Localized prostate cancer: Risk stratification and choice of initial treatment

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INTRODUCTION

Prostate cancer is the second most common cancer in males worldwide, according to data from the GLOBOCAN database. In developed areas, prostate cancer is increasingly being diagnosed when the tumor is confined to the prostate, due at least in part to screening with prostate-specific antigen (PSA). However, prostate cancers confined to the gland may become less frequent than more invasive tumors as PSA screening rates fall [1].

For males with newly diagnosed prostate cancer, the most important factors in selecting the initial treatment include the following:

- Anatomic extent of disease (tumor, node, metastasis [TNM] stage)
- Histologic grade (Gleason score/grade group) and molecular characteristics of the tumor
- Serum PSA level
- Estimated outcome with different treatment options
- Potential complications with each treatment approach
- The patient's general medical condition, age, and comorbidity, as well as individual preferences

Risk stratification and its implications for the initial treatment of males with newly diagnosed localized prostate cancer are presented here. Screening for prostate cancer, clinical presentation, diagnosis, and initial evaluation of these males are discussed separately. (See

"Clinical presentation and diagnosis of prostate cancer" and "Initial staging and evaluation of men with newly diagnosed prostate cancer".)

RISK STRATIFICATION

Overview — The initial management of males with newly diagnosed prostate cancer needs to incorporate a consideration of the prolonged natural history of the disease and the risk for progression to disseminated, potentially fatal disease.

The initial evaluation should include clinical staging based on a digital rectal examination by an experienced clinician to assess the extent of disease, the pretreatment serum prostate-specific antigen (PSA), the Gleason score/grade group in the initial biopsy, and the number and extent of cancer involvement in the biopsy cores. This allows the stratification of males into risk categories according to the primary tumor. There is ongoing debate as to the optimal risk stratification system to be used in the selection of treatment for prostate cancer. We use the risk categories as defined by the National Comprehensive Cancer Network (NCCN) (table 1), which have been used in guidelines from the American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO), and the NCCN [2-4]. However, others disagree.

As an example, the European Society for Medical Oncology uses a three-tiered system for risk stratification of localized prostate cancer [5]:

- **Low-risk** – T1-T2a and Gleason score ≤6 and PSA ≤10 ng/mL
- **Intermediate-risk** – T2b and Gleason score 7 and/or PSA 10 to 20 ng/mL
- **High-risk** – ≥T2c or Gleason score 8 to 10 or PSA >20 ng/mL

In some cases, this may also be supplemented by the molecular characteristics (genomic profile) of the tumor. (See 'Germline testing' below and 'Tissue-based molecular assays' below.)

Imaging studies (radionuclide bone scan, computed tomography [CT] of the abdomen and pelvis, multiparametric magnetic resonance imaging [MRI]) are used selectively to assess for extraprostatic extension, regional adenopathy, or distant metastases, depending on the initial clinical staging and estimate of risk; imaging for distant metastases is not routinely recommended for very low- and low-risk disease according to the clinical staging system described above, while it is recommended for more advanced disease. Bone imaging and pelvic imaging, with or without abdominal imaging, are recommended for those with intermediate- and high-risk disease [2]. MRI of the prostate is often obtained in males with low- and very low-

risk disease to ensure that high-grade disease has not been overlooked. (See "Initial staging and evaluation of men with newly diagnosed prostate cancer".)

On the basis of imaging, patients can be further classified as having regional (regional nodes) or metastatic (distant sites or nonregional lymph nodes) disease (table 2).

This initial evaluation (stage, biopsy Gleason score/grade group, serum PSA, imaging, and genomic profile) provides information for clinical staging, as distinct from pathologic staging (figure 1), and forms the basis for the initial treatment decisions. The initial evaluation may significantly under or overestimate the extent and/or aggressiveness of disease. Factors that need to be considered when relying upon clinical staging include variability in the interpretation of findings on digital rectal examination, variability in assigning Gleason grade on the biopsy, and sampling errors in the prostate biopsy that may lead to missing areas with Gleason 4 or 5 disease. Use of multiparametric MRI may improve targeting of prostate lesions for transrectal ultrasound-guided biopsy and thus decrease the risk of missing areas with Gleason 4 or 5 disease [6]. However, this technique is subject to variability in the interpretation of imaging and the experience of the clinician performing the biopsy. (See "The role of magnetic resonance imaging in prostate cancer", section on 'Methods for MRI-targeted prostate biopsy'.)

TNM staging and Gleason grade group — The standard staging system for newly diagnosed prostate cancer is that of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) (table 2 and table 3).

This system incorporates the anatomic extent of disease based upon the primary tumor (T), regional lymph nodes (N), and distant metastases (M). The staging system also incorporates the pretreatment serum PSA and histologic grade group, based upon the Gleason score, to divide patients into prognostic categories. This information about prognostic categories is combined with patient age, life expectancy, overall medical condition (including performance status and comorbidities), presence or absence of symptoms, and patient preferences to make decisions for the optimal treatment for an individual patient.

The Gleason grades for the two most prevalent differentiation patterns are combined to create the Gleason score, and Gleason score is now incorporated into the newly adopted grade group system [7]. In the grade group system, tumors are separated into five categories based upon the primary and secondary Gleason pattern (see "Interpretation of prostate biopsy", section on 'Gleason grading system'):

- Grade group 1 (Gleason score 3+3)
- Grade group 2 (Gleason score 3+4)
- Grade group 3 (Gleason score 4+3)

- Grade group 4 (Gleason score 4+4, 3+5, or 5+3)
- Grade group 5 (Gleason score 4+5, 5+4, or 5+5)

Percentage of positive biopsies — An estimate of tumor volume in the prostate needle biopsy can provide additional useful information [8-14]. The percentage of positive cores is now incorporated into the division of intermediate-risk prostate cancer into favorable and unfavorable subsets in the NCCN system [15].

The best method to assess the volume of cancer in the prostate biopsy is unknown [13], but this parameter can be quantified using the maximal percentage of a core involved with cancer, the percentage of cores that are positive, or the pathologist's estimate of the percentage of biopsy tissue containing cancer overall. The generic term "percentage of positive biopsies" is often applied to any of these quantitative measures. (See "Interpretation of prostate biopsy", section on 'Estimated tumor volume'.)

The influence of prostate biopsy tumor volume on outcome was illustrated by a report of 960 surgically treated males in which 80 percent of those in the intermediate-risk group (clinical stage T2b, biopsy Gleason grade 7 [grade group 2 or 3], or preoperative serum PSA between 10 and 20 ng/mL) could be classified into two separate risk groups based upon the fraction of prostate biopsies that were found to contain cancer [8]:

- Patients with >50 percent positive biopsies had an 11 percent likelihood of PSA control at four years.
- Patients with <34 percent positive biopsies had an 86 percent likelihood of PSA control at four years.

Similar refinement in prognostication was demonstrated for patients in the high-risk group. By contrast, the percentage of positive biopsies provided no additional prognostic value in patients at low risk for recurrence.

Another report showed that males at low risk of recurrence with >50 percent positive biopsies were significantly more likely to be pathologically upgraded at surgery from Gleason ≤6 to Gleason 7 tumors than those with <50 percent positive samples (59 versus 26 percent) [9]. These higher rates of pathologic upgrading translated into significantly lower five-year PSA failure-free survival rates (62 versus 92 percent).

Germline testing — According to the NCCN guidelines, germline testing for alterations in homologous recombination DNA repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*) is suggested for males with very low-risk, low-risk, and intermediate-risk disease if family history is positive for

an inherited cancer predisposition syndrome or if the prostate tumor shows intraductal histology. Intraductal histology is enriched for mutations in homologous recombination DNA repair genes (eg, *BRCA2*). Genetic results may influence the management of males with early stage prostate cancer:

- Germline mutations in *BRCA1, BRCA2, ATM* and *CHEK2* have been associated with lethal prostate cancer [16,17]. (See "Genetic risk factors for prostate cancer", section on 'Prognostic impact'.)

- Males found to have *BRCA* or *ATM* mutations have a higher risk of grade reclassification among males undergoing active surveillance [18]. (See "Active surveillance for males with clinically localized prostate cancer".)

Tissue-based molecular assays — Prognostic tests based on molecular and biomarker analysis of tumor tissue may improve risk stratification of both untreated and treated males with localized prostate cancer. Several of these tests (Oncotype DX, Prolaris, ConfirmMDx, Decipher) have been validated and are clinically available. We agree with guidelines from the NCCN [15] and ASCO [19], which support the use of molecular biomarkers in localized low-risk and favorable intermediate-risk prostate cancer when results are likely to influence treatment decisions (eg, males who are considering active surveillance, or selected males with unfavorable intermediate-risk disease when deciding whether to add androgen deprivation therapy to radiation therapy [RT]).

An increased understanding of prostate cancer biology has led to the development of tissue-based molecular assays that are specifically tailored to prostate cancer in an effort to improve decision making in newly diagnosed males considering active surveillance and in treated males considering adjuvant therapy or treatment of recurrence (table 4). Uncertainty about the risk of disease progression could be reduced if such molecular assays provided accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective studies have shown that these assays provide prognostic information that is independent of NCCN risk stratification group [20] or Cancer of the Prostate Risk Assessment (CAPRA) risk group [21], including the likelihood of death with conservative management (active surveillance). (See 'Post-treatment predictive and prognostic tools' below.)

However, no randomized controlled trials have studied the utility of these tests, and there is disagreement about whether and how these tests should be used in selecting a treatment approach for low-risk prostate cancer.

Recommendations from expert groups — Not surprisingly, there are disparate recommendations from expert groups.

- Consensus-based guidelines from the NCCN [3] state that molecular testing using Decipher, Oncotype DX Prostate, Prolaris, or ProMark may be considered for males who are potential candidates for active surveillance and have low-risk or favorable intermediate-risk disease with a life expectancy ≥10 years.

- Year 2022 updated AUA/ASTRO guidelines state that clinicians may use tissue-based genomic markers selectively in situations where added risk stratification may alter shared decision making [4].

- A year 2019 guideline from ASCO on molecular biomarkers in localized prostate cancer gave "moderate support" for the use of molecular biomarkers as a component of risk stratification for localized prostate cancer when the assay results, considered as a whole with routine clinical factors, are likely to influence treatment decisions [19]. The guideline emphasized that these assays were not indicated for routine use given the paucity of prospective studies assessing short-term and long-term outcomes of patients when these markers are integrated into clinical decision-making.

The various genomic tests and the data supporting their use are discussed separately. (See "Molecular prognostic tests for prostate cancer", section on 'Tests based on molecular characteristics'.)

Clinical versus pathologic staging — For patients who undergo radical prostatectomy, additional information about the extent of disease is obtained from the surgical specimen, and this forms the basis for pathologic staging (figure 1). When this reveals poor prognostic features (Gleason grade higher than the original biopsy, extraprostatic extension, seminal vesicle involvement, or lymph node involvement), additional therapy may be recommended following prostatectomy. (See "Prostate cancer: Postoperative management of pathologic stage T3 disease, positive surgical margins, and lymph node involvement following radical prostatectomy".)

- The potential errors regarding the extent of disease based upon clinical staging alone are illustrated by a series of 25,858 males from the Surveillance, Epidemiology, and End Results (SEER) database who underwent radical prostatectomy in 2010 or 2011 [22]. All had clinical T1 or T2 disease and a biopsy Gleason score of 6 or 7 (grade groups 1, 2, and 3).

  For those with a Gleason score of 6 (grade group 1), the risk of pathologically more advanced disease (T2 margin positive, T3, or T4 at prostatectomy) increased progressively

from 16 percent for those with a PSA <10 ng/mL to 39 percent for those with a PSA 20 to 29.9 ng/mL, and the risk of upgrading of the Gleason score increased from 43 to 61 percent, depending upon the original serum PSA.

For those with a Gleason score of 7 (3+4, grade group 2) on biopsy, the risk of identifying more advanced disease increased from 28 percent (PSA <10 ng/mL) to 49 percent (PSA 20 to 29.9 ng/mL). The risk of more advanced disease was even higher in those with a biopsy Gleason score of 7 (4+3, grade group 3). The risk of identifying Gleason score ≥8 disease ranged from 11 to 19 percent, depending upon the baseline PSA.

- In another series of 12,459 males from the SEER database, patients had T1c or T2 prostate cancer and were managed with radical prostatectomy; 59 percent of patients had Gleason grade group 1 (3+3) disease, and 41 percent had grade group 2 (3+4) disease [23]. Overall, 34 percent were reassigned to a higher grade group based upon pathology from the radical prostatectomy specimen. In those with clinical grade group 1 disease, 6 percent were upgraded to grade group 3 or higher based upon the radical prostatectomy specimen. In those with clinical grade group 2 disease, 4 percent were upgraded to grade group 4 or higher.

Genomic testing may be useful in identifying patients in whom the initial biopsy missed higher grade disease [24]. (See "Molecular prognostic tests for prostate cancer", section on 'Tests based on molecular characteristics'.)

Importance of shared decision making — Treatment decisions for localized prostate cancer are complicated and preference sensitive because of the differences in the specific risks and benefits of the various treatment choices. Patient-clinician shared decision making can facilitate selecting a treatment that best aligns with the patient's personal values, and it is recommended in professional society guidelines [2,4,6]. The best way to facilitate this is unclear. In one randomized trial, a web-based intervention for assessing patient preferences, called Patient Preferences for Prostate Cancer Care (PreProCare), was associated with improved satisfaction with care and decisions about treatment for localized prostate cancer, reduced patient regret about the decision, and better alignment of the treatment choice with cancer risk categories [25]. However, additional studies are needed to evaluate the effectiveness of interventions that formally assess preference, as well as other tools that attempt to reduce decisional conflict [26], in different settings before it can be concluded that tools such as these improve patient-centered decision making and outcomes. An important issue is the disparity between patient expectations and actual treatment outcomes, both in terms of efficacy and toxicity (ie, functional outcomes) [27].

Thus, one of the most important aspects of the decision-making process includes a discussion about the main side effects with each of the main forms of treatment and their time course. The important advantages, disadvantages, and contraindications associated with each approach are summarized in the tables (table 5 and table 6 and table 7).

Data on patient-reported outcomes are available from the ProtecT trial, which was predominantly conducted in males with low-risk disease [28], and discussed elsewhere (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'ProtecT trial'.)

Other data on patient-reported outcomes for a wider range of males with higher-risk disease are available mainly from retrospective analyses [29].

Pretreatment risk stratification tools — For more than six decades, the AJCC has grouped cancer patients by stage of disease (I to IV), which is used to estimate prognosis. For prostate cancer, in addition to the usual local tumor (T stage) extent, anatomic patterns of spread to lymph nodes (N stage), and distant sites (M stage), non-anatomic factors such as grade group and PSA level were incorporated over time into the AJCC prognostic stage groups based on data supporting their significance (table 3). (See 'TNM staging and Gleason grade group' above.)

However, prostate cancer is one of the few cancers for which such stage groupings have not been adopted in national guidelines or in the design of clinical trials.

Numerous pretreatment risk classification tools that predict the long-term chances of dying from prostate cancer with standard curative treatments based on clinicopathologic features have been developed for prostate cancer (see 'Post-treatment predictive and prognostic tools' below). The available tools include:

- The D'Amico classification (PSA level, clinical tumor stage, and grade group) [30]
- The NCCN risk stratification schema, which is based on the D'Amico classification, but includes other factors including the percent of positive biopsy cores (table 1)
- The Cancer of the Prostate Risk Assessment (CAPRA) score [21]
- The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram for males prior to radical prostatectomy [31]
- European Association of Urology/European Society for Radiotherapy and Oncology [32] and American Urologic Association classifications, which are both based on the D'Amico classification

- Cambridge prognostic groups [33]
- Others, which are also based on the D'Amico classification [34,35]
- PREDICT Prostate [36]
- International Staging Collaboration for Cancer of the Prostate (STAR CAP) model [37]

Whether any of these tools is any better than the others at predicting prostate cancer death is unclear. One Swedish nationwide cohort study of over 139,000 males with prostate cancer who were followed for at least 10 years concluded that the MSKCC nomogram, the CAPRA score, and the Cambridge prognostic group systems performed better at discriminating death than any of the D'Amico-derived systems [38]; however, only 35 percent of the included individuals had complete information on all variables used in some of the assessed risk stratification tools. Furthermore, information on cT2 to T3 substages was not recorded in the database.

In 2016, the AJCC set forth criteria for more advanced statistical models to better personalize prognostic estimates [39]. At the time, no model for localized prostate cancer was felt to be sufficiently accurate. However, in 2020, the STAR CAP model proposed a new contemporary pretreatment predictive staging system that meets these criteria [37]. It was developed based upon multivariate analysis of data from over 19,000 males treated for localized prostate cancer with surgery or RT and validated in a dataset of over 125,000 males reported to the SEER database. A point system was assigned for the variables of age, T and N category, Gleason grade, percent positive prostate biopsy cores, and pretreatment PSA levels; and depending on the cumulative point total, a stage from IA to IIIC was assigned, with five-year prostate cancer-specific mortality ranging from 0.1 to 12.4 percent based on stage, and 10-year prostate cancer-specific mortality ranging from 0.3 to 40 percent. The model was shown to have better discriminatory value for prostate cancer-specific mortality than either the AJCC 8th edition or the CAPRA model. The model is available online.

An important point is that all current stratification systems to estimate risk of progression were based on data from patients who did not undergo MRI or targeted (MRI/US) prostate biopsy. As this is becoming more of a standard of care internationally, it is believed that the accuracy of estimating disease risk according to pretreatment assessment will improve over time.

RISK-STRATIFIED APPROACH TO TREATMENT OF ADENOCARCINOMAS

Localized disease — The choice of treatment for an individual patient with a non-high-grade localized prostatic adenocarcinoma depends on an informed patient decision incorporating

knowledge about the potential advantages and disadvantages associated with each approach, along with personal preferences. The basic choices are external beam radiation therapy (RT) with or without brachytherapy, brachytherapy alone, radical prostatectomy, or active surveillance. The important advantages, disadvantages, and contraindications associated with each approach are summarized in the tables (table 5 and table 6 and table 7).

The following treatment options, which are based on the risk stratification provided by the National Comprehensive Cancer Network (NCCN), are consistent with guidelines from the American Urological Association/American Society for Radiation Oncology, the American Society of Clinical Oncology, and the NCCN [2-4,40]. On the other hand, European Society for Medical Oncology guidelines use a three-tiered approach to risk stratification for the purpose of treatment selection [5].

Clinically localized, NCCN very low risk — Patients with very low-risk prostate cancer have disease detected by prostate biopsy based upon serum prostate-specific antigen (PSA) only, without a detectable abnormality on digital rectal examination or imaging. To be classified as very low risk, such patients must have a tumor that is in histologic grade group 1 (Gleason score ≤6) on biopsy and a serum PSA <10 ng/mL. Furthermore, the extent of disease within the prostate must be limited (ie, fewer than three positive biopsy cores, with less than 50 percent involvement in any one core, and a PSA density less than 0.15 ng/mL/gram) [15,41].

In published guidelines, including those of the NCCN [3], active surveillance is usually recommended for males with very low-risk disease and a life expectancy >10 years [2,15,40]. However, this approach is associated with a need for close follow-up and may create significant anxiety, causing many patients to subsequently choose definitive intervention even in the absence of progressive disease. We consider this to be an appropriate approach in the absence of certain histologic features (areas of cribriform or intraductal cancer) and low-risk gene expression profiles for males who meet the biologic criteria of low risk for metastasis and have psychological comfort with active surveillance. Some males may still choose to be treated (RT or radical prostatectomy) even in the presence of very low-risk disease. (See "Molecular prognostic tests for prostate cancer" and "Interpretation of prostate biopsy", section on 'Gleason 8, grade group 4' and "Interpretation of prostate biopsy", section on 'Presence of a special subtype of cancer' and "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Active surveillance' and "Active surveillance for males with clinically localized prostate cancer" and 'Germline testing' above.)

Clinically localized, NCCN low risk — Patients with no palpable tumor in the prostate (ie, diagnosis based upon needle biopsy only) or limited disease in one lobe of the prostate gland, a

serum PSA <10 ng/mL, and grade group 1 (Gleason score ≤6) disease are classified has having low-risk disease (table 1).

The choice of therapy depends upon an informed patient decision incorporating knowledge about the potential advantages and disadvantages associated with the different treatment approaches.

Standard treatment options for these patients include the following:

- Active surveillance, with serial monitoring and the initiation of definitive treatment if there is evidence of progression, is a preferred care option for most males [2]. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Active surveillance' and "Active surveillance for males with clinically localized prostate cancer".)

  We consider active surveillance to be an appropriate approach in the absence of certain histologic features (areas of cribriform or intraductal cancer) and low-risk tissue-based gene expression profiles for males who meet the biologic criteria of low risk for metastasis and have psychological comfort with active surveillance. (See 'Germline testing' above.)

- Clinicians may offer definitive therapy (radical prostatectomy or RT) to patients who may have a high probability of progression on active surveillance [2].

  - If chosen, RT may be delivered by either an external beam source or brachytherapy. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Radiation therapy' and "External beam radiation therapy for localized prostate cancer" and "Brachytherapy for low-risk or favorable intermediate-risk, clinically localized prostate cancer".)

  - If chosen, radical prostatectomy may be carried out with either an open or minimally invasive approach. Lymph node dissection is optional for those with low-risk disease. For patients managed with radical prostatectomy, the surgical pathology specimen may result in a change in staging that suggests additional postoperative therapy may improve the chance for cure. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Radical prostatectomy' and "Radical prostatectomy for localized prostate cancer".)

Although several retrospective reports suggest similar outcomes from these treatments [42,43], the only data directly comparing these approaches in a large randomized trial come from the Prostate Testing for Cancer and Treatment (ProtecT) trial being conducted in the United Kingdom, in which patients were randomly assigned to active surveillance, radical

prostatectomy, or definitive RT [28,44]. Most of the enrollees had very low- or low-risk disease (the median PSA was 4.6 ng/mL, 76 percent had a Gleason score of 6, and 76 percent had stage T1c disease). In the initial report of this trial, there was no significant difference in the 10-year cancer-specific survival or overall survival rates between the different treatment modalities. However, there was an increased frequency of metastatic disease and clinical progression with active surveillance, and there were only a very limited number of deaths related to prostate cancer.

Detailed results and limitations of the ProtecT trial are discussed separately, as are additional data supporting the role of active surveillance from large observational series. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'ProtecT trial' and "Active surveillance for males with clinically localized prostate cancer".)

Ablative techniques (cryotherapy, high-intensity ultrasound, photodynamic therapy with an interstitial laser) have been advocated, but there are inadequate long-term data to consider these to be standard approaches [2], although high-intensity ultrasound is approved for prostate ablation in some countries. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Ablation therapy' and "Cryotherapy and other ablative techniques for the initial treatment of prostate cancer".)

Clinically localized, NCCN intermediate risk — Patients with clinically localized, intermediate-risk prostate cancer can have more extensive tumor in the prostate (ie, involving more than one-half of one lobe of the prostate [T2b] or with bilateral disease [T2c] on initial examination or imaging) but no detectable extraprostatic extension or seminal vesicle involvement (table 2 and table 3).

Favorable versus unfavorable intermediate-risk disease — According to consensus-based guidelines from the NCCN [3], intermediate-risk patients are now divided into favorable and unfavorable subsets as follows:

Favorable intermediate-risk disease:

- T2b to T2c **or**
- Gleason score 3+4 = 7 (grade group 2) **or**
- PSA 10 to 20 ng/mL **and**
- Percentage of biopsy cores <50 percent

Unfavorable intermediate-risk disease:

- T2b to T2c **or**

- Gleason score 3+4 = 7 (grade group 2) or Gleason score 4+3 = 7 (grade group 3) **or**
- PSA 10 to 20 ng/mL

Treatment options for intermediate-risk patients include:

- RT, which may be delivered by an external beam source and/or brachytherapy. Because of the increased risk of recurrence or disseminated disease, androgen deprivation therapy (ADT) is recommended as a component of a combined modality approach [2]. Although patients can be treated with RT alone, the evidence base is less robust than for combined RT plus ADT. The additional prognostic value derived from tissue-based molecular assays may help with this decision [45]. (See 'Tissue-based molecular assays' above and "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Radiation therapy' and "External beam radiation therapy for localized prostate cancer" and "Brachytherapy for low-risk or favorable intermediate-risk, clinically localized prostate cancer".)

- Radical prostatectomy with pelvic lymph node dissection, which may be carried out with either an open or minimally invasive approach. For patients managed with radical prostatectomy, the presence of adverse pathologic features in the surgical staging specimen may be an indication for adjuvant (postoperative) RT. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Radical prostatectomy' and "Radical prostatectomy for localized prostate cancer".)

- Active surveillance is an option for those with favorable intermediate-risk disease, but patients should be informed that this comes with a higher risk of developing metastases compared with definitive treatment [2]. Active surveillance is **not** indicated for males with unfavorable intermediate-risk disease. (See "Active surveillance for males with clinically localized prostate cancer".)

Clinically localized, NCCN high risk — Patients with clinically localized, high-risk prostate cancer have more extensive disease, based upon the presence of presumed extraprostatic extension on digital rectal examination (T3a), or are classified as being at high risk because of a serum PSA ≥20 ng/mL or a grade group of 4 or 5 (Gleason score 8 to 10) (table 2 and table 3 and table 1).

Standard treatment options for these patients include:

- RT using an external beam source combined with brachytherapy, or external beam RT alone. Long-term (18 to 36 months) ADT is generally recommended as well. (See "Initial

management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Radiation therapy'.)

- Radical prostatectomy with extended pelvic lymph node dissection is an option for high-risk patients without fixation to adjacent organs/tissue. For high-risk patients managed with radical prostatectomy, the presence of adverse pathologic features in the surgical staging specimen may be an indication for adjuvant (postoperative) RT, and/or ADT for those with node-positive disease. (See "Radical prostatectomy for localized prostate cancer" and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Radical prostatectomy'.)

- Primary ADT alone may be a reasonable approach if males are not candidates for local definitive therapy (eg, if the patient has a limited life expectancy) and have local symptoms [2]. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Males who are not candidates for definitive local therapy'.)

Clinically locally advanced or NCCN very high risk — Patients whose initial evaluation suggests locally advanced disease (T3b or T4 (table 2)) with seminal vesicle involvement, tumor fixation, or invasion of adjacent organs are classified as being at very high risk for progression or recurrence. In addition, patients with a primary Gleason pattern of 5, or with four or more cores with a Gleason score of 8 to 10 (grade group 4 or 5) are classified as very high risk. These patients are at high risk for lymph node involvement, and they should all undergo imaging of the pelvis (computed tomography [CT] or magnetic resonance imaging [MRI]) prior to treatment.

Biopsy grade group 5 (Gleason score 9 or 10) — Most patients in whom the core biopsies contain areas with Gleason 5 pattern (ie, an overall Gleason score of 9 or 10, histologic grade group 5) will present with clinically locally advanced disease. (See 'Clinically locally advanced or NCCN very high risk' above and "Interpretation of prostate biopsy", section on 'Gleason grading system'.)

However, a small subset of those with a biopsy histologic grade group of 5 have clinically localized disease based on the initial evaluation. In a series of 259 males with Gleason score 9 or 10 disease (grade group 5) on core biopsy who subsequently underwent radical prostatectomy, factors that were useful in predicting more extensive disease at prostatectomy (T3, T4, or lymph node involvement) included the extent of Gleason 9 or 10 disease in the preoperative biopsy cores and the presence of perineural invasion [46].

Patients receiving definitive treatment for prostate cancer with a Gleason score of 9 or 10 (histologic grade group 5) have a worse prognosis than those with a Gleason score of 8 (histologic grade group 4) [7,47,48]. The validation of the new grade group system included 1436 patients with grade group 4 disease and 1014 with grade group 5 disease. On multivariate analysis, the risk of recurrence was significantly higher for patients with grade group 5 disease compared with those with grade group 4 disease, both for those treated with radical prostatectomy and those treated with RT [47].

Treatment options — Treatment options for males with locally advanced or very high-risk disease include:

- External beam RT with long-term ADT. In some cases, the external beam RT may be combined with brachytherapy to increase the radiation dose to the primary tumor. (See "External beam radiation therapy for localized prostate cancer".)

- Radical prostatectomy combined with extended pelvic lymph node dissection may also be an option for very high-risk patients, especially for younger individuals. (See "Radical prostatectomy for localized prostate cancer".)

  In this setting, serum PSA provides important information on whether or not all disease has been resected and whether further therapy is indicated.

  - For patients in whom serum PSA is undetectable following definitive surgery, careful monitoring is indicated, including digital rectal examination and serum PSA every three to six months. (See "Follow-up surveillance after definitive local treatment for prostate cancer".)

  - If the PSA fails to fall to undetectable levels or if the PSA subsequently rises, patients are presumed to have residual or recurrent disease. Such patients should be evaluated for evidence of metastatic disease, and subsequent therapy is dictated by the results of that evaluation. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation" and "Rising or persistently elevated serum PSA following radical prostatectomy for prostate cancer: Management" and "Role of systemic therapy in patients with a biochemical recurrence after treatment for localized prostate cancer".)

- The optimal treatment for patients with grade group 5 disease is unclear, and both radical prostatectomy and RT (external beam RT or external beam RT plus brachytherapy) are included in some contemporary guidelines [15,49], although it was not specifically addressed in the year 2022 AUA/ASTRO guidelines [4,40,50]. We tend to prefer external beam RT plus brachytherapy and long-term ADT for these patients, although

prostatectomy may be preferred for younger individuals. The most extensive data come from a retrospective analysis of 1809 patients, which found that the five-year prostate cancer-specific mortality rates were lower in those treated with a combination of external beam RT plus brachytherapy compared with either external beam RT alone or radical prostatectomy [51]. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Patients with grade group 5 disease'.)

Research efforts are looking at the use of multimodal approaches incorporating systemic therapy and RT in conjunction with surgery to improve outcomes in patients with locally advanced, high-risk, or metastatic disease either to regional lymph nodes or at disseminated sites [52]. These approaches can be considered in the context of a formal clinical trial. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Role of chemotherapy'.)

- Clinicians should not recommend active surveillance for most males with high-risk prostate cancer [2,4]. Watchful waiting should only be considered in asymptomatic males with a limited life expectancy (≤5 years).

Clinical lymph node involvement — Patients with lymph node involvement are classified as having stage IV (metastatic) disease in the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system (table 2 and table 3). Patients with lymph node metastases diagnosed based upon clinical staging but without distant metastases are usually treated with definitive RT plus ADT. However, for young males with minimal regional lymphatic spread suspected, radical prostatectomy as part of a combination strategy that includes postoperative ADT and/or RT is an option. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Clinical evidence of lymph node involvement'.)

Disseminated metastases — The initial approach to the management of disseminated metastases (M1) and for a detectable or rising serum PSA following treatment in those who are not candidates for definitive locoregional therapy generally focuses on ADT, with either a so-called medical orchiectomy (using gonadotropin-releasing hormone) or bilateral orchiectomy. In some cases, ADT may be combined with docetaxel chemotherapy. (See "Initial systemic therapy for advanced, recurrent, and metastatic noncastrate (castration-sensitive) prostate cancer" and "Overview of systemic treatment for advanced, recurrent and metastatic castration-sensitive prostate cancer and local treatment for patients with metastatic disease".)

HIGH-GRADE, LOW-PSA PROSTATE CANCER

High-grade (Gleason score 8 to 10) prostate cancer with a low prostate-specific antigen (PSA; ≤2.5 mg/mL) appears to comprise a distinct but uncommon subset that includes the small cell and large cell prostatic neuroendocrine carcinomas [53]. In such cases, the Gleason score is assigned to the adenocarcinoma component, which in 85 percent of cases, is Gleason >8 [54]. This disease subset typically is aggressive and relatively hormone resistant [55-57]. (See "Interpretation of prostate biopsy", section on 'Neuroendocrine neoplasms'.)

Although the clinical presentation of these prostate cancers when they present with localized disease is similar to that of other prostate cancers, metastases often occur early in the natural history, and symptoms can be due to distant disease. In addition, a range of laboratory abnormalities have been reported with the small cell variant, including paraneoplastic syndromes such as Cushing syndrome, peripheral neuropathy, membranous nephropathy, and hypercalcemia. (See "Clinical manifestations of lung cancer", section on 'Paraneoplastic phenomena'.)

Important differences in the clinical and prognostic characteristics of these patients are illustrated by an analysis that included almost 500,000 males with T1-4N0M0 prostate cancer from the National Cancer Database (NCDB), 136,000 males from the Surveillance, Epidemiology, and End Results (SEER) database, and genomic data from 4960 males from the Decipher Genomics Resource Information Database (GRID) [55]:

- In the overall NCDB series, 0.7 percent of patients had Gleason 8 to 10 disease and a PSA ≤2.5 ng/dL. Among those with Gleason 8 to 10 disease, 6 percent had a PSA ≤2.5 ng/dL.
- In the SEER database, prostate cancer-specific mortality was higher for males with a PSA ≤2.5 ng/dL and Gleason 8 to 10 adenocarcinomas compared with the reference group of those with a PSA 4.1 to 10 ng/dL at diagnosis (hazard ratio [HR] 2.70), and it was similar to that for males with high-grade disease and a PSA >20 ng/dL (HR 2.56 compared with the reference group). The adjusted prostate cancer-specific mortality rate at 47 months after diagnosis was 14 percent in the high-grade, low-PSA subset, compared with 4.9 percent in those with a PSA >2.5 ng/dL.
- Among males with high-grade disease and a low PSA treated with radiation therapy, the use of androgen deprivation therapy was associated with an overall survival benefit for those with a PSA >2.5 ng/dL but not for those with a PSA ≤2.5 ng/dL.

- In GRID, males with a low PSA and high-grade disease were more likely to have a neuroendocrine/small cell pattern compared with those with high-grade disease and a PSA >2.5 ng/dL. (See "Molecular prognostic tests for prostate cancer", section on 'Genomic classifier (Decipher)'.)

In patients diagnosed pathologically as having either large cell or small cell neuroendocrine carcinoma, the prognosis is even worse. As an example, in a series of 241 cases identified from the SEER database over a 30-year period, 60 percent had metastatic disease at presentation. The one-, two-, and five-year survival rates for the entire series were 48, 28, and 14 percent, respectively [58].

The optimal management of patients with high-grade, low-PSA prostate cancer has not been well defined, and the clinical observations in these patients suggest that the standard approach to high-risk and very high-risk disease may not be optimal. Additional research will be required to better categorize this patient subset and define the preferred treatment approach.

- For patients with localized disease, treatment is similar to that for other patients with high-risk or very high-risk disease. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Options for high- and very high-risk disease'.)

- For patients with metastatic disease, there may be an increased role for chemotherapy using regimens similar to those used for small cell carcinoma of the lung. (See "Extensive-stage small cell lung cancer: Initial management", section on 'Initial treatment' and "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Aggressive prostate cancer variants'.)

QUALITY OF LIFE

For patients being treated for localized prostate cancer, there are substantial differences in the side effects associated with radical prostatectomy, radiation therapy, and active surveillance (table 6).

The impact of these factors on quality of life is discussed separately. (See "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Quality of life issues'.)

POST-TREATMENT PREDICTIVE AND PROGNOSTIC TOOLS

As noted above, combining pretreatment clinical, pathologic, and biochemical factors (eg, serum prostate-specific antigen [PSA] level; Gleason score/grade group; clinical tumor, node, and metastasis stage (table 2 and table 3)) allows for risk stratification, a more reliable prediction of pathologic stage, and an estimation of treatment outcome prior to treatment. (See 'Risk stratification' above.)

Increasingly, models are being developed and validated that can be used to predict individualized estimates of biochemical (PSA-only) recurrence and prostate cancer-specific survival [21,59-63] after definitive local treatment of prostate cancer, based on clinicopathologic factors.

Nomograms may offer advantages over risk tables in terms of increased accuracy, whereas risk tables may offer increased simplicity in their application. Validated post-treatment nomograms accessible online can be found using the following links:

- Memorial Sloan Kettering prostate cancer nomograms
- The Palpable Prostate

Models such as these do not take into account genomic tests or molecular markers. As noted above, several tissue-based molecular assays have been developed in an effort to improve decision making in newly diagnosed males considering active surveillance. Uncertainty about the risk of disease progression could be reduced if such assays provided accurate and reproducible prognostic or predictive information beyond National Comprehensive Cancer Network (NCCN) risk group assignment and currently available life expectancy tables and nomograms. Consensus-based guidelines from the NCCN indicate that males with low- or favorable intermediate-risk disease may consider the use of Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification to select optimal candidates for active surveillance (table 4) [20]. (See 'Germline testing' above and "Molecular prognostic tests for prostate cancer".)

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues include balancing the risk from delaying cancer treatment versus harm from COVID-19, minimizing the use of potentially immunosuppressive cancer treatments whenever possible, mitigating the negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources. These and other recommendations for cancer care

during active phases of the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis and management of prostate cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Prostate cancer treatment; stage I to III cancer (Beyond the Basics)" and "Patient education: Treatment for advanced prostate cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Risk stratification**
    - For purposes of selecting treatment, newly diagnosed prostate cancer is risk stratified based on digital rectal examination, serum PSA, prostate biopsy, and imaging studies. In some cases, assessment for germline alterations in homologous recombination DNA repair genes and tissue-based gene expression classifiers also contributes.

- Based on this information patients can be divided into several categories, which provide the basis for treatment decisions. Numerous pretreatment risk classification tools are available for prostate cancer; we use the National Comprehensive Cancer Network stratification scheme, which is outlined in the table (table 1). (See 'Risk stratification' above.)

- **Risk-stratified approach to treatment** – Patient-clinician shared decision making can facilitate selecting a treatment that best aligns with the patient's personal values, and it is recommended in professional society guidelines. (See 'Importance of shared decision making' above.)

  - **Clinically localized, very low-risk prostate cancer** – Active surveillance, is a preferred option for most males with very low-risk disease in the absence of certain histologic features (areas of cribriform or intraductal cancer) and for individuals who have psychologic comfort with active surveillance. Definitive local therapy (radiation therapy [RT], radical prostatectomy) may be offered to select patients who may have a high probability of progression on active surveillance, and to those who prefer definitive treatment even in the presence of very low-risk disease. (See 'Clinically localized, NCCN very low risk' above and "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Very low risk'.)

  - **Clinically localized, low-risk prostate cancer** – For males with low-risk prostate cancer and a life expectancy greater than 10 years, definitive therapy (radical prostatectomy, brachytherapy, or external beam RT) or active surveillance are all appropriate options. The choice of a specific approach requires a consideration of the benefits and risks associated with each approach, the patient's individual preferences and comorbidities, and the histology and gene expression profile of the tumor. (See 'Clinically localized, NCCN low risk' above and "Initial approach to low- and very low-risk clinically localized prostate cancer", section on 'Low risk'.)

  - **Clinically localized, intermediate-risk prostate cancer** – Patients with intermediate-risk disease are divided into favorable and unfavorable subsets based on the percentage of positive biopsy cores and the specific Gleason score or grade group (table 1). (See 'Favorable versus unfavorable intermediate-risk disease' above.)

    RT and radical prostatectomy are both appropriate options for males with intermediate-risk disease. Active surveillance is an option for those with favorable intermediate-risk disease, but patients should be informed that this comes with a higher risk of developing metastases compared with definitive treatment. Tissue-based

molecular profiles may improve risk stratification. (See 'Clinically localized, NCCN intermediate risk' above and 'Tissue-based molecular assays' above.)

- **Clinically localized, high-risk prostate cancer** – Standard treatment options for clinically localized, high-risk prostate cancer includes external beam RT combined with brachytherapy and androgen deprivation therapy (ADT), or radical prostatectomy. The choice of a specific approach requires a consideration of the benefits and risks associated with each approach, individual preferences and comorbidities, and estimated life expectancy. (See 'Clinically localized, NCCN high risk' above and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)

- **Locally advanced and very high-risk prostate cancer** – Tumors with seminal vesicle involvement (T3b), tumor fixation (T4), or invasion of adjacent organs (T4), as well as prostate cancers with a primary Gleason pattern of 5 or with four or more cores with a biopsy grade group of 4 and 5 (Gleason score 8 to 10) are classified as very high risk.

  Treatment options include external beam RT, with or without brachytherapy, and long-term ADT, or radical prostatectomy. For patients with biopsy grade group 5 disease, we prefer external beam RT plus brachytherapy and ADT rather than radical prostatectomy. (See 'Clinically locally advanced or NCCN very high risk' above and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)

- **Lymph node involvement** – Patients with clinical lymph node involvement are usually treated with definitive RT plus ADT. However, for young males with minimal regional lymphatic spread suspected, radical prostatectomy as part of a combination strategy that includes postoperative ADT and/or RT is an option. (See 'Clinical lymph node involvement' above and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)

- **Disseminated disease** – The initial approach for patients with disseminated metastases (M1) generally focuses on ADT, which may be combined with docetaxel. (See 'Disseminated metastases' above and "Overview of systemic treatment for advanced, recurrent and metastatic castration-sensitive prostate cancer and local treatment for patients with metastatic disease".)

- **High-grade, low-PSA prostate cancer** – High-grade (Gleason score 8 to 10) prostate cancer with a low PSA appears to comprise a distinct but uncommon subset that

includes the small cell and large cell prostatic neuroendocrine carcinomas. (See 'High-grade, low-PSA prostate cancer' above.)

- For patients with localized disease, treatment is similar to that for other patients with high-risk or very high-risk disease. (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Options for high- and very high-risk disease'.)

- For patients with metastatic disease, there may be a role for chemotherapy using regimens similar to those used for small cell carcinoma of the lung. (See "Extensive-stage small cell lung cancer: Initial management", section on 'Initial treatment' and "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Aggressive prostate cancer variants'.)

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Topic 6943 Version 61.0

GRAPHICS

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical/pathologic features
Very low	▪ T1c AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND ▪ PSA density <0.15 ng/mL/g
Low	▪ T1 to T2a AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Does not qualify for very low risk
Favorable intermediate	▪ No high or very high risk features ▪ No more than one intermediate risk factor: • T2b to T2c OR • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND ▪ Grade group 1 or 2 AND ▪ Percentage of positive biopsy cores <50%
Unfavorable intermediate	▪ No high or very high risk features ▪ Two or three of the intermediate risk factors: • T2b to T2c • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND/OR ▪ Grade group 3 AND/OR ▪ ≥50% of positive biopsy cores
High	▪ No very high risk features AND ▪ T3a OR

	▪ Grade group 4 or 5 OR ▪ PSA >20 ng/mL
Very high	▪ T3b to T4 OR ▪ Primary Gleason pattern 5 OR ▪ Two or three high-risk features OR ▪ >4 cores with Grade group 4 or 5

PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4.2018.

Graphic 118962 Version 4.0

Prostate cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
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 found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

NOTE: There is no pathological T1 classification.
NOTE: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

Regional lymph nodes (N)

N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional 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. M1c is most advanced.

Prostate-specific antigen (PSA)

PSA values are used to assign this category.

PSA values
<10
≥10 <20
<20
≥20
Any value

Histologic grade group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

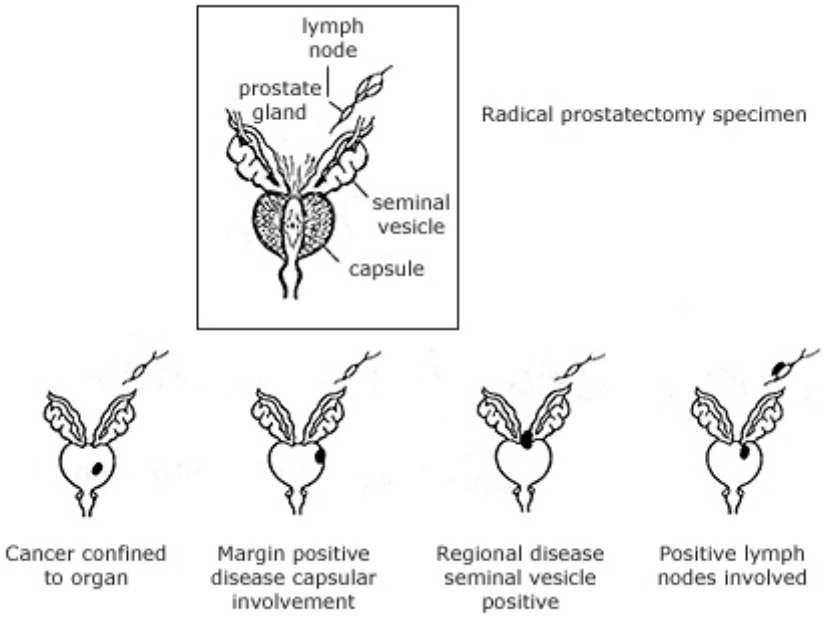
Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, or 5+3

5	9 or 10	4+5, 5+4, or 5+5

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110728 Version 10.0

Pathologic staging of prostate cancer



Radical prostatectomy allows the determination of the extent of cancer in the prostate gland, prostate capsule, seminal vesicle, and lymph nodes because these tissues are removed and examined under the microscope. The likelihood of remaining disease free at 10 years following prostatectomy is related to the extent of capsular penetration, whether the cancer is specimen confined, and whether there is evidence of positive margins.

Adapted with permission from Garnick, M, Patient's Guide to Prostate Cancer, Penguin, New York, 1999, p. 45.

Graphic 80052 Version 2.0

Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is…	And N is…	And M is…	And PSA is…	And Grade Group is…	Then the stage group is…
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

Graphic 110729 Version 10.0

Molecular biomarker prognostic assays commercially available for use in males with clinically localized prostate cancer

Test(s)	Company	List price* (USD)	Sample requirement	Clinical utility/intended use	Comments
Decipher Biopsy and Decipher Postoperative	Decipher Biosciences (formally Genome Dx)	$5150	FFPE tissue from prostate biopsy, or	Categorize patients into low/high risk to stratify patients to surveillance versus treatment (and intensity of treatment)	Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0
			Prostate tissue after RP	Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant therapy, or salvage therapy may be warranted	
Oncotype Dx GPS	Genomic Health	$4520	Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted	Biopsy-based likelihood of adverse pathologic features (grade group ≥3 or extracapsular extension); identify those who may benefit from surveillance versus treatment	GPS ranges from 0 to 100 based on mRNA expression of 17 genes across 4 pathways
Prolaris Biopsy and Prolaris Postprostatectomy	Myriad Genetic Laboratories	$3900	FFPE tissue from prostate tumor biopsy or prostatectomy specimens	Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management	mRNA expression of cell-cycle progression genes is used to calculate the score; clinical factors are subsequently

					added for risk assessment
ProMark, Proteomic Prognostic test for prostate cancer	MetaMark	$3900	Requires tissue collected with patented biopsy kit available from MetaMark	Uses automated image recognition technology to determine the likelihood of grade group ≥2 or stage ≥T3b	Expression of 8 proteins; uses automated image recognition technology to generate a score from 1 to 100 indicating the aggressiveness of prostate cancer

FFPE: formalin fixed, paraffin embedded; RP: radical prostatectomy; mRNA: messenger RNA; GPS: Genomic Prostate Score.

* Cost was not available on the website and was therefore obtained by contacting sales team or customer support for each company during the week of April 22, 2019. List prices do not necessarily reflect prices paid by Medicare or out of pocket by patients, or other discounted rates.

Graphic 126666 Version 3.0

The advantages of the main treatment options for early prostate cancer

External beam radiation therapy (EBRT)
Effective long-term cancer control with high-dose treatments
Very low risk of urinary incontinence
Available for cure of patients over a wide range of ages and in those with significant comorbidity
Brachytherapy
Cancer control rates appear equal to surgery and EBRT for organ-confined tumors
Quicker than EBRT (single treatment)
Available for cure of patients over a wide range of ages and in those with some comorbidity
Radical prostatectomy
Effective long-term cancer control
Predictions of prognosis can be more precise based on pathologic features in specimen
Pelvic lymph node dissection is possible through the same incision
PSA failure is easy to detect
Active surveillance
Reduces overtreatment
Avoids or postpones treatment-associated complications
Has no effect on work or social activities

PSA: prostate-specific antigen.

Modified from: Vogelzang NJ, Scardino PT, Shipley WU, et al. Comprehensive textbook of genitourinary oncology, 3rd Edition, Lippincott Williams & Wilkins 2005.

Graphic 52491 Version 17.0

The disadvantages of the main treatment options for early prostate cancer

External beam radiation therapy
Significant risk of erectile dysfunction
Lack of lymph node removed; late rectal symptoms more common than with brachytherapy or radical prostatectomy
Knowledge of possible metastasis to lymph nodes is not available
Up to one-half of patients have some temporary bladder or bowel symptoms during treatment
Brachytherapy
Significant risk of erectile dysfunction
Lack of lymph node removed; knowledge of possible metastasis to lymph nodes is not available
Up to one-half of patients have some temporary bladder or bowel symptoms with treatment; there may be exacerbation of preexisting lower urinary tract obstructive symptoms
Radical prostatectomy
Significant risk of erectile dysfunction
Risk of operative morbidity
Low risk of long-term incontinence
Active surveillance
Tumor may progress beyond the possibility for cure
Later treatment may result in more side effects
Living with untreated cancer may cause anxiety
Need for follow-up MRI and prostate biopsies to assess for progression

Modified from: Vogelzang NJ, Scardino PT, Shipley WU, et al. Comprehensive textbook of genitourinary oncology, 3rd Edition, Lippincott Williams & Wilkins 2005.

Graphic 51287 Version 21.0

Relative contraindications to the main treatment options for early prostate cancer

External beam radiation therapy
Previous pelvic irradiation
Active inflammatory disease of the rectum
Very low bladder capacity
Chronic moderate or severe diarrhea from any cause
Brachytherapy
Previous pelvic irradiation
Large-volume gland
Marked voiding symptoms
Large or high-grade tumor burdens*
Chronic moderate or severe diarrhea
Active inflammatory disease of the rectum
Radical prostatectomy
Higher medical operative risk
Neurogenic bladder
Active surveillance
Patients with high prostate cancer anxiety
High-grade tumors (>Gleason 6); not stage T1c
Prolonged expected survival

* Brachytherapy may be indicated in combination with external beam radiation therapy.

Modified from: Vogelzang NJ, Scardino PT, Shipley WU, et al. Comprehensive textbook of genitourinary oncology, 3rd Edition. Lippincott Williams & Wilkins 2005.

Graphic 53124 Version 14.0

Contributor Disclosures

Eric A Klein, MD Consultant/Advisory Boards: GRAIL Inc [Multicancer early detection test]; Cleveland Diagnostics [isoPSA as a reflex test for elevated PSA]; Exact Sciences [OncotypeDx prostate]; Exact Imaging [Prostate microultrasond]; Lantheus [PSMA PET scanning]. All of the relevant financial relationships listed have been mitigated. **Nicholas Vogelzang, MD** Equity Ownership/Stock Options: Caris [Genetic testing]. Grant/Research/Clinical Trial Support: AbbVie [Prostate cancer];Amgen [Prostate cancer];Aravive [Advanced renal cancer];Arrowhead [Advanced solid tumors];Arvinas [Metastatic castration-resistant prostate cancer];AstraZeneca [Metastatic castration-resistant prostate cancer];Bristol-Myers Squibb [Renal cancer];Clovis [Prostate cancer];Dendreon [Prostate cancer];Eisai [Renal cancer];Endocyte [Metastatic castration-resistant prostate cancer];Epizyme [Metastatic castration-resistant prostate cancer];ESSA [Metastatic castration-resistant prostate cancer];Exelixis [Renal and prostate cancers];Genentech [Advanced solid tumors];Gilead [Bladder cancer];Kangpu [Metastatic castration-resistant prostate cancer];Kintor Suzhou [Metastatic castration-resistant prostate cancer];MacroGenics [Advanced solid tumors];Merck [Advanced solid tumors];Mirati [Bladder cancer];Modra [Metastatic castration-resistant prostate cancer];Myovant [Hormone-sensitive prostate cancer];Novartis [Renal cancer];Rhovac [Prostate cancer];SDPO [Advanced solid tumors];Seagen [Bladder cancer];Sotio [Prostate cancer];Vasgene [Bladder]. Consultant/Advisory Boards: Arvinas [Metastatic castration-resistant prostate cancer];Astellas [Renal cancer];AstraZeneca [Metastatic castration-resistant prostate cancer];Aveo [Renal cancer];Cancer Expert Now [Advanced solid tumors];Caris [Advanced solid tumors];Clovis [Prostate cancer];Eisai [Advanced solid tumors, renal cancer];ESSA [Metastatic castration-resistant prostate cancer];Exelixis [Advanced solid tumors, renal and prostate cancers];Fujifilm [Bladder cancer];Genentech [Advanced solid tumors];Helsinn [Bladder cancer];Janssen [Prostate cancer];Kintor Suzhou [Metastatic castration-resistant prostate cancer];Merck [Advanced solid tumors, genitourinary cancer];Modra [Metastatic castration-resistant prostate cancer];Novartis/AAA [Renal cancer];OnQuality Pharma [Renal cancer];Pfizer [Genitourinary cancer];Propella [Prostate cancer];Sanofi-Genzyme [Prostate cancer];SDPO [Advanced solid tumors];SWOG [Genitourinary cancer]. Speaker's Bureau: AstraZeneca [Metastatic castration-resistant prostate cancer];Bayer [Prostate cancer];Caris [Advanced solid tumors];Clovis [Prostate cancer];Sanofi Genzyme [Prostate cancer];Seagen [Bladder cancer]. Other Financial Interest: Merck [Legal consulting];Novartis [Legal consulting]. All of the relevant financial relationships listed have been mitigated. **W Robert Lee, MD, MS, MEd** Equity Ownership/Stock Options: Augmenix Inc [Prostate cancer]. All of the relevant financial relationships listed have been mitigated. **Jerome P Richie, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **Diane MF Savarese, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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