Active surveillance for men with early prostate cancer

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Disclosures: Laurence Klotz, MD Nothing to disclose. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelixis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer(investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VNR 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers' Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veriex/Janssen [Renal cancer (enzalutamide, abiraterone, axitinib)]. [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]. Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelixis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent)]; BIND [Prostate cancer (experimental agent); Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEd Consultant/Advisory Boards: Medivation [Prostate cancer (enazlutamide)]; Ferring Pharmaceuticals [Prostate cancer (Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

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INTRODUCTION AND DEFINITION OF TERMS — Active surveillance (expectant management) for men with prostate cancer involves the postponement of immediate therapy, with definitive treatment used if there is evidence that the patient is at increased risk for disease progression. Active surveillance is an accepted option for the initial management of carefully selected men with localized, well-differentiated prostate cancer thought to be at low-risk for progression [1,2].

Active surveillance differs from the older concept of "watchful waiting", which was based upon the premise that some men would not benefit from definitive treatment of apparently localized prostate cancer because of the prolonged natural history of the disease [3]. For patients
managed with watchful waiting, the decision was made at the outset to forego definitive
treatment and to provide symptomatic treatment (either androgen deprivation therapy or local
palliative maneuvers) if disease progressed locally or at distant metastatic sites. Watchful
waiting was largely seen as an alternative to definitive local therapy for elderly men with a
limited life expectancy and for those with substantial comorbidity.

The key considerations in choosing active surveillance for the initial patient management
include:

- Selection of patients who are at low-risk of progression
- Frequency and type of monitoring during active surveillance
- Criteria for switching from surveillance to definitive therapy

The role of active surveillance for patients with localized prostate cancer will be reviewed here.
Other approaches to the management of patients with early prostate cancer are discussed
elsewhere. (See "Initial approach to low- and very low-risk clinically localized prostate cancer".)

RATIONALE — The use of active surveillance as a treatment option in carefully selected men
with early prostate cancer is based upon several assumptions [2]:

- Prostate cancer is often detected when it is not clinically significant.
- Patients who have indolent prostate cancer can be distinguished by
  clinical and/or pathologic parameters from those who will have more aggressive disease
  that will lead to symptoms, metastases, or death.
- All definitive treatments for patients with prostate cancer, including those directed at
  minimal disease, are associated with significant side effects and costs.
- With appropriate surveillance, patients can be reclassified as being at higher risk for
disease progression and receive definitive therapy without substantially decreasing the
  chance of cure.
- The psychological burden of living with prostate cancer without active treatment has less
  impact on quality of life than receiving unnecessary, definitive treatment.

In contrast to most other malignancies, the growth rate of many prostate cancers is slow and
appears to be relatively constant over time. For many men, such disease either never requires
treatment or treatment can be postponed for a prolonged period without significantly decreasing
the chance for cure. (See "Screening for prostate cancer", section on 'Overdiagnosis'.)

Evidence supporting the concept that many men have asymptomatic prostate cancer that is
indolent and does not require immediate treatment comes from a number of sources:

- Autopsy studies have shown that there is a high incidence of occult cancer in the
  prostate of men dying without a known prostate cancer. The frequency of such tumors
  may be as high as 30 percent in men under 40 years, and may approach 70 to 80 percent
  in those 60 to 80 years of age. At least one study has suggested that the prevalence of
  occult prostate cancer may be decreasing since the introduction of the widespread PSA
  screening for prostate cancer [4]. (See "Risk factors for prostate cancer".)
- Epidemiologic studies since the introduction of PSA-based screening indicate that the
  number of cases of prostate cancer is substantially higher than was seen prior to the
  screening era. Extrapolations based upon the frequency of a serum PSA >2.5 ng/mL in
  men 50 to 70 years of age and the rate of a positive biopsy in that population subset
  suggest that there are over 500,000 undiagnosed cases of prostate cancer in this group
  [5].
A high frequency of occult prostate cancer was observed in the Prostate Cancer Prevention Trial, in which men underwent routine prostate biopsy at the completion of the trial [6]. Among those who had received placebo, 15 percent of those without an elevated serum PSA or abnormal digital rectal examination had occult prostate cancer. (See "Chemoprevention strategies in prostate cancer", section on 'Finasteride: Prostate Cancer Prevention Trial'.)

**PATIENT SELECTION** — Identification of those patients whose disease will not progress for an extended period is a critical issue in the choice of active surveillance for men with prostate cancer [2].

**Criteria** — Multiple criteria have been proposed for identifying patients with a favorable prognosis who are candidates for active surveillance, and the clinical criteria applied at different sites and in different studies vary somewhat [2]. All such criteria incorporate an early clinical stage, a relatively low serum prostate specific antigen (PSA), and a Gleason score consistent with well- or moderately-differentiated tumor. Other parameters that are frequently incorporated include the number of positive cores on the original biopsy, the percentage of positive cores, the extent of tumor involvement within a biopsy core, the PSA density, and PSA kinetics.

Although controversial, several sites have recommended a repeat prostate biopsy before committing to a plan for active surveillance, in order to identify patients in whom the original biopsy may have missed evidence of increased risk [7]. In most patients, delaying this biopsy for six months to a year may not have an impact on long term outcome, even if higher grade disease is eventually identified.

Such eligibility criteria, known as the Epstein criteria, were initially developed and validated based upon pathologic findings from radical prostatectomy specimens [8,9]. Although these criteria are useful in identifying men whose disease is likely to be localized and low grade at radical prostatectomy, long-term clinical correlation is required to determine how effective active surveillance is in a clinical setting. A study using contemporary biopsy techniques found that 93 percent of men meeting the Epstein criteria on biopsy had organ confined disease at prostatectomy [10]. However, 20 percent had more aggressive pathologic features including Gleason 7 disease or extraprostatic extension. Despite these findings, no patient meeting these criteria had a clinical or biochemical failure at six years after surgery.

In a prospective experience in Toronto, eligibility criteria consisted of clinical stage T1c or T2a prostate cancer, a Gleason score ≤6, and a serum PSA ≤10 ng/mL [11]. This corresponds to anatomic stage prognostic group I in the seventh (2010) TNM staging system (table 1 and table 2). For patients over age 70 years, slightly less stringent criteria were applied (Gleason score ≤7 [3+4], and/or PSA ≤15 ng/mL). However, active surveillance in these intermediate risk patients has been associated with a decreased overall survival and decreased cancer specific survival compared with low risk patients, and particular caution should be exercised if active surveillance is being considered in men with intermediate risk prostate cancer [12]. (See 'Observational studies' below.)

Nomograms have also been developed as an alternative to a single set of criteria to predict the probability of indolent prostate cancer for an individual patient [13-15]. The applicability of these nomograms is limited by the characteristics of the population in which they were developed, and the results may not apply to asymptomatic younger men detected by PSA screening [16]. (See "Prostate cancer: Risk stratification and choice of initial treatment", section on 'Nomograms'.)
The application of these criteria or of nomograms for helping a patient to decide whether or not to pursue active surveillance must be carefully individualized. Although age alone does not preclude active therapy, active surveillance may be particularly appropriate in older men and those with significant comorbidity, due to the long natural history of prostate cancer and concerns about treatment-related toxicity. Treatment-related toxicity (impotence, incontinence, acute surgical complications) appears to be more frequent in older men, making an active surveillance approach more attractive in this setting [17].

Endorectal coil MRI may eventually be useful as a supplemental way to optimize patient selection for active surveillance. A prospective study imaged 60 consecutive patients who had been selected for active surveillance based upon standard criteria [18]. Patients were subsequently reclassified as needing definitive therapy if a confirmatory biopsy revealed any Gleason 7 tumor, 3 or more cores positive for cancer, or more than 50 percent tumor in any one core. Any MRI finding of a tumor >1 cm in greatest dimension was deemed positive, since this corresponded to a tumor volume of 0.5 cm³.

MRI findings obtained upon study entry were correlated with those of the confirmatory biopsy. Among the 13 patients who had a lesion >1 cm on their MRI (22 percent), repeat biopsy identified 10 who were reclassified based upon their repeat biopsy. Among the 24 patients (40 percent) where the MRI demonstrated a lesion <1 cm, 16 were not reclassified on repeat biopsy and 6 were reclassified as being at increased risk. Overall, 20 of 22 patients who had a normal MRI at baseline were not reclassified on repeat biopsy. These findings need confirmation before MRI can be considered to have a role in determining the appropriateness of active surveillance.

In older patients, a comprehensive geriatric assessment may be useful in determining whether a definitive intervention, active surveillance, or watchful waiting is most appropriate. (See "Comprehensive geriatric assessment for patients with cancer".)

**Ethnicity** — African American ethnicity may be an additional factor to consider in deciding whether or not to use active surveillance as the initial treatment approach in men with low-risk prostate cancer. African American ethnicity is known to be associated with an increased incidence of prostate cancer; in this population prostate cancer has a significantly earlier age of onset, higher PSA levels, worse Gleason scores, and more advanced stage of disease at presentation. These associations are multi-factorial, and may also reflect issues of access to care and early detection as well as inherent genetic and environmental factors. (See "Risk factors for prostate cancer", section on 'Ethnicity'.)

The potential increased risk with active surveillance is illustrated by the outcomes in which a series of African American men who chose radical prostatectomy for very low-risk prostate cancer were compared with a comparable group of men of white or other races [19]. All men had clinical stage T1c disease, biopsy Gleason score ≤6 using contemporary Gleason criteria, no more than two positive biopsy cores, less than 50 percent involvement in any one core, PSA ≤10 ng/mL, and a PSA density ≤0.15 ng/mL/cm³. The African American men had significantly higher rates of upgrading of their Gleason pathology (33 versus 13 percent) and positive surgical margins (19 versus 6 percent). On multivariable analysis, the increased risk of unfavorable findings at prostatectomy was statistically significant compared with the combined results for white and other races.

However, the majority of black men who choose active surveillance are able to avoid overtreatment. Ethnicity is only one of many factors that should be taken into consideration in the selection of active surveillance or active treatment.
Guidelines — Guidelines that have attempted to identify patient groups for whom active surveillance is an appropriate option include:

- The American Urological Association (AUA) considers active surveillance, interstitial brachytherapy, external beam radiation therapy, and radical prostatectomy appropriate treatment options for patients with low and intermediate-risk prostate cancer [20]. These guidelines concluded that the available data on outcomes and complications were insufficient to recommend any one form of treatment over another for any risk category of disease. These guidelines recommend that all men with clinically localized prostate cancer be informed about all three of these treatment strategies, with a discussion of estimated benefit as well as harm from each intervention. We agree with this recommendation.
- The National Comprehensive Cancer Network (NCCN) guidelines define a very low-risk group, which includes the criteria for the TNM anatomic stage prognostic groups I in the 2010 TNM staging system [1]. In addition, these patients must have fewer than three positive biopsy cores, with ≤50 percent cancer in each core, and a PSA density <0.15 ng/mL/g. In this very low-risk group, the NCCN recommends active surveillance as the preferred option for those with a life expectancy less than 20 years. For the low-risk group (anatomic stage prognostic group I), the NCCN recommends active surveillance for those with a life expectancy less than 10 years, and considers active surveillance an option, along with radiation therapy and radical prostatectomy, for those with a longer life expectancy.

SURVEILLANCE STRATEGY — The optimal strategy for men who are being managed with active surveillance has not been defined.

Evidence of progression — The primary parameters available for monitoring include the serum prostate specific antigen (PSA), digital rectal examination, and repeat prostate biopsy, but no clinical studies have defined the appropriate testing intervals and the criteria to trigger active intervention.

Repeat prostate biopsy is usually recommended based upon a concern that histologic grade will worsen. The probability that higher grade disease will be detected is 8 to 28 percent [21,22], and these cases may represent a higher-grade component of the original tumor that was originally not sampled rather than evolution to higher grade disease.

In Toronto, the monitoring plan and criteria for active intervention include [23]:

- Measurement of the serum PSA at three month intervals, to calculate the PSA doubling time. A doubling time of three years or less is used as a criterion for intervention.
- A repeat prostate biopsy is performed at one year, to rule out higher grade disease that may have been missed on the original biopsy or developed as a consequence of tumor progression. Following this, biopsies are repeated every four to five years to look for evidence of biologic progression to Gleason 4+3 or higher. (See "Interpretation of prostate biopsy", section on ‘Gleason score’.)

This approach is consistent with the 2007 American Urological Association (AUA) guidelines as well as those of the National Comprehensive Cancer Network (NCCN), neither of which delineate specific intervals for retesting [1,20].

Prevention of progression — Treatment with dutasteride, a 5-alpha reductase inhibitor, is being studied to determine whether this approach can prevent or delay the progression of prostate cancer in patients being managed with active surveillance. (See "Chemoprevention strategies in prostate cancer", section on ‘5-Alpha reductase inhibitors’.)
In the multicenter REDEEM trial, 302 men were randomly assigned to treatment with either dutasteride or placebo for three years [24,25]. All patients had low-risk disease and met strict criteria for active surveillance (T1c or T2a prostate cancer, PSA <11 ng/mL, a Gleason score ≤6, ≤3 positive cores on biopsy with ≤50 positivity on any one core). Repeat biopsies were performed at 18 and 36 months. The primary endpoint was time to progression (defined by an increase in Gleason score to >6, involvement of >3 cores, >50 percent involvement of any one core, or treatment for prostate cancer [RT, radical prostatectomy, hormonal ablation]).

In an initial report, treatment with dutasteride significantly decreased or delayed the risk of pathologic or therapeutic progression (an increase in volume or grade of disease, or treatment of prostate cancer for any reason) compared with placebo (54 of 144 [38 percent] versus 70 of 145 [48 percent], hazard ratio 0.62, 95% CI 0.43-0.89) [24]. Furthermore, there was no evidence of an increase in the number of patients with high grade prostate cancer on the final biopsy.

A secondary analysis of the 276 patients who underwent a post baseline biopsy found that 94 (34 percent) had pathologic evidence of progression, including 54 (20 percent) with progression based upon volume (four or more positive cores or one core with ≥50 percent involvement), 19 (7 percent) with grade progression (Gleason ≥7), and 21 (8 percent) with both volume and grade progression. In 66 of the 94 cases (70 percent) progression was detected within the first 18 months.

The results of the REDEEM trial require confirmation in larger numbers of patients with longer follow-up. The trial was relatively short term, and has no data on clinical progression.

OUTCOMES — The available data on patient outcomes with active surveillance come from observation studies [2]. Large, randomized trials that compare active surveillance with immediate intervention are in progress. (See ‘Randomized trials’ below.)

Observational studies — Multiple observational studies provide important information about the clinical course of patients managed with active surveillance, although additional longer-term follow-up is needed. These studies consistently have found a low rate of progression to metastatic disease or death from prostate cancer with active surveillance; in addition, the majority of patients did not require definitive therapy within the time frame of these studies [26-31]. These results are illustrated by the following large studies:

●In a prospective study from Toronto, 993 men were initially managed with active surveillance since 1995 [31]. From 1995 to 1999, patients with a favorable risk profile (Gleason score ≤6 and serum PSA ≤10 ng/mL) were managed with active surveillance; less stringent criteria were used for patients over 70 years of age (serum PSA ≤15 ng/mL or a Gleason score 3 + 4). From 2000 to 2005, enrollment was limited to the favorable risk category, regardless of age. Until 2009, definitive treatment was recommended for a prostate specific antigen (PSA) doubling time of three years or less; subsequently, a rapid doubling time was used as an indication for more extensive evaluation.

Results were updated as of 2013, with a median follow-up from first biopsy of 6.4 years. There were 149 deaths, of which 15 (1.5 percent) were attributed to prostate cancer. An additional 13 patients (1.3 percent) had developed metastatic disease, but either were alive or had died of other intercurrent illnesses. The 10 and 15-year cause-specific survival rates were 98 and 94 percent. The rates of remaining on untreated and on active surveillance at 5, 10, and 15 years were 76, 64, and 55 percent, respectively.
In the Health Professionals Follow-up Study, 3331 men were diagnosed with prostate cancer between 1986 and 2007; treatment was deferred for at least one year in 342 (10 percent) [26]. The untreated group included both men managed with active surveillance and those in whom definitive therapy was not planned because of age or comorbidity. One-half of these patients remained untreated at a median follow-up of seven years. Patients deferring treatment were significantly older and had earlier stage disease, lower serum PSA, and lower biopsy Gleason scores. Multivariate analysis (adjusted for age, time of diagnosis, clinical stage, PSA at diagnosis, and Gleason score) found no significant difference in the risk of developing metastases or dying of prostate cancer between the observation and treatment groups (hazard ratio 1.03, 95% CI 0.65-1.23). A separate analysis of 945 of these patients from this center compared outcomes in the 237 patients with intermediate risk disease versus the 708 patients with low risk disease [12]. Cancer specific survival was significantly poorer at 15 years for those with intermediate risk disease (88.5 versus 96.3 percent, hazard ratio [HR] 3.75, 95% CI 1.37-10.28), and there was an increased risk of developing metastatic disease (11 [4.6 percent] versus 6 [0.8 percent]). Overall survival for intermediate risk patients was also worse (15-year overall survival 50 versus 69 percent, HR 2.08, 95% CI 1.49-2.89), although this may reflect differences in the patient populations.

In the randomized Goteborg population-based prostate cancer screening trial, 968 men were diagnosed with screen-detected prostate cancer between 1995 and 2010 [28]. Of these, 469 (48 percent) were managed with active surveillance. The 10-year failure-free, treatment-free, and overall survival rates were 86, 45, and 81 percent, respectively.

In the ongoing PRIAS study, patients with low-risk prostate cancer are being managed with active surveillance according to a predefined protocol consistent with other active surveillance protocols [27]. At the time of a 2013 report, 2494 patients had been enrolled worldwide, and enrollment is continuing. With a median follow-up of 1.6 years, results are consistent with those seen in other observational series.

The reasons men discontinue active surveillance were analyzed in a series of 1729 men in a Swedish database who were followed for a minimum of five years [32]. At five years, 64 percent of the men remained on active surveillance. Discontinuation of active surveillance was due to PSA progression, biopsy progression, or personal preference in 52, 24, and 20 percent of cases, respectively.

Many men who require active intervention actually represent a subset of patients who were under-sampled originally. In a series of 470 men initially included in an active surveillance program at Johns Hopkins, patients underwent annual prostate biopsies to identify evidence of progression [33]. Overall, 51 patients (11 percent) underwent radical prostatectomy. In addition, three-fourths of men who progressed did so within one to two years after the original diagnosis, suggesting undersampling of more aggressive tumor rather than progression of indolent tumor.

Randomized trials — A definitive assessment of the role of active surveillance in favorable-risk prostate cancer patients requires a direct comparison between immediate treatment and active surveillance including definitive treatment for evidence of progression. There are no results to date from randomized trials that compare definitive treatment (radical prostatectomy or radiation therapy) with a contemporary active surveillance approach.

Two large older studies, the Scandinavian Prostate Cancer Group 4 trial [34] and the PIVOT trial [35], compared immediate definitive therapy (radical prostatectomy) with delayed treatment for metastatic disease or symptomatic locoregional progression. Both trials provide insights into the natural history of prostate cancer, but neither trial utilized an active surveillance strategy.
with definitive therapy instituted if there was evidence of progression. (See "Radical prostatectomy for localized prostate cancer", section on 'Survival impact of radical prostatectomy'.)

In the Prostate Testing for Cancer and Treatment (ProtecT) trial that is being conducted in the United Kingdom (NCT00632983), patients were randomly assigned to active surveillance, radical prostatectomy, or definitive radiation therapy [36]. Patients assigned to active surveillance have their PSA monitored every three months during the first year and every six months thereafter. Additional testing is carried out as indicated, and the therapeutic plan is reassessed as clinically indicated. The primary outcome of the trial is survival time, as assessed from the initial presentation.

The trial commenced enrollment in June 2001, and a total of 1643 were randomized by 2009, consistent with the statistical design of the trial. The primary endpoint of the trial is prostate cancer mortality at a median follow-up of 10 years, and this will be analyzed in 2016.

A second trial, the Standard Treatment Against Restricted Treatment (START) trial (NCT00499174), was prematurely terminated because of inadequate patient enrollment [37].

Quality of life — The main advantage of active surveillance is the avoidance or deferral of treatment-associated side effects. These advantages are difficult to quantify. A detailed decision analysis that focused on hypothetical, otherwise healthy 65 year-old men with low-risk, localized prostate cancer used quality of life as the endpoint [38]. In this analysis, active surveillance was associated with a higher quality-adjusted life expectancy than initial treatment with external beam radiation therapy, brachytherapy, or radical prostatectomy. (See "Initial approach to low- and very low-risk clinically localized prostate cancer".)

A decision about whether to choose active surveillance or immediate treatment for early prostate cancer also needs to consider other factors that may affect quality of life:

● Patients who are managed with active surveillance have the psychosocial burden of living with an indolent cancer without active treatment [39,40]. This anxiety can be a significant factor in causing many patients who are being managed with active surveillance to seek active treatment [41]. In the Toronto cohort, approximately one-third of patients sought active treatment for reasons other than disease progression [11]. (See 'Observational studies' above.)

● Patients who are properly educated about the indolent course of good-risk prostate cancer may be better able to avoid some of the psychological complications associated with active surveillance [40]. Improved communication with the medical staff may improve both the acceptability of active surveillance as an initial approach as well as continuing participating in such a program [42,43].

● One observational study found an increased risk of erectile dysfunction in 231 patients who had annual 10 to 12 core prostate biopsies as part of their active surveillance program following the diagnosis of early prostate cancer [44]. This observation requires confirmation.

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.)

- Basics topics (see "Patient information: Choosing treatment for low-risk localized prostate cancer (The Basics)"
- Beyond the Basics topics (see "Patient information: Prostate cancer treatment; stage I to III cancer (Beyond the Basics)"

**SUMMARY AND RECOMMENDATIONS** — Active surveillance for localized prostate cancer entails observation rather than immediate therapy, with curative-intent treatment deferred until there is evidence that the patient is at an increased risk for disease progression. This approach is based upon the prolonged natural history of the prostate cancer and is an attempt to balance the risks and side effects of overtreatment against the possibility of disease progression and a lost opportunity for cure. (See 'Rationale' above and "Radical prostatectomy for localized prostate cancer", section on 'Survival impact of radical prostatectomy'.)

- The three standard therapies for men with organ-confined prostate cancer are radical prostatectomy, radiation therapy (either interstitial brachytherapy or external beam radiation therapy), and active surveillance.
- For men who place a high premium on avoiding the side effects of definitive treatment and who accept the possible increased risk of late metastasis or death, we recommend active surveillance (Grade 1C). (See 'Rationale' above.)
- The optimal criteria for patient selection have not been defined, but generally include the clinical stage, serum PSA, and Gleason score from the diagnostic biopsy. The increased risk of unfavorable disease in men of African American ethnicity may also be a factor to consider in patient selection. (See 'Patient selection' above.)
  - In the prospective cohort in Toronto, the eligibility criteria consisted of clinical stage T1c or T2a prostate cancer (table 1), a Gleason score ≤6, and a serum PSA ≤10 ng/mL [11]. Slightly less stringent criteria were applied for patients over age 70 years (Gleason score ≤7 [3+4], and/or PSA ≤15 ng/mL). However, particular caution should be applied in considering active surveillance for these patients because of an increased risk of disease progression.
- For patients who are being managed with active surveillance, the optimal schedule for monitoring and the criteria for initiating therapy have not been defined (see 'Surveillance strategy' above). Our approach includes:
  - Measurement of the serum PSA at three month intervals, to calculate the PSA doubling time. We use a doubling time of three years or less as a criterion for active intervention.
  - A repeat prostate biopsy is performed at one year, to rule out higher grade disease that may have been missed on the original biopsy. Following this, biopsies are repeated every four to five years to look for evidence of biologic progression to Gleason 4+3 or higher.

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**REFERENCES**


Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis

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**Disclosures:** A Oliver Sartor, MD Nothing to disclose. Steven J DiBiase, MD Nothing to disclose. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelexis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer (investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody); Speakers' Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veridex/Janssen [Renal cancer (enzalutamide, abiraterone, axitinib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]; Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelexis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent)]; BIND [Prostate cancer (experimental agent)]; Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEd Consultant/Advisory Boards: Medivation [Prostate cancer (enzalutamide)]; Ferring Pharmaceuticals [Prostate cancer(Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

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All topics are updated as new evidence becomes available and our peer review process is complete.  
**Literature review current through:** Apr 2015.  |  **This topic last updated:** Jul 15, 2014.

**INTRODUCTION** — The spectrum of clinical manifestations of prostate cancer has changed substantially since the introduction of prostate specific antigen (PSA) screening with a higher percentage of men now having localized disease at presentation. However, metastatic prostate cancer remains an important clinical problem, both in terms of the number of affected men and its impact on quality of life.

The bones of the axial skeleton are the predominant site of metastasis in most men with metastatic prostate cancer ([image 1](#)), and these lesions can cause pain, debility, and/or functional impairment. The clinical manifestations and diagnostic assessment of bone metastases in men with prostate cancer are reviewed here.

An overview of bone metastases is presented separately, as is a discussion of the management of prostate cancer bone metastases. (See "Overview of the epidemiology, clinical presentation, diagnosis, and management of adult patients with bone metastasis" and "Bone metastases in advanced prostate cancer: Management".)

**PATHOPHYSIOLOGY** — Malignant cells are widely disseminated in men with advanced prostate cancer. However, metastases preferentially develop in the bones of the axial skeleton, where red marrow is most abundant. The reasons for this pattern of metastasis are unclear but the leading hypothesis focuses on symbiotic interactions between prostate cancer cells and bone stromal cells such as osteoblasts, osteoclasts, and fibroblasts.

The bone metastases in men with prostate cancer are usually osteoblastic (ie, characterized by new bone formation). However, increases in bone resorption have been consistently
demonstrated histologically and biochemically. Bone destruction is an important factor in the etiology of pain and other complications due to bone metastases, although it is unclear if such bone destruction precedes the development of osteoblastic metastases or is a consequence of increased bone formation.

The mechanisms by which prostate cancer tumor cells induce osteoblastic changes are unclear, but are thought to involve excess activation of osteoblast mitogens, some of which are derived from bone stroma (insulin-like growth factors, transforming growth factor-beta, bone-morphogenic proteins, proteases, fibroblast growth factors, endothelin, other soluble factors) and others from the prostate cancer itself. (See "Mechanisms of bone metastases", section on 'Osteoblastic metastases'.)

**CLINICAL MANIFESTATIONS** — Bone is the predominant site of disseminated prostate cancer in men who present with or subsequently develop metastatic disease. Although bone metastases are often asymptomatic initially, patients can eventually develop complications that require treatment; these skeletal-related complications include pain requiring irradiation, pathologic fractures, spinal cord compression, surgery to bone, and occasionally abnormalities of calcium metabolism.

**Pain** — Pain is the most common manifestation of bone metastases. Pain from bone metastases is typically insidious in onset and slowly increases in severity over weeks to months. However, there are exceptions, such as a pathologic fracture or the sudden onset of back pain that accompanies the collapse of a cancer-containing vertebral body.

Although bone pain due to metastasis is commonly described as aching (like a toothache), nerve root entrapment, a common complication associated with vertebral metastases, may cause a burning and/or radiating type of pain.

Pain located distal to the knees or elbows is less likely to be malignant than that located proximally or centrally because cancers typically spread to bone areas with active marrow function. Arthritic pain is more likely to localize to joints than pain from bone metastases, but history alone cannot reliably distinguish the two. (See "Assessment of cancer pain".)

Uncontrolled pain due to bone metastases results in unnecessary suffering, decreased ability to cope with illness, interference with activities of daily living, and can necessitate extended or repeat hospital admissions. Uncontrolled pain may also delay or disrupt anticancer treatment, compromising its effectiveness. (See "Bone metastases in advanced prostate cancer: Management" and "Cancer pain management: General principles and risk management for patients receiving opioids".)

**Pathologic fractures** — Pathologic fractures are an important but relatively uncommon clinical manifestation of bone metastases from prostate cancer (image 2). Although prostate cancer bone metastases are typically osteoblastic, the structure of osteoblastic bone may be abnormal and there is usually a significant destruction of normal bone cortex (image 3).

Systemic treatment with androgen deprivation therapy (ADT) can contribute to osteoporosis, which increases the risk of fractures. Osteoporotic fractures need to be distinguished from those pathologic fractures caused by bone metastasis. (See "Mechanisms of bone metastases", section on 'Prostate cancer' and "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures'.)
**Spinal cord compression** — Vertebral metastases are a particularly common site of metastatic disease in men with advanced prostate cancer. Such metastases can cause spinal cord compression and severe neurologic deficits.

Pain is usually the first symptom of spinal cord compression, and this generally precedes the development of other symptoms by weeks or even months. A focused neurologic examination is required in men with back pain because of the risk of epidural spinal cord compression. Symptoms occurring later can include motor weakness, sensory findings, bowel and bladder dysfunction, and ataxia. (See "Clinical features and diagnosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Clinical features'.)

Early recognition of the clinical features of epidural spinal cord compression followed by prompt treatment is critical in minimizing the neurologic deficits associated with this complication. (See "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Primary treatment'.)

**Hypercalcemia and hypocalcemia** — Hypercalcemia is relatively uncommon in men with advanced prostate cancer compared with other malignancies where osteolytic disease is more common than osteoblastic disease. Hypocalcemia is more frequent, but is generally asymptomatic. Hypocalcemia may also be due to treatment with bone modifying agents (bisphosphonates, denosumab). (See "Hypercalcemia of malignancy" and "Risks of therapy with bone antiresorptive agents in patients with advanced malignancy", section on 'Hypocalcemia and other electrolyte abnormalities'.)

**Other laboratory abnormalities** — The most common abnormal laboratory findings observed in men with bone metastatic prostate cancer are a rising serum PSA level, an elevation in serum alkaline phosphatase, and anemia. However, these laboratory abnormalities are not useful in either establishing or ruling out the diagnosis of bone metastasis in men with prostate cancer.

- The serum PSA is typically >10 ng/mL in men with metastatic well-differentiated or moderately differentiated tumors [1]. However, some prostate cancers produce little PSA, and lower or even normal PSA values do not exclude bone metastases. Knowledge of serum testosterone is very helpful in interpreting PSA levels. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Prostate cancer with low PSA production'.)
- Osteoblastic metastases are commonly but not inevitably accompanied by elevations in markers of bone turnover (eg, serum bone-specific alkaline phosphatase, urinary hydroxyproline, urinary deoxypyridinoline). However, these are not routinely measured clinically. Although serial measurement of biochemical bone markers may not be useful in men with metastatic prostate cancer [2,3], a significant decline in bone-derived alkaline phosphatase is a reasonably reliable indicator of a favorable therapeutic response. In addition, high levels of bone-associated alkaline phosphatase are associated with a greater risk of adverse skeletal outcomes [2,4,5]. Because elevated serum alkaline phosphatase can be derived from bone or liver, further evaluation to distinguish the site of origin may be warranted. (See "Bone physiology and biochemical markers of bone turnover" and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'.)
- Anemia is common and typically is proportional to the extent of bone involvement. However, anemia may also be caused by a variety of factors including androgen deprivation therapy [6], systemic cytotoxic chemotherapy, disseminated intravascular coagulation, or a combination of poorly defined tumor-related factors.
**Frequency of skeletal-related events** — The risk of progression to metastatic disease at presentation, and hence the risk of subsequently developing bone metastases, is a function of multiple factors, which are incorporated into the American Joint Committee on Cancer (AJCC) staging system. In a prospective study looking at the risk of future bone metastases, the most important factor for men with castrate resistant prostate cancer and non-metastatic disease was a rapidly rising PSA and a baseline PSA of >13.0 ng/ml [7]. (See "Prostate cancer: Risk stratification and choice of initial treatment").

The frequency of skeletal-related complications rises progressively with more extensive disease. The incidence of such events in men with castrate resistant prostate cancer who have developed bone metastases was illustrated by a trial in which 1901 patients were randomly assigned to osteoclast inhibition with either zoledronic acid or denosumab [8]. The median times to first skeletal-related event were 17 and 21 months, respectively. For the entire cohort, the frequencies of bone pain requiring radiation therapy, pathologic fracture, and spinal cord compression were 20, 15, and 3 percent, respectively. In these studies pathologic fracture rates were assessed by skeletal surveys rather than symptoms. In more recent studies that used symptoms rather than skeletal surveys to detect pathologic fractures, the risk of pathologic fracture was 7 percent [9].

**DIAGNOSIS** — Pain is the most common manifestation of bone metastases. Prostate cancer patients with bone pain that cannot be definitively attributed to another condition should be evaluated for bone metastases. Pathologic fracture and spinal cord compression are less common and usually occur in the context of a patient with known bone metastases.

**Asymptomatic patients** — Routine evaluation for occult bone metastases in asymptomatic patients is not indicated in many cases at initial diagnosis or at the first evidence of a rising PSA following definitive therapy because of the low incidence of metastatic disease. (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Evaluation for distant metastases' and "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation".)

**Symptomatic patients** — The development or worsening of bone pain is the primary indication for evaluation for bone metastases but should not automatically be interpreted as due to bone metastasis. Worsening pain from a wide range of nonmalignant conditions (eg, arthritis, disc injury, musculoskeletal discomfort related to physical exertion) and treatment-related complications (eg, nerve root compression from vertebral body collapse due to treatment-related osteoporosis) need to be considered in the differential diagnosis.

The choice of imaging procedure is guided by the clinical setting:

- **Radionuclide bone scan** – Technetium-99 (99Tc)-MDP radionuclide bone scans are typically used as the first test for the evaluation of a patient with suspected bone metastases, but without symptoms or physical findings suggesting a pathologic fracture or incipient spinal cord compression. Bone scans are particularly sensitive for the detection of osteoblastic metastases and are the most useful imaging modality to assess the presence, number, and anatomic distribution of bone metastases in men with prostate cancer (image 4). (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Technetium-99 bone scan'.) Bone scans are most effective in detecting osteoblastic metastases and those with mixed blastic and lytic components. Occasional patients have predominantly osteolytic disease, and a negative bone scan does not rule out bone metastases. Plain radiography or MRI is indicated if bone metastases are suspected following a negative bone scan.
Sodium fluoride-18 (Na18F) PET scan is a more sensitive method of detecting suspected bone metastases. However, the clinical implications of a 99Tc-MDP and Na18F scan are not necessarily the same [10].

● **Plain radiographs** – Plain radiographs are more specific but less sensitive than bone scans. Plain films are the preferred initial imaging procedure when a pathologic fracture or compression fracture is suspected.

Benign lesions can cause increased uptake on a bone scan, and plain radiographic imaging may also be indicated to confirm abnormal or equivocal findings from a radionuclide bone scan. Plain films may also be useful for diagnosing treatment-related osteoporosis and osteoporotic fractures.

● **Magnetic resonance imaging** – Urgent magnetic resonance imaging (MRI) is indicated for patients with a suspected spinal cord compression based upon symptoms or physical findings. (See 'Spinal cord compression' above and "Clinical features and diagnosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Radiologic confirmation'.)

A number of other imaging techniques are being evaluated in an effort to improve upon the sensitivity and specificity of technetium-99 radionuclide bone scans. These are discussed separately. (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Evaluation for distant metastases'.)

**SUMMARY**

● Bone is the predominant site of disseminated disease in men with prostate cancer who present with or subsequently develop metastatic disease. Pain is the most common manifestation of bone metastases. Pain from bone metastases is typically insidious in onset and slowly increases in severity over weeks to months. (See 'Pain' above.)

● Pathologic fractures are an important clinical manifestation of bone metastases from prostate cancer. Although prostate cancer bone metastases are typically osteoblastic, the structure of osteoblastic bone may be abnormal and there is often a significant osteolytic component. (See 'Pathologic fractures' above.)

● Vertebral metastases are a particularly common site of metastatic disease in men with advanced prostate cancer. Such metastases can cause spinal cord compression and severe neurologic deficits. Early recognition of the clinical features of epidural spinal cord compression followed by prompt treatment is the most important step in minimizing the neurologic deficits associated with this complication. (See 'Spinal cord compression' above and "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Primary treatment'.)

● The diagnosis of bone metastases is based upon imaging findings. The choice of imaging procedure is based upon the clinical setting:

  • Routine imaging is not indicated in patients at low risk for the development of bone metastases. (See 'Asymptomatic patients' above and "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Staging evaluation' and "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation".)

  • Technetium-99 (99-Tc) MDP radionuclide bone scan is the current preferred imaging modality for the overall assessment of the number and location of bone metastases. (See 'Pain' above and 'Symptomatic patients' above.)

  • Plain radiographs are particularly useful for the initial assessment of patients thought to have a pathologic fracture. They are also indicated for the assessment of
equivocal findings on bone scan and for patients with purely osteolytic disease. (See 'Pathologic fractures' above and 'Symptomatic patients' above.)

• Magnetic resonance imaging (MRI) is required for prompt evaluation of patients having signs or symptoms suggestive of spinal cord compression. (See 'Spinal cord compression' above and "Clinical features and diagnosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Radiologic confirmation'.)

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INTRODUCTION — The clinical manifestations of prostate cancer at diagnosis have changed substantially since the introduction of prostate specific antigen (PSA) screening. Although a higher percentage of men have localized disease at presentation, metastatic prostate cancer remains an important clinical problem, in terms of the number of men with advanced disease, its impact on quality of life and as a cause of mortality.

Osteoblastic lesions in bone are the most common site of metastasis. These frequently are symptomatic, and can cause pain, debility, and functional impairment. The treatment of bone metastases in men with prostate cancer is palliative. The goals of treatment are to improve survival, relieve pain, improve mobility, and prevent complications (eg, pathologic fractures, epidural spinal cord compression).

The management of bone metastases in men with advanced prostate cancer is reviewed here. Treatment can include treatments directed specifically against the cancer involving bone, osteoclast inhibition to prevent complications from osseous involvement, and systemic therapy directed against the cancer.

The clinical presentation and evaluation of bone metastases and the overall approach to the management of men with advanced prostate cancer are discussed separately. (See "Overview of the epidemiology, clinical presentation, diagnosis, and management of adult patients with bone metastasis" and "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis" and "Overview of the treatment of disseminated prostate cancer").
TREATMENT OF PATIENTS WITH SYMPTOMATIC BONE METASTASES

External beam radiation therapy — External beam radiation therapy (RT) is the treatment of choice for men with castration resistant prostate cancer and bone pain that is limited to one or a limited number of sites. External beam RT is discussed separately. (See "Radiation therapy for the management of painful bone metastases").

Bone-targeted radiopharmaceuticals — Radium-223, an alpha particle emitting agent, prolongs overall survival and decreases symptomatic skeletal events due to bone disease in men with extensive multifocal painful bone metastases and in those with persistent or recurrent pain despite having received external beam RT to maximal normal tissue tolerance (Table 1). Although beta particle emitting radiopharmaceuticals may yield some symptomatic benefit they do not significantly prolong overall survival.

A prerequisite for radiopharmaceutical treatment is the presence of uptake on bone scan due to metastatic disease at the sites that correlate with pain. These radiopharmaceuticals are mainly used in men with advanced prostate cancer and symptomatic osteoblastic bone metastases.

Radium-223 — Radium-223 (223Ra) dichloride is an alpha particle emitting radiopharmaceutical that is indicated for the treatment of patients with castration resistant prostate cancer, symptomatic bone metastases, and no known visceral metastases. Radium is a bone-seeking element, and its decay allows the deposition of high energy radiation over a much shorter distance than with beta particle emitting radioisotopes, thus potentially treating tumor while minimizing toxicity to normal bone marrow.

Radium-223 increased both overall survival and the time to first symptomatic skeletal related event in the phase III ALSYMPCA trial [1,2]. Symptomatic skeletal events were defined as external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.

In the ALSYMPCA trial, all patients had castration resistant prostate cancer with multiple bone metastases and had either progressed on docetaxel chemotherapy or were not candidates for docetaxel chemotherapy. Patients were required to have two or more bone metastases and no known visceral metastases. Overall, 921 patients were randomly assigned in a 2:1 ratio to best supportive care plus radium-223 (one dose every four weeks for six cycles) or best supportive care plus placebo. Best supportive care options included a second-line variety of hormonal therapies and bisphosphonates. Approximately 80 percent had six or more lesions on bone scan and 40 percent had 20 or more lesions. Almost 60 percent had received prior docetaxel chemotherapy.

Key results included the following [1-4]:

- Overall survival, the primary endpoint of the trial, was significantly prolonged with radium-223 compared with placebo (median 14.9 versus 11.3 months, HR 0.70, 95% CI 0.58-0.83) [1]. The survival benefit was consistent across all patient subgroups, including both those who had and had not received prior docetaxel.
- The time to first symptomatic skeletal event (SSE, which included the first use of external beam RT for symptom relief, new pathologic fracture, spinal cord compression, or tumor related orthopedic surgery intervention) was significantly increased (median 15.6 versus 9.8 months, HR 0.66, 95% CI 0.52-0.83) [2]. When the symptomatic skeletal events were analyzed individually, the differences were statistically significant for use of external beam RT for symptom relief (HR 0.67) and for spinal cord compression (HR 0.52). Differences
were not statistically significant for new pathologic fracture (0.62) or for orthopedic surgery intervention (0.72), but the number of such events was limited. Routine radiographs were not utilized during this trial, and thus all SSEs were detected clinically.

- Treatment with radium-223 was associated with a favorable safety profile, with a lower frequency of all adverse events compared with placebo; there were no clinically meaningful differences in the incidence of grade 3 or 4 adverse events. Additional long-term safety data 1.5 years after the last patient’s last injection of radium-223 did not identify any major safety issues [3].
- In a prespecified subset analysis, radium-223 had similar efficacy in those who had received prior docetaxel and those who were docetaxel naïve [4]. Treatment was well tolerated irrespective of prior docetaxel use, although the incidence of grade 3-4 thrombocytopenia was higher in patients who had previously received docetaxel (9 versus 3 percent).
- Treatment with radium-223 was accompanied by a better quality of life during the period of study drug administration [1].

The clinical trial used six doses of radium-223 every four weeks; there are no safety or efficacy data on additional doses of treatment.

There are no randomized trials that compare radium-223 with other agents known to prolong overall survival in patients with metastatic, castration resistant prostate cancer (table 2). The factors influencing the sequencing and combinations of different therapies are discussed separately. (See "Overview of the treatment of disseminated prostate cancer".)

**Beta emitting radiopharmaceuticals** — Multiple beta-emitting radiopharmaceuticals have been evaluated and used clinically prior to the development of radium-223 (table 1). The most widely studied have been strontium-89 and samarium-153. Other isotopes studied include phosphorus-32, rhenium-186, and rhenium-188 [5,6].

- Multiple clinical trials have evaluated the efficacy of strontium-89 in men with prostate cancer bone metastases [7-12]. In the largest of these trials (757 patients), treatment with strontium-89 was integrated with docetaxel chemotherapy [12]. No statistically significant differences were noted in either overall survival or clinical progression-free survival in the intent to treat analysis.
- Two small randomized trials compared samarium-153 with placebo. Both found that treatment with samarium-153 was more effective than placebo in providing pain relief [13,14].

Myelosuppression is the predominant toxicity associated with beta particle emitting radiopharmaceuticals and was more prominent with strontium than samarium. This toxicity has limited their usage, and there is no evidence that beta emitting radiopharmaceuticals prolong survival.

**Focused ultrasound** — Magnetic resonance guided focused ultrasound is a technique to provide palliation for painful bone metastases in patients who have either failed on standard RT or are not candidates for RT [15]. The focused ultrasound waves raise the temperature at the imaged focal point and thus produce thermal tissue ablation.

The regulatory approval of this device was based upon an international multicenter trial that demonstrated the activity and safety of this approach [16]. (See "Image-guided ablation of skeletal metastases", section on ‘Outcomes’.)
Surgery — The use of surgery or kyphoplasty for bone lesions in men with metastatic prostate cancer is generally reserved for patients with pathologic fractures or epidural spinal cord compression. (See "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome" and "Evaluation and management of complete and impending pathologic fractures in patients with metastatic bone disease, multiple myeloma, and lymphoma").

Analgesics — A range of pharmacologic agents are available to treat cancer-related bone pain that is not adequately controlled by measures specifically directed against the metastatic disease. Pain management in cancer patients is discussed separately. (See "Cancer pain management with opioids: Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs" and "Cancer pain management: Adjunctive analgesics (coanalgesics)" and "Psychological, rehabilitative, and integrative therapies for cancer pain").

Systemic anticancer therapy — Systemic anticancer treatment is an important component of care for men with metastatic prostate cancer causing bone metastases. The use of androgen deprivation therapy as initial therapy and various other modalities for castration resistant disease is discussed separately. (See "Overview of the treatment of disseminated prostate cancer").

Systemic treatments can also have an effect on the frequency of symptomatic skeletal events (SSEs) or skeletal related events (SREs). SSEs are clinically detectable events that do not depend on routine acquisition of imaging. SSEs are clinically apparent events rather than radiographic detectable events that are not clinically apparent. Agents that have been demonstrated to decrease the frequency of skeletal events include radium-223, enzalutamide, and abiraterone, as well as the osteoclast inhibitors denosumab and zoledronic acid (table 3). (See "Castration resistant prostate cancer: Treatments targeting the androgen pathway" and "Osteoclast inhibition" below.)

PREVENTION OF BONE METASTASIS COMPLICATIONS

Radium-223 — In addition to its role in treating symptoms that are secondary to known bone metastases, radium-223 has been demonstrated to significantly decrease the incidence of symptomatic skeletal events in patients with symptomatic bone metastases. Symptomatic skeletal events include the first use of external beam RT for symptom relief, new pathologic fracture, spinal cord compression, or tumor related orthopedic surgery intervention. (See 'Radium-223' above.)

The definitive clinical trials with radium-223 were limited to patients with symptomatic disease, and radium-223 has not been explored in the management of patients with asymptomatic bone metastases.

Osteoclast inhibition — The bone metastases observed in prostate cancer are primarily osteoblastic, but there is a significant osteolytic component that is mediated by osteoclasts. Pathologic fractures do occur, although they are generally less frequent than in cancers with predominantly osteolytic disease. In addition, treatment with ADT can cause increased bone resorption and bone loss, which increases the risk of osteoporotic fractures. (See "Mechanisms of bone metastases", section on 'Prostate cancer' and "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures").

Prevention of skeletal related events due to bone metastases — In men with bone-metastatic castration resistant prostate cancer, osteoclast inhibition (with bisphosphonates
or denosumab) can decrease the rate of skeletal related complications, and these agents can be recommended. However, in trials conducted in men with hormone-sensitive metastatic disease, osteoclast inhibition does not significantly decrease the rate of skeletal related events; thus these agents are not indicated in this setting.

**Castration resistant disease**

**Bisphosphonates** — In men with castration resistant prostate cancer and bone metastases, bisphosphonates delay the development of skeletal-related events, which is a composite endpoint that includes pathologic fractures, radiation therapy [RT] to bone, surgery to bone, and spinal cord compression.

The benefit of zoledronic acid in men with bone metastases and castration resistant prostate cancer was demonstrated in a trial in 643 men whose disease was progressing while on ADT [17]. Men were randomly assigned to one of two doses of zoledronic acid (4 mg or 8 mg) or placebo, each given every three weeks. The 8 mg dose of zoledronic acid was reduced to 4 mg early in the trial because of an increased risk of renal toxicity.

At a follow-up of 24 months, there was a significant decrease in the frequency of skeletal related events with zoledronic acid compared to placebo (38 versus 49 percent), and the median time to develop a skeletal related event was significantly longer with zoledronic acid (488 versus 321 days) [18]. Pain and analgesic scores were significantly lower in men who received zoledronic acid compared with placebo, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups.

Other bisphosphonates are not equally effective [19]. Clinical studies with clodronate have yielded equivocal results [20-22], and two trials with pamidronate did not identify a statistically significant benefit in terms of skeletal related events or pain control [23].

Zoledronic acid is approved in the United States for use in men with castration resistant prostate cancer and bone metastases. The European Committee for Proprietary Medicinal Products has approved zoledronic acid for all men with bone metastases from prostate cancer.

**Denosumab** — Denosumab is a fully humanized monoclonal antibody that binds to the RANK ligand, a key factor in the pathway for osteoclast formation and activation. (See "Mechanisms of bone metastases", section on 'RANKL and OPG' and "Denosumab for osteoporosis".)

Denosumab has been evaluated in a range of clinical settings. Denosumab is approved for the prevention of skeletal related events in men with prostate cancer bone metastases and for the treatment of bone loss in men receiving ADT.

Denosumab is more effective than zoledronic acid in preventing skeletal related events in men with established bone metastatic castration resistant prostate cancer, although it does not improve overall survival or time to disease progression.

In a double-blind phase III trial 1901 men with castration resistant prostate cancer and at least one bone metastasis were randomly assigned to denosumab (120 mg) or zoledronic acid (4 mg), each given every four weeks [24]. Patients on both treatment arms were advised to use calcium and vitamin D supplements. The primary objective of the study was time to first skeletal-related event (pathologic fracture, need for radiation therapy or surgery, or spinal cord compression).

At a median follow-up of approximately 12 months, results included the following:
● The time to first skeletal-related event was significantly delayed with denosumab compared to zoledronic acid (median 20.7 versus 17.1 months, HR 0.82, 95% CI 0.71-0.95).

● There was no statistically significant difference in either overall survival (19.4 versus 19.8 months, HR 1.03) or time to disease progression (8.4 months with both regimens, HR 1.06).

● Both treatments were well tolerated. Osteonecrosis of the jaw trended toward being more frequent with denosumab compared with zoledronic acid (2.3 versus 1.3 percent) although these differences were not statistically significant. Hypocalcemia was also significantly more frequent with denosumab (13 versus 6 percent).

In addition, hypophosphatemia can occur more than 25 percent of the time in denosumab treated patients [25].

Castration sensitive disease — In contrast to the results in men with castration resistant disease, no benefit was seen when zoledronic acid was started during initial treatment with ADT in men with bone metastases. In the CALGB 90202 trial, 645 men were randomly assigned to zoledronic acid or placebo [26]. The trial was discontinued prematurely when the corporate sponsor withdrew support. With a median follow-up of 24 months, there was no statistically significant difference in the time to first skeletal related event (median 31.9 versus 29.8 months, hazard ratio [HR] 0.97). Overall survival also was not significantly different (median 38 versus 36 months, HR 0.88; 95% CI 0.70-1.12).

There are no data on denosumab for the prevention of skeletal related events in patients with castration sensitive disease.

Prevention of ADT-related bone loss — Both bisphosphonates and denosumab significantly decrease bone turnover and increase bone mineral density in men receiving androgen deprivation therapy (ADT) for prostate cancer. The results of randomized trials in this setting are discussed separately. (See "Side effects of androgen deprivation therapy", section on ‘Bisphosphonates’ and "Side effects of androgen deprivation therapy", section on ‘Denosumab’.)

Prevention or delay of bone metastases — Randomized trials with both bisphosphonates and denosumab have failed to demonstrate a favorable risk/benefit ratio for men with non-metastatic castration resistant prostate cancer.

Bisphosphonates — Although preclinical data suggest that bisphosphonates have an antitumor effect in prostate cancer, the adjuvant use of bisphosphonates in men with castration resistant prostate cancer without bone metastases has never been shown to significantly decrease the incidence of bone metastases.

In the phase III ZEUS trial, 1433 patients with high risk prostate cancer (PSA ≥20 ng/mL, Gleason 8-10, or node positive disease) were randomly assigned to zoledronic acid (4 mg every 3 months) for four years [27]. After a median follow-up of 4.8 years, there was no significant difference in the incidence of bone metastases (four year incidence, 14.7 with zoledronic acid versus 13.2 percent in the control group).

A smaller trial using clodronate also failed to demonstrate a decrease in the incidence of bone metastases [28].

Denosumab — Although denosumab delays the time to first bone metastasis in non-metastatic castration resistant prostate cancer, it does not improve overall survival or overall progression-free survival and is associated with osteonecrosis of the jaw in a significant number of cases.
Denosumab has not been approved for this indication. However, denosumab can be considered in patients without bone metastases but, with a rising PSA, and a PSA doubling time less than six months.

In a phase III trial, 1432 men with non-metastatic castration resistant prostate cancer were randomly assigned to denosumab or placebo [29]. All patients either had undergone bilateral orchietomy or had received continuous treatment with a gonadotropin releasing hormone agonist or antagonist for at least six months. Patients were castration resistant, based upon three consecutive rising PSA determinations. Patients were classified as high risk for the development of bone metastases based upon a serum PSA ≥8.0 mcg/L or a PSA doubling time <10 months.

**Denosumab** significantly increased the bone metastasis-free survival compared with placebo (29.5 versus 25.2 months, HR 0.85, 95% CI 0.73-0.98). A similar four month increase was observed in the time to first bone metastasis. However, there was no significant difference in overall survival (median 44 versus 45 months, HR 1.01).

A subsequent exploratory analysis of this trial found that patients with a rapid PSA doubling time had a shorter time to the development of bone metastases [30]. Furthermore, the impact of denosumab in delaying the development of bone lesions was more pronounced. For patients with a PSA doubling time ≤6 months, the median time to bone metastases was 25.9 months with denosumab versus 18.7 months with placebo (HR 0.77, 95% CI 0.64-0.93).

Osteonecrosis of the jaw was observed in 5 percent of patients treated with denosumab and was not observed with placebo. Hypocalcemia was more common with denosumab (1.7 versus 0.3 percent).

**Calcium and vitamin D** — Calcium and vitamin D levels should be assessed and low levels corrected prior to initiating therapy with an osteoclast inhibitor. If there are no contraindications (eg, preexisting hypercalcemia, recurrent renal stones), all patients receiving an osteoclast inhibitor should receive calcium and vitamin D supplementation to prevent secondary hyperparathyroidism and hypocalcemia and to ensure sufficient calcium for bone repair/healing.

**Side effects** — Although the benefits of osteoclast inhibition have been well established in large randomized clinical trials, these agents can cause serious toxicity in rare cases. Important potential side effects include:

- Osteonecrosis of the jaw (ONJ)
- Hypocalcemia
- Renal impairment is a concern with bisphosphonates but not denosumab

The potential risk for complications should not preclude the use of osteoclast inhibitors. Careful patient selection, avoidance of the use of these agents in patients in high risk settings, and continued awareness of the potential for complications during treatment are important to minimize the risk of serious complications [31,32].

The prevention and management of complications associated with osteoclast inhibitors (bisphosphonates and denosumab) are discussed separately. (See “Risks of therapy with bone antiresorptive agents in patients with advanced malignancy”.)

**SUMMARY AND RECOMMENDATIONS**

- Osteoblastic bone lesions in the axial skeleton are the most frequent site of metastasis in men with advanced prostate cancer. Treatment is palliative, with the goal of prolonging
survival, relieving pain, improving mobility, and preventing complications such as pathologic fractures or epidural cord compression.

- Systemic therapy is an important component of patient management for controlling symptoms and slowing progression of bone metastases. (See "Overview of the treatment of disseminated prostate cancer".)
- For patients whose pain is not controlled with systemic therapy and who have either a single or limited number of focal symptomatic bone metastases, we recommend external beam radiation therapy (Grade 1B). (See "Radiation therapy for the management of painful bone metastases".)
- For patients with castration resistant prostate cancer and multifocal symptomatic osteoblastic bone metastases that are not controllable with systemic therapy or external beam RT, bone-targeting radiopharmaceuticals may offer significant palliative benefit (See 'Bone-targeted radiopharmaceuticals' above.)
  - **Radium-223** is an alpha particle emitting agent that offers significant advantages because of its localized deposition of radiation. In a phase III trial, radium-223 improved overall survival and decreased skeletal-related events in men with advanced castration resistant disease with multifocal bone metastases without visceral disease. (See 'Radium-223' above.)
- For men with castration resistant prostate cancer and bone metastases, we recommend an osteoclast inhibitor (denosumab or zoledronic acid) to reduce the risk of skeletal complications in patients with bone metastases (Grade 1A). For most patients, we suggest denosumab rather than zoledronic acid based upon superior efficacy in a large randomized trial (Grade 2A). For patients in whom cost and/or reimbursement are important considerations, zoledronic acid is an appropriate alternative. (See 'Bisphosphonates' above and 'Denosumab' above.)
- Treatment of cancer-related bone pain that is not adequately controlled by measures specifically directed against the metastatic disease is an important component of overall patient management. (See "Cancer pain management with opioids: Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal antinflammatory drugs" and "Cancer pain management: Adjuvant analgesics (coanalgesics)" and "Psychological, rehabilitative, and integrative therapies for cancer pain".)

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Chemotherapy in castrate-resistant prostate cancer

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INTRODUCTION — For men with advanced prostate cancer, androgen deprivation therapy usually can provide disease control for a substantial period of time. However, the vast majority of men eventually develop progressive disease that is resistant to further hormonal treatment.

Prior to the development of the taxanes, cytotoxic chemotherapy was considered to be relatively ineffective in men with castrate-resistant prostate cancer. In early trials, objective response rates were 10 to 20 percent, and median survival generally did not exceed 12 months. However, taxane-based regimens have been associated with higher rates of objective tumor regression and biochemical (prostate specific antigen [PSA]) response, as well as longer overall survival.

Contemporary research has led to the development of multiple active treatment modalities for men with advanced prostate cancer. The use of cytotoxic chemotherapy for the treatment of castrate-resistant prostate cancer will be reviewed here. An overview of the management of advanced prostate cancer is presented separately. (See "Overview of the treatment of disseminated prostate cancer".)

CHEMOTHERAPY-NAIVE PATIENTS: DOCETAXEL — The activity of taxanes in men with castrate-resistant prostate cancer was initially suggested by multiple phase II studies in which docetaxel, with or without prednisone, was given on either a weekly or every three week...
schedule. These trials led to the evaluation of docetaxel in a number of combinations, including a phase III comparison to mitoxantrone, which established the combination of docetaxel plus prednisone as the standard of care for initial chemotherapy in men with castrate-resistant prostate cancer [1].

**Docetaxel versus mitoxantrone** — In the TAX-327 trial, 1006 men with chemotherapy-naïve metastatic castrate-resistant prostate cancer were randomly assigned to docetaxel (75 mg/m² every three weeks), docetaxel (30 mg/m² weekly), or mitoxantrone (12 mg/m² every three weeks) [2]. All patients received prednisone 5 mg orally twice a day. Patients were continued on maintenance gonadal androgen suppression, but antiandrogens were discontinued at least four weeks prior to chemotherapy. Overall survival was the primary endpoint of the trial. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Continuation of ADT'.)

Key results from the trial included the following:

- With an extended follow-up that included death of 86 percent of the patients, the benefit of the every three week schedule of docetaxel plus prednisone has persisted for overall survival (median 19.2 versus 17.8 and 16.3 months for the weekly docetaxel and mitoxantrone regimens, respectively) [3]. The three-year survival rates were higher in those treated with the two docetaxel schedules (18.6 and 16.6 versus 13.5 percent with mitoxantrone, respectively).
- In subset analyses, survival benefits were present in those older and younger than 65 years of age, in those with and without pain at baseline, and in those whose baseline PSA was greater than or less than the median (115 ng/mL).
- Both docetaxel plus prednisone treatment schedules were associated with a higher PSA response rate than with mitoxantrone (45 and 48 versus 32 percent) and a higher pain response rate (35 and 31 versus 22 percent, respectively).
- Grade 3 or 4 neutropenia was most common with docetaxel every three weeks compared with weekly docetaxel and mitoxantrone (32 versus 2 and 22 percent). Neutropenic infection was uncommon with all three regimens (3, 0, and 2 percent, respectively). Discontinuation of treatment due to adverse effects was uncommon with all three regimens (11, 16, and 10 percent, respectively).

Dexamethasone (8 mg) was administered 12, 3, and 1 hour prior to infusion with docetaxel to minimize toxicity. Although some have speculated that the dexamethasone, rather than the docetaxel, may be responsible for the activity of this combination [4], at least one study found no benefit from dexamethasone alone [5].

These results have established docetaxel (75 mg/m² every three weeks) plus daily prednisone (5 mg twice a day) as the standard of care for men with castrate-resistant prostate cancer.

**Alternative docetaxel schedules** — For patients who are unlikely to tolerate docetaxel on an every three week schedule, more frequent administration of docetaxel may offer a better tolerated alternative. In a phase III trial, patients were randomly assigned to docetaxel 50 mg/m² every two weeks or to docetaxel 75 mg/m² every three weeks, both given with prednisone [6]. The every two week schedule was associated with an improved time to treatment failure and overall survival compared with the every three week schedule, and there was a decrease in the incidence of severe neutropenia (53 versus 36 percent) and febrile neutropenia (14 versus 4 percent).
However, weekly use of docetaxel, as in the TAX-327 trial, was not superior to treatment with mitoxantrone [2]. (See 'Docetaxel versus mitoxantrone' above.)

Other docetaxel combinations — Multiple large phase III trials have failed to demonstrate an improvement in overall survival by adding other agents to the docetaxel prednisone regimen. Approaches tested include the following:

- Vascular growth factor inhibition (bevacizumab [7], aflibercept [8])
- Lenalidomide [9]
- Dasatinib [10]
- Endothelin receptor antagonists (atrasentan [11], zibotentan [12])
- Calcitriol [13]

Other docetaxel-based combinations with older cytotoxic agents have been evaluated in a more limited way in phase II, but none of these has an established role. These include combinations with vinorelbine [14], capecitabine [15], epirubicin [16], and carboplatin [17].

CABAZITAXEL — Cabazitaxel is a semisynthetic taxane derivative that was developed for its activity in patients with resistance to docetaxel. Cabazitaxel has been shown to prolong survival in patients who have progressed on docetaxel and is only indicated for use in combination with prednisone for patients who have previously been treated with a docetaxel-containing regimen [18].

In the phase III TROPIC trial, 755 men, all of whom had progressed on docetaxel, were randomly assigned to oral prednisone (10 mg/day) plus either cabazitaxel (25 mg/m² as an intravenous infusion every three weeks) or mitoxantrone (12 mg/m² every three weeks) [19]. Premedication to prevent severe hypersensitivity reactions included antihistamines, steroids, and an H2 antagonist. Antiemetic prophylaxis was recommended and was given either orally or intravenously as needed.

Men treated with cabazitaxel plus prednisone had an increased overall survival compared with those treated with mitoxantrone plus prednisone (hazard ratio [HR] 0.70, 95% CI 0.59-0.83, median survival 15.1 versus 12.7 months). Progression-free survival was also significantly prolonged (2.8 versus 1.4 months, HR 0.74, 95% CI 0.64-0.86). On subset analysis, the survival benefit was greater in patients who had been most heavily exposed to docetaxel compared with those with the lowest exposure (HR 0.51 versus HR 0.96 for those with >900 mg/m² compared with those who had received <225 mg/m²). With additional follow-up, the two-year estimated survival was greater than two years in 27 percent of patients treated with cabazitaxel versus 16 percent in those treated with mitoxantrone [20].

The cabazitaxel regimen was significantly more toxic than mitoxantrone. Potential treatment-related deaths were more frequent in the 30 days after last treatment for cabazitaxel compared with mitoxantrone (4.9 versus 2.4 percent). Grade 3 or greater neutropenia was observed in 82 percent of patients with cabazitaxel and febrile neutropenia was seen in 8 percent. In addition, diarrhea was reported in 47 percent of patients and was greater than or equal to grade 3 in 6 percent.

Prophylaxis with colony-stimulating factors is indicated to prevent febrile neutropenia for patients older than 65 years and for those with extensive prior radiation therapy, as well as in other high-risk groups. In addition, prophylaxis to prevent infusion reactions is recommended. (See "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced
neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation* and “Infusion reactions to systemic chemotherapy”.

Additional phase III clinical trials in castrate-resistant prostate cancer are comparing cabazitaxel with docetaxel as the initial chemotherapy regimen (NCT01308567), and comparing a dose of 20 mg/m² versus 25 mg/m² (NCT01308580) to determine whether comparable efficacy can be achieved with less myelotoxicity.

**OTHER CHEMOTHERAPY REGIMENS** — There are no chemotherapy regimens that have an established role based upon randomized clinical trials for patients who have progressed on the standard docetaxel prednisone regimen and potentially with the taxane cabazitaxel. However, many of these patients may be candidates for additional chemotherapy when their disease cannot be managed with secondary endocrine therapies. (See “Secondary endocrine therapies for castration resistant prostate cancer”.*

**Platinum-based regimens** — The most widely used contemporary regimens for docetaxel-resistant disease incorporate a platinum compound (carboplatin, oxaliplatin, cisplatin), often in conjunction with estramustine, capecitabine, or paclitaxel.

**Carboplatin** — Carboplatin had some clinical activity against castrate-resistant prostate cancer in relatively small phase II trials that were conducted prior to the development of the standard docetaxel prednisone regimen [21-25].

The potential role of carboplatin is illustrated by two contemporary phase II studies limited to patients who had progressed on docetaxel prednisone:

- The combination of carboplatin plus paclitaxel was evaluated in 38 patients, 24 of whom had received two or more prior chemotherapy regimens [26]. A clinical and/or biochemical response was seen in 26 percent of cases and an additional 34 percent had stable disease. The median duration of response and median time to progression were 6 and 3.6 months, respectively, and the median overall survival was 10 months.
- In a second phase II study, carboplatin was given in combination with docetaxel to 34 men who had progressed during or within 45 days after the completion of docetaxel-based chemotherapy [17]. Biochemical responses were observed in 18 percent of cases, the median progression-free survival was 3 months, and median overall survival was 12 months.

**Oxaliplatin** — The clinical activity of oxaliplatin was initially suggested in a phase II study in which oxaliplatin was combined with infusional 5-fluorouracil in men with castrate-resistant prostate cancer [27].

Two subsequent studies have evaluated the combinations using oxaliplatin in men who had progressed after docetaxel-based chemotherapy:

- In a study in 47 men, oxaliplatin was combined with pemetrexed [28]. A biochemical (PSA) response was observed in 64 percent of cases, and an objective response was seen in 10 of the 40 men with measurable disease. The median progression-free survival was 6 months and median overall survival was 12 months.
- In another phase II, 14 men were treated with the combination of oxaliplatin plus capecitabine [29]. A PSA response was observed in 8 of 14 cases (57 percent) and the median overall survival was 24 weeks.
Cisplatin — Older trials suggested that cisplatin had some activity in combination with either an anthracycline [30] or with estramustine plus ifosfamide [31] in men with castrate-resistant prostate cancer.

In a phase II study, 25 men who had docetaxel refractory disease were treated with the combination of cisplatin plus prednisone [32]. Biochemical responses were observed in 20 percent of cases, and 3 of 13 patients with measurable disease had a partial response. Median progression-free survival was 6 months and median overall survival was 55 weeks.

Other agents

Mitoxantrone — Although mitoxantrone is approved for the treatment of men with advanced prostate cancer, the approval was based upon symptom palliation and not an increase in overall survival in patients who had castrate-resistant disease [33-35].

Mitoxantrone retains some activity in patients who have progressed on docetaxel, although the availability of cabazitaxel and other agents that prolong survival minimize its role in this setting. In the phase III trial comparing cabazitaxel with mitoxantrone in patients who had previously been treated with docetaxel, mitoxantrone had a 4 percent objective response rate and an 18 percent PSA response rate [19]. (See "Overview of the treatment of disseminated prostate cancer", section on 'Castration resistant disease'.)

Estramustine — Estramustine, either as single agent or in combination therapy, has a minimal, if any, role in the overall management of metastatic castrate-resistant prostate cancer.

Estramustine is a conjugate of an alkylating agent to estradiol. Although estramustine has some activity as a single agent in men with castrate-resistant prostate cancer [36-40], its use is complicated by an increased risk of arterial and venous thromboembolic events [41]. Although daily aspirin and low-dose warfarin have been proposed as prophylaxis, a decrease in thromboembolic complications using these strategies has not been demonstrated.

Although the combination of estramustine plus docetaxel improved overall survival in a phase III trial compared with mitoxantrone plus prednisone [42], this combination was associated with excessive toxicity and does not have an established role.

Paclitaxel — The taxane paclitaxel has been less extensively evaluated than docetaxel in men with castrate-resistant prostate cancer. Paclitaxel does not have an established role in these patients, but appears to have activity that is schedule dependent. Experience in men with docetaxel-refractory disease comes primarily from combinations with platinum compounds. (See 'Platinum-based regimens' above.)

Miscellaneous agents — A number of older drugs were evaluated and showed evidence of at least limited activity. These included antimetabolites (fluorouracil, gemcitabine), cyclophosphamide, ixabepilone, and topoisomerase I inhibitors alone or in various combinations [43-52]. Objective response rates were generally 10 to 20 percent or less, and the use of these agents has been supplanted by the development of taxanes and platinum compounds.

PROSTATE CANCER WITH LOW PSA PRODUCTION — Some men with aggressive metastatic prostate cancer have low serum PSA values [53-55]. These patients are more likely to have visceral and osteolytic metastases rather than osteoblastic bone lesions. In this setting, serum PSA cannot be used as a marker to assess the response to treatment.
There are no randomized trials to guide management of patients with castrate-resistant prostate cancer and a low serum PSA. Our approach to treatment in these patients varies depending upon the histology:

- Patients with tumors that contain neuroendocrine (small cell) features are relatively sensitive to chemotherapy regimens that are used for small cell cancer involving the lung (e.g., platinum/etoposide combinations), with response rates of over 50 percent. Nevertheless, the optimal treatment regimen is unknown, and clinical studies are sparse. (See "Extensive stage small cell lung cancer: Initial management" and "Extrapulmonary small cell cancer", section on 'Prostate ESCC'.)
- Patients with poorly differentiated adenocarcinoma tend to have a clinically aggressive course. Although a combination of paclitaxel, estramustine, and carboplatin may be useful in those without neuroendocrine features [21,22], there are no data demonstrating that this is more effective than docetaxel plus prednisone.

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 information: Treatment for advanced prostate cancer (Beyond the Basics")

SUMMARY AND RECOMMENDATIONS

- For chemotherapy-naive men with castrate-resistant prostate cancer without neuroendocrine (small cell) features who are candidates for cytotoxic chemotherapy, we recommend docetaxel (75 mg/m² every three weeks) plus oral prednisone (5 mg twice a day) rather than other chemotherapy regimens (Grade 1B). This docetaxel plus prednisone regimen has been included in the Cancer Care Ontario Practice guidelines, which have been endorsed by the American Society of Clinical Oncology (ASCO). (See 'Docetaxel versus mitoxantrone' above.)
  - This schedule of docetaxel plus prednisone significantly increased survival compared with mitoxantrone plus prednisone in the TAX-327 trial. Giving docetaxel on a two weekly schedule may offer a better tolerated alternative, but the improvement in survival with a weekly schedule of docetaxel was not statistically significant compared with mitoxantrone. (See 'Docetaxel versus mitoxantrone' above.)
  - Gonadal androgen suppression, but not antiandrogens, should be continued during chemotherapy. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Continuation of ADT'.)

- For patients with castrate-resistant prostate cancer who have progressed on treatment with docetaxel plus prednisone, there are a number of treatment options that have been shown to prolong overall survival (table 1). For those who are candidates for second-line
cytotoxic chemotherapy, we recommend cabazitaxel (Grade 1B). Cabazitaxel plus prednisone significantly increased overall survival compared with mitoxantrone plus prednisone. For patients who are not candidates for cabazitaxel or who may benefit from other regimens, platinum-based regimens may have useful activity. (See ‘Cabazitaxel’ above and ‘Platinum-based regimens’ above.)

● Patients with castrate-resistant prostate cancer and a low serum PSA are more likely to have aggressive disease, including the presence of visceral metastases rather than bone metastases. There are no randomized trials to guide therapy in this setting:
  • For patients with poorly differentiated adenocarcinoma without neuroendocrine features, we suggest a combination of docetaxel plus prednisone (Grade 2C). A combination of paclitaxel, estramustine, and carboplatin may be an alternative. (See ‘Prostate cancer with low PSA production’ above.)
  • Those patients whose tumors have a substantial component with neuroendocrine features may benefit from treatment with a chemotherapy regimen similar to that used for patients with small cell lung cancer. (See “Extensive stage small cell lung cancer: Initial management” and "Extrapulmonary small cell cancer", section on ‘Prostate ESCC’.)

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REFERENCES


Follow-up surveillance during and after treatment for prostate cancer

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Disclosures: David F Penson, MD, MPH Nothing to disclose. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelexis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer (investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers' Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veridex/Janssen [Renal cancer (enzalutamide, abiraterone, axitinib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]. Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelexis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; Janssen [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent); BIND [Prostate cancer (experimental agent); Blue Earth [Prostate cancer (diagnostic investigational agent)]]]. W Robert Lee, MD, MS, MEd Consultant/Advisory Boards: Medivation [Prostate cancer (enzalutamide)]; Ferring Pharmaceuticals [Prostate cancer(Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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Literature review current through: Apr 2015. | This topic last updated: Sep 18, 2013.

INTRODUCTION — The widespread availability of highly sensitive testing for serum prostate specific antigen (PSA) has led to major shifts in the epidemiology of prostate cancer. These shifts have been manifested by an increased number of cases, a younger age, and an earlier clinical stage at diagnosis.

Thus, clinicians are managing an increasing number of men with localized prostate cancer who have received definitive treatment of their primary tumor (generally with radical prostatectomy or radiation therapy [RT]). These men require follow-up to detect local recurrence or disseminated disease, as well as for complications of their treatment. (See 'Localized prostate cancer' below and "Initial approach to low- and very low-risk clinically localized prostate cancer" and "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer").

In addition, men who have metastatic disease require follow-up to assess the efficacy of their treatment and identify patients who might benefit from alternative treatments. (See 'Metastatic prostate cancer' below and "Overview of the treatment of disseminated prostate cancer").

The follow-up surveillance for men who have received definitive treatment for prostate cancer as well as those being treated for metastatic disease is discussed in this topic. The natural history and follow-up of patients who have a rising serum PSA following definitive treatment and the follow-up of those being managed initial with active surveillance are discussed separately. (See "Active surveillance for men with early prostate cancer", section on 'Surveillance strategy' and "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation".)
LOCALIZED PROSTATE CANCER — Most men with newly diagnosed prostate cancer have localized disease and undergo definitive therapy with curative intent (radical prostatectomy, external beam RT, brachytherapy). A subset of carefully selected patients with low risk disease may be managed with active surveillance, with definitive therapy deferred until there is evidence of progressive disease. (See "Initial approach to low- and very low-risk clinically localized prostate cancer").

For patients who do develop either a local or disseminated recurrence, disease generally is detected biochemically by a rise in the serum PSA, a highly specific marker for prostate tissue. The development of an overt local recurrence or distant metastases usually occurs significantly later than a rise in the serum PSA. (See 'Serum PSA' below and "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

There are no randomized trials that have defined the optimal follow-up strategy for men following their initial treatment for localized prostate cancer. Regular monitoring of the serum PSA is indicated following definitive therapy, with possible early intervention if a recurrence is detected, since many recurrences following initial treatment can be successfully treated. The natural history of many prostate cancers from the time from biochemical recurrence to symptomatic disease or death is often prolonged and, as such, not all biochemical failures require aggressive treatment. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Risk of metastases or death'.)

When considering surveillance strategies for prostate cancer, the impact of therapy for recurrent disease on both overall survival and quality of life should be discussed with the patient. The patient's individual preferences and overall health status are of primary importance in choosing a surveillance strategy after treatment for localized prostate cancer. If a man does not desire additional treatment or if his life expectancy is limited due to comorbid conditions, early detection of recurrent disease would only cause psychological distress and could detract from quality of life, while not affecting overall survival.

Surveillance strategies

**History and physical examination** — The majority of recurrences following radical prostatectomy or RT for localized prostate cancer are asymptomatic and manifested only by a rising serum PSA. While regular physician visits may serve to reassure the patient, they are of questionable utility in detecting recurrent tumor. Nevertheless, periodic evaluation by a health care provider is important to evaluate potential complications of therapy and for overall health care. The value of serial digital rectal exams in this setting is unclear, particularly after surgery.

**Serum PSA** — Serum PSA is the mainstay of surveillance testing in men who have undergone therapy for localized prostate cancer. There are no clinical trials that define the optimal frequency of measuring the serum PSA. Guidelines from the NCCN recommend that the serum PSA be monitored every 6 to 12 months for the first five years, and annually thereafter [1].

Serum PSA is a sensitive marker for recurrent prostate adenocarcinoma in this setting and is elevated in 95 percent of men with recurrent disease. While the use of PSA for cancer screening is controversial, there is little debate that it is an excellent tumor marker in men with an established diagnosis of prostate cancer.

**Definition** — The definition of a PSA recurrence depends upon the initial treatment:
Surgery – All prostate tissue is removed during a successful radical prostatectomy. Thus, any detectable PSA in the serum using the standard immunoassay (the typical limit of detection is 0.1 ng/mL) theoretically indicates remaining prostate tissue, and presumably represents persistent or recurrent disease. Ultrasensitive PSA assays may detect lower levels of PSA, but the use of lower levels to base treatment decisions is not recommended. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'After radical prostatectomy'.)

Radiation therapy – The definition of a biochemical failure following RT is more complicated, since there is benign prostate tissue remaining after RT. The American Society for Radiation Oncology (ASTRO) has established guidelines to define PSA recurrence following RT. The 1996 ASTRO and 2005 Phoenix criteria are presented separately. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'After radiation therapy'.)

The interpretation of an increase in serum PSA following RT is further complicated by the observation that serum PSA levels can fluctuate ("bounce") significantly after RT (particularly brachytherapy), before returning toward the posttreatment nadir. Thus increases in PSA must be interpreted with caution and do not necessarily indicate recurrence. The PSA bounce phenomenon is discussed separately. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'PSA bounce'.)

Natural history of PSA-only recurrence — The natural history of prostate cancer disease in men with a PSA-only (biochemical) recurrence is often prolonged, and a biochemical recurrence alone is not necessarily an indication for therapy. Because PSA is a specific tumor marker following local therapy, the absence of a rise in PSA can provide significant psychological reassurance. If "PSA-only failure" occurs, other clinical characteristics, such as time to biochemical recurrence or PSA doubling time, can be used to counsel patients and help guide treatment decisions regarding secondary therapy. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Risk of metastases or death'.)

Digital rectal examination — Digital rectal examination (DRE) is considered a regular component of the physical examination since the examination is inexpensive and has little or no risk associated with it. However, monitoring serum PSA rather than DRE is the "gold standard" for early detection of recurrence following definitive local therapy in patients with localized prostate cancer.

- Following radical prostatectomy, the prostatic fossa should be empty on DRE. However, DRE is not sensitive enough to detect local recurrence early [2-5]. As an example, in a retrospective analysis of 501 men who had undergone radical prostatectomy, 72 had a rising PSA [2]. Only 4 of the 501 men (0.8 percent) had an abnormal DRE, and the PSA was elevated in each of these cases.
- In men treated initially with RT, the role of DRE is also unclear. DRE was used routinely prior to the availability of PSA, but this outcome is now seldom reported. However, the clinical significance of a change in DRE following RT is unclear. Furthermore, there is considerable intraobserver variability in assessing change in DRE, which limits the utility of this endpoint.

Imaging studies — Imaging studies do not have a routine role in surveillance for recurrence in patients who have undergone definitive therapy for localized prostate cancer in the absence of a
rising serum PSA or specific symptoms. A variety of imaging studies are potentially useful in identifying the specific sites of recurrence in men with biochemical evidence of recurrence (rising PSA) or in evaluating symptoms suggestive of recurrent disease. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation" and "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

**Bone scan** — The technetium-99 radionuclide bone scan is a sensitive and reliable test for detecting the presence of skeletal metastases. However, bone scan has been replaced by PSA testing for the early detection of asymptomatic recurrence.

In a retrospective study of 118 men who were followed with both serial bone scans and serum PSA after radical prostatectomy for localized disease, 75 percent had no evidence of disease by either study, 9 percent had an elevated PSA with a negative bone scan, and 9 percent had an abnormal bone scan, all of whom had an abnormal PSA [6]. The remaining seven patients with positive or indeterminate bone scans and negative PSA were determined to have recurrent disease.

Bone scans are more likely to detect metastases when the serum PSA level is markedly elevated [7]. However, almost all men are evaluated when they are castrate-sensitive and the serum PSA is much lower (often <1.0ng/mL). In this setting the bone scan is unlikely to identify bony metastases in the absence of symptoms referable to bone. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation", section on 'Imaging studies' and "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

**Transrectal ultrasound** — There is no role for transrectal ultrasound (TRUS) of the prostate or prostatic fossa as a screening test for recurrence of localized prostate cancer. However, in men with a suspected biochemical recurrence and no evidence of systemic disease, TRUS with biopsy may be useful for confirming a local recurrence and in planning secondary treatment. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation", section on 'Prostate biopsy'.)

**Pelvic CT** — Pelvic CT is not indicated for routine surveillance of men who have received definitive treatment for localized prostate cancer because of the limited sensitivity of CT to detect low volume recurrent disease [8].

**Immunoscintography** — Immunoscintigraphy using a radiolabeled monoclonal antibody imaging test may be helpful in determining the site of recurrence (local versus distant) in men with a PSA-only recurrence after radical prostatectomy. However, it has no utility in posttreatment surveillance. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation".)

**Monitoring for complications of therapy** — One of the most important aspects of follow-up care for men who have undergone definitive local treatment for prostate cancer is the identification of therapy-related complications. The complications of both radical prostatectomy and radiation therapy are discussed elsewhere. (See "Initial approach to low- and very low-risk clinically localized prostate cancer").

**Treatment options following recurrence** — The detection of early asymptomatic recurrence following treatment for localized prostate cancer is useful only if it decreases morbidity or mortality. While data directly addressing this issue are lacking, there is some indirect evidence that early detection and treatment of a recurrence can improve outcomes. Treatment options
are dictated by whether the recurrence is local or systemic, and whether the initial treatment was surgery or radiation.

**Local recurrence following radical prostatectomy** — For men with a local recurrence following radical prostatectomy, radiation therapy (RT) is a reasonable option for salvage therapy in some cases. Salvage RT is most successful when the disease burden is low and when the relapse-free interval is 12 months or longer. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation" and "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Risk of metastases or death'.)

The role of salvage RT for the treatment of locally recurrent disease is discussed separately. (See "Rising or persistently elevated serum PSA following radical prostatectomy for prostate cancer: Management").

**Local recurrence following RT** — Radical prostatectomy or ablation with cryotherapy may provide effective salvage therapy in appropriately selected cases for men with a local recurrence following RT. (See "Rising serum PSA after radiation therapy for localized prostate cancer: Salvage local therapy").

**Systemic recurrence** — For men with a systemic recurrence of prostate cancer or who are not candidates for salvage therapy because of age or comorbidity, systemic treatment may be indicated. However, the optimal timing of such treatment is uncertain, since treatment-related side effects can adversely affect quality of life (QOL). (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy").

**METASTATIC PROSTATE CANCER** — For men with metastatic prostate cancer, surveillance should be geared toward identifying signs and symptoms of disease progression as an indication of treatment failure. While there are no data to guide the frequency of clinician visits, it is common clinical practice to examine men at three to six month intervals, which often coincide with the time of administration of long-acting gonadotrophin agonist therapy [1].

The onset of new symptoms during therapy may suggest the need for further diagnostic evaluation (eg, back pain with neurologic abnormalities due to spinal cord compression, bone pain due to pathologic fracture) or specific site-directed therapy (eg, radiation therapy to a painful bone metastasis). (See "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Although serial PSA testing in men with metastatic disease has not been shown to prolong life expectancy, rising PSA is an indication of treatment failure, signaling the need to consider alternative therapies. Serial PSA testing can also provide reassurance to patients of a continuing response to treatment.

Measurement of serum PSA in men with metastatic disease every three to six months is reasonable; more frequent evaluation, potentially including imaging studies, is indicated if the serum PSA begins to rise or the patient complains of symptoms. More frequent testing, as well as imaging studies, is often required for men participating in research protocols.

Not all prostate cancers make significant amounts of PSA. Some of these are neuroendocrine tumors that may respond to cisplatin-based chemotherapy rather than hormonal manipulation. Others lack neuroendocrine features, but are poorly differentiated prostatic adenocarcinomas with a serum PSA <10 ng/mL. Objective responses in such patients are difficult to measure but their response duration and median survival tend to be shorter after initial androgen ablation.
compared to men with PSA-producing prostate adenocarcinoma [9]. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Prostate cancer with low PSA production'.)

An important component of follow-up in men with advanced prostate cancer is monitoring for the adverse effects of androgen ablation, including gynecomastia and loss of bone and lean muscle loss. Bisphosphonates such as zoledronic acid can prevent treatment-related bone loss in men who are receiving ADT, and can reduce the number of skeletal events and need for radiation therapy in men with bony metastases. (See "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures' and "Bone metastases in advanced prostate cancer: Management", section on 'Osteoclast inhibition'.)

RISING PSA AFTER INITIAL DEFINITIVE THERAPY — For patients who have a rising serum PSA following initial definitive therapy with surgery or radiation therapy, the natural history of prostate cancer can be highly variable and does not necessarily constitute an indication for treatment. The roles of surveillance and evaluation in this setting are discussed separately. (See "Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation", section on 'Imaging studies' and "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Risk of metastases or death'.)

ACTIVE SURVEILLANCE FOR EARLY PROSTATE CANCER — Active surveillance (expectant management) for men with prostate cancer involves the postponement of immediate therapy, with definitive treatment used if there is evidence that the patient is at increased risk for disease progression. Follow-up for patients being managed with active surveillance and the criteria for therapeutic intervention are discussed separately. (See "Active surveillance for men with early prostate cancer", section on 'Surveillance strategy'.)

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 (see "Patient information: Prostate cancer treatment; stage I to III cancer (Beyond the Basics)"

SUMMARY

- There are no randomized trials that define the optimal surveillance strategy following definitive therapy for localized prostate cancer. The mainstay of follow-up in all patients is PSA testing and clinical evaluation. (See 'Surveillance strategies' above.)
  - For men who have undergone definitive therapy for localized disease, we suggest monitoring the serum PSA every 6 to 12 months for five years and then annually thereafter. (See 'Serum PSA' above.)
  - Routine imaging procedures are not indicated in the absence of symptoms or a rising serum PSA. (See 'Imaging studies' above.)
In patients with metastatic prostate cancer, surveillance should be geared toward the detection of progressive disease and the side effects of long-term androgen deprivation therapy. A physician visit and serum PSA level every three to six months is reasonable. (See 'Metastatic prostate cancer' above.)

References


Initial approach to low- and very low-risk clinically localized prostate cancer

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Disclosures: Eric A Klein, MD Nothing to disclose. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelexis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer (investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers’ Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veridex/Janssen [Renal cancer (enzalutamide, abiraterone, axitinib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]. Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelexis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent)]; BIND [Prostate cancer (experimental agent); Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEd Consultant/Advisory Boards: Medivation [Prostate cancer (enzalutamide)]; Ferring Pharmaceuticals [Prostate cancer (Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

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Literature review current through: Apr 2015. | This topic last updated: Apr 13, 2015.

INTRODUCTION — Most prostate cancers now are diagnosed while clinically localized, based in part upon the widespread use of serum prostate specific antigen (PSA) measurement. Treatment planning needs to incorporate the natural history of the disease and the risk of progression, since many of these cancers are biologically indolent and may never threaten the health or life of the patient.

For patients diagnosed with prostate cancer confined to the prostate, standard management options include radical prostatectomy, radiation therapy (external beam, brachytherapy), and, for carefully selected patients with very low or low-risk disease, active surveillance.

Key factors in choosing treatment for a man with low-risk prostate cancer include the likelihood of recurrence or metastasis following treatment (risk stratification), the patient's age and life expectancy, the presence or absence of significant comorbidity, and patient preferences. (See "Prostate cancer: Risk stratification and choice of initial treatment", section on 'Risk stratification'.)

This topic discusses the initial management approach for men with low-risk prostate cancer. The approach to treatment of men with intermediate and high-risk prostate cancer, locally advanced (very high risk) disease, and stage IV disease (clinical lymph node involvement or disseminated metastases) are discussed separately:

- (See "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer").
- (See "Overview of the treatment of disseminated prostate cancer").
RISK STRATIFICATION — The management of men with newly diagnosed prostate cancer needs to incorporate a consideration of the prolonged natural history of prostate cancer and the risk for progression to disseminated, potentially fatal disease.

Risk stratification uses the clinical stage of disease, baseline serum prostate specific antigen (PSA), the Gleason score, and the extent of prostate involvement (including the number of biopsy cores containing cancer) to divide patients into prognostic categories (table 1A-B). Although there are fairly arbitrary boundaries between these prognostic categories, prostate cancer is a broad continuum. Risk stratification is combined with patient age, overall medical condition, the presence or absence of symptoms, and patient preferences in guiding initial therapy decisions. (See "Prostate cancer: Risk stratification and choice of initial treatment".)

- Patients with very low-risk clinically localized prostate cancer have disease detected by prostate biopsy only, without detectable abnormality on digital rectal examination or imaging. To be classified as very low-risk, such patients must have a 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) [1].
- Low-risk prostate cancer — Patients with low-risk, clinically localized prostate cancer either have disease limited to one lobe of the prostate (T2a) or no apparent tumor by DRE (T1, diagnosis based upon a biopsy only, with no abnormal findings on imaging or palpation), a serum PSA <10 ng/mL, and a Gleason score ≤6.
- Intermediate-risk prostate cancer — Men with intermediate-risk clinically localized 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 without extracapsular extension or seminal vesicle involvement. In addition, patients with clinical stage T1 or T2a disease are classified as having intermediate risk disease based upon a serum PSA between 10 and 20 ng/mL or a Gleason score 7 on biopsy.
- High-risk prostate cancer — Patients with high-risk, clinically localized prostate cancer may have more extensive disease, based upon the presence of extracapsular extension (T3a). In addition, some patients with less extensive disease are classified as high risk because of a serum PSA >20 ng/mL or a Gleason score of 8 to 10.
- Very high risk prostate cancer — Patients whose initial evaluation suggests locally advanced disease (T3b or T4) diagnosed based upon clinical staging but without lymph node involvement (N0) or distant metastases (M0) are at very high risk of local recurrence or distant metastases.
- Patients with lymph node involvement or disseminated metastases are classified as having stage IV disease.

The initial approaches to treatment for men with very low or low-risk prostate cancer are discussed here. The management approaches to patients with intermediate or high-risk prostate cancer are discussed separately. (See "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer".)

TREATMENT APPROACHES — The relative advantages and disadvantages of different treatment approaches for men with newly diagnosed low-risk and very low-risk prostate cancer are discussed in this section. Standard treatment approaches include active surveillance in selected cases, radical prostatectomy, external beam RT, and brachytherapy.
**Active surveillance** — Active surveillance is defined as the postponement of immediate definitive therapy, with curative-intent treatment instituted if there is clinical evidence of disease progression. Active surveillance is an appropriate treatment option for some patients with prostate cancers that are small, have a low Gleason grade, and thus are thought to have a relatively low-risk of progression (TNM anatomic prognostic group I ([table 1A](#) and [table 1B](#)).

The goal of active surveillance is to avoid treatment-related complications for men whose cancers are not likely to progress. For many men, such disease either never requires treatment or treatment can be postponed for a prolonged period without significantly decreasing the chance of cure. (See "Active surveillance for men with early prostate cancer", section on 'Rationale'.)

Active surveillance must be distinguished from "watchful waiting", which is based upon the premise that some men will not benefit from definitive treatment of their localized prostate cancer [2]. For patients managed with watchful waiting, the decision is made at the outset that the patient is not a candidate for definitive therapy and to provide palliative treatment (typically androgen deprivation therapy, ADT) if and when symptomatic progression requires therapy. Watchful waiting may be an acceptable alternative for men with short life expectancy based upon age and/or substantial comorbidity. (See "Prostate cancer in elderly patients" and "Radical prostatectomy for localized prostate cancer", section on 'Survival impact of radical prostatectomy'.)

There are no results from randomized clinical trials that have compared immediate definitive treatment (radical prostatectomy or RT) with active surveillance (ie, deferred definitive therapy). (See "Active surveillance for men with early prostate cancer", section on 'Randomized trials'.)

Because of the potential for side effects associated with aggressive treatment of indolent disease, active surveillance is an option for patients with very low-risk prostate cancer and an estimated life expectancy less than 20 years [1]. Immediate definitive treatment with radiation therapy or radical prostatectomy is an alternative for patients desiring a more aggressive approach. Active surveillance may also be an option for patients with low-risk disease and a life expectancy of less than ten years.

Although active surveillance avoids side effects in the short term, it does induce significant concerns and anxiety. Many men who initially choose active surveillance decide on definitive treatment within one to two years despite the absence of progression.

The key issues for patients who may be candidates for active surveillance include:

- Appropriate patient selection
- Frequency and type of monitoring required during surveillance and the ability and desire to comply with a surveillance schedule
- Criteria for initiating definitive therapy

These issues are discussed elsewhere. (See "Active surveillance for men with early prostate cancer".)

**Radiation therapy** — The goal of RT for men with localized prostate cancer is to deliver a therapeutic dose of radiation to the tumor while minimizing radiation to normal tissues. Both external beam RT and brachytherapy are widely used as a single modality for clinically localized low-risk prostate cancer. When used as the primary treatment modality, results with RT are similar to those with radical prostatectomy. (See "External beam radiation therapy for localized
The definition of biochemical failure after RT is complex since some normal prostatic glandular tissue remains and serum PSA levels are unlikely to fall to undetectable levels following a course of RT. The Phoenix criteria define biochemical failure after either external beam RT or brachytherapy as a PSA rise of 2 ng/mL or more above the nadir PSA after treatment. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'After radiation therapy'.)

**External beam RT** — External beam RT utilizes an external source of radiation to treat the prostate gland and a margin of adjacent normal tissue. External beam RT is generally used alone (ie, without androgen deprivation therapy or brachytherapy boost) for low-risk clinically localized prostate cancer. (See "External beam radiation therapy for localized prostate cancer".)

**Technique** — Three-dimensional conformal RT (3D-CRT) techniques are considered standard and have replaced older two dimensional approaches for the definitive treatment of localized prostate cancer. (See "External beam radiation therapy for localized prostate cancer", section on 'External beam RT techniques'.)

Multiple technical refinements of 3D-CRT may facilitate the administration of higher doses of radiation to the tumor and decrease toxicity to normal tissues:

- **Intensity-modulated RT (IMRT)** is an advanced form of 3D-CRT that has replaced older 3D-CRT techniques in many areas [3]. IMRT utilizes a beam with varying intensity, in contrast to older forms of 3D-CRT techniques in which the dose rate is constant. Thus, IMRT can target a complex and irregular tumor volume more effectively. (See "Radiation therapy techniques in cancer treatment", section on 'Intensity-modulated radiation therapy'.)
- **Image-guided RT** — Image-guided RT (IGRT) uses two- or three-dimensional imaging prior to each treatment to precisely locate the tumor and surrounding organs. IGRT thus further minimizes the margin of normal tissue that would otherwise need to be irradiated to allow for changing anatomic relationships.
- **Proton-beam RT** — Proton-beam RT uses charged particles (protons) to deliver high doses of RT to the target volume while limiting the "scatter" dose received by surrounding tissues. Although proton beam therapy is being more widely used in men with prostate cancer as new treatment facilities become available, there is currently no evidence that this approach offers any advantages over IMRT or IGRT. (See "External beam radiation therapy for localized prostate cancer", section on 'Particle irradiation'.)

**Complications** — The morbidity of external beam RT is low with contemporary 3D-CRT techniques. The main complications are briefly reviewed here and discussed in detail elsewhere. (See "External beam radiation therapy for localized prostate cancer", section on 'Complications'.)

- **Gastrointestinal** — Acute radiation proctitis of moderate or greater severity is reported in approximately 20 percent of men, depending upon its definition, the radiation dose, and treatment volume [4]. This estimate is supported by an analysis from the Surveillance, Epidemiology, and End Results (SEER) database that found that approximately 17 percent of patients required a procedure such as colonoscopy following EBRT for prostate cancer [3]. If the pelvic lymph nodes are included in the treatment volume, radiation enteritis may also be observed. (See "External beam radiation therapy for localized..."
Symptoms can include abdominal cramping, tenesmus, urgency, and frequent defecation. They can usually be controlled with antidiarrheal agents or topical antiinflammatory preparations. After RT is completed, acute symptoms usually subside within three to eight weeks.

Long-term intestinal side effects persist in a low percentage of patients, manifested by persistent diarrhea, tenesmus, rectal urgency, or hematochezia. Rectal or anal strictures, ulcers, and perforation are rare. (See "Clinical manifestations, diagnosis, and treatment of radiation proctitis" and "Gastrointestinal toxicity of radiation therapy").

● Urinary – Approximately one-half of patients experience urinary frequency, dysuria, or urgency due to cystitis, urethritis, or both during external beam RT. Symptoms typically resolve within several weeks after the completion of therapy. Late side effects are uncommon. (See "External beam radiation therapy for localized prostate cancer", section on 'Urinary symptoms' and "Cystitis in patients with cancer", section on 'Radiation cystitis'.)

● Erectile dysfunction – The frequency of erectile dysfunction increases over time. By two years after external beam RT, 60 to 70 percent of men report moderate or more severe difficulties with sexual functioning [4]. Other factors that can contribute to erectile dysfunction in this population include older age, intercurrent diseases (hypertension, cardiovascular disease, diabetes), and the use of neoadjuvant ADT. (See "External beam radiation therapy for localized prostate cancer", section on 'Sexual dysfunction'.)

**Brachytherapy** — Brachytherapy directly implants a radioactive source within the prostate to treat the cancer, thus providing the highest dose of radiation over a very limited distance. Brachytherapy maximizes irradiation of the tumor while minimizing radiation to normal structures. Brachytherapy requires only a one or a limited number of treatments, rather than the daily therapy required by external beam RT. (See "Brachytherapy for localized prostate cancer".)

The radiation source is inserted into the prostate using a transperineal approach under transrectal ultrasound guidance.

- Low dose rate brachytherapy is delivered with permanently implanted radioactive seeds, typically using either iodine-125 or palladium-103.
- High dose rate brachytherapy uses a temporary radiation source such as iridium-192, which is inserted into the prostate through hollow catheters or needles that have been appropriately positioned and later removed. This form of brachytherapy typically requires a 48 hour hospitalization, in contrast to low dose rate brachytherapy, which can be completed in a single 90 minute outpatient procedure.

**Patient selection** — The appropriateness of brachytherapy for individual patients is based upon technical feasibility, the absence of coexistent urinary conditions, and the ability to adequately irradiate all disease. Brachytherapy alone is an appropriate option for men with low or intermediate-risk disease [5,6] (table 1A and table 1B). (See "Brachytherapy for localized prostate cancer", section on 'Patient selection'.)

A large prostate gland (>60 g) is associated with a higher rate of treatment-related complications, including acute urinary retention, and is a relative contraindication to
A course of ADT prior to brachytherapy is sometimes used prior to brachytherapy to reduce the volume of the prostate gland, although there is no evidence to demonstrate that this approach adds value and has the down side of exposing patients to the acute side effects of ADT. (See "Brachytherapy for localized prostate cancer", section on 'Patient selection'.)

Complications — The main complications following brachytherapy are genitourinary and gastrointestinal. (See "Brachytherapy for localized prostate cancer", section on 'Complications'.)

- Urinary symptoms – Transient urinary frequency, urgency, and dysuria occur in the majority of patients, generally developing several days after implantation. Acute prostatic swelling causing urinary retention and requiring catheterization is uncommon. Late complications can include incontinence, urethral strictures, and urinary retention.
- Erectile dysfunction – The reported incidence of erectile dysfunction varies widely among men who were potent prior to brachytherapy (table 3). The patient-reported frequency of erectile dysfunction is time dependent and similar to that for RT and radical prostatectomy [4]. (See "Brachytherapy for localized prostate cancer", section on 'Sexual dysfunction'.)
- GI symptoms – Gastrointestinal toxicity is less common than genitourinary toxicity following brachytherapy. Late gastrointestinal complications of brachytherapy are seen in less than 10 percent of patients and include rectal urgency, bleeding or ulceration, bowel frequency, and prostatorectal fistulas [4].

Radical prostatectomy — Radical prostatectomy is an established option to treat localized prostate cancer, based upon high rates of long-term cancer control, acceptable perioperative morbidity and mortality, and side effects profile.

The most widely used surgical techniques are the open retropubic radical prostatectomy and a minimally invasive radical prostatectomy. (See "Radical prostatectomy for localized prostate cancer".)

All prostate tissue is removed during a successful radical prostatectomy. Postoperatively, detectable serum PSA using standard immunoassays is indicative of residual prostatic tissue, which presumably represents residual tumor tissue. The most widely accepted criterion for defining biochemical failure after radical prostatectomy is that of the American Urological Association (AUA), which defines a biochemical recurrence as a serum PSA ≥0.2ng/mL that is confirmed by a second determination with a PSA ≥0.2 ng/mL [7]. Biochemical recurrence has a variable natural history, and not all men with a detectible PSA after RP require therapy. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'After radical prostatectomy'.)

Pathologic T3, margin positive disease, and microscopic lymph node involvement — Clinical staging based upon the digital rectal examination and potentially supplemented by imaging may fail to detect extracapsular extension, seminal vesicle involvement, or lymph node involvement. The management of patients with more extensive disease or positive surgical margins based upon pathologic staging is discussed separately. (See "Prostate cancer: Pathologic stage T3 disease or positive surgical margins following radical prostatectomy".)

Complications — The complications of most concern to men who undergo prostatectomy are urinary incontinence and impotence, which are due to damage to the urinary sphincter and penile nerves. The frequency of incontinence and erectile dysfunction depend in part upon the experience and expertise of the surgeon, and not whether the technique is performed by the
open or minimally invasive approach. (See "Radical prostatectomy for localized prostate cancer", section on 'Complications and quality of life'.)

**Urinary incontinence** — The incidence of urinary incontinence following radical prostatectomy depends upon the definition of incontinence, the time elapsed since surgery, whether or not a nerve-sparing approach was used, and the source of the data (patient or physician reported). Based upon patient queries, some symptoms may be present in up to 25 percent or more of patients at one year and later, and 5 to 10 percent consider this to be a moderate or more severe problem [4]. (See "Radical prostatectomy for localized prostate cancer", section on 'Urinary incontinence'.)

Urinary incontinence is most common immediately after surgery, and there is a gradual return of function thereafter. Conservative measures (eg, pelvic floor muscle training and biofeedback) are often used in the months following radical prostatectomy in an effort to control symptoms while sphincter function is returning. For men with significant persistent incontinence, options include a urethral sling procedure or artificial urinary sphincter.

**Erectile dysfunction** — The frequency of erectile dysfunction following retropubic radical prostatectomy depends upon the patient's age, preoperative level of sexual functioning, and whether or not nerve-sparing surgery was performed (table 4). Erectile dysfunction is nearly universal if the erectile nerves are not preserved at surgery. (See "Radical prostatectomy for localized prostate cancer", section on 'Impotence'.)

The return of potency following a nerve-sparing procedure is gradual, and men may benefit from regular use of a phosphodiesterase-5 (PDE5) inhibitor. Although potency rates as high as 80 percent have been reported from individual centers performing nerve-sparing surgery on carefully selected men, the potency rates in broader populations are substantially lower. Furthermore, patient estimates of the frequency of erectile dysfunction are generally higher than physician-reported data.

Erectile dysfunction can be treated with PDE-5 inhibitors, penile injection therapy, vacuum erection devices (VED), and implantation of a penile prosthesis. (See "Treatment of male sexual dysfunction" and "Surgical treatment of erectile dysfunction".)

**Other approaches**

**Ablation therapy** — Cryotherapy and high-intensity focused ultrasound (HIFU) have been used to selectively destroy tissue, either by freezing or by generating local thermal energy. These ablation techniques can be applied either to the entire prostate gland or to focally destroy the part of the prostate gland thought to be involved by tumor. (See "Cryotherapy and other ablative techniques for the initial treatment of prostate cancer".)

The role of ablation with cryotherapy or HIFU as an alternative to radical prostatectomy or RT remains uncertain. Potential advantages in men with localized disease include the ability to destroy cancer cells using a relatively noninvasive procedure. As such, these procedures are associated with minimal blood loss and pain. There is also a more rapid posttreatment convalescence.

Whether the long-term outcomes are equivalent to those with definitive surgery or RT is uncertain however. Additional experience and longer follow-up are required to compare the rate of disease control and side effects profiles with other treatment modalities. HIFU is not available in the US outside of clinical trials.
Androgen deprivation therapy alone — Guidelines from the NCCN and the AUA both recommend that primary androgen deprivation therapy (ADT) alone not be included among standard options for the initial treatment of men with localized prostate cancer [1,6].

Androgen deprivation therapy (ADT) alone has been advocated for patients seeking active therapy but wishing to avoid the side effects of radical prostatectomy or RT. Studies advocating ADT alone for localized prostate cancer are retrospective, include limited patient numbers, have a short follow-up duration, and lack critical assessment of the side effects associated with ADT [8].

Large database studies have found an increase in all cause mortality when primary ADT is used to treat prostate cancer:

- A study from the Surveillance, Epidemiology, and End Results (SEER) database included over 46,000 men diagnosed with localized prostate cancer between 1992 and 2009 and not treated with either RT or radical prostatectomy [9]. In this cohort, 39 percent were managed with primary ADT and 61 percent with observation. Treatment with ADT was associated with a significant increase in all cause mortality compared with those not given ADT (hazard ratio [HR] 1.37, 95% CI 1.20-1.56).
- A similar conclusion was drawn from a cohort from the National Center for Prostate Disease Research database, which included 2313 men with biopsy-confirmed, clinically localized (T1-T2) prostate cancer, of whom 569 chose ADT and 1744 chose expectant management [10]. In a preliminary report, treatment with ADT was a significant predictor of all-cause death after controlling for follow-up time, year of diagnosis, age, race, PSA level, tumor characteristics, comorbidity, and secondary treatment.

Antiandrogen monotherapy — Primary antiandrogen monotherapy is not recommended for localized prostate cancer. Antiandrogen monotherapy was most extensively evaluated in the Early Prostate Cancer program in which 8113 men with localized (T1, T2) or locally advanced (T3, T4) nonmetastatic prostate cancer were randomly assigned to bicalutamide or placebo in addition to standard care (watchful waiting, RP, or RT) [11]. At a median follow-up of 10 years, the improvement in progression-free survival in men with localized (T1, T2) disease was not statistically significant regardless of the initial management approach. In addition, there was no statistically significant difference in overall survival. In men with locally advanced (T3, T4) disease, PFS was improved but there was no statistically significant difference in overall survival.

PROGNOSIS — There are no randomized clinical trials that provide adequate data comparing active surveillance, radiation therapy, brachytherapy, and radical prostatectomy for men with clinically localized, low-risk prostate cancer [12]. Thus comparisons between different treatment modalities rely upon interpretation of large, observational databases.

Proper interpretation of observational series requires that studies have adequate follow-up, stratify patients based upon pretreatment criteria, utilize standard definitions for treatment success or failure, and contain adequate numbers of patients. The Prostate Cancer Results Study Group reviewed all studies published between 2000 and 2010 for published reports meeting those criteria [12]. That analysis suggested that brachytherapy was associated with better biochemical progression-free survival at five years, although it is unclear whether this may simply reflect differences in patient selection.

Radical prostatectomy, external beam radiation therapy (RT), and brachytherapy all provide biochemical relapse free survival of 80 percent or more in studies with follow-up of 5 to 10
years. Furthermore, more than 95 percent of patients remain free of local recurrence and distant metastases. Representative large observational studies illustrate the results in men with limited risk prostate cancer.

**Radical prostatectomy** — The results using radical retropubic prostatectomy to treat prostate cancer are illustrated by a retrospective series of 3283 men with low-risk prostate cancer who were treated at the Mayo Clinic between 1987 and 2003 [13]. Approximately two-thirds of these cases had clinical stage T1c disease and the remainder had T2a primary tumors; the mean pretreatment PSA was 5.4 ng/mL. Median follow-up was 7.7 years.

At five years, 90 percent of men were free from biochemical relapse, and at 10 years 82 percent remained progression free. Even among those who experienced a biochemical relapse, the prognosis for these low-risk patients was highly favorable. The overall rates of freedom from local recurrence at 5 and 10 years were 98 and 97 percent, respectively, and the freedom from systemic progression at 5 and 10 years was 99.6 and 99 percent, respectively.

Additional data on the efficacy of radical prostatectomy come from a multi-institutional series of over 23,000 men who underwent radical prostatectomy for prostate cancer [14]. In an analysis based upon surgical staging, the prostate cancer specific mortality for those with Gleason 6 or less lesions was approximately 1 percent at 15 years; similarly for those with pathologic T2N0 lesions, prostate cancer specific mortality was 0.8 to 1.5 percent at 15 years. Similar results have been reported in a large single institution experience with 4478 men treated over a 30 year period [15].

The prognosis for patients found to have tumor involvement of one or more regional lymph nodes is less favorable, with a biochemical recurrence rate at 15 years of 52 percent and a clinical recurrence rate of 33 percent [16]. (See "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer", section on 'Prognosis'.)

**External beam RT** — The outcomes with external beam RT as a single modality are illustrated by a single institution series of 2047 men treated between 1998 and 2004 [17]. The series included 446 patients with low-risk disease. RT was administered either by 3D-CRT or IMRT, with doses ranging from 66 to 86 Gy.

The seven-year PSA relapse-free survival rate for low-risk disease patients was 90 percent. Both the distant metastasis-free and the cause-specific survival rates at seven years for the men with low-risk disease were 99 percent. There was no statistically significant difference in outcome as a function of radiation dose.

**Brachytherapy** — The results with low dose rate brachytherapy using permanent seed implantation are illustrated by a multi-institution series of 2693 treated between 1988 and 1998 [18]. Median follow-up was five years. Within this series, 1444 had low-risk disease. Two-thirds of patients were treated with iodine-125 and the remainder with palladium-103.

The eight-year PSA relapse-free survival rate was 82 percent according to the American Society for Radiation Oncology (ASTRO) definition (three successive increases in the PSA after nadir reached) and 74 percent according to the Phoenix (nadir +2 ng/mL) definition. The eight-year distant metastasis free survival for the low-risk patients was 98 percent. Multivariate analysis confirmed the importance of an adequate dose of radiation.

**CHOICE OF THERAPY** — For men with low-risk clinically localized prostate cancer, brachytherapy, external beam radiation therapy (RT), and radical prostatectomy all provide an extremely high degree of freedom from local or distant recurrence with prolonged follow-up. For
carefully selected patients with low or very low-risk of recurrence, active surveillance with
delayed definitive treatment if necessary is also an appropriate option. (See ‘Active
surveillance’ above.)

The choice of therapeutic approach depends upon an informed patient decision incorporating
knowledge about the potential advantages and disadvantages associated with each approach
along with personal preferences. Important advantages, disadvantages, and contraindications
associated are summarized in the appended tables (table 5 and table 6 and table 7).

Large, non-randomized studies have shown differences in overall survival favoring radical
prostatectomy over RT or brachytherapy, but have not demonstrated statistically significant
differences in prostate cancer mortality [19,20]. Furthermore, these findings may reflect a
selection bias with younger, healthier patients choosing radical prostatectomy [21].

There are no data from large randomized clinical trials that compare the different treatment
approaches in men with low-risk prostate cancer. A large, German phase III trial
(PREFERE, NCT01717677) has been initiated to compare prostate cancer specific survival
after radical prostatectomy, external beam RT, brachytherapy, and active surveillance in
patients with low- or intermediate-risk prostate cancer [22].

Early differences in effects on quality of life are illustrated by a multi-institutional, observational
study of 1201 men treated for clinical T1/T2 prostate cancer from 2003 to 2006 [4]. Active
treatment for these men included radical prostatectomy (n = 601), external beam RT (n = 292),
or brachytherapy (n = 306). Key observations from this study included the following:

● Urinary symptoms – Symptoms of urinary irritation or obstruction (dysuria, weak stream,
  frequency) were seen after RT and were more common after brachytherapy than external
  beam RT. The incidence of these symptoms peaked at two months and was less common
  by two years after treatment. In contrast, incontinence was frequent after radical
  prostatectomy, with approximately two-thirds of patients requiring at least some pad use
  after two months. By two years, symptoms had resolved in most patients, although 20
  percent still required some use of pads. Incontinence was much less common in patients
  treated with external beam RT or brachytherapy.

● Bowel function – Bowel symptoms, primarily urgency and frequency, were reported by 10
to 20 percent of patients treated with either external beam RT or brachytherapy. Although
the incidence was highest at two months after treatment, symptoms persisted at two years
in 7 to 16 percent of cases. Bowel symptoms were rare after radical prostatectomy.

● Sexual function – In patients managed with radical prostatectomy, some sexual
dysfunction was present in approximately 90 percent of patients after two months and was
a moderate or major problem in 60 percent. Some problems persisted in 60 percent after
two years and was a moderate or big problem in 43 percent. For patients treated with RT
(either external beam RT or brachytherapy), approximately 60 percent had some sexual
dysfunction at two months, which persisted at two years.

Similar differences were seen in an observational study of 1655 men treated with either radical
prostatectomy or RT between 1994 and 1995, in which functional status was assessed at
baseline, 2, 5, and 15 years [23]. Urinary symptoms and erectile dysfunction were significantly
more frequent following radical prostatectomy, while bowel symptoms were more frequent
following RT. However, there was a progressive decline in function in all three domains over
time for both groups, and the differences were not statistically significant at 15 years.
POST-TREATMENT SURVEILLANCE — Follow-up surveillance after initial definitive treatment is an important component of patient management. Although most patients with low-risk clinically localized prostate cancer will remain disease-free, a minority will relapse with local and/or distant disease.

With the availability of sensitive testing for serum PSA, this may result in detection of recurrence at a time when successful salvage therapy is feasible.

Follow-up after definitive treatment is discussed separately. (See "Follow-up surveillance during and after treatment for 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.)

- Basics topics (see "Patient information: Prostate cancer (The Basics)" and "Patient information: Choosing treatment for low-risk localized prostate cancer (The Basics)"
- Beyond the Basics topics (see "Patient information: Prostate cancer treatment; stage I to III cancer (Beyond the Basics)" and "Patient information: Treatment for advanced prostate cancer (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

- The clinical assessment of the anatomic extent of disease, serum prostate specific antigen (PSA), and biopsy Gleason score are used for risk stratification which then guides the initial choice of therapy in conjunction with patient age, comorbidity, and personal preferences (table 1A and table 1B). (See "Prostate cancer: Risk stratification and choice of initial treatment".)
- For men with clinically localized, very low-risk prostate cancer and a life expectancy of less than 20 years, we suggest active surveillance rather than immediate definitive therapy (Grade 2C). However, this approach is associated with a need for close follow-up and can create significant anxiety, causing many patients to subsequently choose definitive intervention even in the absence of progressive disease. Radiation therapy and radical prostatectomy are acceptable alternatives for patients preferring immediate definitive therapy. (See ‘Active surveillance’ above.)
- For men with low-risk prostate cancer and a life expectancy of greater than 10 years, definitive therapy (radical prostatectomy, brachytherapy, or external beam radiation therapy (RT)), or active surveillance may all be appropriate options. The choice of a specific approach requires a consideration of the benefits and risks associated with each approach, taking into account the patient’s individual preferences and comorbidities. (See‘Radiation therapy’ above and ‘Radical prostatectomy’ above and ‘Active surveillance’ above.)
• For patients with a more limited life expectancy (less than 10 years) we suggest active surveillance (Grade 2C). (See ‘Active surveillance’ above.)

● Although disease control with radical prostatectomy and radiation therapy are similar, there are important differences in the patterns of toxicity associated with these treatments. The advantages, disadvantages, and contraindications with each treatment modality are summarized in the attached tables (table 5 and table 6 and table 7) (See ‘Choice of therapy’ above.)

• Irritative and obstructive urinary symptoms are more common after RT, particularly brachytherapy. Incontinence is more frequent after radical prostatectomy, but generally improves gradually after surgery.

• Bowel symptoms (urgency, frequency) are more common after external beam RT and brachytherapy than with radical prostatectomy.

• Erectile dysfunction is most frequent immediately after radical prostatectomy. Bilateral nerve-sparing surgery diminishes but does not eliminate this risk. Erectile dysfunction is also common after both external beam RT and brachytherapy, and the incidence rises gradually following treatment. At 24 months, sexual symptom scores are similar among men treated with RP, RT, and brachytherapy.

● Follow-up surveillance after initial definitive treatment is an important component of patient management since salvage may be feasible if recurrence is detected early. (See “Follow-up surveillance during and after treatment for prostate cancer”.)

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Initial therapy for castration sensitive metastatic prostate cancer

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Disclosures: Richard J Lee, MD, PhD Nothing to disclose. Matthew R Smith, MD, PhD Nothing to disclose. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelexis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer(investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigational agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers' Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dexereon; GSK, Veridex/Janssen [Renal cancer (enzalutamide, abiraterone, arixitnib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)], Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelexis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)], [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent)]; BIND [Prostate cancer (experimental agent)]; Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEdConsultant/Advisory Boards: Medivation [Prostate cancer (enzalutamide)]; Ferring Pharmaceuticals [Prostate cancer(Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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INTRODUCTION — The critical role of androgens in stimulating prostate cancer growth was established in 1941 by Charles Huggins [1,2]. These findings led to the development of androgen deprivation therapy (ADT) as the treatment for patients with advanced prostate cancer.

Although androgen deprivation therapy (ADT) is palliative, it can normalize serum levels of prostate specific antigen (PSA) in over 90 percent of patients and can produce objective tumor responses in 80 to 90 percent. This antitumor activity can improve quality of life (QOL) by reducing bone pain as well as the rates of complications (eg, pathologic fracture, spinal cord compression, ureteral obstruction).

The duration of response to ADT for patients with metastatic disease is highly variable, and most prostate cancer patients eventually experience disease progression despite treatment. Patients who have progressed while on ADT are said to have castration resistant disease, although such tumors may remain responsive to additional therapies directed against androgenic stimulation of the prostate cancer.

Docetaxel was subsequently shown to prolong survival in men with castration resistant prostate cancer. Contemporary research has demonstrated that chemohormonal therapy combining docetaxel with ADT offers a clinically meaningful survival advantage for patients with castration sensitive disease and a high tumor burden. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Chemotherapy-naive patients: Docetaxel' and 'Chemohormonal therapy' below.)
The initial therapy for men with castration sensitive metastatic prostate cancer will be reviewed here. An overview of the treatment of disseminated prostate cancer is presented separately, as are special considerations for patients whose only manifestation of disseminated disease is a rising serum PSA. (See "Overview of the treatment of disseminated prostate cancer" and "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy".)

**ANDROGEN DEPRIVATION THERAPY** — Androgen deprivation therapy (ADT) with lowering of serum testosterone levels to castrate levels remains the primary approach to the systemic treatment of castration sensitive metastatic prostate cancer and a low tumor burden. In addition, ADT is an integral component of therapy along with docetaxel chemotherapy for men with a high tumor burden. (See 'Chemohormonal therapy' below.)

ADT can be accomplished either by surgical orchiectomy (castration) or medical orchiectomy (using either a gonadotropin releasing hormone [GnRH] agonist or a GnRH antagonist). In some cases, antiandrogens have been combined with a GnRH agonist to block the effects of androgen produced by the adrenal gland and produce a combined androgen blockade. Both medical orchiectomy and surgical orchiectomy are appropriate methods for lowering serum testosterone levels in men with advanced castration sensitive prostate cancer [3-5]. The decision between medical and surgical treatment is based upon a variety of factors including patient preference, cost, and treatment availability. (See 'Surgical orchiectomy' below and 'Medical orchiectomy' below and 'Combined androgen blockade with antiandrogens' below.)

Historically, estrogens were also used to suppress serum testosterone levels. Estrogens inhibit the release of GnRH from the hypothalamus, thus suppressing pituitary luteinizing hormone release and thereby reducing testicular production of testosterone. Diethylstilbestrol (DES) was extensively studied as an alternative to surgical orchiectomy for the initial management of metastatic prostate cancer prior to the development of GnRH agonists. However, two large randomized trials conducted by the Veterans Administration Cooperative Urological Research Group (VACURG) found that DES at a dose of 5 mg/day significantly increased the risk of dying from heart disease or stroke, and that DES did not provide any advantage compared with surgical orchiectomy in terms of overall survival [6,7].

Guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) recommend ADT using either medical orchiectomy or surgical orchiectomy as the initial hormonal therapy for men with advanced prostate cancer [3-5]. The decision between medical and surgical treatment is based upon a variety of factors including patient preference, cost, and treatment availability.

**Surgical orchiectomy** — Bilateral orchiectomy is a relatively simple, cost-effective procedure [8]. Following surgery, serum testosterone levels rapidly decrease to castrate levels [9], and this is usually associated with improvements in bone pain and other disease-related symptoms [2].

Although orchiectomy is used much less frequently than medical castration in North America and Europe, it remains a useful alternative when an immediate decrease in testosterone is necessary (eg, impending spinal cord compression) or when costs or adherence to medical therapy are an issue. In many countries, bilateral orchiectomy remains the standard of care for initial hormone therapy of metastatic prostate cancer.

The psychological impact of surgical castration is also an important factor for men choosing between surgery and medical treatment. In a study of 159 men with metastatic prostate cancer
who were provided with standard information regarding the costs, benefits, and risks of orchiectomy, only 22 percent chose orchiectomy \[10\]. However, the benefits of lower overall cost, avoidance of injections for continued medical castration, and potentially fewer clinic visits may make orchiectomy more appealing in the current era of escalating health care costs.

The psychological effects of orchiectomy may be ameliorated with placement of testicular prostheses or with modification of the total orchiectomy to a subcapsular orchiectomy, in which the tunica albuginea and epididymis remain intact, providing a cosmetic effect in the scrotum \[11,12\].

**Efficacy of initial ADT** — The efficacy of ADT as the initial therapy in the contemporary era where patient management includes established secondary agents (such as docetaxel) is illustrated by the control arm of the STAMPEDE trial \[13\]. In that ongoing trial that began in 2005, over 8000 men are being randomly assigned to ADT (medical or surgical orchiectomy) or one of a number of experimental arms as their initial systemic therapy. An analysis included data from 917 men with metastatic disease managed with ADT alone with a median follow-up of 20 months. The median failure-free survival duration following ADT was 20 months, while the median overall survival was 42 months.

**Medical orchiectomy**

**Gonadotropin releasing hormone agonists** — Medical castration using a gonadotropin releasing hormone (GnRH) agonist was first reported in 1982 \[14\].

**Mechanism of action** — Synthetic GnRH analogs have greater receptor affinity, reduced susceptibility to enzymatic degradation, and are approximately 100-fold more potent than the natural GnRH molecule \[15\]. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), which causes a subsequent increase in testosterone production from testicular Leydig cells (figure 1).

This transient rise in LH when GnRH therapy is initiated can cause a surge in serum testosterone, which may stimulate prostate cancer growth. This "flare" may cause an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer \[16\]. Thus, initial treatment with GnRH alone is contraindicated in men with severe urinary tract obstruction or painful bone metastases. The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone \[8\]. (See 'Combined androgen blockade with antiandrogens' below.)

After about one week of therapy, GnRH receptors are down-regulated on the gonadotropin-producing cells, with a decline in the pituitary production of LH and FSH \[17\]. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within three to four weeks after the start of treatment \[18\]. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors \[19,20\].

**Formulations** — GnRH agonists approved for parenteral administration include leuprolide, goserelin, triptorelin, buserelin, and histrelin. Buserelin is available in both a parenteral and nasal formulation.
Depot formulations are widely used. These initially were available to suppress testosterone levels for about one month; even longer acting formulations are now available and commonly used. The longest lasting is a leuprolide formulation delivered by a small osmotic pump encased in a titanium cylinder. This is implanted subcutaneously in the upper arm where it can deliver the drug for up to one year. Castrate levels of testosterone are achieved and sustained for the entire year of implantation [21,22]. Annual removal and replacement is a short, outpatient procedure.

**Serum testosterone level** — The objective of ADT is to lower the serum testosterone level at least to the same extent as that achieved with surgical orchiectomy [23]. Historically, this has correlated with a level of 1.7 nmol/L (<50 ng/dL), although contemporary laboratory testing indicates that testosterone levels decline to 0.7 nmol/L (<20 ng/dL) after orchiectomy [9].

The potential relationship between suppression of the serum testosterone and clinical outcome is illustrated by a secondary analysis of the JPR.7 trial in which 626 evaluable men were treated with continuous ADT for a rising PSA and followed for a median of eight years [24,25]. The risk of dying was lowest in those with the greatest suppression of serum testosterone in the first year. Compared with a first year minimum testosterone nadir <0.7 nmol/L, those with a nadir testosterone of 0.7 to 1.7 nmol/L had an increased risk of dying (hazard ratio [HR] 2.08, 95% CI 1.28-3.38), as did those a nadir >1.7 nmol/L (HR 2.93, 95% CI 0.77-4.70). However, it is unclear whether further hormonal manipulation to achieve a deeper suppression of serum testosterone would result in improved outcomes [26].

Our practice is consistent with the current guidelines from the National Comprehensive Cancer Network (NCCN), which use a serum testosterone level of 1.7 nmol/L (<50 ng/dL). Additional hormonal maneuvers can be considered if this level of suppression of serum testosterone cannot be achieved with initial treatment [27]. Rechecking the serum testosterone level is especially important if the anticipated clinical or biochemical response to treatment has not been achieved.

**GnRH agonists versus orchiectomy** — Unlike orchiectomy, medical castration with GnRH agonists offers the potential for reversing hypogonadal symptoms upon cessation of therapy. In addition, GnRH agonists avoid the psychological issues associated with surgical castration.

A meta-analysis of 10 trials involving 1908 patients comparing a GnRH agonist with orchiectomy found equivalence in overall survival, progression-related outcomes, and time to treatment failure [28]. At two years, survival with a GnRH agonist was not statistically worse (HR for death 1.13, 95% CI 0.92-1.39, compared with orchiectomy). In this meta-analysis, there were no significant differences in efficacy between leuprolide, goserelin, and buserelin.

GnRH agonists are frequently used with antiandrogens to produce combined androgen blockade either during the initial period of treatment to prevent a disease flare; they also may be used in conjunction with antiandrogens for long-term therapy. (See 'Combined androgen blockade with antiandrogens' below.)

**GnRH antagonists** — Pure GnRH antagonists (eg, degarelix) were developed to suppress testosterone while avoiding the flare phenomenon observed with GnRH agonists. GnRH antagonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, but do not stimulate an initial release of LH or FSH.

The efficacy of degarelix was established in a phase III trial in which 610 men with prostate cancer were randomly assigned to degarelix (240 mg for one month, followed by monthly
maintenance with doses of either 80 mg [n = 207] or 160 mg [n = 201]) or to leuprolide (7.5 mg per month) [29]:

- **Degarelix** suppressed testosterone levels within three days in 96 percent of patients, an outcome not achieved in patients treated with leuprolide. Suppression of serum testosterone levels was maintained for the duration of the 12-month trial.
- An update from the 2011 Genitourinary Cancers Symposium indicated that the incidence of PSA failure during the study on the degarelix 240/80 schedule was significantly lower than on the leuprolide arm (8.9 versus 14.1 percent, p = 0.05) [30]. However, the incidence of PSA failure during the study on the degarelix 240/160 schedule was 14.2 percent.
- Secondary analyses from the phase III trial reported a greater suppression of serum alkaline phosphatase with degarelix compared with leuprolide. However, the mean baseline serum alkaline phosphatase was lower in the leuprolide arm in all three of the subgroups that were examined, with small numbers of patients per subgroup. Furthermore, whether greater control of serum alkaline phosphatase translates into better control of skeletal metastasis is not known [31,32].
- Local injection site reactions were more frequent with degarelix than with leuprolide (40 versus <1 percent), although no systemic allergic reactions were reported. A secondary analysis of cardiovascular complications in the phase III trial found a similar cardiovascular safety profile for both agents [33].
- In a follow-up study, patients initially assigned to degarelix were continued on maintenance therapy for up to five years, and those originally assigned to leuprolide were given the opportunity to cross over to degarelix [34]. Treatment with degarelix was well tolerated during this maintenance phase and testosterone suppression was sustained throughout this period.

An individual patient meta-analysis of randomized trials compared degarelix with either leuprolide or goserelin in 1925 men in five trials [35]. Progression-free survival was longer in those treated with degarelix (18 versus 25 percent with progression, p = 0.04). However, treatment in these trials was limited to either 3 or 12 months, and there were only four deaths due to prostate cancer. Additional clinical trials are in progress to determine the long-term clinical outcomes and optimal application of degarelix in men with metastatic prostate cancer.

The need for monthly degarelix injections and long-term experience with GnRH agonists makes the latter the preferred approach in many practices.

**Combined androgen blockade with antiandrogens** — First generation antiandrogens (eg, flutamide, bicalutamide, nilutamide) bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. Antiandrogens alone do not block the hypothalamic pituitary axis; testosterone levels are normal or increased. Available antiandrogens and their use as second line endocrine therapies are discussed separately. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogens'.)

Antiandrogens are not indicated for monotherapy in previously untreated patients with advanced prostate cancer. However, antiandrogens have a role in conjunction with either medical or surgical castration to produce a combined androgen blockade, which may be useful either to block the side effects associated with the flare phenomenon at the initiation of ADT or for long-term treatment to increase the efficacy of ADT.

**Initiation of ADT** — We use antiandrogens in the management of men with disseminated prostate cancer during the initiation of treatment with a GnRH agonist, in order to prevent a
disease flare due to the transient increase in testosterone levels [8]. (See 'Mechanism of action' above.)

A placebo-controlled trial demonstrated that antiandrogens decrease bone pain at the initiation of GnRH agonists for patients with metastatic prostate cancer [36]. In practice, antiandrogen therapy is often started seven days prior to GnRH agonist initiation for men at high risk of flare symptoms, or concurrently for asymptomatic patients. Antiandrogen therapy is then continued for two to four weeks.

**Long-term combined androgen blockade** — Long-term administration of antiandrogens has been combined with medical or surgical castration to block the effects of adrenal testosterone in a combined androgen blockade. However, both toxicity and costs are higher and limit the potential benefits of this approach. Our approach is to use monotherapy with a GnRH agonist rather than combined androgen blockade. Both NCCN and ASCO guidelines consider combined androgen blockade an appropriate option but do not make a specific recommendation [3,4].

Numerous randomized trials have compared combined androgen blockade with monotherapy; these are illustrated by two of the largest of these trials:

- Intergroup trial INT 0036 randomly assigned 603 men with metastatic disease to leuprolide plus flutamide or leuprolide alone [37]. Men treated with the combination had significantly longer progression-free and median survival compared with leuprolide alone (16.5 versus 13.9 months and 35.6 versus 28.3 months).
- Intergroup trial INT 0105 randomly assigned 1387 men with metastatic disease to orchiectomy and either flutamide or placebo [38]. Although more patients treated with the combined approach achieved a serum PSA <4ng/mL (74 versus 62 percent with placebo), the differences in median and progression-free survival were not statistically significant (34 versus 30 months, and 20 versus 19 months, respectively). Withdrawal from the study due to toxicity was significantly more common in those assigned to flutamide (33 versus 10 patients with placebo).

The reasons for the differences in outcome between these two trials are not certain. In INT 0105, ADT utilized orchiectomy [38], while in INT 0036, ADT relied upon daily injections of leuprolide [37]. Lack of adherence to the leuprolide regimen may have led to incomplete androgen deprivation, and therefore a larger benefit when an antiandrogen was added to the treatment in the combined androgen blockade arm [38]. Castrate levels of testosterone were not systematically confirmed in INT 0036.

Several meta-analyses suggest a benefit in five-year survival but not at earlier time points for combined androgen blockade [39-42]. The largest of these, which was conducted by the Prostate Cancer Trialists' Collaborative Group, analyzed individual patient data from 27 randomized trials that included 8275 men (88 percent with metastatic disease) [39]. Combined androgen blockade was associated with a trend toward decreased five-year mortality (70.4 versus 72.4 percent, hazard ratio [HR] 0.96; 95% CI 0.91-1.01). When the seven studies using the steroidal antiandrogen cyproterone acetate were excluded, the reduction in mortality with combined androgen blockade was statistically significant (72.4 versus 75.3 percent; HR 0.92). These data do not resolve the question of whether combined androgen blockade is preferable to medical or surgical orchiectomy alone, since toxicity and costs are higher and potential benefits limited with combined androgen blockade.
There are no data to support the use of more potent androgen receptor antagonists such as **enzalutamide** alone or in combination with a GnRH agonist, but such approaches are under investigation.

**Intermittent androgen deprivation** — Intermittent androgen deprivation (IAD) attempts to minimize the adverse effects of medical castration by withdrawing treatment in patients who have responded to ADT and then reinstituting ADT when there is evidence of recurrent or progressive disease.

The biological rationale is twofold. First, prolonged ADT theoretically may facilitate progression from androgen dependence to androgen independence. In addition, many of the acute and chronic side effects of ADT are due to castrate levels of testosterone. Periods of time when men are off therapy may be associated with decreases in these side effects, thereby improving quality of life.

IAD typically involves treatment for either a fixed interval of time or until a maximal response is achieved based upon serum PSA levels. ADT is then withdrawn, and patients are followed for evidence of recurrence. As testosterone production resumes, the side effects of ADT are mitigated, but the risk of disease progression also increases. The patient is followed with PSA measurements, and ADT is reinitiated based on a predefined threshold level of serum PSA (which varies with different practices, but is often between 10 and 20 ng/mL), or with evidence of new metastatic disease.

**Metastatic disease** — The Intergroup trial INT 0162 (S9346, [NCT00002651](https://clinicaltrials.gov/ct2/show/NCT00002651)) compared the impact of IAD with continuous ADT for its impact on overall survival and quality of life in patients with metastatic, hormone sensitive prostate cancer and a serum PSA ≥5 ng/mL [43]. Patients were treated with a combination of a GnRH analog and antiandrogen for seven months. Patients who achieved a PSA ≤4 ng/mL were then randomly assigned to either continuous ADT or IAD. Patients assigned to IAD remained off therapy until they met a prespecified criterion (serum PSA either ≥20 ng/mL or back to original baseline), at which point ADT was resumed. Patients who responded to resumption of ADT could be managed with additional cycles off therapy.

Of the 3040 patients who were enrolled, 1749 patients were randomized and 1535 patients were available for analysis at a median follow-up of 9.8 years:

- INT 0162 was designed as a noninferiority trial based upon overall survival. Survival with IAD was to be considered noninferior if the 95% confidence interval for the hazard ratio excluded 1.20 (ie, a 20 percent difference roughly equal to one year).
- Overall survival measured from the time of randomization was longer with continuous ADT than with IAD (median 5.8 versus 5.1 years, HR 1.10, 95%CI 0.99-1.23). Based upon these results, IAD could not be considered noninferior compared with continuous ADT. In unplanned subset analyses, results were consistent across all subgroups except for those with extensive metastatic disease, where IAD did meet the criteria for noninferiority.
- Quality of life parameters (erectile function, libido, vitality, physical functioning, mental health) were assessed at baseline, and 3, 9, and 15 months after randomization. There were statistically significant improvements in erectile function and mental health at three months with IAD but not at later time points.

IAD was also compared with continuous ADT in a smaller phase III trial from the South European Uroncological Group [44]. Although this trial demonstrated noninferiority in terms of
Overall survival, only 11 percent of patients had metastatic disease, while the remainder had clinical T3 or T4 disease and were not candidates for definitive therapy.

Based upon the results of the INT 0162 trial, continuous ADT remains the standard of care for patients with metastatic disease.

**Rising PSA** — The North American JPR.7 trial studied 1386 men with a rising serum PSA but without detectable metastases following definitive radiation therapy [24]. This trial met predetermined criteria for noninferiority for IAD compared with continuous ADT in terms of overall survival. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'Continuous versus intermittent androgen deprivation'.)

**Timing of ADT**

**Symptomatic metastases** — For patients with symptomatic metastases, androgen deprivation therapy should be initiated promptly, both to palliate symptoms and to prevent severe complications (eg, pathologic fractures, spinal cord compression) [5].

**Asymptomatic metastases** — Treatment for metastatic prostate cancer is not curative and treatment-related side effects can adversely affect quality of life. Therefore, a major question remains for asymptomatic patients whether to start therapy as soon as metastatic disease is diagnosed or whether to delay treatment until significant symptoms are present.

The optimal timing for therapeutic intervention has been addressed in a number of randomized trials. However, the interpretation of these trials is limited by their heterogeneous patient populations, which often included large numbers of patients with locally advanced disease but without evidence of disseminated metastases. Furthermore, some of the patients in these trials did not receive deferred treatment as originally planned.

A 2007 meta-analysis combined the results from 3065 patients in four randomized trials [3]. In this analysis, early ADT was associated with a statistically significant decrease in prostate cancer-related deaths (relative risk [RR] 0.84; 95% CI 0.77-0.92), although there was no significant benefit in overall survival (RR 0.98; 95% CI 0.95-1.01).

The completed trials did not incorporate prognostic factors that are associated with disease progression, such as PSA doubling time, Gleason score, and PSA response to ADT. Additional studies will be required to determine if there are subsets of patients with asymptomatic metastases in whom therapy initiation can be deferred.

We suggest that early treatment be used to reduce the morbidity from potential complications of untreated disease (eg, ureteral obstruction, pathologic fractures, spinal cord compression, urethral obstruction, extraskeletal metastases).

**Rising serum PSA** — The factors affecting the optimal timing of treatment for men whose only manifestation of disseminated prostate cancer is an elevated serum PSA are discussed separately. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'When to initiate ADT'.)

**Other hormonal approaches** — Other hormonal approaches have been studied as a means to achieve similar anti-tumor efficacy in hormone sensitive patients without the toxicities associated with androgen deprivation therapy (ADT). These approaches either have not proven equivalent to ADT or remain experimental, and ADT remains the standard of care.

**Antiandrogen monotherapy** — A meta-analysis of eight trials that compared antiandrogens alone with medical or surgical castration found a trend toward shorter overall survival with
antiandrogen monotherapy compared with castration that approached, but did not reach, statistical significance (HR 1.22, 95% CI 0.99-1.40) [28]. Antiandrogens, particularly bicalutamide, have been extensively studied. Based upon extensive clinical trials, the use of these agents is generally restricted to combination with GnRH analogs as a component of combined androgen blockade or for secondary endocrine therapy in patients with castration resistant disease. (See Combined androgen blockade with antiandrogens above and "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogens'.)

**Enzalutamide** — Enzalutamide binds to the androgen receptor and blocks the intracellular effects of androgen; randomized trials have established its efficacy in patients with advanced castration resistant disease. (See“Castration resistant prostate cancer: Treatments targeting the androgen pathway”, section on 'Enzalutamide'.)

The activity of enzalutamide as initial therapy was assessed in a phase II study in 67 men with hormone sensitive disease that would normally be treated with ADT [45]. At week 25, 62 patients (93 percent) achieved a ≥80 percent decrease in serum prostate specific antigen (PSA). The most common side effects were gynecomastia, fatigue, nipple pain, and hot flashes (36, 34, 19, and 18 percent, respectively). A determination of the ultimate duration of activity and the efficacy relative to standard ADT will require comparative clinical trials and longer follow-up. The use of enzalutamide in men with hormone sensitive prostate cancer remains experimental.

**CHEMOHORMONAL THERAPY** — Historically, androgen deprivation therapy (ADT) alone has been the standard of care for the initial treatment of men with metastatic castration sensitive disease. However, contemporary results have demonstrated a statistically significant and clinically meaningful overall survival benefit for chemohormonal therapy combining ADT with docetaxel chemotherapy, compared with ADT alone, in men with high volume metastatic castration sensitive prostate cancer. Thus, chemohormonal therapy is the preferred option for this patient subset for men who are candidates for docetaxel chemotherapy.

The most extensive data come from the CHAARTED trial, in which 790 men with previously untreated, castration sensitive metastatic prostate cancer were randomly assigned to ADT plus docetaxel (six cycles of 75 mg/m² given every three weeks) or to ADT alone [46]. Approximately 65 percent of patients had high volume disease, defined by visceral metastases and/or four or more bone metastases (including at least one bone metastasis beyond the pelvis or axial skeleton). The primary endpoint of the trial was overall survival.

Preliminary results were presented at the 2014 ASCO meeting. At a median follow-up of 29 months, overall survival for the entire study population was significantly increased with chemohormonal therapy compared with ADT alone (median 58 versus 44 months, hazard ratio [HR] 0.61, 95% CI 0.47-0.80). In men with high volume disease, overall survival was significantly increased (median 49 versus 32 months, HR 0.60, 95% CI 0.45-0.81). In men with low volume disease, a similar overall survival benefit was observed, but there were too few deaths to be meaningful and additional follow-up will be required (median not reached for either treatment regimen, HR 0.63, 95% CI 0.34-1.17, p = 0.14).

Secondary trial endpoints also showed a benefit from chemohormonal therapy compared with ADT alone. Achieving a serum PSA <0.2 ng/mL was significantly more frequent at both 6 and 12 months with chemohormonal therapy compared with ADT alone (28 versus 14 percent, and 23 versus 12 percent, respectively). The median time to clinical progression was also
significantly longer with chemohormonal therapy (33 versus 20 months, HR 0.49, 95% CI 0.37-0.65).

Additional information will be required to fully interpret the results of this trial, including longer follow-up to assess potential delayed toxicity associated with this approach. Furthermore, the trial was conducted prior to the availability of some of the newer therapeutic approaches, and the relative value of aggressive initial therapy in this context will require ongoing evaluation.

In the smaller GETUG-AFU 15 trial, 385 men with metastatic prostate cancer were randomly assigned to ADT (either a gonadotropin releasing hormone [GnRH] agonist or orchiectomy) plus docetaxel (75 mg/m² every three weeks for up to nine cycles) or to ADT alone [47]. Results were updated at the 2015 American Society of Clinical Oncology (ASCO) Genitourinary Cancer symposium [48]. At a median follow-up of 83 months, there was a statistically significant increase in biochemical progression-free survival with the addition of chemotherapy to ADT (median 22.9 versus 12.9 months, HR 0.7, 95% CI 0.6-0.9). The difference in progression-free survival was noted in both those with low and high volume disease. However, the increase in overall survival with chemohormonal therapy compared with ADT alone was not statistically significant (median 61 versus 47 months, HR 0.9, 95% CI 0.7-1.2).

In the ongoing STAMPEDE trial (NCT00268476), multiple combination regimens, including docetaxel plus ADT, are being compared with ADT alone. No results are currently available.

PREVENTION OF OSTEOPOROSIS — Androgen deprivation therapy (ADT), with either medical or surgical orchiectomy, increases bone turnover, decreases bone mineral density, and increases the risk of clinical bone fractures in men with prostate cancer [49-51]. (See "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures'.)

We recommend dietary calcium intake (food and supplements) of 1000 to 1200 mg daily and supplemental vitamin D 800 to 1000 international units daily for all men receiving ADT. We also recommend weight bearing exercise, decreased alcohol consumption, and smoking cessation [52-55]. Estimates of fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/) with or without bone density measurements may provide guidance in consideration of medical therapies to prevent fracture. (See "Side effects of androgen deprivation therapy", section on 'Lifestyle modification'.)

Baseline and periodic measurement of bone density are also useful in detecting early evidence of osteoporosis [5].

The roles of concurrent therapy with an osteoclast inhibitor (denosumab, bisphosphonates) in men with and without bone metastases are discussed separately. (See "Bone metastases in advanced prostate cancer: Management", section on 'Osteoporosis and bone fractures' and "Side effects of androgen deprivation therapy", section on 'Osteoclast inhibition'.)

SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY — The side effects of androgen deprivation therapy, including prevention and management, are discussed in detail separately. (See "Side effects of androgen deprivation therapy".)

SURVEILLANCE DURING TREATMENT — Surveillance strategies during treatment for disseminated prostate cancer are discussed separately. (See "Follow-up surveillance during and after treatment for prostate cancer", section on 'Metastatic 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 topic (see "Patient information: Treatment for advanced prostate cancer (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

- Androgen deprivation therapy (ADT) (ie, lowering the serum testosterone level to castrate levels) is an integral component of the initial treatment of men with castration sensitive metastatic prostate cancer. (See 'Androgen deprivation therapy' above.)
  - For men with asymptomatic metastatic disease, we suggest early rather than delayed treatment (Grade 2B). Although early treatment may not improve overall survival, this approach is associated with improved progression-free survival. (See 'Asymptomatic metastases' above.)
  - For men with low volume disease (ie, no visceral metastases and less than four bone metastases), we suggest treatment with ADT alone rather than chemohormonal therapy (Grade 2B). (See 'Androgen deprivation therapy' above.)
  - For men with high volume disease (visceral metastases and/or four or more bone metastases), we recommend chemohormonal therapy combining ADT with docetaxel chemotherapy rather than ADT alone (Grade 1B). (See 'Chemohormonal therapy' above.)

- ADT can be accomplished either by surgical orchiectomy (castration) or medical orchiectomy (using either a gonadotropin releasing hormone [GnRH] agonist or a GnRH antagonist). Newer modalities that have been demonstrated to prolong survival in men with metastatic disease have only been evaluated in men who have progressed after ADT (ie, castration resistant disease) and are not indicated in this setting (table 1). (See 'Surgical orchiectomy' above and 'Medical orchiectomy' above and "Overview of the treatment of disseminated prostate cancer".)
  - For patients managed with medical orchiectomy, we suggest using an antiandrogen for two to four weeks during GnRH agonist initiation to prevent a disease flare due to the transient increase in testosterone levels (Grade 2B). Use of the GnRH antagonist degarelix is an alternative. (See 'Initiation of ADT' above and 'GnRH antagonists' above.)
    - After the initial treatment induction, we suggest monotherapy using a GnRH agonist rather than combined androgen blockade with a GnRH agonist plus an antiandrogen (Grade 2B). Long-term combined androgen blockade may have a modest survival benefit compared with GnRH agonist monotherapy, but combined androgen blockade has more side effects and greater cost. (See 'Combined androgen blockade with antiandrogens' above.)
    - We recommend continuous therapy rather than intermittent androgen deprivation (Grade 1B). (See 'Intermittent androgen deprivation' above.)
Because of the increased bone turnover and decreased bone mineral density, dietary calcium intake (food and supplements) of 1000 to 1200 mg daily and supplemental vitamin D 800 to 1000 international units daily, as well as lifestyle modifications (weight bearing exercise, decreased alcohol consumption, smoking discontinuation), are indicated for all men beginning ADT and for those who undergo surgical orchectomy. (See "Side effects of androgen deprivation therapy", section on 'Prevention'.)

For men whose only evidence of disseminated disease is an elevated or rising serum PSA, issues regarding the optimal timing of initiating treatment and the use of continuous versus intermittent ADT are discussed separately. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy").

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REFERENCES


**Interpretation of prostate biopsy**

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**Disclosures:** Ximing J Yang, MD, PhD
Nothing to disclose. Nicholas Vogelzang, MD
Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelixis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer (investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers' Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veridex; Janssen [Renal cancer (enalutamide, abiraterone, axitinib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]. Consultant/Advisory Boards: Amgen; Celgene; Medivation; Novartis; Eisai; Exelixis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; [Prostate cancer immunotherapy (cabo antinib)]; Cerulean [Renal cancer (experimental agent); BIND [Prostate cancer (experimental agent)]; Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEd
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Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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**Literature review current through:** Apr 2015. | **This topic last updated:** Jun 23, 2014.

**INTRODUCTION** — Prostate cancer is the second most common cancer in men worldwide, with an estimated 1,100,000 cases and 307,000 deaths in 2012 [1].

The increasing frequency of prostate cancer over the last decade is due in part to widespread screening with serum prostate specific antigen (PSA) (figure 1). However, the incidence of the disease was increasing even before the introduction of this test (table 1) [2-4]. The reasons for this increase are not known; both genetic and environmental factors have been implicated. (See "Risk factors for prostate cancer").

A histologic diagnosis of prostate cancer is generally required prior to instituting therapy for any stage of disease. Needle core biopsy of the prostate under ultrasound (US) guidance is the most common method of obtaining diagnostic tissue. More than one million prostate needle biopsies are performed in the United States each year, and cancer will be diagnosed in approximately 20 to 30 percent of men undergoing prostate needle biopsies in clinical settings.

Other potential sources of diagnostic tissue include material from transurethral resection of the prostate (TURP), prostatectomy or cystoprostatectomy specimens, or biopsies from metastatic sites (most often lymph nodes and/or bone).

This topic review will discuss biopsy interpretation in prostate cancer. Specific issues related to clinical presentation, diagnosis, staging, and treatment of prostate cancer are discussed separately. (See appropriate topic reviews).
BIOPSY TECHNIQUE — The technique for prostate biopsy and the diagnosis of prostate cancer are discussed separately. (See “Clinical presentation and diagnosis of prostate cancer” and “Prostate biopsy”.)

HISTOLOGIC FEATURES — Adenocarcinoma accounts for more than 95 percent of malignancies of the prostate. Other types of cancers (e.g., transitional cell carcinoma, carcinosarcoma, basal cell carcinoma, lymphomas or stromal sarcoma) do occur within the prostate. Here we will focus on the diagnostic features of prostatic adenocarcinoma; more comprehensive discussions of prostate biopsy interpretation are described elsewhere.

Adenocarcinoma — The diagnosis of prostatic adenocarcinoma, particularly on limited material from needle core biopsy, is based upon a constellation of architectural and cytological features, and no single feature is sensitive and specific enough to establish diagnosis of prostatic adenocarcinoma in all the cases.

Prostatic adenocarcinoma can be diagnosed by the presence of small infiltrating glands with prominent nucleoli. Architecturally, malignant cells form glands that are typically smaller than benign glands (acini or ducts), and the tumor cells tend to grow in an infiltrative and haphazard manner. In less differentiated tumors, the glandular pattern is irregular, less organized, fused or even absent, and the tumor cells tend to grow in cords, nests, or sheets, more often in cribriform patterns.

Cytologically, the cytoplasm of tumor cells is often purple and darker than the pale cytoplasm of the benign epithelium on hematoxylin and eosin (H&E)-stained sections. Tumor cells often display nuclear enlargement, irregularity, and hyperchromasia, and large nucleoli can be seen in the majority of cases. Intraluminal crystalloids, amorphous secretion, or blue-tinged mucin are frequently present in malignant glands, which are uncommonly found in benign glands. The common morphologic features associated with the diagnosis of malignancy as reported in one series of 250 needle biopsies performed at a single institution are listed in the following table.

Immunohistochemistry — Immunohistochemistry (IHC) using PSA has a limited role in pathologic diagnosis of prostate cancer on needle biopsy, because both adenocarcinomas and benign prostatic epithelium are reactive. PSA IHC may be applied in biopsy material to confirm the prostatic origin of epithelial cells, rather than determining whether they are benign or malignant. PSA-positive cells derived from lymph nodes, bone, or from the prostate bed following prostatectomy are more likely to represent malignant cells than are those taken from an intact prostate.

IHC for high molecular weight cytokeratin (34bE12) can be performed in selected cases to identify basal cells, which are present in benign prostatic glands, but absent in prostatic adenocarcinomas. This immunostain should be used with caution because some cancer cells are positive, and some benign prostatic glands display only weak staining.

Another molecule, alpha-methylacyl-CoA racemase (AMACR), also known as P504S, is identified as a molecular marker for prostatic adenocarcinoma by cDNA microarray technology. AMACR is a useful marker for tissue diagnosis of prostate cancer in several studies reported by us and others. We recommend a combination of 34bE12 (negative for prostatic adenocarcinoma) and AMACR (positive for prostatic adenocarcinoma) in selected prostate cases when diagnostic uncertainty is encountered.

More recently, p63, a nuclear protein present in prostatic basal cells and absent in prostatic adenocarcinomas, has also been shown to be a more reliable marker than 34bE12 because its...
prominent nuclear staining [18]. We often used an IHC "cocktail" which includes AMACR, p63, and 34be12 antibodies.

ERG is a nuclear protein encoded by the ERG gene (ETS related gene). The fusion between ERG and TMPRSS has been found in prostatic adenocarcinoma. ERG immunostaining has been used to detect the TMPRSS-ERG fusion protein [19]. ERG nuclear staining is detected in approximately 50 percent of prostatic adenocarcinoma cases in this country. The rate of ERG fusion in prostate cancer is even lower for African Americans or Asians compared to Caucasians [20]. The low sensitivity of ERG immunoreactivity may limit its clinical utility in diagnosis of prostate cancer [21]. However, this fusion gene product is fairly specific for prostate cancer [22]. The clinical value of the ERG fusion in prostate cancer is still under investigation.

**Small cell (neuroendocrine) carcinoma** — Neuroendocrine cells are normally present in a benign prostatic acinus or duct [23]. Small cell (neuroendocrine) carcinoma, a rare primary tumor of the prostate, is an aggressive and fatal disease [24]. Approximately 50 percent of small cell carcinomas of the prostate coexist with typical adenocarcinomas. (See "Extrapulmonary small cell cancer".)

The pathologic diagnosis requires the presence of significant number of small undifferentiated (oat cell) carcinoma cells demonstrating neuroendocrine features that are histologically identical to small cell carcinoma of the lung (picture 8). (See "Pathology of lung malignancies", section on 'Small cell carcinoma'.)

Small cell neuroendocrine tumors must be differentiated from carcinoid, a well differentiated tumor with neuroendocrine differentiation, which can also be found in the prostate either as primary or secondary involvement [25]. The histological diagnosis is not different from that for carcinoid tumors seen in other organs. (See "Clinical characteristics of carcinoid tumors".)

Neuroendocrine differentiation can be confirmed by IHC for neuroendocrine markers such as chromogranin, synaptophysin, or neuron specific enolase. Like small cell cancer involving the lung, small cell carcinoma of the prostate can be positive for thyroid transcription factor-1 (TTF-1); however, the rate of positivity is lower than that of pulmonary small cell carcinoma [26,27].

Because small cell carcinomas of the prostate are typically resistant to hormonal therapy designed for prostatic adenocarcinoma [28], care should be taken to differentiate this entity from adenocarcinoma with focal neuroendocrine differentiation.

**Adenocarcinoma with focal neuroendocrine differentiation** — Focal neuroendocrine differentiation can be observed in several types of prostatic tumors that may have different biologic and biochemical features [29-31]. As an example, focal neuroendocrine differentiation may be seen in 47 to 100 percent of cases of typical prostatic adenocarcinomas [29,30] particularly in high grade tumors. Prostatic adenocarcinoma with neuroendocrine differentiation can be seen in isolated tumor cells as eosinophilic granules.

The contribution of focal neuroendocrine differentiation to clinical behavior is uncertain [32,33]. With currently available information, there is insufficient evidence to support treating these cases differently from typical high grade prostatic adenocarcinoma. We do not routinely perform IHC for neuroendocrine markers to search for focally positive areas of neuroendocrine differentiation in prostate cancer.

**Urothelial (transitional cell) carcinoma** — Urothelial carcinoma involving the prostate is relatively common. Most of these tumors are due to direct extension into prostatic urethra or prostatic ducts from urothelial carcinoma of urinary bladder, and prostate involvement may be
identified in 12 to 48 percent of patients who undergo radical cystectomy for urothelial bladder cancers [34]. (See "Clinical presentation, diagnosis, and staging of bladder cancer").

Primary urothelial carcinoma of the prostate without bladder involvement is rare. Based on the old literature, primary urothelial carcinoma of the prostate was estimated at 1 to 4 percent of prostatic malignancies [34]. However, these numbers for primary prostatic urothelial carcinoma were obtained before the radical prostatectomy era, and therefore the actual incidence may be lower.

Urothelial carcinoma is not infrequent in prostate needle core biopsy, because the needle biopsy samples areas mostly in the prostatic peripheral zone. Because of the differences in clinical management, it is important to recognize urothelial carcinoma, which displays morphologic and immunohistochemical characteristics different from prostatic adenocarcinoma.

Distinguishing primary prostatic urothelial carcinoma from the secondary involvement of the prostate by bladder cancer is very difficult on biopsy specimens. Therefore, clinical investigation of the bladder and urinary tract is necessary if urothelial carcinoma is initially detected in the prostate. The presence of prostatic stromal invasion of urothelial carcinoma, which is associated with worse prognosis, should be evaluated in the case of prostatic urothelial carcinoma in addition to the grade and location of the tumor.

**KEY COMPONENTS OF THE PATHOLOGY REPORT**

**When cancer is present** — The histologic diagnosis of prostate cancer on a biopsy specimen must be made without any uncertainty. Any equivocal diagnostic term, such as "possible", "likely", "suspicious", or "atypical" should not be accepted as definitive diagnosis of malignancy. Therapy should not be initiated for a patient based on an equivocal or uncertain diagnosis. (See 'Cases with diagnostic uncertainty' below.)

When prostatic adenocarcinoma is present on needle biopsy, it is not sufficient to simply confirm its presence. The following important features should be included in the pathology report:

**Gleason score**

**Scoring system** — The Gleason grading system, which is based solely upon architectural features of prostate cancer cells, closely correlates with clinical behavior. A higher score indicates a greater likelihood of having non-organ confined disease, as well as a worse outcome after treatment of localized disease [35,36]. The Gleason score is the preferred system for grading tumors and has been incorporated as a key prognostic factor in the 2010 TNM staging system for prostate cancer (table 3 and table 4). (See "Prostate cancer: Risk stratification and choice of initial treatment").

Based upon the growth pattern and degree of differentiation, tumors are graded from 1 to 5, with grade 1 being the most, and grade 5 the least differentiated (figure 2) [37]. The composite Gleason score is derived by adding together the numerical values for the two most prevalent differentiation patterns (a primary grade and a secondary grade). As an example, if a biopsy consists of predominantly grade three and secondarily grade four disease, the combined score is "three plus four" or seven. Gleason scores of two, three, and four are typically considered well-differentiated or low-grade cancers; scores of five, six, or seven represent moderately differentiated cancers; and scores of eight, nine, or ten represent poorly differentiated or high-grade cancers.
Is a Gleason 6 lesion prostate cancer? — Questions have been raised whether prostatic adenocarcinoma with Gleason score 6 should be considered prostate cancer [38,39]. The short answer for that question is definitively "yes". Prostatic adenocarcinoma with Gleason 6 (3+3) is the most common form of prostate cancer.

Key issues that clarify this confusion include:

- Gleason grading of prostate cancer is based on the architectural features not cytological features of the tumor cells. In other words, Gleason grade 6, Gleason 7, and Gleason grade 8 are all composed of malignant cells with similar cytological features but with different architectural patterns.
- The features of Gleason grade 6 adenocarcinoma include uncontrolled growth, invasive nature, and the lack of basal cells as discussed earlier. All these are the characteristics of a malignant neoplasm, which are very similar to those of prostatic adenocarcinomas of Gleason 7 or above.
- However, it is well documented that Gleason 6 adenocarcinoma can progress into Gleason 7 or higher grade cancer, and subsequently lead to metastases and eventually death without proper treatments.
- A small subset of Gleason 6 adenocarcinomas do give rise to metastatic disease, but with current techniques, we cannot determine which cases of Gleason 6 adenocarcinoma will progress and which will not. In a multicenter study of 100 cases of metastatic adenocarcinoma of the prostate, only 10 percent of the metastatic tumors were derived from Gleason 6 adenocarcinomas, while 90 percent were derived from primary adenocarcinomas with Gleason score 7 or higher, although the percentage arising from Gleason score 6 would be lower with current grading systems [9].
- Furthermore, needle core biopsy is subject to sampling errors as well as to errors in interpretation. Errors of these types may lead to the subsequent diagnosis of Gleason 7 adenocarcinoma, or the subsequent clinical presentation with more advanced, high grade disease. The patients that meet the Epstein criteria of "insignificant cancer" on biopsy may harbor higher grade carcinoma without being sampled in the prostate at the time of needle core biopsy diagnosis.
- Patients with Gleason 6 adenocarcinoma frequently are considered for management with active surveillance. The results from these programs clearly have shown that some of these patients will progress to Gleason 7 disease and require definitive treatment. The criteria for defining which cancers are appropriate for active surveillance are discussed separately. (See "Active surveillance for men with early prostate cancer".)
- A modified Gleason system for prediction of prognosis based upon pathology of a prostatectomy specimen has been proposed [39]. In this system, grade 1 corresponds to a Gleason ≤6, grade 2 to Gleason 7 (3 + 4), grade 3 to Gleason 7 (4 + 3), grade 4 to Gleason 8, and grade 5 to Gleason 9 or 10. These grades corresponded with progressively decreased five-year recurrence-free survivals (95, 83, 65, 63, and 35 percent, respectively).

In summary, prostatic adenocarcinoma with Gleason 6 is a common form of prostate cancer. If it is of a small volume, Gleason 6 adenocarcinoma may be considered as the early phase of prostate cancer that can be clinically "insignificant". Significant percentages of cases with Gleason 6 on needle core biopsies will progress to higher grades and higher volume tumor if not treated, although the latent period of progression is uncertain. The patients who meet strict criteria of "clinically insignificant cancer" can choose to be on the active surveillance program,
but close follow-up with PSA density, free PSA, and repeat biopsy is necessary to detect early progression to high grade tumors in this group of patients.

**Gleason 7** — Gleason score 7 prostate cancer is a heterogeneous entity. In most series, men with Gleason 4 + 3 tumors (where grade 4 is more prevalent than grade 3) have a less favorable outcome than do those with Gleason 3 + 4 disease, where grade 3 is more prevalent [40-45]. As an example, multivariate analysis of a single institution series of 1333 men with Gleason 7 prostate cancer found a significantly increased risk of seminal vesicle invasion in those with Gleason 4 + 3 disease (20 versus 9 percent, odds ratio [OR] 2.26) [45]. This observation appears to be more reliable when applied to a prostatectomy specimen rather than one from a biopsy [46,47].

**Tertiary Gleason scores** — In some cases, a tumor may contain a small component of higher grade tumor in addition to the two predominant patterns; the grade of this minor component is referred to as the tertiary Gleason grade. Traditionally, the tertiary Gleason grade has been noncontributory to the overall Gleason score in biopsy specimens. However, in 2005, the International Society of Urologic Pathology consensus conference recommended that men with biopsy Gleason score 3 + 4 or 4 + 3 prostate cancer and a tertiary pattern 5 should have their cancers classified as Gleason score 8 or 9, respectively [48]. These men have a higher pathologic tumor stage and an increased risk of biochemical and clinical recurrence compared to men who have Gleason score 7 disease without a tertiary grade 5 component [44,49-51].

The percentage of a tumor consisting of high-grade prostate cancer (ie, combined Gleason pattern 4 or 5) may provide additional prognostic information [52]. In a series of 504 consecutive patients undergoing prostatectomy, an increasing percentage of high-grade tumor was associated with a statistically significant poorer cancer specific survival.

**Clinical application of gleason score** — The use of the numerical Gleason score is preferable to the three-tiered grading system of low, intermediate, or high grade disease (also known as grade lumping), especially for the initial diagnosis of prostate cancer. The numerical Gleason score is of clinical relevance, since it is a component of most nomograms and tables that estimate prognosis based upon pretreatment variables (table 5). In contrast, these descriptive terms may be acceptable for men with known, previously treated prostate cancer, or for those with metastatic disease where tumor grading is difficult. (See "Prostate cancer: Risk stratification and choice of initial treatment").

Some investigators have proposed "grade compression" by lumping prostate cancer into three groups: well differentiated or low grade (Gleason scores of two, three, or four); moderately differentiated or intermediate grade (Gleason scores of five, six, or seven) and poorly differentiated or high grade (Gleason scores of eight, nine, or ten). Grade compression is problematic since Gleason score 6 and 7 tumors are very different in their behaviors. Therefore, for individual patients, the Gleason score is a better indicator than a compressed grade. However, grade compression could be used when a small number of cases are available for study.

A diagnosis of prostate cancer with a single digit Gleason grade should be avoided. For example, a diagnosis of "prostatic adenocarcinoma, Gleason grade 4" is confusing. It could mean a tumor with Gleason score "2 + 2" or four, which is a low grade tumor with limited aggressive behavior, or it could mean a tumor with Gleason score "4 + 4" or eight, which is very aggressive. A Gleason score should be reported even for a single small focus of cancer on needle biopsy [53].
Several studies suggest that contemporary Gleason grade readings may be significantly higher than they were 10 years ago [54-56]. The effect of this subtle upgrading of Gleason scores over time could be an apparent improvement in outcome for all categories of men with clinically localized prostate cancer (the so-called Will Rogers phenomenon). This issue has the potential to impact on the interpretation of studies that suggest improvements in outcome from treatment over time.

There can be substantial interobserver variability in the Gleason grading of a biopsy specimen, particularly for pathologists with less experience interpreting prostate biopsies. In a study in which the interpretations from 29 pathologists were compared with that of an expert in prostate cancer pathology on an average of 278 samples, only 68 percent of samples were correctly classified as Gleason score <7, 7, or >7 [57]. Therefore, additional training may be necessary for those pathologists who are unfamiliar with the Gleason grading system.

Furthermore, there can be significant discrepancies between the Gleason score, as determined on the prostate biopsy, and the Gleason score based upon the final, pathologic specimen. This issue is discussed separately. (See "Prostate cancer: Risk stratification and choice of initial treatment", section on 'Risk stratification'.)

**Side and location of the tumor** — Because a partial prostatectomy is not practical, some pathologists do not record which side harbors the tumor. However, documentation of tumor side and location is critical for urologists performing a nerve-sparing radical prostatectomy [58]. Based upon this information, one or both neurovascular bundles may be spared, with a potentially significant impact on postprostatectomy potency rates. (See “Radical prostatectomy for localized prostate cancer”, section on 'Nerve-sparing approach'.)

**Estimated tumor volume** — An estimate of tumor volume (often generically termed the "percentage of positive biopsies") can add clinically significant information to other factors such as the biopsy Gleason score in predicting outcome following therapy for early stage prostate cancer [59-63]. (See "Prostate cancer: Risk stratification and choice of initial treatment", section on 'Percentage of positive biopsies'.)

Simply stated, tumor involving the majority of five cores sampled on the sextant biopsy represents a more significant disease burden than tumor involving a small portion of one core only. Therefore, both the number of involved cores, and extent of tumor within each core should be included in the pathology report. Tumor involvement within a core can be estimated by measuring either the percentage or the length by centimeter of tumor involvement [59,60].

**Perineural invasion** — The presence of perineural invasion (PNI) in a prostate biopsy should be reported, since it represents information that may be used by the clinician in planning therapy (picture 9) [64,65]. PNI in a core biopsy is an important predictor of pathologic stage, with most [59,64,66-70] but not all studies [71] finding a correlation between PNI on biopsy and extraprostatic extension at the time of prostatectomy. The presence of PNI on pretreatment core biopsy is also associated with a significantly higher likelihood of disease recurrence after radiation therapy [70,72].

Finding PNI in a prostatectomy specimen is very common. Although this finding has limited independent predictive value for clinical outcomes, PNI found in a prostatectomy specimen is correlated with a higher volume of prostate cancer in our own experience.

**Extraprostatic extension** — Although extraprostatic extension is usually documented only at the time of radical prostatectomy, direct extension of tumor cells beyond the confines of the prostatic capsule into periprostatic adipose tissue can occasionally be observed in needle
biopsy specimens (picture 10). As an example, in one series of 150 malignant needle biopsy specimens, invasion of fat was only detected in one case (table 2) [6].

The presence of extraprostatic extension is clinically significant, because it changes the tumor stage to a T3 lesion, which constitutes locally advanced disease (table 3 and table 4). (See "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer").

Involvement of skeletal muscle or ganglions or individual nerves by tumor cells should not be considered to represent extraprostatic extension because these structures can be also observed within the normal prostate gland.

Seminal vesicles, and their continuation within the prostate (the ejaculatory duct), can sometimes be seen on needle biopsy specimens. The clinical implication of finding tumor invading the ejaculatory duct on a biopsy specimen is identical to that of a cancer invading the seminal vesicle. The epithelial cells of the seminal vesicles are characterized by the presence of hyperchromatic and pleomorphic nuclei with intracellular golden-brown lipofuscin pigment. A diagnosis of tumor involvement of the seminal vesicles must be made cautiously unless the biopsy is specifically indicated as from the seminal vesicle [73]. Although targeted biopsy of the seminal vesicle is not a routine component of tumor staging, it is occasionally performed. (See "Clinical presentation and diagnosis of prostate cancer").

Presence of a special type of cancer — Occasionally, the presence of special types of malignant tumor cells may be observed coexisting with conventional prostatic adenocarcinoma. The reason to include these tumor components in the diagnostic report is that they are all associated with a poor prognosis, which may require special management [5].

These components may include but are not limited to:

- Ductal adenocarcinoma, characterized by the presence of tall columnar tumor cells
- Small cell carcinoma, characterized by the presence of small cell neuroendocrine components, which should be confirmed using IHC markers
- A sarcomatoid component along with the carcinoma (carcinosarcoma or sarcomatoid carcinoma), which is characterized by the presence of high-grade spindle tumor cells in addition to typical carcinomatous components

When cancer is absent — Even if invasive cancer cannot be determined with certainty on the diagnostic prostate biopsy, several benign features warrant mention in the pathology report.

PIN — The presence of high-grade prostatic intraepithelial neoplasia (PIN) in the needle biopsy specimen is clinically significant and should be included in the report, although it does not represent an invasive cancer.

High-grade PIN is believed to be a precursor to prostatic adenocarcinoma. The presence of high-grade PIN traditionally mandates a follow-up core biopsy to rule out the presence of a coexisting cancer. However, more recent studies have shown that the risk of finding cancer in a patient with isolated high-grade PIN was only slightly higher than that in a patient with a benign prostate biopsy. In contrast, the presence of low-grade PIN is not usually reported, because of its lack of clinical significance and possible confusion with high-grade PIN. (See "Precancerous lesions of the prostate: Pathology and clinical implications").

Inflammation — Inflammation, particularly if it is acute, can contribute to an elevated serum PSA; therefore its presence should be specified in the pathology report [74,75]. In core biopsy specimens of prostate tissue, a severe inflammatory reaction can mask the diagnostic histologic
features of an adenocarcinoma; therefore extreme care should be taken to exclude the presence of a cancer. Nonspecific granulomatous prostatitis, which is characterized by infiltrates of histiocytes and other inflammatory cells along with destruction of the prostate glandular structures, can be misdiagnosed as high-grade prostate cancer [76].

Infarction — If an infarct is present in biopsy tissue, it should be included in the diagnosis because it could be responsible for an elevated PSA level, presumably as a result of tissue necrosis releasing massive amounts of PSA into the serum. Prostatic infarcts are uncommon and in the past have only been reported on TURP material. However, infarcts may be identified in a small number of prostate core needle biopsies (eg, two cases in 2959 biopsies in one series [77]). Histologically, a relatively fresh prostatic infarct is characterized by defined areas of coagulative necrosis with or without hemorrhage, intermediate aged infarcts have reactive stroma and epithelium without necrosis, and older infarcts are characterized by replacement of the stroma by dense fibrosis, and reparative changes (eg, squamous metaplasia at the infarct edges) [77].

BPH — The "diagnosis" of BPH on a needle biopsy specimen should be avoided since it may give a false impression that this is the cause of serum PSA elevation. Another common condition that might contribute to an elevated serum PSA is benign prostatic hyperplasia (BPH) [78]. Some pathologists routinely diagnose BPH in every prostate needle biopsy specimen without sufficient histologic evidence. However, BPH cannot be reliably diagnosed in such specimens because histologic diagnosis requires the presence of hyperplastic nodules, which cannot be assessed on needle core tissue [79].

Cases with diagnostic uncertainty — When a prostate biopsy is undertaken, a definitive pathologic diagnosis prostate cancer is usually needed for clinical management. Unfortunately, definitive diagnosis is not always possible [80].

For the diagnosis of invasive cancer to be made, there must be absolutely no doubt on the part of the consulting pathologist. A firm diagnosis of limited prostate cancer on needle core biopsy is one of the most difficult areas in surgical pathology. The histologic features of prostatic adenocarcinoma are complex and may be subtle [73]. An error in any step of tissue processing, including tissue fixation, dehydration, embedding, even staining, may interfere with a proper diagnosis.

Even if tissue processing is perfect, a definitive diagnosis of cancer may still be difficult for even an experienced pathologist. One of the most common problems that interferes with the ability to make a definitive diagnosis is the size of the suspicious lesion. Most pathologists do not feel comfortable making a diagnosis of malignancy when the focus of concern contains only a few atypical glands or acini.

In the situation where the pathologist is suspicious but not totally convinced about a diagnosis of prostate cancer, the term "atypical glands suspicious for, but not diagnostic of, prostatic adenocarcinoma" is often applied. Although other pathologists prefer the diagnostic term "atypical small acinar proliferation suspicious for prostatic adenocarcinoma (ASAP)" [81], this phrase has been criticized because it may be confused with a definite cancer [82, 83].

Between 1 and 23 percent of needle biopsy pathology specimens (average 5 percent) have a diagnosis of atypical foci suspicious for carcinoma [84]. This is not a pathologic entity but a diagnostic term that is used when there is suspicion for but not sufficient evidence to make a definitive diagnosis of cancer. Because the average risk of subsequently documenting cancer following an atypical or suspicious diagnosis is approximately 40 percent [84], repeat biopsy is
necessary within three to six months in all cases. Repeat biopsy should include more sampling of the initial atypical site as well as other areas. Some urologists prefer saturated biopsy methods, in which more than 24 cores are taken.

The incidence of an uncertain atypical diagnosis is lower when immunohistochemical staining for high molecular weight cytokeratin (34bE12), p63, or AMACR is applied. (See 'Immunohistochemistry' above.) The significance of finding ASAP in men high-grade PIN in a needle biopsy specimen is discussed elsewhere. (See "Precancerous lesions of the prostate: Pathology and clinical implications", section on 'Clinical significance'.)

Regardless of the terminology, the following options are available for cases with diagnostic uncertainty:

- Examine multiple deeper tissue sections. Typically, a total of 10 slides with 30 sections are generated from each prostate tissue core for further evaluation. On deeper levels, a minute suspicious lesion might show sufficient evidence to permit a diagnosis of cancer.
- Perform IHC for 34bE12 or p63 (negative for prostatic adenocarcinoma) and AMACR (positive for prostatic adenocarcinoma) However, IHC stains may be false positive or false negative, and the diagnosis of prostatic adenocarcinoma should always be primarily based upon the histological features from H and E-stained slides, rather than IHC stains alone. (see 'Immunohistochemistry' above)
- Rebiopsy of the prostate if clinically indicated. Approximately one-half of men with atypical or suspicious foci will have cancer identified on repeat biopsy [85-88].
- Send the slides to a pathologist with greater experience and expertise on prostate lesions for a second opinion to avoid an unnecessary second biopsy.

EFFECT OF TREATMENT ON BIOPSY SPECIMENS

Hormone therapy — Androgenic influences are important for both the growth and malignant transformation of prostatic tissue. The testes account for 90 to 95 percent of total circulating testosterone, while the adrenal glands produce the remainder. In the prostate, testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase (figure 3). DHT is the primary androgen that stimulates the growth of both benign and malignant prostate tissues.

Huggins and Hodges were the first to show that palliation of metastatic disease could be achieved by androgen ablation, which can be accomplished surgically (orchiectomy) or medically by administration of gonadotropin releasing hormone (GnRH) analogs, estrogens, or androgen receptor blockers (anti-androgens) [89,90]. Although androgen ablation is usually reserved for the treatment of advanced or metastatic prostate cancer, it may be used in men with less advanced disease (i.e., clinically organ-confined, or locally advanced) as an adjunct to radiation therapy or surgery. (See "Initial therapy for castration sensitive metastatic prostate cancer").

Androgen ablation — Regardless of the method of androgen ablation, the histologic changes in the prostate gland are indistinguishable. The effects can be shown both in normal secretory epithelium, as well as in adenocarcinoma cells, the vast majority of which maintain the secretory epithelial phenotype (table 6) [91,92]. Regression and degenerative changes, such as pyknotic nuclei, clear cytoplasm or vacuolated cytoplasm, are evident, while the features of cytologic atypia (e.g., nuclear enlargement and prominent nucleoli) that are typically present in adenocarcinoma cells are diminished or absent. These changes can cause difficulty in assessment of prostate biopsies, and may result in underestimation of the extent of disease if hormone therapy was administered prior to a biopsy or prostatectomy. Furthermore, because of
the severe histologic changes in tumor cells caused by prior hormonal therapy, the assignment of a Gleason score is unreliable in this situation and is usually withheld.

Despite this, the infiltrating pattern of a prostatic adenocarcinoma is mostly retained and can be recognized. In particular, identification of scattered individual malignant epithelial cells in the stroma is diagnostic evidence of prostatic adenocarcinoma (picture 11). Immunostaining for keratins or for PSA may be helpful in identifying the individual tumor cells in this situation to confirm the diagnosis [93].

Other nonspecific histologic changes, including basal cell hyperplasia, transitional cell and squamous cell metaplasia in benign epithelium, and chronic inflammation, may also be present. These nonspecific histologic changes in benign prostatic epithelial cells often provide the pathologist with a clue as to the use of prior hormonal therapy.

**Estrogens** — Administration of estrogen is rarely done; diethylstilbestrol is no longer commercially available. However, estrogens can cause severe squamous metaplasia of benign and malignant prostatic cells in addition to the atrophic changes described above (table 6) [94,95].

**Finasteride and dutasteride** — The 5-alpha reductase inhibitors finasteride and dutasteride, which are widely used in the treatment of benign prostatic hyperplasia, are considered to be weak anti-androgens. (See "Medical treatment of benign prostatic hyperplasia", section on '5-alpha-reductase inhibitors'.)

Both finasteride and dutasteride appear to have a limited effect on the histologic appearance of prostatic adenocarcinomas in biopsy specimens in contrast to the steroidal anti-androgens (table 6) [96-100]. Therefore, the histologic diagnosis of prostate cancer on biopsy specimens from men receiving finasteride or dutasteride is not difficult.

However, it has been suggested that 5-alpha reductase inhibitors have the potential to alter the Gleason score of prostate cancers [101]. This hypothesis was proposed largely to explain the findings of the Prostate Cancer Prevention Trial, in which men treated with finasteride had fewer prostate cancers overall but significantly more tumors of Gleason score 7 to 10 compared with the control group [102]. However, this observation was not confirmed in two other trials and the relationship between 5-alpha reductase inhibitors and Gleason score in incident prostate cancer remains unsettled. (See "Chemoprevention strategies in prostate cancer", section on '5-Alpha reductase inhibitors'.)

Administration of a 5-alpha reductase inhibitor may complicate the diagnosis of a prostate cancer because these agents produce a nearly 50 percent decrease in serum PSA concentrations during the first three months of therapy, which persists as long as the drug is continued (See 'Measurement of prostate specific antigen", section on 'Medications'.)

**Radiation therapy** — Posttreatment prostate biopsy is not commonly performed to assess local control after irradiation for prostate cancer. Positive results on rebiopsy do not add significant clinical information to that provided by sequential serum PSA measurements following therapy. Rebiopsy is not routine following RT and is indicated only if the PSA is rising and salvage surgery or brachytherapy is being considered. (See "Rising serum PSA after radiation therapy for localized prostate cancer: Salvage local therapy", section on 'Patient selection'.)

The majority of series describing the histologic appearance of the irradiated prostate gland were derived from patients receiving external beam radiation therapy (RT) [103,104]. Histologic
changes following brachytherapy are qualitatively similar but may be more pronounced \([104,105]\). (See "Brachytherapy for localized prostate cancer".)

Several weeks after RT has begun, prostatic cells undergo severe degenerative changes, including nuclear shrinkage and cytoplasmic damage. Occasionally, small foci of necrosis will be evident, both in benign and malignant glands. Acute inflammatory cells such as neutrophils, macrophages, and later lymphocytes, accumulate. Gradually, the infiltration of reactive cells subsides and fibrosis develops in areas of tissue damage. This acute phase of reaction to RT is rarely seen in biopsy material because so few patients undergo routine biopsy, and those who do generally have their biopsy at least six months after RT. At that time, residual cancer cells may or may not be evident in the biopsy specimen (see below).

In response to RT, benign epithelial and stromal cells develop cytologic atypia, with the epithelial cells having prominent nuclear irregularity, hyperchromasia, and polymorphic changes \((table 6)\). Because of the presence of smudged nuclei, prominent nucleoli are not commonly seen. Irradiated benign epithelial cells often show a slightly spindled appearance termed "streaming" histology. Despite marked nuclear atypia, benign glands still retain their lobular pattern \(\text{(picture 12)}.\)

Nonspecific histologic changes such as chronic inflammation, basal cell proliferation, or stromal fibrosis may also be present to varying degrees. Postradiation changes in the benign glands may persist for a long time following prostatic RT, causing difficulty interpreting prostate biopsies in irradiated men \([105]\). In diagnostically difficult cases, immunostaining specific for basal cells may be helpful, often showing positive staining in the benign atypical cells but not in malignant cells.

In contrast to the benign glands, the characteristic haphazard infiltrating architectural pattern and cytologic features of malignant prostate glands are often retained \((table 6)\) \([5]\). Irradiated tumor cells may display clear cytoplasm and other degenerative changes or they may show no apparent histological changes from the radiation \(\text{(picture 13)}.\)

The presence of malignant cells six months following RT to the prostate should not be interpreted as treatment failure. The long doubling time of many prostate tumors, coupled with radiobiologic data indicating that cell death following RT is a postmitotic event, suggests that the time course of disappearance of viable cancer from the prostate is prolonged. As a result, false positive biopsies may be due to delayed tumor regression and indeterminate biopsies (usually showing radiation effect in viable tumor cells) are of uncertain significance. In one series, for example, 30 percent of indeterminate biopsies showed eventual clearance of tumor at a mean time of 30 months following RT \([106]\). A higher number of indeterminate biopsies may convert to negative in men undergoing brachytherapy \([107]\).

A biopsy that demonstrates the presence of tumor cells beyond 18 to 24 months is more likely to indicate active disease (either persistence or a local recurrence) \([107-109]\), however, even this is not absolute. In at least one series, 22 of 46 men who underwent routine prostate biopsy after combined external beam RT and brachytherapy had evidence of residual tumor cells; however, 16 had no evidence of an elevated serum PSA (biochemical failure) \([109]\).

Whether the Gleason grade of recurrent adenocarcinoma following a course of RT is of any significance accurately reflects tumor aggressiveness or clinical behavior is uncertain \([109]\). Further studies are necessary to evaluate this issue.

**SUMMARY**
Core needle biopsy of the prostate is used to determine whether or not cancer is present in men with an elevated serum PSA level and/or an abnormal digital rectal examination. The standard is to take multiple core biopsies under transrectal ultrasound guidance. Primary diagnosis of prostate cancer by using fine needle aspiration is not acceptable in the United States, although it was widely used in other countries in the past. (See "Clinical presentation and diagnosis of prostate cancer", section on 'Diagnosis'.)

More than 95 percent of malignancies arising in the prostate are adenocarcinoma. The remaining types include urothelial carcinoma, basal cell carcinoma, small cell carcinoma, lymphoma, and sarcomas. (See 'Histologic features' above.)

When prostate cancer is present in the biopsy, the combined Gleason score, based upon architectural features of the prostate cancer cells, should be reported because it correlates closely with clinical behavior and has been incorporated into the tumor, node, metastasis (TNM) prognostic group staging system (Table 3 and Table 4). (See 'Gleason score' above and "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Staging system'.)

Additional information that may be derived from the prostate biopsy includes the number of positive cores, the percentage (or length) of cancer in the positive core, the presence of perineural invasion or extraprostatic extension, and the presence of histologic types other than conventional adenocarcinoma. (See 'When cancer is present' above.)

Many benign conditions can mimic prostate cancer. The accuracy of pathological diagnosis of prostate cancer can be improved by using immunohistochemistry (IHC) markers; correct interpretation of the IHC results is critical for success. New biomarkers to diagnose prostate cancer and provide prognostic information are promising but require further evaluation before being used in routine clinical practice.

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Overview of the treatment of disseminated prostate cancer

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Disclosures: Nancy A Dawson, MD Speaker’s Bureau: Bayer [Prostate cancer (Radium-223)]; Dendreon [Prostate cancer (Sipuleucel-T)]; Janssen [Prostate cancer (Abiraterone)]; Astellas [Prostate cancer (Enzalutamide)]; Sanofi-Aventis [Prostate cancer (Docetaxel, Cabazitaxel)]; Amgen [Prostate cancer/Bone metastases (Denosumab)]; Consultant/Advisory Boards: Amgen [Prostate cancer/Bone metastases (Denosumab)]. Nicholas Vogelzang, MD Grant/Research/Clinical Trial Support: Bayer [Prostate cancer (Radium 223)]; Novartis [Renal cell cancer (everolimus, dovitinib)]; Exelixis [Prostate/thyroid cancer (cabozantinib)]; Progenics [Prostate cancer (investigational agent anti PSMA)]; Janssen [Prostate cancer (ARN prostate)]; Bavarian Nordic [Prostate cancer (Prostvac)]; Viamet [Prostate cancer (VN 417)]; Astex [Prostate cancer (HSP inhibitor)]; Merck [Melanoma (investigative agent pembrolizumab)]; Genentech (investigational agent PDL-1 antibody). Speakers’ Bureau: Astellas; Johnson and Johnson; Pfizer; Novartis; Dendreon; GSK; Veridex/Johnson & Johnson; Janssen [Renal cancer (enzalutamide, abiraterone, axitinib)]; [Renal, circulating tumor cells (Provenge, Radium 223, pazopanib)]. Consultant/Advisory Boards: Amgen; Caris; Celgene; Medivation; Novartis; Eisai; Exelixis; Roche [Bladder cancer, prostate cancer, renal cancer, (denosumab)]; [Prostate cancer immunotherapy (cabozantinib)]; Cerulean [Renal cancer (experimental agent)]; BIND [Prostate cancer (experimental agent)]; Blue Earth [Prostate cancer (diagnostic investigational agent)]. W Robert Lee, MD, MS, MEd Consultant/Advisory Boards: Medivation [Prostate cancer (enzalutamide)]; Ferring Pharmaceuticals [Prostate cancer (Degarelix)]. Jerome P Richie, MD, FACS Nothing to disclose. Michael E Ross, MD Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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INTRODUCTION — Although most cases of prostate cancer are diagnosed and treated while disease is localized, some men have evidence of metastatic prostate cancer at presentation and others develop disseminated disease after their definitive treatment. Contemporary research has led to the development of multiple active treatment modalities for men with advanced disease. Management of men with advanced prostate cancer involves the sequential use of these and older approaches, with the goals of prolonging survival, minimizing complications, and maintaining quality of life.

An overview of treatment options for patients with disseminated prostate cancer and considerations for the proper sequencing of the various treatment options are presented here.

The initial management of men with localized prostate cancer is discussed separately:

● (See "Initial approach to low- and very low-risk clinically localized prostate cancer").
● (See "Initial management of regionally localized intermediate, high, and very high-risk prostate cancer").

PATIENT POPULATIONS — Some men with prostate cancer will have overt metastases either at presentation or as their first sign of recurrence following definitive therapy. In the vast majority of cases, such metastases are predominantly osteoblastic lesions in the axial skeleton. However, in some cases the only manifestation of disseminated disease is an elevated or rising serum PSA after definitive therapy.
Systemic therapy options for men in whom the only evidence of disseminated disease is an elevated PSA are the same as those for men with overt metastases. However, disease manifested only by an elevated serum PSA may have a very prolonged natural history, which has significant implications for the timing and choice of therapy. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Natural history after biochemical failure' and "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy").

SEQUENCE OF SYSTEMIC THERAPIES

Androgen deprivation therapy — Previously untreated prostate cancer is dependent upon androgen at least initially for its continued growth in most cases. Androgen production occurs primarily in the testes, which account for 90 to 95 percent of total circulating testosterone; testicular production of androgen is regulated by the hypothalamic pituitary axis. The adrenal glands produce the remainder of the circulating androgens. These observations provide the rationale for androgen deprivation therapy (ADT). ADT can be accomplished with either bilateral orchiectomy (surgical castration) or medical orchiectomy [1-3]. (See ‘Androgen deprivation therapy’ below.)

Castration sensitive disease — ADT is a standard component of the initial approach for patients with metastatic prostate cancer or an elevated serum PSA when systemic therapy is indicated.

- ADT is generally given alone for patients with low volume disease. ADT alone is also used as systemic therapy in some patients when the only evidence of recurrent or residual disease is a rising serum PSA. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy").
- For patients with high volume disease (ie, visceral metastases and/or >4 bone metastases), the combination of ADT plus docetaxel chemotherapy significantly improves overall survival. (See ‘Androgen deprivation therapy’ below and "Initial therapy for castration sensitive metastatic prostate cancer").

Castration resistant disease — Patients being managed with ADT who have evidence of disease progression (increasing serum PSA, new clinical metastases, progression of existing metastases) in the presence of adequately depressed serum testosterone are considered to have castration resistant disease.

Contemporary research in men with castration resistant prostate cancer has led to the development of multiple agents that improved overall survival in phase III trials (table 1). These include agents that interfere with androgenic stimulation of prostate cancer growth (abiraterone, enzalutamide), taxane chemotherapy (docetaxel, cabazitaxel), immunotherapy (sipuleucel-T), and a bone targeted radiopharmaceutical (radium-223). In addition, there are a number of older endocrine approaches that may retain utility in selected situations and have not been adequately studied in randomized trials. (See ‘Castration resistant disease’ below.)

These newer therapeutic approaches have each been evaluated in a relatively limited segment of the potential patient population and have not been compared with each other in randomized trials. The observed benefit in survival with each is of similar magnitude and results cannot be directly compared because of differences in patient populations.

The proper sequencing of these newer approaches requires a consideration of multiple factors (table 1). The sites and extent of disease involvement, along with the rate of disease progression, are particularly important considerations in choosing therapy.
• None of the newer modalities has been adequately evaluated in men whose only evidence of disseminated disease is an elevated or rising serum PSA. The optimal management of patients whose only evidence of disease is a rising or elevated PSA thus is extrapolated from patients with more extensive disease. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy".)

• Sipuleucel-T — The dendritic cell vaccine sipuleucel-T was studied only in the context of asymptomatic or minimally symptomatic men with metastases. This approach has not been studied in men whose only evidence of disease is an elevated PSA or in those with symptomatic metastases. Furthermore, treatment with sipuleucel-T does not affect the serum PSA, restricting this approach to patients with slowly progressive disease where a relatively rapid response to treatment is not required. (See "Immunotherapy for castration-resistant prostate cancer", section on 'Sipuleucel-T'.)

• Abiraterone and enzalutamide — Both abiraterone and enzalutamide act by interfering with the androgenic stimulation of tumor growth. The initial phase III trial with each of these agents was conducted in patients who had progressed after treatment with docetaxel chemotherapy. Subsequent trials have demonstrated activity in patients who are chemotherapy naïve. (See "Castration resistant prostate cancer: Treatments targeting the androgen pathway", section on 'Abiraterone' and "Castration resistant prostate cancer: Treatments targeting the androgen pathway", section on 'Enzalutamide'.)

• Taxane chemotherapy — Cytotoxic chemotherapy with a taxane is generally reserved for patients with relatively rapidly progressive, symptomatic disease for which less toxic approaches are not an appropriate option. Docetaxel is the preferred agent in this setting. Cabazitaxel has been shown to prolong survival in docetaxel resistant patients and is being compared with docetaxel as the initial chemotherapy agent in a phase III trial. (See "Chemotherapy in castrate-resistant prostate cancer".)

• Radium-223 — The bone-seeking radiopharmaceutical radium-223 is appropriate only for patients with extensive bone metastases but without other visceral metastases, and its evaluation in clinical trials was limited to this setting. (See "Bone metastases in advanced prostate cancer: Management", section on 'Radium-223'.)

Other factors that may influence the choice of therapy include the route and frequency of administration, side effects, regulatory status, cost, insurance reimbursement, and patient preferences.

In addition, older endocrine approaches (eg, antiandrogens, ketoconazole, steroids) may have an important role, particularly in the management of patients with slowly progressive disease, as a way to forestall using more toxic or expensive alternatives. (See 'Other endocrine approaches' below.)

Patients should be included in clinical trials whenever possible.

CASTRATION SENSITIVE DISEASE

Androgen deprivation therapy — Androgen deprivation therapy (ADT) is the standard initial approach for patients when systemic therapy is indicated for metastatic prostate cancer or evidence of disseminated disease based upon serum PSA. ADT can be accomplished either with bilateral orchiectomy (surgical castration) or medical orchiectomy. (See "Initial therapy for castration sensitive metastatic prostate cancer".)

Bilateral orchiectomy — Bilateral orchiectomy (surgical castration) is a simple, cost-effective procedure. Following surgery, serum testosterone levels rapidly decrease to castrate levels. In many countries, bilateral orchiectomy remains the standard of care for initial hormone therapy of
metastatic prostate cancer. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Surgical orchiectomy'.)

Surgical castration may be particularly useful when an immediate decrease in testosterone is necessary (eg, impending spinal cord compression, urinary tract outlet obstruction) or when cost or adherence to medical therapy are an issue.

Medical orchiectomy — Medical orchiectomy decreases testicular production of testosterone by its effects on the hypothalamic pituitary axis. The most widely used approach is continuous treatment with a gonadotropin releasing hormone (GnRH) agonist, which suppresses luteinizing hormone production and therefore the synthesis of testicular androgens. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Mechanism of action'.)

With the initiation of treatment with GnRH agonists, there is a transient surge of luteinizing hormone before the luteinizing hormone levels fall. This surge can cause an increase in serum testosterone, which may result in a worsening of disease. This "flare phenomenon" may be of particular concern in clinical settings such as impending epidural spinal cord compression or urinary tract outflow obstruction. Antiandrogens (eg, flutamide, bicalutamide) may be useful in preventing the flare phenomenon. (See 'Combined androgen blockade' below.)

A number of GnRH agonists are available (leuprolide, goserelin, buserelin, triptorelin). Depot formulations are frequently used to permit less frequent treatment administration. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Formulations'.)

The GnRH antagonist degarelix binds to the GnRH receptors on pituitary gonadotropin-producing cells but does not cause an initial release of luteinizing hormone. Degarelix suppresses testosterone production and avoids the flare phenomenon observed with GnRH agonists; a GnRH antagonist may be a useful alternative to a GnRH agonist when an immediate decrease in testosterone levels is required. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'GnRH antagonists'.)

Combined androgen blockade — Antiandrogens bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. The use of antiandrogens with a GnRH agonist thus produces a combined androgen blockade. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Combined androgen blockade with antiandrogens'.)

Combined androgen blockade is widely used for two to four weeks during the initiation of treatment with a GnRH agonist in order to prevent a disease flare due to the transient increase in testosterone levels. Combined androgen blockade is sometimes considered for long-term therapy to improve on the efficacy of a GnRH alone, although its long-term use is limited by costs and increased toxicity. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Combined androgen blockade with antiandrogens'.)

Continuous versus intermittent ADT — Many of the side effects of ADT are due to castrate levels of serum testosterone. When treatment is withdrawn, serum testosterone levels gradually return toward normal; discontinuation of long-acting GnRH agonists may be associated with a very slow testosterone recovery. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Serum testosterone level'.)

Intermittent ADT has been proposed as a way to minimize the side effects of medical castration by withholding active therapy once patients have responded to treatment. ADT can then be
reinstituted when there is evidence of progression. The time when men are off therapy may be associated with decreased side effects, thereby improving quality of life.

- **Metastatic disease** – Despite the theoretical advantages of this approach, intermittent ADT is not indicated in patients with metastatic prostate cancer unless survival is considered secondary to quality of life. A phase III intergroup trial found that intermittent ADT could not be considered noninferior compared with continuous ADT in terms of overall survival [4]. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Combined androgen blockade with antiandrogens'.)

- **Rising or elevated PSA only** – Intermittent ADT may be appropriate for a subset of men whose only manifestation of disseminated prostate cancer is an elevated or rising serum PSA. A preliminary report of large randomized trial suggested that intermittent ADT was noninferior in terms of overall survival, but additional data are required to assess the long-term value of this approach [5]. In this setting, intermittent ADT should be limited to well-informed patients who understand the potential risks and benefits of this approach. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'IAD for PSA only recurrence'.)

**Side effects of ADT** — ADT is associated with a wide range of side effects that can significantly impair quality of life. Important and/or frequent side effects include:

- Loss of lean body mass, increased body fat, and decreased muscle strength.
- Sexual dysfunction – Loss of libido in men receiving GnRH agonists usually develops within the first several months and is followed by erectile dysfunction.
- Loss of bone mineral density, which can result in bone fracture due to osteoporosis. This effect may be compounded by the presence of bone metastases.
- Vasomotor instability, which is manifested by hot flashes.
- Gynecomastia, decreased body hair, and smaller penile and/or testicular size.
- Fatigue or lack of energy.
- Behavioral and neurologic effects.
- Cardiovascular and metabolic abnormalities.

Although these side effects are potentially significant, they should not preclude the use of ADT in appropriate clinical settings. (See "Side effects of androgen deprivation therapy" and "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Prevention of osteoporosis' and "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Side effects of androgen deprivation therapy'.)

**Timing of treatment** — The optimal time to initiate systemic therapy is uncertain. Hormone therapy for disseminated prostate cancer is not curative and immediate therapy has not been shown to prolong survival compared with delayed therapy. Furthermore, treatment-related side effects can adversely affect quality of life.

- In the setting of patients with overt metastatic disease, several randomized trials and a meta-analysis found that immediate compared with delayed ADT was associated with a statistically significant decrease in prostate cancer-related death, although there was no overall survival benefit [1]. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Timing of ADT'.)

- The optimal timing for the initiation of ADT for patients with a rising serum PSA is controversial. Proponents of early treatment argue that this approach can delay disease progression and may prolong survival. Others contend that treatment is best deferred until
clinical metastases or symptoms develop since there is no consistent evidence for a significant survival benefit with ADT in this setting. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'When to initiate ADT'.)

**Chemohormonal therapy** — Sequential therapy with ADT alone and the later addition of docetaxel to ADT remains the standard of care in most settings. However, contemporary research has shown that the combination of ADT plus docetaxel offers a clinically meaningful and statistically significant benefit for men with castration sensitive disease and high volume disease. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Chemohormonal therapy'.)

**CASTRATION RESISTANT DISEASE** — Patients who have evidence of disease progression (eg, increase in serum PSA, new clinical metastases, progression of existing metastases) while being managed with androgen deprivation therapy (ADT) are considered to have castration resistant disease. This section discusses the definition of castration resistance and the various treatment options available. The approaches discussed here are consistent with the 2014 American Society of Clinical Oncology (ASCO) and Cancer Care Ontario Clinical Practice guidelines [6].

**Definition and implications** — There are no widely accepted criteria to define castration resistant disease outside of a clinical trial setting, particularly when the only evidence is an increase in serum PSA, and the decision requires judgment on the part of the treating physician. In some clinical trials, this has been defined by a serum PSA greater than 2 ng/mL and rising over one month, although others initiate a discussion of treatment modification with the patient as soon as the PSA has risen twofold.

The presence of castration resistant disease does not imply that disease is totally independent of androgens and resistant to further therapies directed at the androgen stimulation of tumor growth. For patients whose initial ADT was a medical orchiectomy (gonadotropin releasing hormone [GnRH] agonist or antagonist), such treatment should be continued even when additional systemic treatment is initiated. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Continuation of ADT'.)

Prostate cancer can have a long natural history, and its management may require the sequential use of multiple treatment options. Factors to consider in sequencing these options are discussed separately. (See ‘Sequence of systemic therapies’ above.)

**Interference with androgenic stimulation** — An improved understanding of the role of androgens in stimulating the growth of prostate cancer has lead to the development of abiraterone and enzalutamide, both of which have significantly improved overall survival compared with placebo in phase III trials in patients with castration resistant prostate cancer previously treated with docetaxel-based chemotherapy.

There are only limited data on the activity of enzalutamide in patients who have previously been treated with abiraterone and on the activity of abiraterone after treatment with enzalutamide.

**Abiraterone** — Androgens produced in the testis can cause “autocrine/paracrine” signaling that results in tumor progression. Abiraterone is an orally administered small molecule that irreversibly inhibits the products of the CYP17 gene (including both 17,20-lyase and 17-alpha-hydroxylase). In doing so, abiraterone blocks the synthesis of androgens in the tumor as well as in the testis and adrenal glands. Patients treated with abiraterone are at risk for adrenal insufficiency and require concurrent steroid replacement therapy. (See "Castration resistant prostate cancer: Treatments targeting the androgen pathway", section on 'Abiraterone'.)
In two phase III trials, abiraterone plus prednisone prolonged overall survival compared with prednisone alone in men who had previously been treated with docetaxel [7] and in those who were chemotherapy naïve [8]. Abiraterone is approved for patients who have metastatic castration resistant prostate cancer. Abiraterone is generally well tolerated, although fluid retention, hypokalemia, and hypertension may require treatment. (See "Castration resistant prostate cancer: Treatments targeting the androgen pathway", section on 'Abiraterone'.)

Abiraterone plus prednisone has limited activity in men with castration resistant prostate cancer who have previously been treated with both docetaxel and enzalutamide [9,10]. As an example, 10 to 20 percent of such patients in a retrospective case series had a decrease in serum PSA during treatment with abiraterone [9]. The median progression-free survival was 2.7 months.

Enzalutamide — Enzalutamide is an orally administered agent that acts at multiple sites in the androgen receptor signaling pathway, including blocking the binding of androgen to the androgen receptor, inhibition of nuclear translocation of the androgen receptor, and inhibition of the association of the androgen receptor with nuclear DNA. Unlike abiraterone, concurrent treatment with steroids is not required.

Enzalutamide has been compared with placebo in two phase III trials, one in men who had previously been treated with docetaxel [11] and the other in those who were chemotherapy naïve [12]. Overall survival was significantly prolonged in both trials. Enzalutamide is approved for patients with metastatic castration resistant prostate cancer. Treatment with enzalutamide has been associated with seizures in rare cases, and its use is contraindicated in patients with a seizure disorder. (See "Castration resistant prostate cancer: Treatments targeting the androgen pathway", section on 'Enzalutamide'.)

Enzalutamide has limited activity in men with castration resistant prostate cancer who have previously been treated with both docetaxel and abiraterone [13,14]. As an example, in a retrospective case series, approximately 10 percent of such patients had a ≥50 percent decrease in serum PSA during treatment with enzalutamide [13].

Other endocrine approaches — Older secondary endocrine treatment options include the addition of first generation antiandrogens to patients treated with a GnRH antagonist alone or with surgical orchietomy, withdrawal of antiandrogen therapy for patients who have been on an antiandrogen, suppression of adrenal androgen production with ketoconazole or steroids, and estrogens or progesterones. Overall response rates, generally based upon changes in serum PSA, vary from 20 to 60 percent, and responses tend to be of relatively short duration. (See "Secondary endocrine therapies for castration resistant prostate cancer".)

Specific secondary endocrine treatment approaches generally have not been compared with each other in large randomized trials, nor has a survival benefit been demonstrated with these approaches. However, the sequential use of such endocrine treatments prior to switching to chemotherapy often is preferred because of the generally less severe side effects. These alternative approaches may be used immediately after ADT in patients who have evidence of slow progression as manifested only by an increasing PSA or have asymptomatic metastases. Secondary endocrine approaches may also have a role after chemotherapy in the later phases of disease when there are no other treatment options.

Antiandrogens — Antiandrogens block the effects of circulating androgens with fewer adverse effects (hot flashes, loss of libido, impotence) than are associated with surgical or medical castration. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogens'.)
Antiandrogens may be useful in patients whose initial ADT included either medical orchiectomy with a GnRH agonist alone or surgical orchiectomy. There is incomplete cross-resistance between antiandrogens, and substitution of one antiandrogen for another occasionally is useful.

Available nonsteroidal antiandrogens include flutamide, bicalutamide, and nilutamide. The steroidal antiandrogen cyproterone acetate is approved for this indication outside the United States.

**Antiandrogen withdrawal** — The so-called "antiandrogen withdrawal syndrome" refers to a decline in serum PSA that is sometimes observed following the withdrawal of an antiandrogen in men who had progressed while being managed with complete androgen blockade. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogen withdrawal'.)

Approximately 20 percent of men progressing after complete androgen blockade have a PSA or "biochemical" response when antiandrogens are withdrawn, and some experience symptomatic or objective improvement. For men who have progressed while on complete androgen blockade, the first therapeutic maneuver is the discontinuation of the antiandrogen. Other therapy generally should not be initiated until adequate time has elapsed to assess for a possible withdrawal response.

**Ketoconazole** — Ketoconazole (200 to 400 mg three times per day) is an antifungal agent that inhibits adrenal androgen synthesis. Ketoconazole also has a direct cytotoxic effect on prostate cancer cells. Serum testosterone levels decline to castrate levels within 24 hours and antitumor efficacy is rapid. Adverse effects (nausea and vomiting, skin rash, fatigue, asthenia) and drug interactions may limit the use of ketoconazole in some patients. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Ketoconazole'.)

**Glucocorticoids** — Glucocorticoids (eg, prednisone, dexamethasone, hydrocortisone) reduce pituitary production of ACTH, resulting in suppression of adrenal steroidogenesis, including adrenal androgens. Several studies have shown significant subjective and objective improvement in men with castration resistant prostate cancer who receive glucocorticoids. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Glucocorticoids'.)

**Estrogens and progesterones** — Estrogens inhibit the release of GnRH from the hypothalamus, thus suppressing pituitary luteinizing hormone release and thereby reducing testicular production of testosterone. Diethylstilbestrol (DES) is no longer used at a dose of 5 mg/day in men with prostate cancer because of the increased risk of cardiovascular disease. However, DES at a dose of 1 mg/day is useful in some patients. Other estrogen preparations and progestogens also may have a role in occasional patients. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Estrogens' and "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Megestrol acetate'.)

**Sipuleucel-T** — Sipuleucel-T is a dendritic cell vaccine that is prepared from peripheral blood mononuclear cells obtained by leukapheresis. These cells are exposed ex vivo to a novel recombinant protein immunogen, which consists of prostatic acid phosphatase (PAP) fused to human granulocyte macrophage colony-stimulating factor. These activated cells are then infused back into the patient approximately three days after the original harvesting. (See "Immunotherapy for castration-resistant prostate cancer", section on 'Sipuleucel-T'.)
In randomized trials, sipuleucel-T prolonged overall survival compared with placebo in men with minimally symptomatic, metastatic prostate cancer [15]. There are no data on the effectiveness of sipuleucel-T in men whose only evidence of disease is an elevated PSA or in those with symptomatic metastatic disease. Treatment is contraindicated in patients who are on steroids or opioids for cancer-related pain, and should be used with caution in patients with liver metastases.

Although sipuleucel-T prolonged overall survival, it did not significantly increase progression-free survival or affect the serum PSA. Thus, assessing the impact of therapy on an individual patient can be difficult or impossible.

Chemotherapy — Taxanes are the only cytotoxic chemotherapy agents that significantly prolonged overall survival in clinical trials in men with castration resistant prostate cancer. (See "Chemotherapy in castrate-resistant prostate cancer".)

Docetaxel — Docetaxel (75 mg/m²) given every three weeks in combination with daily prednisone (5 mg twice a day) significantly prolonged overall survival compared with mitoxantrone plus prednisone in the TAX 327 phase III trial [16]. Based upon those results, docetaxel plus prednisone has become the standard initial regimen when chemotherapy is indicated for castration resistant prostate cancer [17]. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Chemotherapy-naive patients: Docetaxel'.)

Docetaxel causes significant myelosuppression and requires premedication to minimize the risk of infusion reactions. Therapy with prednisone is also required in combination with docetaxel. Contraindications include underlying hepatic dysfunction or compromised bone marrow function.

Cabazitaxel — Cabazitaxel is a synthetic taxane derivative developed to have activity in patients who progressed after treatment with docetaxel. In a phase III trial, cabazitaxel plus prednisone significantly increased survival compared with mitoxantrone plus prednisone in men whose disease had progressed on docetaxel [18]. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Cabazitaxel'.)

Cabazitaxel can cause significant myelosuppression and requires premedication to minimize the risk of infusion reactions. Therapy with prednisone is also required in combination with cabazitaxel. Contraindications include underlying hepatic dysfunction or compromised bone marrow function.

Mitoxantrone — Mitoxantrone was the first chemotherapy agent approved for use in men with castration resistant prostate cancer. Mitoxantrone was approved based upon improvement in symptoms, and not a prolongation of survival. Its use now is generally limited to patients requiring chemotherapy who have progressed on or are not candidates for taxane chemotherapy. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Mitoxantrone'.)

Radium-223 — Radium-223 is an alpha particle emitting radiopharmaceutical. Radium is a bone-seeking element, and radium-223's radioactive decay allows the deposition of high energy radiation over a much shorter distance than with beta-emitting radioisotopes, thus minimizing toxicity to normal bone marrow and to other organs. (See "Bone metastases in advanced prostate cancer: Management", section on 'Radium-223'.)

In a phase III trial, treatment with radium-223 was well tolerated and increased both overall survival and time to first symptomatic skeletal-related event (external beam radiation therapy to
relieve skeletal symptoms, new symptomatic pathologic fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention) in patients with symptomatic bone metastases and no known visceral metastases [19]. Because of its mechanism of action, its use is limited to patients who have bone metastases without other clinically significant sites of disease.

SURVEILLANCE DURING TREATMENT — Surveillance strategies during treatment for disseminated prostate cancer are discussed separately. (See "Follow-up surveillance during and after treatment for prostate cancer", section on 'Metastatic prostate cancer'.)

OLIGOMETASTATIC DISEASE — After prior definitive therapy, patients will occasionally present with metachronous oligometastatic disease. There are no high quality data on the optimal management of patients in this situation. In most cases this was diagnosed using positron emission tomography (PET)/computed tomography (CT).

The role of metastasis directed therapy (eg, surgery and/or radiation therapy [RT] for an isolated lymph node, stereotactic RT for bone metastasis) remains uncertain, and the decision regarding treatment requires a consideration of a wide range of patient-specific factors (eg, site of metastasis, disease-free interval, patient age, comorbidity).

A systematic review of the literature identified 15 case series that included information on 450 patients [20]. Isolated metastases were identified in lymph nodes or bone in 78 and 21 percent of cases, respectively. Approximately one-half of patients were progression free one to three years after metastasis directed therapy. Interpretation of these results is difficult since most of these also received adjuvant androgen deprivation therapy (ADT).

Additional data from prospective studies are required to determine the role of metastasis directed therapy.

PROGNOSTIC FACTORS

Clinical parameters in castration resistant disease — The most important factor influencing survival in men with prostate cancer is the site of metastatic involvement. This was illustrated by a meta-analysis that included data from approximately 4000 men treated with docetaxel for castration resistant disease in five randomized trials [21]. Overall survival decreased progressively with involvement of lymph nodes, bone, lung, and liver (27, 20, 17, and 12 months, respectively).

A number of other factors can also influence survival. Two large phase III trials were used to develop and validate a model to predict overall survival in men with castration resistant prostate cancer who were treated with chemotherapy [22]. Factors associated with a shorter overall survival included poorer performance status, the presence or absence of visceral metastases other than bone, use of opioids for pain relief, an elevated serum LDH, increasing serum PSA, increasing serum alkaline phosphatase, lower serum albumin, and a lower hemoglobin level. These factors were combined into a nomogram to classify patients as being at low, intermediate, or high risk.

Prognostic biomarkers — A variety of markers are being studied for their ability to identify subsets of patients with advanced prostate cancer who have significantly different prognoses. The most extensive data come from analyses of circulating tumor cells (CTCs); more recently, studies have looked at gene expression profiles. Ultimately, these different approaches may be combined. Currently, these studies cannot be used in individual patients.
Circulating tumor cells — CTCs can be detected in the systemic circulation of men with prostate cancer, and the presence of increasing numbers of CTCs assessed using the CellSearch assay has been associated with shorter overall survival in two large trials:

- In the phase III trial comparing abiraterone plus prednisone with placebo plus prednisone in men with castration resistant metastatic prostate cancer who had progressed on docetaxel chemotherapy, CTCs were measured in 972 of 1195 patients at baseline and/or serially thereafter [23]. Median overall survival was significantly longer in those with baseline CTCs <5 per 7.5 mL compared with those with CTCs ≥5 per 7.5 mL (22.1 versus 10.9 months in those assigned to abiraterone and 19.7 versus 8.2 months in those assigned to placebo).
- In a second phase III trial, CTCs were assayed in 238 patients with castration resistant metastatic prostate cancer randomly assigned to treatment with docetaxel or docetaxel plus atrasentan [24]. Median overall survival was significantly longer in those with <5 CTCs per 7.5 mL compared with those with ≥5 CTCs per 7.5 mL at baseline (26 versus 13 months).

The significance of circulating prostate cancer cells in men at the time of their initial diagnosis is discussed elsewhere. (See "Prostate cancer: Risk stratification and choice of initial treatment".)

Markers of bone metabolism — New bone formation and bone resorption are ongoing processes that may be disordered in the presence of bone metastases. Markers of bone metabolism provide information that may be useful either as prognostic factors or to identify subsets of patients that may be responsive to particular agents.

The potential utility of such markers was most extensively studied in a phase III trial in patients with metastatic castration resistant prognosis who were treated with docetaxel/prednisone, plus either the experimental agent atrasentan or placebo [25]. In that trial, sera were collected at baseline and in follow-up from 778 patients, and assayed for two markers of bone resorption (N-telopeptide, pyridinoline) and two markers of bone formation (C-terminal collagen propeptide, bone alkaline phosphatase).

For each of the four markers, a higher serum level at baseline (defined as greater than the median) was associated with a significantly shorter overall survival (medians 22 to 23 versus 15 to 16 months). Increasing levels of these biomarkers after nine weeks of treatment were associated with significantly poorer prognosis.

The potential utility of this approach to identify subsets of patients who may benefit from a specific therapeutic approach was also observed. Among those patients who received the experimental agent atrasentan rather than placebo, overall survival was significantly increased in those who had significant elevations of all four biomarkers (median 13 versus 5 months), whereas there was no difference in overall survival when the remainder of the patients were analyzed. (See "Investigational approaches for the treatment of advanced prostate cancer", section on 'Endothelin receptor antagonists'.)

Gene expression panels — Multiple studies have looked at the use of gene expression panels as a way to identify patient subsets with differing prognoses.

- In one report, a six-gene panel was initially developed in a group of 62 men with castration resistant prostate cancer [26]. The prognostic utility was then validated in an independent cohort of 138 patients. The use of the panel was able to divide this cohort into low and high risk groups, with median survivals of 9.2 and 18.5 months, respectively.
In another study, a nine-gene panel was assessed in a two step process [27]. A patient subset (LPD1) was identified from the initial study. In the validation cohort, this panel found that those in this subset had a significantly poorer prognosis (median overall survival 11 versus 26 months).

**SMALL CELL CANCER OF PROSTATE** — For patients with castration resistant disease in whom small cell cancer is suspected, biopsy is indicated whenever possible. If the biopsy confirms that the tumor is a small cell malignancy, chemotherapy with a small cell regimen is indicated. (See "Extrapulmonary small cell cancer", section on 'Prostate ESCC'.)

**MANAGEMENT OF BONE METASTASES** — Osteoblastic metastases to the axial skeleton are the predominant site of metastases in most men with prostate cancer. These lesions are frequently symptomatic and can cause pain, functional impairment, and debility. The goals of treatment are to relieve pain, improve mobility, and prevent complications such as pathologic fractures or epidural spinal cord compression. (See "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis".)

Systemic antitumor therapy may alleviate symptoms from bone metastases, but other treatments may also be needed. (See "Bone metastases in advanced prostate cancer: Management").

**Radiation therapy**

- External beam radiation therapy (RT) — External beam RT is indicated for men with either a single or a few focally symptomatic bone metastases, when pain cannot be controlled with moderate analgesics. Local field RT provides some benefit in 80 to 90 percent of cases, and 50 to 60 percent have complete relief of symptoms. Repeated use of palliative RT, especially when given to areas encompassing much of the active marrow, can cause bone marrow suppression, which may impair quality of life and limit the use of palliative chemotherapy. (See "Radiation therapy for the management of painful bone metastases", section on 'External beam RT'.)

- Radiopharmaceuticals — The alpha-particle emitting radiopharmaceutical radium-223 decreases bone pain and delays or prevents the complications of bone metastases. (See 'Radium-223' above and "Bone metastases in advanced prostate cancer: Management", section on 'Radium-223'.)

  The beta-particle emitting radioisotopes samarium-153 (153Sm) and strontium-89 (89Sr) have been used for palliative treatment of patients with multifocal, painful osteoblastic bone metastases and those with persistent or recurrent pain despite receiving external beam RT to maximal normal tissue tolerance. However, the role of these agents is less clear with availability of radium-223. (See "Bone metastases in advanced prostate cancer: Management", section on 'Beta emitting radiopharmaceuticals'.)

- **Osteoclast inhibition** — For men with bone metastases, the use of an osteoclast inhibitor (denosumab, zoledronic acid) is an important adjunct to reduce the risk of skeletal complications of bone metastases. (See "Bone metastases in advanced prostate cancer: Management", section on 'Osteoclast inhibition'.)

- **Analgesics** — The presence of pain in men with advanced prostate cancer should prompt immediate and aggressive management with analgesics while local or systemic treatments that directly address the cause of the pain are pursued. The use of nonopioid analgesics, opioids, and analgesic adjuvants is discussed elsewhere. (See "Cancer pain management with opioids").
Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs" and "Cancer pain management: Adjuvant analgesics (coanalgesics)."

PALLIATION OF PELVIC DISEASE — Advanced prostate cancer can cause pelvic symptoms that significantly impair quality of life. These include lower urinary tract symptoms, pelvic pain, hematuria, and obstructive rectal symptoms. Systemic therapy is the primary approach for the control of such symptoms. (See 'Androgen deprivation therapy' above and 'Castration resistant disease' above.)

Although there are no prospective clinical studies in patients with castration resistant prostate cancer, retrospective series indicate that radiation therapy (RT) may be useful for symptom palliation [28-30]. As an example, in one series, 58 men were treated with 20 Gy in five fractions [28]. Four months after RT, 31 of 35 patients (89 percent) had complete resolution of symptoms. In a second series, a more protracted RT schedule (2 Gy fractions, median dose 60 Gy) gave similar results [29].

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.)

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

SUMMARY AND RECOMMENDATIONS

- Although most men with prostate cancer are diagnosed and successfully treated while disease is localized, some will present with or subsequently develop disseminated disease. This is often manifested initially by an increasing PSA in patients who are being closely followed for evidence of recurrence after definitive treatment. In other cases, however, overt metastatic disease may be present when the patient is first diagnosed or at some time after definitive treatment for locoregional disease. The same treatment options are generally used for men with overt metastases and those whose only evidence of disease is an elevated or rising serum PSA. (See 'Patient populations' above.)
- Previously untreated prostate cancer generally is dependent upon androgen for its continued growth. This observation provides the basis for androgen deprivation therapy (ADT) as a component of the initial systemic therapy. Treatments targeting androgenic stimulation of the tumor are also used in several subsequent treatment modalities. (See 'Androgen deprivation therapy' above and 'Interference with androgenic stimulation' above.)
- We recommend initial treatment with either medical or surgical orchiectomy (ADT) to suppress serum testosterone levels for all patients requiring systemic therapy (Grade 1A).
This approach replaced estrogen therapy, which was associated with increased cardiovascular toxicity in randomized trials. Other modalities that have been shown to prolong survival in men with castration resistant disease have not been evaluated as initial therapy and are not indicated in this setting (table 1). (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Surgical orchiectomy' and "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Medical orchiectomy'.)

- The optimal timing for initiating treatment depends upon the extent of disease as well as patient specific factors:
  - For men whose only evidence of disseminated disease is an elevated or rising PSA following definitive locoregional therapy, the optimal timing for initiation of ADT is problematic and involves a consideration of the prolonged natural history of the disease, as well as patient specific factors including age and personal preferences. (See "Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification", section on 'Natural history after biochemical failure' and "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'When to initiate ADT'.)
  - For men with overt metastases, we suggest immediate rather than delayed treatment (Grade 2B). This approach has been shown to significantly decrease prostate cancer-related deaths, but the difference in overall survival was not statistically significant. (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Timing of ADT'.)
    - For men with low volume disease (ie, no visceral metastases and less than four bone metastases), we suggest treatment with ADT alone rather than chemohormonal therapy (Grade 2B). (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Androgen deprivation therapy'.)
    - For men with high volume disease (visceral metastases and/or four or more bone metastases), we recommend chemohormonal therapy combining ADT with docetaxel chemotherapy rather than ADT alone (Grade 1B). (See "Initial therapy for castration sensitive metastatic prostate cancer", section on 'Chemohormonal therapy'.)

- Castration resistant prostate cancer is defined by the occurrence of disease progression after surgical or medical orchiectomy. The presence of castration resistant disease does not imply that disease is totally independent of androgens and resistant to further therapies directed at blocking androgen stimulation. ADT should be continued when additional systemic therapy is used in men with castration resistant disease. (See 'Castration resistant disease' above and "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Continuation of ADT'.)

- For men with castration resistant prostate cancer, we recommend that therapy sequentially incorporate modalities that have been demonstrated to improve overall survival, and the choice of therapy should be guided by the patient population studied in clinical trials (table 1). Potential options include interference with androgenic stimulation of tumor growth (abiraterone, enzalutamide), sipuleucel-T, taxane chemotherapy (docetaxel, cabazitaxel), and radium-223. Older approaches that may have a role in selected cases include antiandrogens, antiandrogen withdrawal, suppression of adrenal steroidogenesis with ketoconazole or steroids, estrogens, and progesterones. (See 'Castration resistant disease' above.)
Factors that should be considered include the site and extent of disease, rate of disease progression, symptomatology, comorbidities, regulatory status and availability of the modality, side effects of the treatment, and contraindications.

(See 'Sequence of systemic therapies' above.)

●Osteoblastic lesions in the axial skeleton are the predominant site of metastases in the majority of cases. For men with bone metastases, the use of an osteoclast inhibitor is an important adjunct to systemic therapy to reduce the risk of skeletal complications (pathologic fracture, epidural spinal cord compression). In addition, external beam radiation or radiopharmaceuticals may provide important symptom palliation for men with severe pain at one or more sites due to bone metastases. (See "Bone metastases in advanced prostate cancer: Management".)

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REFERENCES


