PSA and prostate cancer:
In patients with prostate cancer, prostate specific antigen (PSA) levels may be elevated due to increased production, as well as due to a disruption of tissue barriers between the gland lumen and capillaries. Studies have shown that high PSA levels can precede clinical disease by 5 – 10 years or even longer. The overlap of PSA levels in patients with cancer and those with benign conditions can cause diagnostic dilemmas.

20% – 50% of men with newly diagnosed cancer in the USA have serum PSA values below 4 ng/ml. These cancers that are detected when PSA levels are < 4 ng/ml are more likely to be organ confined and have a better prognosis.

1) Clinical presentation and diagnosis of prostate cancer:
- Symptoms are an unusual presentation, and may be difficult to differentiate from benign conditions. Patient age, prostate volume, digital rectal examination (DRE) findings, and family history must all be considered.
- Most patients who undergo biopsy do so because of a PSA determination, despite the current controversy surrounding screening.
- Although the likelihood of having a biopsy positive for cancer increases as the PSA levels rise, there is no absolute value that can be used as a threshold to determine the need for a biopsy.
- Monitoring trends in PSA over a period of time is helpful. A change from prior values (an increase of more than 0.35 ng/ml/year for a PSA of < 4.0 ng/ml OR more than 0.75 ng/ml/year if the PSA is > 4 ng/ml) should be considered suspicious.
- DRE retains an important role for early detection. About 20% of cases have a prostate nodule that prompts a biopsy. An abnormal DRE, especially if there is asymmetry, nodularity or induration, should prompt a biopsy regardless of the PSA level.
- Diagnosis requires a tissue biopsy, which should be preceded by measurement of PSA levels.

2) Evaluation of the newly diagnosed patient:
The initial evaluation of the newly diagnosed patient with prostate cancer and the standard staging system of the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) both incorporate the pre-treatment PSA level, together with other entities like the Gleason score and imaging studies. These parameters are used in algorithms for risk stratification, and treatment selection. For details on staging kindly refer to Prostate (Chapter 41). In: AJCC Cancer Staging Manual, Edge S, et al. (Eds), Springer-Verlag, New York 2010.

3) Active surveillance:
Active surveillance for localised prostate cancer entails observation rather than immediate intervention. The parameters used are PSA monitoring, DRE and repeat biopsy. In Toronto (using guidelines consistent with the American Urological Society (AUA) and the National Comprehensive Cancer Network (NCCN)), the monitoring plan and criteria for active intervention are:
- Measurement of PSA at 3 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 biopsy after 1 year to rule out higher grade disease that may have been missed originally, or developed as a consequence of tumour progression.

Figure 1: Probability of dying of prostate cancer according to number of PSA doublings per year: ²²
Treatment and follow-up:
The mainstay of follow-up in all patients after therapy for cancer is clinical evaluation and PSA testing.
- The NCCN guidelines for men who have undergone definitive therapy for localised disease suggests monitoring PSA levels every 6 – 12 months for 5 years, and then annually thereafter.
- Routine imaging procedures are not indicated in the absence of symptoms or a rising PSA level.
- In metastatic disease, surveillance should be geared towards the detection of progressive disease, and the side effects of long term androgen deprivation therapy. Physician visits and serum PSA monitoring every 3 – 6 months is reasonable.

PSA-only (biochemical) recurrence:
PSA is a sensitive and specific marker after diagnosis of prostate cancer. Monitoring levels after treatment of localised cancer can lead to the identification of men with a PSA-only recurrence, when there are no symptoms or signs of locally recurrent or metastatic disease.
- For patients that have undergone a radical prostatectomy, the AUA defines a biochemical recurrence as a PSA ≥ 0.2 ng/ml, which is confirmed by a second determination with a PSA ≥ 0.2 mg/ml.
- For patients initially treated with radiation, the American Society for Therapeutic Radiology and Oncology has developed the Phoenix Criteria. A PSA recurrence is defined as an increase of 2 ng/ml or more above the nadir PSA, regardless of whether the patient receives androgen deprivation therapy. The date of failure is defined in the Criteria by the time the rise in PSA is noted.
- A PSA-only recurrence does not predict the development of metastatic disease, and is not necessarily an indication for treatment.

Other tests in patients with prostate cancer:

A. Serum free and bound PSA:
In men with a normal prostate, the majority of free PSA in the serum reflects the mature protein that has been inactivated by proteolytic cleavage. In contrast, the cleaved fraction is relatively decreased in men with prostate cancer. Thus, the percentage of free PSA (f/t PSA) is lower in the serum of men with prostate cancer compared to those that have a normal prostate or BPH.

The f/t PSA has been used to improve the sensitivity of cancer detection when the total PSA is in the normal range (< 4ng/ml) and to increase the specificity when total PSA is in the grey zone (4.1 – 10 ng/ml). In the latter group, the lower the value of f/t PSA, the greater the likelihood that an elevated PSA represents cancer, and not BPH. As with PSA, there is no absolute f/t PSA cut off that completely discriminates cancer from BPH.

Free PSA may be useful for risk stratification in prostate cancer. A lower percentage of f/t PSA may be associated with a more aggressive form of prostate cancer.

B. Complexed PSA (cPSA):
The amount of cPSA is higher in men with prostate cancer compared to men with a normal prostate or those with BPH. Some reports suggest that cPSA outperforms both total PSA and the ratio of f/t PSA, with a similar sensitivity but a higher specificity. It is also used in the monitoring of prostate cancer patients.

C. PSA density and velocity:
PSA density (PSA divided by prostate volume measured by transrectal ultrasound) and PSA velocity (rate of change of PSA over time) are emerging concepts. The use of these techniques is not consistent and remains under debate.

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