CURRENT TRENDS IN UROLOGY

Volume 1

EDITED BY

Martin I. Resnick, M.D.

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CURRENT TRENDS IN UROLOGY

Volume 1

DEDICATION

To Vicki, Andy and Jeff

Preface

Changing concepts in urology, as in other areas of medicine, develop with one's personal experience, advances in laboratory and clinical research, and thoughtful interchange between interested individuals. Developments in specialized diagnostic techniques, new forms of medical and surgical therapy, and altered concepts of disease etiology tend to evolve slowly and result from the ideas and efforts of many diverse individuals. It is difficult to clearly pinpoint when a new modality or thought undergoes a transition to the point at which it is accepted and used in everyday clinical practice. Also, and probably rightfully so, it seems that many common practices continue to remain controversial and are not the accepted dogma that we would like to believe them to be.

It is the intent of this new series, *Current Trends in Urology*, to present a group of essays that provide a critical review of changing topics that are of importance to all practicing urologists. The authors are all recognized experts in their particular areas of interest and each of the articles reflects their broad experience and thoughts. I am most pleased to have the opportunity to edit this new series and I hope it will contribute to the care of patients with disorders of the genitourinary system. It is also anticipated that as this series develops with time, it will be a constant expression of the development of new ideas and concepts important to us all.

Martin I. Resnick, M.D.

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CHAPTER 1

Current Concepts in the Staging of Prostatic Cancer

Ronald W. Sadlowski

Almost 25 years ago Whitmore[1] introduced the concept of four clinical categories for staging adenocarcinoma of the prostate. An enormous amount of information concerning the natural history of the various forms of prostatic cancer and comparative methods of treatment has been collected as a result of this staging system. The newer information has in turn led to modifications and refinement of the original staging system in order to acknowledge the importance of the grade as well as the volume of tumor present. As newer staging tools become available further modifications are certain to be adopted. The role of surgical staging has become more refined, and the importance of this procedure is more widely recognized. The newer technology of immunologic assay for acid phosphatase is under active investigation and almost certainly will necessitate further modifications of the staging systems. Current prospective studies using the stratification provided by the present staging systems will further refine our understanding of this disease. Such knowledge will in turn improve our ability to determine the best mode of therapy for any single patient according to his manner of presentation. This review will concentrate on explaining the staging systems as currently constructed and it will also examine in detail some of the newer staging modalities that are currently under investigation.

INITIAL WORK-UP

The diagnosis of prostatic carcinoma is made from the microscopic histologic examination of an adequate biopsy specimen of the prostate by an experienced pathologist. Clinical findings such as prostatic induration on rectal examination, osteoblastic lesions on plain film radiographs of bone, and elevated serum acid phosphatase determinations are all suggestive but without exception require histologic confirmation prior to definitive treatment. Preliminary work-up usually includes a thorough history and physical examination followed by several radiologic, laboratory, and nuclear medicine studies. A history of weight loss or bone pain, if caused by prostatic cancer, usually implies advanced disease and a guarded prognosis. Voiding symptoms are usually related to associated benign prostatic hyperplasia, but if related primarily to prostatic carcinoma portend a poorer prognosis because the stage is usually more advanced. The rectal examination is of primary staging importance because the finding of induration histologically confirmed as prostatic cancer implies at least a stage B classification and if the induration is beyond the limits of the capsule the disease is at least stage C. A good bimanual examination under anesthesia allows the physician to determine if the prostate is movable or fixed and if there

are any pelvic masses suggestive of metastatic disease. Concomitant cystoscopy will confirm or exclude invasion of the bladder neck, trigone, and ureteral orifices by direct extension. An intravenous pyelogram and chest film are routinely obtained. Tomograms of the lungs are usually reserved for evaluation of suspicious lesions noted on posteroanterior or lateral views. The finding of partial or complete ureteral obstruction or the finding of ureteral deviation due to direct extension or extensive nodal metastases usually is indicative of stage D or at least very advanced local disease. Liver function studies, blood urea nitrogen, creatinine, complete blood count, and platelet count are routinely obtained. Liver scans are usually reserved for further evaluation of an abnormal liver on physical examination or abnormal liver function studies. An elevated blood urea nitrogen or creatinine will require the collection of a 24-hour urine for creatinine clearance. The finding of anemia will require hematologic investigation to confirm or exclude metastatic bone marrow replacement as a possible cause. Bone marrow biopsy or aspiration is not a routine staging tool but is reserved for the evaluation of suspected metastatic deposits found on plain radiographs or bone scan or in the evaluation of anemia. The bone scan has all but replaced the metastatic bone survey in the initial evaluation of patients with prostatic cancer and should be obtained in every case as part of the initial staging evaluation and as a baseline for follow-up examinations. Abdominal ultrasonography and computerized axial tomography scanning are still usually reserved for the evaluation of previously determined masses and are not routinely performed in the initial work-up. The role of lymphangiography and surgical staging will be discussed in detail in the text.

STAGING SYSTEMS

Although several clinical staging systems have been proposed since the A through D system was introduced by Whitmore in 1956, none have received universal acceptance.[1] This is largely a reflection of the continued increase in knowledge over the past 25 years of the natural history of prostatic cancer. Discovery of differences in the biologic behavior of more refined subgroups of patients with prostatic cancer has caused a further stratification in the staging systems proposed. Advances in technology have also altered these viewpoints and will continue to do so. For example, although originally it was believed that patients with either stage C or D disease would have elevated serum acid phosphatase (SAP) levels, more recently the Veterans Administration Uro-Oncology Research Group (VA UORG) studies have categorized all patients with elevated SAP into stage IVA (stage D1) with changes to IVB (stage D2) if lymph nodes were positive for tumor and IVC (stage D3) if there was evidence of bony metastases. The development of the radioimmunoassay for prostatic acid phosphatase (PAP) will require an additional accommodation in the staging system because of the increased chance of elevation in patients with earlier stage disease. Until large series of patients are studied using all of these newer modalities, the currently available systems will continue to be useful.

Despite minor variations among the most commonly used staging systems, enough uniformity exists to allow invaluable comparison of data from the clinical series of a diverse group of institutions and cooperative groups.

The TNM system (Table 1.1) for staging prostatic cancer was approved in 1974 by the International Union Against Cancer (I.U.C.C.).[2] Although this system has not been extensively used as such in the United States, many of its important features have been incorporated as early as 1959 by the American Joint Committee of Cancer Staging and End Results Reporting.[3] This led to the use of Roman numerals I, II, III, and IV instead of the corresponding letters A, B, C, and D to make it more consistent with the TNM (tumor, nodes, metastases) classification. However, it has been pointed out that the use of letters has the advantage of avoiding confusion between tumor stage and tumor grade.[4,5] The subsequent splitting of these stages into a growing number of subgroups has enhanced our knowledge of the natural history of the disease, although it continues to restrict the accumulation of sufficient data to referral institutions seeing large numbers of such patients or cooperative research groups.[6]

The details of individual staging systems should be referred to in the literature, but what follows is an attempt to explain the assumptions common to most of them.[1-3, 4, 7, 8] Both clinical and pathologic data are combined in these criteria with some emphasis on grading (Table 1.2).

Stage A

This is prostatic cancer that is clinically inapparent on rectal examination. The disease is localized within the capsule of the prostate and the SAP is usually in the normal range. The disease is detected only incidentally upon examining the tissue removed during transurethral or enucleation surgery for what is thought to be benign disease or in autopsy specimens. Histologic examination of all surgical specimens of prostatic tissue thought to be benign by the surgeon preoperatively will reveal about a 10%, incidence of malignancy.[5, 12, 13] This stage has been subdivided into stage A1 when the histology is low grade (well differentiated) and three or fewer chips or roughly less than 5%[6] to less than 20%[7] of the total specimen is involved by tumor.[3, 8] The degree of accuracy in assigning this stage obviously becomes a function of the extent of sampling.[14] Unfortunately, no sampling standards are available that have universal acceptance. In stage A2, the tumor is more diffuse throughout the specimen and tends to be moderately well or poorly differentiated histologically.[14a] According to the VA UORG studies, roughly 5% of patients admitted to their studies with newly diagnosed prostatic cancer were classified as stage A,[15] although others report as high as 37 and 53%.[16, 17]

Stage B

In this stage the tumor is clinically evident as an indurated area on the surface of the posterior lobe on digital rectal examination. This is a clinical stage usually with a normal range SAP and definitely a normal bone scan. Surgical findings of involved pelvic lymph nodes would upstage the patient to stage D. The subgroup B1 limits the induration to less than 50% of one lobe and includes the classic nodule that is less than 1½ cm in diameter and surrounded by compressable tissue on at least two and sometimes three sides.[3] Some authors even give the nodule a separate category, B1N.[4] In stage B2, there is induration in both lobes, but the disease is still clinically thought to be intracapsular. About 5% of the

Table 1.1
U.I.C.C. Classification of Prostatic Cancer

T—Primary Tumor
- TX The minimum requirements to assess fully the extent of the primary tumor cannot be met
- T0 No tumor palpable. This category includes those cases of the incidental finding of a cancer in an operative or biopsy specimen
- T1 Tumor intracapsular surrounded by palpably normal gland
- T2 Tumor confined to the gland. Smooth nodule deforming contour but lateral sulci and seminal vesicles not involved
- T3 Tumor extending beyond the capsule with or without involvement of the lateral sulci and/or seminal vesicles
- T4 Tumor fixed or invading neighboring structures

N—Regional and Juxta-Regional Lymph Nodes
The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries. The juxta-regional nodes are the inguinal nodes, the common iliac and para-aortic nodes.
- NX The minimum requirements to assess the regional lymph nodes cannot be met
- N0 No evidence of involvement of regional lymph nodes
- N1 Involvement of a single regional lymph node
- N2 Involvement of multiple regional lymph nodes
- N3 There is a fixed mass on the pelvic wall into a free space between this and the tumor
- N4 Involvement of juxta-regional nodes

M—Distant Metastases
- MX The minimum requirements to assess the presence of distant metastases cannot be met
- M0 No evidence of distant metastases
- M1 Distant metastases present
  - M1a Evidence of occult metastases by biochemical an d/or other tests
  - M1b Single metastasis in a single organ site
  - M1c Multiple metastases in a single organ site
  - M1d Metastases in multiple organ sites

Table 1.2
Staging of Prostatic Cancer

Stage A1	Clinically inapparent, well differentiated cancer found in three or fewer chips; less than 20% of total gland is thought to be involved by cancer[3, 6, 9]
Stage A2	Clinically inapparent, moderately well to poorly differentiated cancer found in more than three chips; greater than 20% of the total gland is thought to be involved by cancer[3, 6, 9]
Stage B1N	Nodule less than 1½ cm confined to one lobe with compressable tissue on at least two and sometimes three sides[3, 4]
Stage B1	Palpable induration confined within one lobe of the prostate; intracapsular disease[3, 4]
Stage B2	Palpable induration in both lobes but still intracapsular disease[3, 4]
Stage C1	Palpable induration beyond the capsule, less than 70 g in size; normal SAP and bone scan; negative lymph node biopsy[5, 10]
Stage C2	Palpable induration beyond the capsule, greater than 70 g in size; bladder neck, trigone, or seminal vesicles may be involved; normal SAP and bone scan; negative lymph node biopsy[5, 10]
Stage D1	Any stage with elevated colorimetric SAP, negative pelvic lymph node biopsy and negative bone scan[11]
Stage D2	Any stage with positive pelvic lymph nodes and negative bone scan; SAP may or may not be elevated[11]
Stage D3	Positive bone scan or evidence of soft tissue metastases (lung or liver) or lymph nodes positive above the aortic bifurcation; SAP may or may not be elevated[11]

patients entered into the VA UORG studies were stage B,[15] although in military institutions where yearly rectal exams are more routinely performed, the distribution rises to 22 and 25%.[16, 17]

Stage C

This stage represents contiguous spread beyond the limits of the capsule, but without clinical evidence of metastases. Subdividing this into two categories (C1 and C2) is based on the finding that if the local lesion is less than 35 g the incidence of positive pelvic lymph nodes is 20% whereas in larger lesions the incidence more than doubles, rising progressively to 92% in local lesions larger than 150 g.[5, 18] The C2 lesion includes tumors larger than 70 g or invasion of the bladder neck, trigone, or seminal vesicles.[10] Whitmore[19] originally held that patients with stage C disease might have an elevated SAP. More recent staging systems acknowledge the poorer prognosis associated with an elevated colorimetrically determined SAP and this finding now puts the patient in the stage D category.[4, 5, 11, 20] The bone scan is always normal. About 50% of the VA UORG patients were stage C.[15]

Stage D

This stage represents metastatic carcinoma to bone or lymph nodes and includes patients with elevated colorimetrically determined SAP in the most recent VA UORG study.[11] In stage D1 (IVA) the SAP is elevated, but the bone scan is normal and the pelvic lymph nodes are negative. Stage D2 (IVB) includes patients with positive lymph nodes, but negative scans and the SAP may or may not be elevated. In stage D3 (IVC) the bone scan or bone survey is positive for metastatic disease with or without an elevated SAP.[11] Others avoid the SAP problem and assign D1 to patients with metastases to the pelvic lymph nodes below the aortic bifurcation and D2 to patients with metastasis to lymph nodes above the aortic bifurcation, to bone, or to other soft tissues such as lung or liver.[7] Locally advanced cancer involving the bladder, ureters, or rectum or extending laterally to the pelvic wall is categorized as D1 by McCullough's staging or D2 by the VA UORG staging system, according to Schmidt and Pollen's criteria.[7, 10, 11] About 40% of patients entering the VA UORG study were classified as stage D.[15]

BONE SCANS

Since the introduction of bone scans nearly 20 years ago, improved techniques using modern radionuclides have relegated bone surveys largely to a secondary role in the detection of bony metastases.[21] Generally, a polyphosphate compound labeled with technetium-99m has been used since 1971. It has been estimated that 12 to 30% of patients with bone scans positive for metastatic prostatic cancer also have normal bone surveys.[22, 23] It is now common practice to evaluate for bony

metastases with a bone scan and not perform any radiographs other than the plain film of the intravenous pyelogram if the scan is negative.[7, 24]

The value of bone scanning as an initial staging procedure is illustrated by the report of 40% positive scans in 201 men presenting with prostatic cancer.[23] In the same series, of 61 patients investigated 67 times by both radiogaphs and ^{99m}Tc-polyphosphate scans, radiographs missed isotopically detected metastases in 12% of the cases, but in only one case (1.5%) did the scan miss radiographically evident metastases.[23] Although bone scans are the most sensitive means currently available for detecting metastatic bone deposits, their lack of specificity deserves emphasis. An isotope "hot spot" is a nonspecific indicator of abnormal metabolic bone activity and can be seen in any metabolically active lesion, including Paget's disease, arthritis, and fractures.

Patients presenting with stage I or II disease have a 7% yield of positive studies while in stage III disease, the yield rises to 18%.[25]

Bone surveys are less sensitive than bone scans for detecting metastatic deposits for several reasons. At least 30 to 50% of the normal bone mineral must be lost in order to demonstrate an early metastatic lesion.[26] In the vertebrae, at least, it has been estimated that a lesion must be over 1.5 cm in size[27] and have a bone loss of 50 to 70% before a deposit may be seen on plain radiograph.[28] Since the kidneys are the main route for the excretion of the radionuclide, occasionally hydronephrosis is first detected on a bone scan, especially in follow-up studies of patients with prostatic cancer.[29]

The bone scan may occasionally be falsely positive as well as falsely negative. Unfortunately, no data exist in the literature to date to identify the rate of true positives from false positives in patients presenting with positive scans in previously undetected prostatic cancer.[25] Similarly, no data exist to determine the rate of conversion from a normal to an abnormal bone scan during the follow-up.[25] In the author's limited experience, a series of 50 consecutive patients with all stages of disease were followed with scans at 6-month intervals for an average of 2.2 years and no significant changes were noted in any of the scans.

Falsely negative scans can occur, especially with metastases that appear symmetrically in the bones.[7] Osteolytic metastases may appear as areas of decreased uptake.[30] Fewer than 2% of patients with radiographic evidence of bone metastases have normal bone scans.[31, 32]

An abnormal bone scan explained by a benign process, however, is considered a true negative scan. Paget's disease, various arthritides, fractures, osteomyelitis, osteoporosis, and areas of previous surgery, all of which can cause a scan to be positive, can usually be confirmed by plain radiographs, often with the help of special views and tomograms.[3] Occasionally a "hot spot" on a bone scan appears normal or unexplained on subsequent radiographs and a bone biopsy is then required to verify whether a metastatic deposit is present.[34]

More than 80% of metastases visualized on radiographs are of the osteoblastic variety, most commonly mixed osteolytic and osteoblastic, while osteolytic lesions alone are unusual or rare.[4, 10] Osteoblastic metastases are said to be a result of simultaneous destruction and reactive osteoblastic hyperplasia of bone.[4] The most frequent sites of bony metastases are the pelvis, lumbar vertebrae, and proximal femurs.[4]

The radionuclide ^{99m}Tc-polyphosphate has largely replaced other radioisotopes for bone scanning. Once the components of the kit are activated, it has a half-life of about 6 hours. About 10 to 15 mCi are injected and then 2 to 4 hours are allowed for the blood activity to decrease. Total imaging time is less than 30 minutes.[35]

LYMPHANGIOGRAPHY

Lymphangiography has been advocated as a useful staging tool since its introduction by Kinmonth in 1952.[36] Dorsal bipedal lymphangiograms are performed by cutting down on and cannulating an isolated lymphatic channel on the dorsum of the foot with a 30-gauge needle. About 7 ml of an oily iodinated contrast material such as ethiodol is then slowly injected with the aid of an infusion pump. A radiograph at 2 hours will show contrast material in the retroperitoneal lymphatic channels and thoracic duct and the 24-

hour films will demonstrate the filled lymph nodes.

Absolute contraindications to pedal lymphangiography include a history of allergy to iodinated contrast material, a right to left cardiac shunt, and significantly decreased pulmonary function.[37] Pulmonary capillaries trap the oily contrast material that is not taken up by the lymph nodes. Multiple small pulmonary emboli result which primarily cause an impairment in pulmonary diffusion capacity and to a lesser degree a decrease in vital capacity. Maximum impairment is seen at 36 hours postinjection with recovery complete usually by 3 to 5 days.[38] Pulmonary function tests are recommended if significant pulmonary disease is suspected. Injection of the second foot 5 days after the first has been recommended if modest pulmonary impairment exists.[37]

Only the external iliac, common iliac, and para-aortic nodes are thought to be visualized on pedal lymphangiograms and the obturator, internal iliac, and presacral nodes are generally not thought to be well visualized.[7, 39] Recent data, however, show 87% of the internal iliac and 94% of the obturator nodes to have histologic evidence of retained contrast material within the lymph node specimens, although this was not correlated with the radiographic interpretation.[6] Merrin et al.[40] radiographed 50 samples of nodes taken from around the obturator nerve from 25 patients with preoperative bipedal lymphograms and found radiopaque contrast material present in all samples. Herman et al.[41] have shown that the internal iliac (hypogastric) lymph nodes are only visualized about one-half of the time by pedal lymphograms. They also demonstrate that the external iliac nodes visualized by pedal lymphograms consists of three nodal chains: (1) external iliac chain, (2) middle chain, and (3) internal chain.[40–42] Confusion sometimes arises as the most medial of the three nodal chains comprising the external iliac nodes are the nodes which surround the obturator nerve and are commonly called the obturator nodes by clinicians but occasionally are referred to as the internal chain or internal iliac chain, thus confusing them with the internal iliac (hypogastric) lymph nodes.[40]

Several criteria have been defined for the correct interpretation of the lymphangiogram. Metastases to lymph nodes from prostatic cancer tend to produce peripheral filling defects which will not be visualized unless they are 5 mm or larger.[37, 43] Nodes may also fail to opacify if the metastasis becomes so large that it totally obstructs the lymphatic channel and collateral lymphatic vessels may then be visualized. The radiograph taken 2 hours postinjection will determine whether any channels traverse subsequently noted filling defects since these channels should not pass through a malignant deposit.

Although multiple filling defects are usually observed with metastases, small defects are less reliable since they may also be caused by fibrosis, fatty replacement, reactive hyperplasia, and irregularly shaped lymph nodes.[24, 37, 39] Microscopic deposits including all those less than 5 mm in diameter are the main reason for the relatively high falsely negative rate. Castellino[44] states that microscopic metastases to the subcapsular marginal sinus are the cause for most falsely negative lymphograms. The best current estimates are that the overall accuracy of pedal lymphangiography in prostatic cancer is between 70 and 80% with a 5 to 10% incidence of falsely positive and a 15 to 20% incidence of falsely negative results.[6, 42, 44–46]

Recent experience with fine needle aspiration lymph node biopsy postlymphangiography has given a new dimension to the role of lymphograms in the staging of prostatic cancer. Cytologic confirmation of nodes suspected of containing tumor is thereby obtained. In this technique, pedal lymphangio graphy is performed in the usual manner and biopsy is performed within the following week, often as an outpatient procedure. A fine 23-gauge, 15-cm needle is advanced transabdominally and transperitoneally under local anesthesia with the patient in the supine position (Fig. 1.1). Fluoroscopic control is used to help guide the tip of the needle into the nodal filling defect or suspected nonopacified node. The stylet is then withdrawn and suction applied with a 12-ml syringe while the needle is moved up and down through a 1-cm excursion in order to aspirate as much material as possible. The withdrawn needle is then

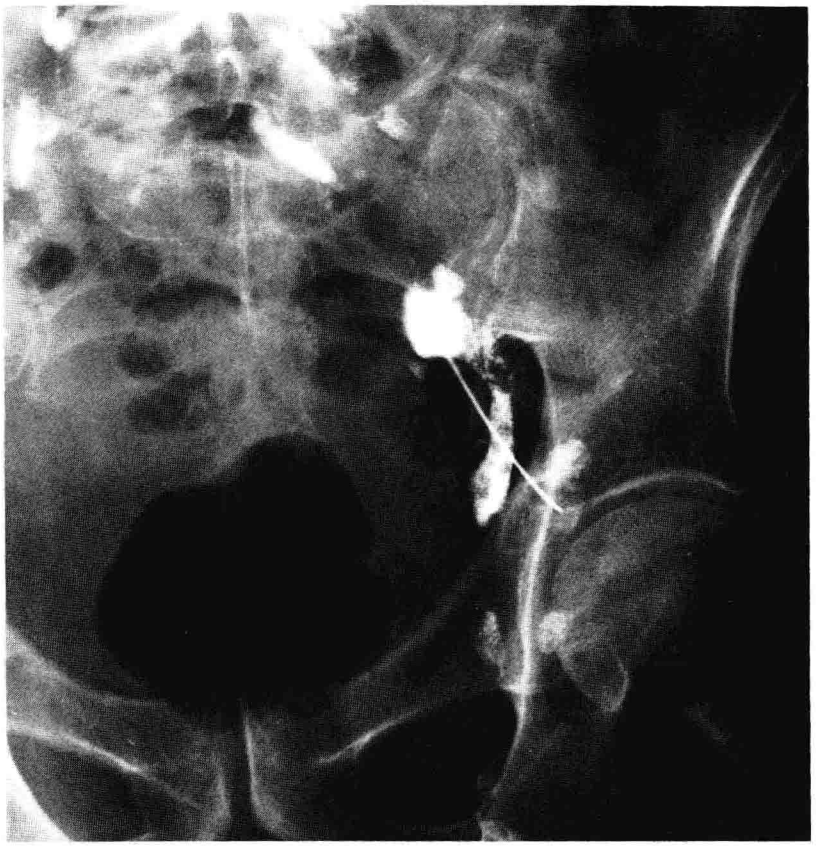

Figure 1.1. Tip of fine needle is inserted transperitoneally into suspicious lymph node overlying acetabulum in this film. (Photograph courtesy of Dr. Stavros C. Efrimidis, Mount Sinai School of Medicine, New York, NY.)

irrigated with sterile saline and the specimen is sent for cytologic examination. After observation for 1 to 2 hours, the patient is usually discharged.[37, 47–49a] Satisfactory biopsies were obtained in 37 of 42 patients in one series and in 5 out of 5 patients in another.[47, 48] Neither series reported any complications. This technique should prove invaluable for decreasing the falsely negative rate while simultaneously allowing for the application of strict diagnostic criteria for malignancy in order to minimize the falsely positive determinations. The histologic confirmation of tumor in an equivocal area seen on lymphogram will spare some patients the need for open pelvic lymph node biopsy for staging prior to selection of the most appropriate therapy regimen.

ULTRASONOGRAPHY

Although transabdominal ultrasonography has not been of great value in helping to determine whether prostatic carcinoma extends locally beyond the prostatic capsule, the technique of transrectal ultrasonography with its enhanced local resolution appears to offer much promise. Since it has been estimated that from 12 to 16% of patients thought to have malignancy confined to the prostate will have involvement of the periprostatic and periseminal vesical tissue at the time of radical prostatectomy, the development of a reliable, noninvasive, easily performed, and relatively inexpensive technology for detecting this sub-

population clinically would be most welcome.[50, 51] Transrectal ultrasonography seems to offer the best hope except for the expense factor. Special probes and adaptive equipment are necessary and currently are available only in a limited number of research-oriented institutions (Fig. 1.2). In the study by Resnick et al.[52] 23 patients with biopsy proven prostatic carcinoma had transrectal ultrasonography prior to radical perineal prostatectomy. Thirteen of 13 patients thought to have stage C disease by finger as well as sonogram examinations were confirmed histologically. Of the remaining 10, all were thought to be stage A or B by conventional staging, but four of these patients were thought to have extention around the seminal vesicles by ultrasonography and this was confirmed histologically.[52]

There are some discrepancies noted on comparing the study of Resnick to the study by Peeling et al.[53] They found that 6 of 7 patients thought to have prostatic cancer confined within the prostatic capsule had a perforation anteriorly. This was not confirmed histologically and is contrary to most clinical experience. In addition, the seminal vesicles were seen in only about two-thirds of 69 examinations. Further experiences hopefully will confirm the accuracy of this modality for detecting otherwise clinically inapparent stage C prostatic carcinoma. The value of computerized axial tomography for the solution of the same problem is currently under investigation, but suffers from the same problem of expense.[54, 55] Comparative studies of transrectal ultrasonography versus computerized axial tomography for the detection of clinically inapparent stage C disease are currently unavailable but would be extremely useful.

ACID PHOSPHATASE (AP)

For more than 40 years SAP has had an important although somewhat enigmatic role in the staging of prostatic cancer. Between 70 and 90% of patients with bony metastases from carcinoma of the prostate have an elevated SAP.[56, 57] To complicate matters, from 5 to 30% of patients without demonstrable metastases also have an elevated SAP. These figures, although commonly quoted, date back to the days before bone scans and pelvic lymph node biopsies were available to more accurately stage patients. Clinicians have long been aware of the vagaries of trying to interpret a minimally elevated SAP in patients with prostatic cancer. Multiple determinations and the aid of the other staging tools help to develop a proper perspective in any single patient. The recent review by Henneberry et al.[58] is an excellent overview of the subject. This review will concentrate on the role of AP in the staging of prostatic cancer.

COLORIMETRIC METHODS

Since the early use by the Gutmans of phenylphosphate as a substrate for measuring SAP, at least six other substrates have come into common usage.[56, 58] Because of the lack of organ specificity of these substrates, an attempt was made to concomitantly use an organ-specific inhibitor to improve the specificity of the substrate.[59, 59a, 61]

The most common inhibitor in general use is L-tartrate. Approximately 95% of PAP activity is inhibited by L-tartrate while no inhibition is seen with erythrocyte AP. Because of this, the tartrate-inhibited fraction of SAP has been advocated as a specific index for the AP activity of prostatic origin.[59] However, it has been pointed out that this specificity is limited by the fact that L-tartrate also inhibits the AP from the spleen, liver, platelets, and kidney.[58, 60–62] The clinical usefulness of the separation of the L-tartrate fraction from the total SAP has been questioned by others.[60, 60a]

Although a lack of consensus on the usefulness of a specific inhibitor prevails, a newer substrate, sodium thymolphthalein monophosphate has gained increasingly wider acceptance. Compared to five of the other most commonly used substrates, thymolphthalein monophosphate was found to be hydrolyzed least rapidly by the nonprostatic APs. Therefore, this new substrate was touted as the least affected by the nonprostatic APs. Even the platelet and erythrocyte APs, commonly released by the clotting process and hemolysis in the collecting tube, respectively, contributed a minimal fraction of the total AP activity so that neither L-tartrate nor formaldehyde