

CARCINOMA OF THE PROSTATE GLAND

EUGENE F. POUTASSE, M.D.

Department of Urology

CONSIDERABLE progress has been made in the treatment of cancer of the prostate in the last decade.¹ This advancement is based upon control of the cancer by eliminating the testicular androgenic stimulus for growth and by utilizing the inhibitory action of estrogens. Striking clinical improvement in advanced cases usually results from such hormonal therapy. When the cancer is localized within the prostate it can be removed completely by extirpation of the gland. The pathology, diagnosis, and treatment of prostatic cancer will be discussed herein and the necessity for early, accurate diagnosis stressed before the carcinoma has extended beyond the gland and become widespread.

Incidence. According to a Public Health Report in which figures are standardized for age and sex, carcinoma of the prostate ranks next in frequency to malignancy of the stomach and skin.² The incidence of cancer of the prostate gland actually is much higher because of the large number of cases unrecognized clinically. Rich³ reported finding cancer in 41 out of 292 prostate glands from consecutive autopsies examined by single section, an incidence of 14 per cent. Moore⁴ found the incidence to be 21 per cent in the prostate glands of men over 50 years of age in whom the diagnosis was not made clinically or in the gross findings at autopsy. Kahler⁵ reported an incidence of 17 per cent, and Baron and Angrist⁶ discovered cancer in 23 of 50 prostate glands examined similarly by serial block examination, an incidence of 46 per cent. These pathologic studies show that the occurrence is much higher than recognized, a fact of increasing importance as life expectancy increases. In a series of 100 patients with cancer of the prostate gland recently reviewed,⁷ 10 cases were not recognized clinically or at the time of operation, the cancer having been discovered only on pathologic study. In an additional 10 patients, cancer developed 1 or more years after prostatic surgery for benign enlargement. The latter cases may have existed as clinically unrecognized foci at the time of the original operation or may have developed subsequently.

Age Distribution. Although prostatic cancer seldom is encountered in patients younger than 50, its occurrence is frequent enough to demand consideration when evaluating the prostate gland of a man in the lower age group. Approximately 10 per cent of all clinically recognized cases are in patients between 50 and 60 years of age, but the majority (75 per cent) are discovered between the ages of 60 and 80. The remaining 15 per cent are found in men past 80 years of age. As shown by Moore,⁴ the clinically unrecognized or "occult" carcinomas of the prostate gland follow, in general, the same age distribution; however, the incidence of these unrecognized cancers increases after 80 years of age.

Pathology. The cancer most commonly encountered is adenocarcinoma which comprises 95 per cent of all cases⁸ and is derived from epithelial glandular

elements of the true prostate. The majority of these neoplasms are composed of proliferative, invasive acini and are known as *adenocarcinoma*. A few of the lesions form small subsidiary acini within a larger acinus, and sometimes are referred to as medullary carcinomas. A small percentage are so dedifferentiated that lumen formation is absent; these are known as undifferentiated carcinomas and are usually of scirrhus type. A mixture of the various types may occur in the same gland.

According to Lewis,⁸ less than 5 per cent of cases of carcinoma of the prostate gland arise from the modified transitional cell epithelium lining of the prostatic ducts. These are best known as *transitional cell carcinoma* although some authors use the term squamous cell carcinoma, despite the fact that these tumors show no keratinization or squamoid characteristics. Squamous metaplasia is frequently observed in the prostate gland and is usually related to areas of previous infarction or to prolonged hormonal therapy. Sarcoma of the prostate rarely is encountered, most of the cases occurring in boys before the tenth year of life.

Origin. Much discussion has arisen concerning the origin of prostatic neoplasms. Benign enlargement of the prostate develops from the prostatic ducts and the periurethral glands of Albarran,^{9,10} consisting of a new growth of fibrous, muscular and glandular tissue arranged in lobules along the prostatic urethra. This enlargement, as shown by Le Duc,¹¹ pushes the true prostatic glands and parenchyma outward, thereby forming the surgical capsule of the prostate which extends from the apex to the base and laterally around the urethra to include the anterior commissure. With few exceptions, cancer has been found to have arisen from the atrophic prostatic glands in any part of this capsule, microscopic foci having been observed in all parts of the capsule.⁴ It is generally agreed, however, that about 70 per cent of the lesions arise originally from the posterior lamella or lobe, although after extensive growth has occurred it is impossible to determine the origin. In a series of more than 200 prostate glands removed by perineal prostatectomy for early cancer, Lewis⁸ found the lesion in the posterior lamella in all cases; in this location it is readily palpable on rectal examination. There is, as yet, no adequate means of diagnosing early carcinoma arising in the anterior commissure or adjacent lateral lobes unless the growth is palpable.

No known relationship exists between adenomatous enlargement and carcinoma of the prostate gland, the two conditions occurring as often together as not. Neither is there a recognized affinity between chronic prostatic infection or calculi and neoplasm. It is believed generally that the prostatic glands first must undergo atrophy before malignant change can occur; nevertheless adenocarcinomas have been found in men of 35 to 50 years of age. Although it is now a well-established fact that androgens provide the stimulus for growth of established prostatic neoplasms, the relationship of androgens or other hormonal influences to initiation of the malignant change is unknown.

Course of Metastasis. There are several possible routes of metastatic spread of prostatic carcinoma. Venous involvement permits widespread dis-

semination throughout the body and, as shown by Batson,¹² ready access via the vertebral veins to the pelvis, spine, ribs and skull. An abundant lymphatic and perineural lymphatic supply exists within the prostate, which usually is invaded early. Metastasis by the regular lymphatic channels to the lymph glands within the pelvis is an important route of generalized spread. Invasion of the perineural lymphatics, according to Warren, Harris and Graves,¹³ provides a course of entry to the pelvis and lower spine, and occasionally around the rectum, along the periprostatic and larger nerve trunks. Direct extension of prostatic cancer to the adjacent structures, bladder base, seminal vesicles and urethral bulb is also common.

Symptoms. Early or localized prostatic cancer is usually unaccompanied by symptoms. Discovered only by systematic rectal examination of all patients, regardless of symptoms, its presence is demonstrated by a small nodule or indurated area within the gland, as shown in the following case.

Case Report

A 64 year old man was referred to the Cleveland Clinic because of a dermatologic problem. Rectal examination revealed a localized area of firm induration within the prostate gland. There were no significant urologic symptoms. Thorough investigation disclosed no evidence of spread outside the gland. Perineal biopsy was performed, the diagnosis of carcinoma confirmed, and complete removal of the gland carried out.

The diagnosis of early cancer can be established in this manner and complete eradication offered the patient. In early cases obstructive urinary symptoms exist only when associated adenomatous enlargement is present. The advanced stages of prostatic neoplasm, conversely, usually produce obstructive urinary symptoms or complete retention of urine. This is not always true, however, as demonstrated by the sizeable group of patients having metastasis but relatively unimportant, or no urinary symptoms. These patients may manifest other indications of the disease such as weight loss, weakness, paralysis or pain. The pain is characteristically progressive, unremitting, and localized most commonly in the back, pelvis, perineum, or thighs.

Diagnosis. The earliest recognizable malignant lesions consist of small, indurated, nodular areas the size of a pea or larger, within the posterior lamella of the gland. Careful palpation with attention to the anatomic details of the gland will reveal additional information regarding the character and extent of the lesion. In a man more than 45 years of age such findings, regardless of localization, must be viewed with suspicion, particularly if there is no history or evidence of prostatitis or tuberculosis, and roentgenograms fail to show the presence of prostatic calculi. It should be remembered, however, that cancer can develop independently in the presence of any of these diseases. Cancer probably exists when a hard, rounded nodule is felt within the prostate. In the advanced stages prostatic cancer is easily recognizable as a hard, irregular, fixed tumor with infiltration into the surrounding tissues.

A small percentage of prostatic malignancies are not characteristically hard on rectal palpation; in these instances diagnosis may be especially difficult. Occasionally in prostatic cancer cystic degeneration occurs, with a nontender cystic mass occupying the region of the gland. The first clue to correct diag-

nosis under these circumstances may be derived from an elevated serum acid phosphatase determination or by roentgenographic evidence of typical osseous metastasis.

Palpation of the prostate with a rigid instrument or cystoscope in the urethra, particularly if performed under an anesthetic, is decidedly helpful in delineating these areas of induration and determining fixation of the gland. Fixation is usually an index of metastatic spread outside the capsule. Typical cystoscopic findings are generally lacking unless there is extension of the process around the vesical neck.

The phosphatase enzymes, capable of splitting phosphates, show maximum activity in either an acid or alkaline range. Acid serum phosphatase is present in small quantities in the blood of normal persons. It is present in normal adult prostates and usually is found in large amounts in neoplastic prostatic tissue. Under certain conditions it enters the blood stream where it is detectable and diagnostically important. As this phenomenon occurs only when the carcinoma has extended beyond the capsule of the prostate, the test is valueless as a diagnostic adjunct in cases of early localized carcinoma. The real value of an increased serum acid phosphatase determination is to support the diagnosis of extensive prostatic carcinoma or to differentiate various bone lesions. In patients with extensive prostatic cancer, but no roentgenographic evidence of metastases, about one-third may have an elevated serum acid phosphatase or alkaline phosphatase or both. In patients with roentgenographic evidence of metastasis, two-thirds may have an elevated acid phosphatase and the majority an abnormal alkaline phosphatase. A normal acid phosphatase value, however, does not disprove the presence of metastasis because the tumor tissue in some patients may not produce sufficient phosphatase to cause elevation of the normal serum level. Slight elevations of the serum acid phosphatase level infrequently are seen in patients with severe hyperparathyroidism, advanced Paget's disease, osseous metastasis from other types of cancer,¹⁴ or as the immediate result of prostatic massage.

Osseous metastases, may occur either early or late in the course of the disease, and are determined by roentgenographic study of the bones. The commonest sites of bone metastases are the spine, pelvis, femur, ribs and skull. The lesions are characteristically osteoblastic although osteolytic metastases are found occasionally, and must be distinguished from the bony lesions of Paget's disease. The latter produces thickening of the cortex of the bone with increased trabecular markings, whereas prostatic cancer produces mottled sclerotic lesions with loss of the trabecular markings. Parenchymal lung lesions generally are a late manifestation of the disease. Unusual but not uncommon findings in advanced cases are edema of the legs due to pelvic lymphatic obstruction by tumor, palpable abdominal masses, skin metastasis, and paralysis due to metastasis involving the nervous system.

Under investigation is the cytologic examination for tumor cells of prostatic fluid obtained by massage.¹⁵ Although this test holds promise, the interpretation of the material is difficult and the results of various workers thus far

have shown it not entirely reliable. Needle biopsies of the prostate prove successful only in cases of extensive cancer, thus serving to confirm the clinical diagnosis. Transurethral biopsies are secured easily when there is evidence of tumor about the vesical neck or prostatic urethra.

Treatment. The treatment of patients with prostatic cancer is based on a careful evaluation of each case. Factors to be considered are the extent of the cancer, age and life expectancy of the patient, presence of associated or unassociated disease, debility, and severity of symptoms. The biologic behavior of the cancer is under various known and unknown hormonal influences and seems related to the age of the patient. Its susceptibility to treatment is often dramatic and long-lasting but not uniform and relapses are common.

Although, when first seen, the majority of patients with prostatic cancer show evidence of extensive infiltration by the tumor, a lesser number have the neoplasm localized within the gland and frequently present difficult problems in diagnosis and therapy. In many respects, the management of these early neoplasms of the prostate is similar to that of breast nodules in women. Suspicious nodular areas in the prostate should be subjected to perineal exposure and biopsy. If the diagnosis of malignancy can be established from frozen section or the operator is convinced of its presence by exploration, total prostatectomy with removal of the adjacent bladder neck and seminal vesicles should be performed immediately. If it is necessary to wait for permanent section, the incision may be closed and surgical therapy specified by the final pathologic diagnosis. If the suspected lesion proves, beyond doubt, to be non-malignant on adequate exploration and frozen section, the operation can be terminated, unless enucleation of enlarged adenomatous lobes is indicated. Patients who undergo a simple perineal prostatic biopsy need remain in the hospital only a few days.

Young,¹⁶ Colston,¹⁷ and others have reported series of total prostatectomies for carcinoma with corrected 5 year survival rate of more than 50 per cent, most of these operations having been performed before antiandrogenic therapy was known. As soon as the diagnosis of cancer is made or suspected clinically, estrogenic therapy should be instituted for a few weeks prior to operation. Softening and reduction of localized nodular areas occur within a short period, making the operation less difficult and reducing the likelihood of spreading the cancer cells. Despite this apparent regression by hormonal therapy, the cancer is still present as illustrated by the following case.

Case Report

A man, aged 56, was first seen in October 1950 with the complaint of lower abdominal pain resulting from chronic constipation. Examination disclosed a hard nodule in the right lobe of the prostate. No definite extension beyond the prostate could be determined. The acid phosphatase determination was normal and no osseous metastases were demonstrable. Stilbestrol, 3 mg. daily was prescribed for a period of 2½ months, and the hard nodule diminished noticeably leaving only a trace of induration. Perineal biopsy of this area revealed carcinoma and a total prostatectomy was performed. Pathologic examination of the specimen disclosed adenocarcinoma throughout the right posterior portion of the gland and extending into the tip of the adjacent seminal vesicle.

It is generally believed that hormonal therapy should be continued subsequent to operation. As in all cases demonstrating cancer, the patients must be followed at regular intervals.

The treatment of extensive prostatic cancer is palliative; it is based on the elimination by orchiectomy of the testicular androgenic stimulus for its growth, the use of the inhibitory action of estrogens, or both. These measures effect improvement in practically all patients. Relief of symptoms is usually striking and prompt; however relapses may occur in more than 50 per cent within a 2 year period¹⁸ although a small group of men, particularly in the older age group, enjoy prolonged improvement.

Opinions vary as to the efficacy of each type of hormonal therapy. In the collective series of 1818 patients with extensive prostatic cancer observed by the Urosurgical Club, reviewed recently by Nesbit and Baum,¹⁹ the combination of orchiectomy and estrogen therapy provided a statistically significant advantage over either form of treatment used individually in patients without osseous metastasis. Forty-four per cent were alive after 5 years, in contrast with an untreated control group survival of 10 per cent; with either form of antiandrogenic therapy used singly, about 30 per cent will survive 5 years. The same report indicated that patients with bone metastases did not demonstrate as satisfactory an outcome. The 5 year survival of the patients treated either with combined orchiectomy and estrogens, or orchiectomy alone, was 20 per cent in contrast to a survival rate of 10 per cent on estrogens alone and 6 per cent in the untreated control group. The popularity of each type of antiandrogenic therapy has fluctuated since its advent a decade ago. At present, because of the generally satisfactory response, low cost, and ease of administration, the trend is to use estrogens alone. Stilbestrol in daily doses of 3 to 5 mg., or ethinyl estradiol 0.15 to 0.3 mg. daily, may be used. Stilbestrol often produces breast enlargement and, in rare cases, carcinoma of the breast has been induced by this drug.

When urinary obstruction exists, surgical intervention is often necessary. This may be accomplished by transurethral resection in suitable cases. In debilitated patients with advanced renal failure, prolonged suprapubic drainage by means of suprapubic trocar cystostomy is indicated. Many patients with obstructive urinary symptoms, but without significant retention of urine, obtain relief after a short period of hormonal therapy which reduces the size of the primary lesion.

Symptomatic improvement with continuous hormonal therapy prevails for a varying period, older patients deriving the longest and most satisfactory benefit. Most patients subsequently undergo reactivation of the cancer with return of former symptoms, elevation of the serum acid phosphatase, and re-appearance or extension of bone metastasis. At this stage the tumor is largely insensitive to hormonal influence, apparently having undergone certain biologic changes. No satisfactory treatment for this problem has been devised. Increasing the amount of estrogens provides little lasting benefit. Radiation therapy or cordotomy, where indicated, may provide alleviation of pain.

Conclusion

Carcinoma of the prostate is the third ranking malignancy in frequency of clinical recognition in men. The incidence of unrecognized or occult prostatic carcinoma, disclosed at the time of autopsy, is in excess of 20 per cent. Approximately 75 per cent of prostatic cancers arise in the posterior portion of the gland. Small early prostatic carcinomas are diagnosed by rectal palpation and consist of firm nodules or nodular areas within the posterior lamella. Localized prostatic cancers can be eradicated only by total perineal prostatectomy. Antiandrogenic therapy alters the growth of prostatic carcinomata and offers palliation of symptoms and temporary regression of the lesion. The efficacy of various types of antiandrogenic therapy is herein discussed.

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