict OC and NOC PCa shows that TRUS does not add any significant or unique information in determining the correct PCa stage. This observation demonstrates that TRUS has no useful role in the clinical staging of PSA-detected PCa.

CT and MRI scans

Several investigators have evaluated the ability of CT scan, MRI scan, and pedal lymphangiography (PL) to stage accurately patients with newly diagnosed PCa. These staging studies not only fail to distinguish OC from extraprostatic disease but also do not detect approximately 50% of pelvic lymph node metastases. For this reason the majority of the investigators do not include these examinations in the routine staging evaluation of patients with newly diagnosed PCa.

CT and MRI scans have been used in several different settings in an attempt to identify local extraprostatic extension and/or lymph node metastases. Both scans have shown a high rate of false-negative and false-positive results in the assessment of extraprostatic disease [18, 94, 105]. MRI, however, does appear to be more precise than CT in evaluating the local extent of PCa, but this slight gain in sensitivity and specificity is insufficient to warrant routine use of this most expensive technique. The use of fine needle aspiration (FNA) in combination with the CT scan to assess pelvic lymph node status has decreased the false-positive rate to nearly zero, although the false-negative rate remains at the 75% level. The technical inability to combine MRI with FNA prevents the use of this methodology in evaluation of pelvic lymph nodes.

Although the CT scan should not be used routinely, there is a small subset of patients characterized by a total PSA level of >25 ng/ml and a Gleason score of >6 for whom this imaging modality may be helpful in assessing lymph node status. In one study, 13 of 17 positive CT scans were found in patients with a PSA level of >25 ng/ml, a Gleason score of >6, and a positive DRE; in this subset of patients, 13 of 71 (18.3%) had lymphatic metastases identified by CT scan [81]. The combination of this information with the results reported by Von Poppel et al. [99], showing a sensitivity of 78% for the combined application of the CT scan and FNA for identification of positive lymph nodes, defines a useful staging recommendation for this subset of patients.

In summary, patients with a PSA value of >25 ng/ml and a Gleason score of >6 should undergo a CT scan with FNA of any lymph node that is at least 1.0 cm in size. Otherwise, a CT or MRI scan should not be recommended as a staging procedure. This approach should eliminate the use of these imaging studies in over 90% of men with newly diagnosed PCa.

Bone scan

The radionuclide bone scan has played a traditional role in PCa staging, even for clinically localized disease, since there is no way to predict which patient will present with bone metastases. Nevertheless, PCa management has been revolutionized with the advent of PSA testing, making it necessary to review the routine use of bone scan for PCa staging.

During the past few years, several investigations have addressed the ability of PSA screening to predict bone metastases in men with PCa [19, 61]. The data available from these investigations compare PSA results with radionuclide bone scan findings, and these findings suggest that PSA testing is as reliable as and much more cost-effective than the bone scan for most patients. In modern urology the use of the radionuclide bone scan as a staging procedure for PCa should be restricted to well-defined clinical situations.

Chybowski et al. [19] analyzed 521 randomly selected newly diagnosed PCa patients from their data base. Prior to treatment, all patients were assessed with DRE (local clinical stage), prostate biopsy (tumor grade), serum PAP and PSA measurement, and radionuclide bone scan. The statistical analysis indicated that local clinical stage, tumor grade, PAP, and PSA directly correlated with a positive bone scan ($P < 0.0001$). Results were plotted on a receiver operating characteristic (ROC) curve, and PSA was found to be the best predictor of radionuclide bone scan results (Fig. 1). None of the patients with a serum PSA level of < 15 ng/ml had a positive bone scan, and only one man with a PSA value of between 10 and 20 ng/ml (18.2 ng/ml) presented with a positive examination. The observed false-negative rate was zero for PSA values of ≤10 ng/ml and 0.3% for PSA levels of ≤20 ng/ml (95% confidence interval). The authors concluded that radionuclide bone scans are not necessary in the staging evaluation of men with previously untreated PCa who have no skeletal symptom and a serum PSA level of ≤10 ng/ml. In another independent study, after reviewing 852 patients with untreated PCa and a PSA level of < 20 ng/ml, Oesterling and coworkers [61] also found that PSA was capable of predicting bone scan findings. Only 7 (0.8%) patients were found to have a positive bone scan, and 5 (71%) of them presented with symptoms related to the location of the positive findings on the bone scan. One patient reporting no skeletal symptom and a PSA level of < 10 ng/ml had a positive bone scan. On the basis of these results, these investigators again concluded that the staging radionuclide bone scan is unnecessary in patients with (1) newly diagnosed PCa, (2) a PSA value of ≤ 10 ng/ml, and (3) no skeletal symptom.

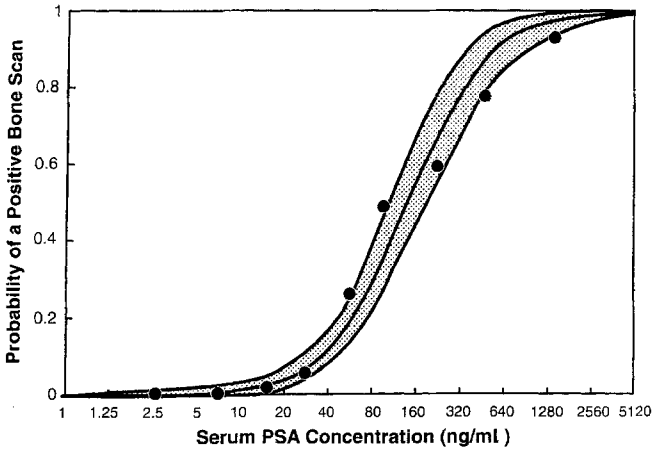


Fig. 1. Probability plot. Predicted percentage of newly diagnosed, untreated prostate cancer patients with positive bone scan (*solid line*) as based on a logistic regression model using the natural logarithm of serum PSA concentration. Confidence limits (95%) for predicted percentages are based on PSA groupings determined by cutoff points of 5, 10, 20, 40, 80, 160, 320, and 640 ng/ml in 521 patients (from Chybowsky et al. [19], with permission)

Similarly, Rees et al. [81] determined that elimination of the radionuclide bone scan could be safely achieved under some PSA- and Gleason-score-based conditions. These researchers reviewed 392 patients diagnosed with PCa, who had pretreatment serum PSA measurements and staging bone scans. None of the patients under the following criteria showed evidence of bone metastases: (1) a serum PSA level of ≤5 ng/ml, (2) a Gleason score of ≤5, or (3) a combination of a PSA value of ≤ 25 ng/ml, a Gleason score of ≤7, and a negative DRE (stage T1c) [81].

Gleave and colleagues [33] retrospectively analyzed pretreatment PSA levels and bone scans on 490 patients with recently diagnosed PCa. None of the 290 patients having a PSA value of ≤10 ng/ml displayed bone metastases. Of the patients with PSA levels of between 10 and 20 ng/ml, 4.5% presented with bone metastases. The positive predictive value was highest for patients with PSA levels of > 50 ng/ml, among whom 19 of 48 (40%) patients presented with skeletal metastases. These authors also observed a higher rate of bone scan positivity in patients with T3 disease (19%) as compared with stage T2 disease (1%) or T1 disease (4%). Furthermore, they found that patients with poorly differentiated cancers (18%) versus moderately different disease (4%) versus well-differentiated disease (1.5%) were more likely to have bone metastases.

In summary, the radionuclide bone scan, although the gold standard for the detection of bone metastases, should not be recommended for asymptomatic patients with PCa who meet at least one of the following criteria: (1) a serum PSA level of ≤ 10 ng/ml, (2) a Gleason score of ≤ 5, or (3) a combination of a PSA value of ≤ 25 ng/ml, a Gleason score of ≤ 7, and a negative DRE.

Bilateral pelvic lymph node dissection

In 1997 the bilateral pelvic lymphadenectomy remains an important and essential procedure in the staging evaluation of newly diagnosed PCa. Reducing the number of unnecessary lymph node dissections while preserving the quality of the cancer therapy, however,

would result in less morbidity for the patient and considerable financial savings for the health-care system.

Recent reports indicate that the rate of metastatic nodal involvement for localized PCa is presently somewhere between 3% and 15%, which represents a major downward shift from the incidence rate of 30% reported in the early 1980s [10, 49, 74, 78, 81, 86, 89]. Kramer and colleagues [48] reviewed their data base and reported that no patient with a Gleason score of between 2 and 4 was found to have lymph node metastases, regardless of the clinical stage. Conversely, patients with a Gleason score of 8–10 had a 93% probability of having lymph node involvement. Other authors have clearly demonstrated that lymph node status correlates directly with clinical stage [24, 64]. Smith and co-workers [87] observed that patients with stage A1 disease and well-differentiated stage B1 tumors had an incidence of positive lymph nodes of zero and 4%, respectively. On the basis of these low rates, they suggested that pelvic lymphadenectomy could be avoided in this subset of patients. Meanwhile, men with poorly differentiated stage C tumors should be assumed to have metastatic disease and should undergo a pelvic lymph node dissection, since 93% of the patients evaluated in this study were found to have nodal involvement. Zincke and colleagues [107] have found that although the biopsy-determined Gleason score directly correlates with the pathologic stage, this variable alone is not sufficiently accurate to predict lymph node status on an individual basis.

Recent reports have proposed the combination of PSA, clinical stage, and Gleason score as the better predictor of metastatic disease to the pelvic lymph nodes. Addressing this issue in 1994, Bluestein et al. [10] examined the ability of preoperative serum PSA concentration, primary Gleason grade (biopsy specimen), and local clinical stage (DRE) to predict accurately the pelvic lymph node status of patients with clinically localized PCa. The medical records of 1630 patients with PCa, who underwent a staging bilateral pelvic lymphadenectomy at the Mayo Clinic between 1988 and 1991, were reviewed. Three distinctively different patient groups were identified in this patient population: (1) 1586 men who underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy, regardless of the node status; (2) 30 patients who underwent pelvic lymphadenectomy and no further exploration due to metastatic disease; and (3) a group comprising 16 patients who underwent staging lymphadenectomy and definitive radiation therapy. Through logistic regression analysis, serum PSA was found to be the best predictor of nodal involvement ($P < 0.0001$). The predictive power of PSA testing could be significantly enhanced by the consideration of clinical stage ($P < 0.001$) and primary Gleason grade ($P < 0.001$). On the basis of these findings and variables, the authors developed a statistical model allowing the practicing urologist to estimate the relative risk of pelvic nodal disease on an individual basis (see Table 3, Fig. 2). Given a cutoff point of ≤3% as an acceptable false-negative rate, 61% of the patients with clinical stage T1a–T2b may be spared an open or laparoscopic staging bilateral pelvic lymphadenectomy [10].

Using a similar mode, Rees et al. [81] proposed a model capable of generating a subset of patients who would have a low chance of harboring metastatic lymph node disease. On the basis of such a model, the authors recommend the elimination of pelvic lymph node dissection in patients with the following criteria: (1) a PSA level of < 5 ng/ml , (2) a Gleason score not exceeding 5, or (3) a combination of a PSA value of < 25 ng/ml, a Gleason score of 7 at the most, and a negative DRE. Application of these criteria should result in a reduction of up to 60% in the number of unnecessary pelvic lymphadenectomies carried out in patients with clinically localized (T1a–T2b) PCa.

Fine needle aspiration (FNA) of lymph nodes under CT guidance is a technique that combines cross-sectional imaging and aspiration biopsy of enlarged (> 1.0 cm) pelvic lymph nodes. It has 70% sensitivity and 100% specificity in detecting lymph node metastatic disease. Its cost-effectiveness and low morbidity rate

Table 3. Relationship of serum PSA, primary Gleason grade, and clinical stage with pelvic lymph node status[a]

Primary Gleason grade	PSA (ng/ml)						
	<2	2–4	4.1–10.0	10.1–20	20.1–50	50.1–100	≥100
1	6 (0)	8 (12.5%)	26 (7.7%)	10 (0)	9 (0)	1 (0)	1 (100%)
2	45 (0)	63 (0)	202 (2.5%)	113 (8%)	52 (13.5%)	9 (44.9%)	7 (42.9%)
3	33 (3%)	62 (2.4%)	276 (4%)	176 (19.3%)	121 (16.5%)	22 (32.4%)	15 (60%)
4	7 (0)	21 (9.5%)	104 (11.5%)	79 (15.2%)	73 (30.4%)	30 (53.3%)	10 (40%)
5	1 (100%)	2 (50%)	8 (12.5%)	4 (25%)	6 (16.7%)	6 (16.7%)	3 (66.7%)
Clinical stage							
T1a	5 (0)	3 (0)	7 (0)	1 (100%)	0 (–)	0 (–)	0 (–)
T1b	16 (6.3%)	6 (0)	11 (0)	7 (14.3)	5 (0)	1 (0)	1 (0)
T1c	5 (0)	7 (0)	88 (0)	53 (3.8%)	40 (10%)	3 (0)	2 (0)
T2a and T2b	33 (0)	53 (1.4%)	121 (0.8%)	58 (6.9%)	20 (15%)	1 (0)	1 (0)
T2c	43 (0)	78 (2.6%)	319 (5.3%)	215 (17.7%)	137 (19.7%)	37 (40.7%)	20 (60%)
T3a	4 (25%)	16 (12%)	69 (17%)	50 (26%)	58 (41%)	26 (53%)	12 (58%)

[a] Values are reported as total numbers of patients per subgroup (percentage of positive nodes) (from Bluestein et al. [10a], with permission)

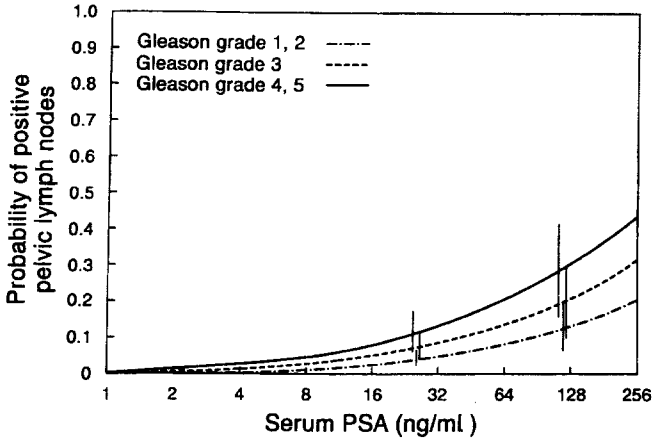
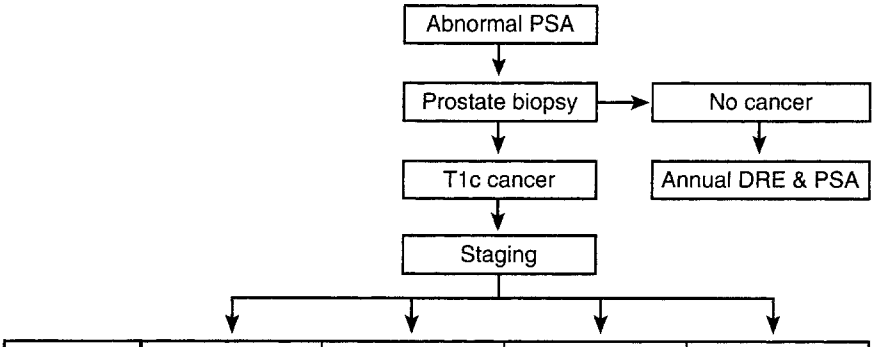


Fig. 2. Probability of positive lymph nodes in patients with clinical stage T1a–T2b (A1–B1) prostate cancer, plotted as a function of serum PSA concentration and primary Gleason grade. *Vertical lines* indicate 95% confidence intervals for probabilities for serum PSA concentrations of 20 and 100 ng/ml. The probability plot was determined from logistic regression analysis (from Bluestein et al. [10a], with permission)

warrant its recommendation whenever an enlarged, clinically significant lymph node (1.0 cm) can be identified on CT scan. The incidence of complications is considerably lower following FNA as compared with open lymphadenectomy.

Surgical assessment of the pelvic lymph nodes can be obtained through the use of two well-established methods – open bilateral lymphadenectomy and laparoscopic bilateral lymphadenectomy. The first and more traditional method, performed in conjunction with radical retropubic prostatectomy, is the open pelvic lymphadenectomy. Some potential complications related to this surgical procedure include obturator nerve injury, trauma to major vessels, thromboembolic events, lymphocele formation, and lymphedema. The laparoscopic approach, which carries less morbidity than the more traditional approach, is more time-consuming and, in the short-term analysis, is not cost-effective. The complication rate after a laparoscopic lymphadenectomy is reported to be 15%, according to Kavoussi et al. [46]; complications may occur either intraoperatively (25%) or postoperatively (75%), and 24% of them require open surgical management. This procedure is particularly appealing in the consideration of radical perineal prostatectomy or radiation therapy as the treatment approach for clinically localized PCa.

In summary, lymph node dissection via either an open or a laparoscopic approach should be indicated in the following situations: (1) a prebiopsy serum PSA level of >5 ng/ml, (2) a poorly differentiated tumor with a Gleason score of >7 [17, 99], (3) five or more positive systematic sextant biopsies or a total linear percentage of involvement of ≥280% [10], (4) a positive seminal vesicle



Staging modality	PSA: ≤ 5 (ng/ml)	5 < PSA ≤ 10 (ng/ml)	10 < PSA ≤ 25 (ng/ml)	PSA: > 25 (ng/ml)
PAP	not useful	not useful	not useful	not useful
TRUS	not useful	not useful	not useful	not useful
MRI scan	not useful	not useful	not useful	not useful
CT scan	not recommended	not recommended	may be useful	advised
Bone scan	unnecessary	unnecessary	advised	advised
Lympha-denectomy	unnecessary	recommended if Gleason > 7	strongly advised	strongly advised
Fine needle aspiration	—	—	—	possible when node ≥ 1.0 cm
RT-PCR	investigational	investigational	investigational	investigational

Fig. 3. Algorithm for the appropriate staging evaluation of newly diagnosed, PSA-detected prostate cancer (state T1c)

biopsy, (5) the presence of palpably advanced local disease of stage T3 or T4, and (6) the presence of enlarged pelvic lymph nodes as determined by pelvic imaging.

Conclusions

This document has reviewed a number of parameters available to and commonly used by the urologist for accurate staging of newly diagnosed, PSA-detected PCa. When used alone, however, none of the staging parameters discussed has sufficient accuracy per se in predicting NOC disease for the *individual* patient. DRE-driven TNM classification of PCa is the logical initial step of clinical staging in all patients. However, due to its lack of sensitivity, specificity, and overall accuracy, it is necessary to combine DRE T-staging with other parameters to improve the performance of clinical staging, ultimately resulting in better therapeutic planning. The most useful and minimally required variables to be associated with DRE are total serum PSA concentration, Gleason score, and other findings from the systematic prostate biopsy. Partin et al. [74] have reported nomogram tables based on total serum PSA, Gleason score, and local clinical stage that provide predictive probabilities for OC disease, NOC cancer, seminal vesicle invasion, and lymph node metastases (Table 2). The systematic sextant biopsy of the prostate can add a number of staging parameters that, once combined into a biopsy-based staging system, may become useful in therapeutic planning.

The indication for seminal vesicle biopsy remains controversial. Available data suggest that it may be useful in staging patients with large palpable tumors (T2b–c). A positive seminal vesicle biopsy associated with findings such as a PSA value of >20 ng/ml, a high Gleason score (8–10), and five or more positive biopsy cores indicates a poor prognosis. Nevertheless, on a regular basis this procedure should not be recommended or performed in a patient with stage T1c PCa.

Radiography studies play a very restricted role in the staging of the newly diagnosed PCa. The available data indicate that imaging studies (TRUS, CT scan, and MRI scan) are not sufficiently accurate to determine the local extent of this disease. Assessment of lymph node status is cost-effective only for patients at high risk for pelvic lymph node metastases. Radionuclide bone scan evaluation is necessary for the man with newly diagnosed PCa only if the total serum PSA level exceeds 10 ng/ml or if he has skeletal symptoms.

The algorithm developed by Bluestein and co-workers [10] to assess the risk of lymph node metastases is valuable for safely deciding which patients do not require a lymph node biopsy or formal pelvic lymph node dissection.

There is no doubt that more efforts are necessary toward improving the currently available multivariate, clinical staging method for stage T1c PCa. A consensual rationalization of what is felt to be an appropriate, cost-effective staging evaluation of T1c PCa in 1997 is presented in Fig. 3. The application of a systematic rationalized staging protocol could result in a significant impact on the quality of care and in more appropriate utilization of economic resources in the management of stage T1c PCa.

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