

CHAPTER 15

PROSTATE CARCINOMA

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Prostate carcinoma is the most common life-threatening cancer affecting men in the Western world. In the United States, it is estimated that almost 250,000 new cases are diagnosed annually and that approximately 1 in 10 will ultimately die of the disease despite improved methods of early diagnosis, evaluation, and management. Prostate cancer is the second highest cause of cancer-related death per year, second only to bronchogenic carcinoma in the United States.¹ Rates of detection vary widely, with the incidence in South and East Asia less frequent than in Europe and United States.² Prostate carcinoma tends to develop in men over the age of 50; it is diagnosed in 80% of men by the age of 80. Recently, there has been recognition that the disease in older men may not merit the same vigorous intervention as in younger men. This insight evolves from greater understanding of the complex biology and clinical course of this tumor.

In the development of prostate cancer, many factors have been implicated: genetics and diet among them. The American Dietetic Association and Dieticians of Canada report a decreased incidence of prostate cancer in men who follow a vegetarian diet.³ However, there is no established relationship between any environmental factor and the incidence or aggressive nature of prostate carcinoma.

In the majority of cases, in the early stages, prostate cancer is harmless and symptom free. This leads to the assumption that appropriate and sensitive diagnostic procedures are crucial for a good survival rate. The serum marker prostate specific antigen (PSA) provides an early clue to the presence of prostate carcinoma but it is a nonspecific biomarker. It is increased in the serum of men as they age and the prostate enlarges, as well as in patients with prostatitis. Nevertheless, an elevated PSA value should lead to other diagnostic procedures such as digital rectal examination, endorectal ultrasound (US) and biopsy resulting in earlier detection of malignancy than had been the case prior to the availability of PSA determinations. The earlier and improved detection of prostate carcinoma has contributed to an apparent increase in the incidence of prostate malignancy. Nevertheless, clinical management remains complex including the choice of therapeutic intervention. This depends somewhat on the age of the patient at the time of detection as well as the nature (degree of aggressiveness) and extent of disease. In recent years, a variety of imaging modalities have become available: US, computed tomography (CT), and magnetic resonance imaging (MRI) improve detection of disease within the prostate gland but they do not identify nodal or distant metastases early in the course of the disease nor do they characterize the degree of aggressiveness of the tumor. Identification of lymph node involvement by either CT or MRI is based primarily on size criteria; nor do these modalities determine the degree of aggressiveness of the tumor, a feature that would be useful to guide therapy. In summary, the following represents needs that are not satisfied by conventional imaging methods (CT, MRI).

- Early detection and localization of tumor within the prostate gland (to avoid false-negative biopsies)
- Characterization of the degree of aggressiveness of the tumor foci (to avoid under- or overestimating therapeutic options)
- Early detection of lymph node metastases
- Early detection of distal metastases

CLINICAL FEATURES OF PROSTATE CARCINOMA

Early disease is detected by elevation of a serum PSA value leading to a workup that involves a digital rectal examination, referral

to a urologist, endorectal US, and biopsy. In addition to providing a diagnosis of malignancy, biopsy material provides a means to assign a Gleason grade. The Gleason scoring system is based upon the microscopic architecture which provides a measure of the degree of aggressiveness of the malignant tissue and serves as a prognostic indicator, thus assisting in determining management strategy. The grades range from 1, with small closely packed, relatively orderly pattern, to 5, with larger poorly differentiated cells, lack of glandular architecture, and considerable disarray. The sum of the two most common patterns provides the overall Gleason score from 2 to 10. Higher Gleason scores (i.e., a Gleason score of 7 and above) are associated with poorer prognosis.

With the widespread availability of serum PSA, patients are now seen early in the course of disease where many patients will not have obvious findings of pelvic or distal involvement. Treatment in these cases is focused on the prostate gland. This involves either surgical prostatectomy or external beam radiation or brachytherapy (insertion of radioactive seeds directly into the prostate). In recent years, other techniques to remove tumor without sacrificing the entire prostate gland (such as cryosurgery) have become available but they are not widely used. Improved mapping of the intraprostatic distribution of tumor and characterization of the degree of aggressiveness of the tumor would enable better informed decision making and perhaps modify surgical and subsequent clinical management. These options may be accompanied by hormonal therapy; that is, elimination of androgen hormones that have a stimulating or supportive effect on prostate tissue and tumors. It is no longer necessary to surgically castrate these patients; the hormonal suppression of testosterone is sufficient to be considered pharmacologic castration. The serum PSA value falls to very low or undetectable levels and is measured periodically. In approximately one of three patients, after a quiescent period up to 5 years after initial treatment with no biochemical (PSA) evidence of disease, a rise in the serum PSA is detected. If the PSA level rises, the next challenge is to identify the location and extent of the source:

- prostate bed recurrence and/or
- pelvic lymphadenopathy and/or
- distal osseous and/or
- soft tissue involvement

Obviously, if the patient has not undergone surgical prostatectomy, the assessment of recurrent disease in residual prostate gland tissue is another challenge.

Each of these possibilities, from extent of disease at presentation to the reappearance of PSA in the treated patient, presents many decisions and choices for the patient and urologist or oncologist. Until recently, US, CT, MRI, and ^{99m}Tc methylene diphosphonate [^{99m}Tc-MDP] bone scintigraphy were the only imaging procedures available to assess the extent of disease in patients with prostate carcinoma. Radionuclide bone scintigraphy, of course, was only useful to determine if bone metastatic disease was present. Regardless of whether it was positive or negative, it did not exclude soft tissue involvement. In the United States, In-111 pentetide caproate [*Prostascint*], a radiolabeled monoclonal antibody, has been approved for its use to determine the extent of disease in newly identified patients who were at high risk for early metastatic disease based on the Gleason score of biopsied tissue and to identify the source of rising PSA values in patients who had undergone surgical prostatectomy. The technique, however, has had limited utility.

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strides toward development and clinical applications of advances using SPECT and PET imaging agents with excellent sensitivity and specificity. The first of these advances, an ^{111}In -labeled anti-PSMA antibody, had limited access and application. Although prostate carcinoma was sometimes identified with FDG PET, it was found not to be sufficiently sensitive to detect all foci. Currently, the most sensitive agent for the detection of intraprostatic tumor, lymph node, and distal involvement appears to be ^{18}F -Fluorocholine [^{18}F -FCH] although it is not specific for PSMA nor does it differentiate between aggressive, higher Gleason score foci and less aggressive disease. Since it ^{18}F has a 2-hour half-life, it can be prepared in regional centers and distributed similar to FDG. In fact, ^{18}F -FCH is commercially available in Europe. In the United States, ^{11}C -Choline has been approved by the FDA on a site-by-site basis. Approval of ^{18}F -FDG is a more complex issue but it is certainly probably that the FDA requirements can be met. When it is approved and can be reimbursed, it is likely that ^{18}F -FCH will become widely available for clinical applications. Although this would be a major contribution to the management of patients with prostate carcinoma, there are several drawbacks. First, ^{18}F -Fluorocholine uptake is neither prostate tumor-specific nor does the degree of uptake reflect the degree of tumor aggressiveness. Since PSMA expression is somewhat proportional to the degree of tumor aggressiveness, tracers that bind PSMA with high affinity are likely to provide quantitative or semiquantitative information about the aggressiveness of primary and metastatic prostatic carcinoma foci. Although radiolabeled fragments of the anti-PSMA antibody, J591, that recognize the extracellular epitope of PSMA are being evaluated, the agent most likely to fill this niche is one of the small molecules that have high affinity binding to the enzymatic component of PSMA. The already developed $^{99\text{m}}\text{Tc}$ -versions of this class of compounds provide excellent resolution images capable of distinguishing discrete foci within the prostate as well as characterizing the degree of aggressiveness and locating local and distal metastases. At this point, it is not possible to predict whether the $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals will be supplanted in time by a positron-emitting version.

Targeted radionuclide therapy also has made great strides, predominantly with the antibody J591, radiolabeled with ^{177}Lu . Although the clinical trials have been performed in only a limited number of Medical Centers, a Phase II trial of a divided dose regimen using ^{177}Lu -DOTA-J591 is nearing completion after which it could become more widely available as a Phase III trial and potentially an approved form of therapy. In addition, there are several ongoing Phase I trials to assess the role of ^{177}Lu -DOTA-J591 to treat earlier phases of recurrent disease as well as an adjuvant trial which would require participation of larger numbers of centers.

In summary, radiolabeled small molecules are likely to emerge as imaging agents to identify prostate carcinoma. It is unclear at this point if the comparatively long circulating time of radiolabeled antibodies which results in a larger fraction of the administered dose being delivered to tumor sites, thus increasing the radiation absorbed dose will be more effective than the total radiation delivered by very high affinity radiolabeled small molecules that are retained by tumor sites.

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