

Diagnosis and treatment of prostate cancer

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Many controversies surround the management of prostate cancer to include screening practices, diagnosis, and treatment options [1,2]. Although various medical organizations do not recommend routine screening for this malignancy [3], other organizations, such as the American Urological Association and the American Cancer Society, have published screening guidelines for the early detection of prostate cancer [4,5]. Results from the PLCO (Prostate, Lung, Colorectal and Ovarian Cancer Screening) trial in the United States, sponsored by the National Cancer Institute, and the European Randomized Study on Screening, should provide definitive answers to the question of whether or not prostate-specific antigen (PSA) screening can ultimately reduce mortality from prostate cancer [6]. The current screening recommendation of the American Urological Association and American Cancer Society is for all men 50 years or older to be offered a PSA measurement annually along with a digital rectal examination (DRE). African American men and those with a family history of prostate cancer (one or more first-degree relative with prostate cancer) should consider beginning their annual screening at age 40. Those individuals who elect to proceed with screening and are eventually diagnosed with prostate cancer face many uncertainties when deciding which course of action to follow. The lack of randomized prospective studies comparing the various definitive treatment modalities currently available occasionally can make the decision process challenging for patients and their providers.

In this setting of controversy, the cost of treating clinically localized prostate cancer is significant. It is estimated that the cost of treating early stage prostate cancer in the United States ranged from \$1.72 to \$4.75 billion

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annually during the 1990s [7]. Demographic trends in the United States, increased awareness, and improved diagnostic approaches are expected to increase the economic burden that this disease places on the health care system [8]. With an estimate of 189,000 new cases of prostate cancer and 30,200 new prostate cancer–related deaths in 2002 [9], the disease will continue to have a major impact on society. In the face of these unanswered questions, this article summarizes some important principles regarding the diagnosis and treatment of prostate cancer. For the purpose of this discussion, the review is limited to the diagnosis and management of clinically localized disease.

Diagnostic and staging approach

Early detection issues

Most men diagnosed with clinically localized prostate cancer have no symptoms that can be attributed to this disease [10]. The suspicion of prostate cancer is usually raised by an elevated serum PSA, an abnormal DRE, or a combination of both. The presence of bladder outlet obstructive symptoms, irritative voiding symptoms, hematospermia, decreased ejaculatory volume, or impotence may suggest locally advanced disease, but the presence of these symptoms in the general population is rarely caused by prostate cancer. Metastatic prostate cancer may present with bone pain, anemia, lower extremity edema, obstruction of the upper urinary tracts, paraneoplastic syndromes, or disseminated intravascular coagulation. Often-times, patients with advanced disease have a prolonged period of weight loss, inanition, and ultimate development of painful bony metastases. The goal of early detection of prostate cancer is to identify those men with clinically significant prostate cancer that has the potential to cause morbidity and to control the disease with treatment [5]. Particular emphasis is placed on the detection of moderate- or high-grade tumors in younger men because the risk of dying from prostate cancer is highest in this group of men. The definition of a clinically significant tumor is controversial (Table 1) [11–13]. Tumors with a Gleason’s sum of 7 or greater seem to be the most aggressive, however, but generally it is related to tumor volume; PSA (which is often a surrogate for volume); and tumor grade. Generally, volumes greater than 0.5 cm³ and Gleason’s sum 7 or greater tumors are thought to have a high risk of disease progression [14,15].

Table 1
Definition of indolent (clinically insignificant) prostate cancer

Series	Definition
Smith and Catalona, 1994 [11]	Impalpable, focal, no Gleason grade, 3, 4, or 5
Ohori et al, 1994 [12]	Tumor volume <0.5 cm ³ , confined, no Gleason grade 4 or 5
Epstein et al, 1994 [14]	Tumor volume <0.5 cm ³ , confined, no Gleason grade 4 or 5

Despite of the fact that PSA is currently the best single test for the early detection of prostate cancer, approximately 20% of tumors may be missed by using the traditional upper limit of normal of 4 ng/mL [16]. There are a variety of methods available to improve on the sensitivity of PSA for prostate cancer detection. To improve on the sensitivity of PSA screening, some investigators have recommended lowering the upper limit of normal in younger patients [17]. Reviewing available data, Richardson and Oesterling [18] recommended using 2.5 ng/mL as the upper limit of normal for white men younger than 50 years of age, and 2 ng/mL for African American and Asian men in the same age group. Another strategy to improve sensitivity is to consider performing biopsy on those individuals with a rapidly rising serum PSA level. Carter et al [19] introduced in 1992 the concept of PSA velocity to increase the sensitivity of PSA for prostate cancer detection. These investigators recommended at least three PSA measurements over a 2-year period or measurements spaced at least 12 to 18 months apart to obtain maximal benefit from this approach. A PSA velocity of greater than 0.75 ng/mL/y was found to be strongly suggestive of cancer.

Various approaches have been suggested to improve specificity of PSA testing and to avoid unnecessary prostate biopsies in certain men. Richardson and Oesterling [18] recommended using higher PSA cutoffs in men over 60 years of age as part of their age-specific PSA reference ranges. Alternatively, Benson [20] introduced the concept of PSA density to account for the fact that prostate cancer is known to release more PSA per volume unit into the circulation than benign prostatic hyperplasia tissue. The use of PSA density is limited, however, by the fact that this calculation requires the performance of transrectal ultrasound (TRUS)-determined prostate volume measurements. Finally, the use of percent free-PSA levels also improves the specificity of PSA testing. Investigators have found that men with free-total PSA ratios greater than 20% to 25% are at significantly lower risk of prostate cancer on subsequent biopsy [21].

Transrectal ultrasound-guided needle biopsy of the prostate

In 1989, Hodge et al [22] introduced the systematic random sextant biopsies for the detection of prostate cancer. For almost a decade, this strategy remained the gold standard for biopsy technique. This is a procedure that is easy to learn, well tolerated by patients, and is associated with minimal risks [23]. Various institutions, however, have reported that the false-negative rate of a single set of sextant biopsies as originally described by Hodge et al [22] ranges around 20% to 25% [24,25]. Recent refinements in biopsy techniques to improve prostate cancer detection include directing the needles more laterally to sample more of the peripheral zone and increasing the number of biopsy cores [26]. In one clinical series, Presti et al [26] reported an overall 42% cancer detection rate. The traditional sextant biopsy scheme missed

about 20% of the cancers, whereas their recommended biopsy scheme detected 96% of the cancers.

Clinical staging

Pretreatment clinical staging assists both the patient and physician with treatment decisions. **Boxes 1 and 2** display the current AJCC (American Joint Committee on Cancer) staging system for adenocarcinoma of the prostate.

Clinical staging is based primarily on the presence or absence of a prostatic nodule on DRE. Clinical staging also differentiates those cancers detected by transrectal ultrasound and biopsy (TRUS/Bx) as opposed to those detected incidentally during transurethral resection of the prostate. Currently, most prostate cancers are detected in men who present with an elevated serum PSA and a normal DRE (ie, clinical stage T1c). To assist with treatment planning, investigators have developed nomograms that use clinical information to predict pathologic stage. Partin et al [27] has recommended using a combination of PSA level, clinical stage, and Gleason's score from the biopsy specimen to predict the likelihood of organ-confined disease, presence of seminal vesicle invasion, and presence of pelvic lymph node involvement with prostate cancer. Sebo et al [28] has suggested a role for percent of positive needle biopsy cores as a predictor of pathologic stage and tumor volume found at radical prostatectomy.

Relying solely on clinical stage, Gleason's grade, and PSA level to predict pathologic stage has its limitations. Approximately one third of the patients presumed to have localized prostate cancer at the time of diagnosis have extraprostatic disease [27]. Because metastatic prostate cancer is virtually incurable, improved pretreatment staging modalities are constantly being sought. The role of various radiographic imaging techniques in prostate cancer staging in the newly diagnosed patient has been extensively studied. Some of these imaging modalities include TRUS, MRI, CT, and radio-nuclide bone scanning.

Transrectal ultrasonography has greatly facilitated prostate biopsy schemes [22,24–26]. The ability of TRUS adequately to screen for extraprostatic tumor spread, however, is limited. In one study, overall staging accuracy by TRUS was estimated to be around 58% and there was no advantage of MRI over TRUS in local staging [29]. Perrotti et al [30] subsequently demonstrated that using endorectal MRI criteria for extraprostatic disease, approximately 20% of patients ultimately found to have organ-confined disease would have been excluded from surgery because of false-positive MRI results.

Evaluation with CT scanning of the abdomen and pelvis is usually not indicated in men with localized prostate cancer when the PSA level is less than 25 ng/mL [31]. In a series of 980 patients who underwent radical retropubic prostatectomy with pelvic lymph node dissection for clinically localized prostate cancer, Tiguert et al [32] concluded that lymph node size

Box 1. Clinical staging of prostate cancer (6th edition AJCC staging)

Primary tumor (T)

- TX - Primary tumor cannot be assessed
- T0 - No evidence of primary tumor
- T1 - Clinically unapparent 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 (eg, 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 vesicles
- T4 - Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

Regional lymph nodes (N)

- NX - Regional lymph nodes were not assessed
- N0 - No regional lymph node metastasis
- N1 - Metastasis in regional lymph nodes

Distant metastasis (M)

- MX - Distant metastasis cannot be assessed (not evaluated by any modality)
- M0 - No distant metastasis
- M1 - Distant metastasis
 - M1a - Nonregional lymph nodes
 - M1b - Bones
 - M1c - Other sites with or without bone disease

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Box 2. Pathologic staging of prostate cancer (6th edition AJCC staging)**Primary tumor (T)^a**

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 vesicles

T4 - Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

Regional lymph nodes (N)

NX - Regional lymph nodes were not sampled

N0 - No regional lymph node metastasis

N1 - Metastasis in regional lymph nodes

Distant metastasis (M)

MX - Distant metastasis cannot be assessed (not evaluated by any modality)

M0 - No distant metastasis

M1 - Distant metastasis

M1a - Nonregional lymph nodes

M1b - Bones

M1c - Other sites with or without bone disease

^a There is no pathologic T1 classification.

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determined preoperatively by CT scanning does not correlate with the presence of metastatic prostate cancer.

Radionuclide bone scans have been one of the most important imaging techniques in prostate cancer staging. Current data suggest, however, that bone scans are not necessary for those patients with a PSA level less than 10 ng/dL at the time of diagnosis [33]. In a retrospective series of 2064

consecutive patients evaluated at the Mayo Clinic, Oesterling et al [33] found only three patients with an abnormal bone scan among the 561 presenting with a PSA less than 10 ng/mL. None of the 467 patients with a PSA less than 8 ng/dL had an abnormal bone scan. The authors recommended obtaining a radionuclide bone scan regardless of PSA value on those patients with skeletal symptoms. Some investigators recommend a routine bone scan only if the PSA level is greater than 20 ng/dL [34]. Other authors recommend a baseline bone scan at the time of diagnosis to document pre-existing findings, such as fractures and degenerative joint disease, to facilitate the interpretation of future bone scans on patients with a PSA rise or skeletal symptoms following definitive therapy [35]. The challenge with this approach is the high prevalence of nonmalignant causes of increased radioisotope uptake (eg, prior trauma, degenerative joint disease, and so forth) in a group of patients at a very low risk of metastasis.

Indium 111 capromab pendetide scanning (ProstaScint) was approved by the Food and Drug Administration for the evaluation of newly diagnosed prostate cancer patients considered to be at high risk for metastasis. This is a radiolabeled monoclonal antibody scan that targets prostate-specific membrane antigen, an antigen expressed to a greater extent in prostate cancer cells than in normal prostate [36]. Early studies suggested a positive predictive value ranging between 50% and 62% [37,38]. Unfortunately, false-positive and false-negative results and difficulty in image interpretation have led to limited clinical applications [39]. Various other molecular staging techniques are currently in use under investigational protocols [40]. One of these involves examination of blood for cells with mRNA for PSA production. Because of a high false-positive rate among men with what ultimately was proved to be localized disease, this testing has had limited clinical application.

Staging pelvic lymph node dissection

The role of pelvic lymphadenectomy in the management of the newly diagnosed prostate cancer patient has changed significantly over the last decade as the understanding of pretreatment prognostic factors continues to grow. This procedure can be performed concurrently at the time of a radical retropubic prostatectomy or as a separate procedure before another alternative treatment option, such as a radical perineal prostatectomy or radiotherapy. In an effort to decrease morbidity from the classically described incision, various groups have advocated a laparoscopic approach or a minilaparotomy incision [41,42]. Laparoscopic pelvic lymphadenectomy has also been advocated as a useful adjunct in the management of patients at high risk for nodal metastatic disease at the time of diagnosis to select patients better for curative local or regional therapies [43]. Although a staging pelvic lymphadenectomy can provide significant information to assist in the management of prostate cancer patients, issues concerning its cost and morbidity (including obturator nerve or vascular injury and lymphocele

formation) raise the question of whether or not this staging procedure is indicated in all newly diagnosed prostate cancer patients [44]. The use of nomograms, such as Partin tables, that predict the likelihood of lymph node involvement based on clinical stage, PSA, and Gleason's score provides a starting point for the counseling physician when deciding if a staging pelvic lymphadenectomy is indicated [27]. It is reasonable to recommend against a staging pelvic lymphadenectomy when considering definitive therapy for patients with clinical T1 or T2 tumors with a PSA less than 10 ng/dL or with a PSA less than 20 ng/dL and a Gleason's sum less than 6 [5,45].

Treatment options for clinically localized prostate cancer

In 1995 The American Urological Association published the conclusions reached by the Prostate Cancer Clinical Guidelines Panel. This expert panel was convened to review the literature regarding the treatment options for clinically localized prostate cancer and to make practice policy recommendations based on available treatment outcomes data [46]. The panel reviewed the peer-reviewed, published literature including all articles from 1966 to 1993 on stage T2 (B) prostate cancer to analyze outcomes for radical prostatectomy, radiation therapy, and surveillance as treatment options. They found the data to be insufficient to allow a comparison between the treatment options. Counseling patients with newly diagnosed clinically localized prostate cancer should include reviewing of all the currently available treatment options with particular attention to all the potential risks and benefits of each individual treatment. Review of treatment options for clinically localized disease should include discussion of watchful waiting, radical prostatectomy, radiation therapy, and cryotherapy in some cases as choices [47]. Unfortunately, a great degree of bias can be present at the time of counseling [48].

Radical prostatectomy

The first planned radical prostatectomy for the treatment of prostatic adenocarcinoma was performed by Billroth [49] through a perineal approach in the 1860s. It was not until 1949 that the first radical retropubic prostatectomy was reported by Memmelaar [50]. During the early 1980s, Walsh and Donker [51] described the anatomy of the pelvic nerves and developed techniques to preserve these nerves to preserve erectile function after radical retropubic prostatectomy.

Multiple series have demonstrated that radical prostatectomy provides excellent cancer control for patients with localized prostate cancer [52–54]. These series reported 10-year actuarial cancer-specific survival rate ranging between 90% and 94%, 10-year actuarial metastasis-free rates between 82% and 87%, and 10-year actuarial PSA progression-free rates between 52% and 68%. Fifteen-year follow-up data indicate rates for actuarial cancer-specific

survival, metastasis-free survival, and PSA progression-free survival between 82% and 90%, 76% and 82%, and 40% and 66%, respectively [54,55].

Currently, most radical prostatectomies performed in the United States are performed through a retropubic approach. The ability to predict the likelihood of lymph node metastasis [27] and attempts to avoid morbidity directly related to the retropubic approach sparked a renewed interest in radical perineal prostatectomy, however, during the early 1990s. Several series have compared both surgical approaches to determine overall cancer control and complication rates [56–58]. Both surgical approaches provide equivalent cancer control rates, and complication rates seem to be similar between both procedures except for higher intraoperative blood loss in the retropubic prostatectomy group and a higher risk for rectal injury in the perineal group [58]. A report on a large contemporary series of patients undergoing radical retropubic prostatectomy demonstrated that this procedure carries minimal risk for complications intraoperatively and during the immediate postoperative period [59]. The incidence of intraoperative complications in this series was 0.8% with rectal injuries being reported as the most common intraoperative complication. Only 1.4% of the patients suffered from any other complication during their hospitalization with a mean hospitalization of 2.3 days. Similarly, a recent report by Walsh [60] demonstrated that, at 18-months follow-up, 93% of a series of 62 patients were continent, and 86% of the patients were able to achieve unassisted intercourse with or without the use of sildenafil. Conversely, an analysis of the Prostate Cancer Outcomes Study found a higher incidence of post-prostatectomy impotence and incontinence [61]. Men with at least 18-months follow-up had an 8.4% incidence of incontinence and a 59.9% incidence of impotence.

Radiation therapy

Radiation therapy, administered as external beam therapy, brachytherapy, or a combination of the two, is frequently used as a treatment option for localized prostate cancer. Risk stratification using pretreatment factors to include PSA level, biopsy Gleason's score, and clinical stage should be considered to assist with patient selection for the various forms of radiation therapy [62]. Those patients with cT1c to cT2a tumors, PSA levels of 10 ng/mL or lower, and biopsy Gleason score of 6 or lower are considered to have low-risk tumors with an expected greater than 85% 5-year PSA failure-free survival. Intermediate-risk patients (cT2b stage, PSA >10 ng/dL but ≤20 ng/dL, or biopsy Gleason score of 7) have about a 50% 5-year PSA failure rate-free survival. Finally, high-risk patients (cT3a or higher, PSA >20 ng/dL, or biopsy Gleason score ≥8) have an expected 33% 5-year PSA failure-free survival. Combination hormonal therapy (neoadjuvant and continued for 2 to 3 years posttreatment) for the treatment of high-risk patients should

be considered because of improved outcomes demonstrated in randomized controlled trials [63].

Based on the premise that survival rates in prostate cancer patients are favorable regardless of primary definitive treatment (surgery versus radiation), investigators with the Prostate Cancer Outcomes Study evaluated differences in posttreatment quality-of-life measures between the two treatments [64]. The investigators found that almost 2 years after treatment, men receiving radical prostatectomy were more likely than men receiving radiotherapy to suffer from urinary incontinence (9.6% versus 3.5%; $P < .001$) and to have higher rates of impotence (79.6% versus 61.5%; $P < .001$). It should be noted that the investigators also found large, statistically significant declines in sexual function in both treatment groups. Men receiving radiotherapy reported greater declines in bowel function than did men treated with radical prostatectomy.

Cryosurgery

Cryosurgical tissue ablation can be achieved by the direct effect of cooling and subsequent warming on the cells, and by the delayed effect of vascular insufficiency and destruction of tissue structure from the treatment [65]. Cryosurgical ablation of the prostate is increasingly being recognized as an option for the treatment of clinically localized prostate cancer. A recent review of the literature recommended consideration of cryosurgical ablation of the prostate in high-risk patients (defined as PSA level >10 , Gleason score ≥ 7 , or clinical stage $\geq cT2b$) [66]. Improved cancer control rates and acceptable side effect profiles are reported in this select group of patients. A prospective comparison with other treatment modalities, however, has not been performed.

Future developments

Laparoscopic radical retropubic prostatectomy is a new surgical technique for the treatment of localized prostate cancer initially described in 1997 [67]. It is not known if this approach provides any additional benefit over an open radical retropubic prostatectomy. In the meantime, interest continues in the refinement of other existing treatment modalities, such as cryosurgical ablation of the prostate and brachytherapy, and the development of novel treatment modalities, such as high-intensity focused ultrasound and radiofrequency interstitial tumor ablation [68].

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