contribution of benign prostatic tissue to serum PSA levels. It is calculated by dividing the total serum PSA level by the estimated gland volume (usually determined by transrectal ultrasound measurements) to estimate the PSA produced per gram of prostate tissue. As men age, their prostates tend to enlarge with BPH. One would then anticipate that, overall, older men would have higher serum PSA levels than younger men. The upper *age-specific PSA* reference ranges are 2.5 ng/mL for men 40 to 49 years of age, 3.5 ng/mL for men 50 to 59 years, 4.5 ng/mL for men 60 to 69 years, and 6.5 ng/mL for men 70 to 79 years. Consequently, a serum PSA value of 3.5, while it will appear as a normal value on a laboratory test, is a worrisome finding in a man in his 40s, warranting additional evaluation. Another means of interpreting serum PSA tests is to assess PSA velocity or the rate of change of PSA. Men with prostate cancer demonstrate a more rapid increase in PSA levels over time than do men who do not have prostate cancer. The rate of change in PSA that best distinguishes between men with and without prostate cancer is 0.75 ng/mL per year. For this measurement to be valid, at least three PSA measurements must be performed over a period of 1.5 to 2 years, as there is substantial short-term variability (up to 20%) between repeat PSA measurements. A man who has a significant increase in serum PSA levels, even if the latest serum PSA test is below the normal cut-off (<4 ng/mL), should undergo additional work-up. Studies have revealed that immunoreactive PSA (the form detected by the widely used antibody test) exists in two forms: a major fraction bound to α_1-antichymotrypsin and a minor free fraction. The percentage of free PSA (free PSA/total PSA × 100) is lower in men with prostate cancer than in men with benign prostatic diseases.

Because many small cancers localized to the prostate may never progress to clinically significant invasive cancers, there is considerable uncertainty regarding the management of small lesions that are detected because of an elevated PSA level. This has created controversy about the role of widespread screening for prostate cancer. Much effort is therefore focused in devising criteria by which those localized lesions most likely to advance can be distinguished from those that remain innocuous.

In contrast to its role in screening, there is no controversy about the value of serial measurements of PSA in assessing the response to therapy. For example, a rising PSA level after radical prostatectomy or radiotherapy for localized disease is indicative of recurrent or disseminated disease. Immunohistochemical localization of PSA on tissue sections can also help the pathologist to determine whether a metastatic tumor originated in the prostate.

In addition to prostate specific antigen, other genes that may serve as biomarkers in prostate cancer have emerged. *PCA3* is a noncoding RNA which is overexpressed in 95% of prostate cancers. A diagnostic test that quantifies urine PCA3 is currently used as an additional biomarker in patients suspected to have prostate cancer because of elevated PSA, but who have had a negative prostate biopsy. Elevated urine PCA3 scores have been shown to be associated with an increased risk of a positive repeat biopsy in this setting. The combination of urinary PCA3 with screening of urine for *TMPRSS2-ERG* fusion DNA (see earlier) may have increased sensitivity and specificity compared to PSA screening alone.

Cancer of the prostate is treated by surgery, radiation therapy, and hormonal manipulations. More than 90% of patients who receive such therapy can expect to live for 15 years. Currently, the most common treatment for clinically localized prostate cancer is radical prostatectomy. The prognosis following radical prostatectomy is based on the pathologic stage, margin status, and Gleason grade. Alternative treatments for localized prostate cancer are either external-beam radiation therapy or interstitial radiation therapy, the latter consisting of placing radioactive seeds throughout the prostate (brachytherapy). External-beam radiation therapy is also used to treat prostate cancer that is too locally advanced to be cured by surgery. Since some prostate cancers have a relatively indolent course, wherein it may take 10 years to see benefit from surgery or radiation therapy, active surveillance is appropriate for many older men or those with significant co-morbidity or even some younger men with low serum PSA values and limited lower grade cancer on biopsy. Advanced, metastatic carcinoma is treated by androgen deprivation therapy. Androgen deprivation may be achieved by orchiectomy, or by administration of synthetic analogs of luteinizing hormone-releasing hormone (LHRH) which suppress normal LHRH, achieving, in effect, a pharmacologic orchiectomy. Other agents decrease levels of local and circulating androgens by inhibiting systemic steroid hormone synthesis. Finally, pharmacologic blockade of the androgen receptor constitutes an additional means of treatment. Although androgen deprivation therapy induces remissions, eventually tumors become resistant to testosterone withdrawal, an event that is a harbinger of disease progression and death.

KEY CONCEPTS

Carcinoma of the Prostate

- Carcinoma of the prostate is a common cancer of older men between 65 and 75 years of age. Aggressive, clinically significant disease is more common in American blacks than in whites, while clinically insignificant occult lesions appear to occur at equal frequencies in these two races.
- Prostate carcinomas range from indolent lesions that will never cause harm to aggressive fatal tumors.
- The most common acquired genetic lesions in prostatic carcinomas are *TPRSS2-ETS* fusion genes and mutations or deletions that activate the PI3K/AKT signaling pathway.
- Carcinomas of the prostate arise most commonly in the outer, peripheral gland and may be palpable by rectal examination.
- Microscopically, they are adenocarcinomas with variable differentiation. Neoplastic glands are lined by a single layer of cells.
- Grading of prostate cancer by the Gleason system correlates with pathologic stage and prognosis.
- Most localized cancers are clinically silent and are detected by routine monitoring of PSA concentrations in older men. Bone metastases, often osteoblastic, typify advanced prostate cancer.

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