Testicular Carcinomas and Carcinoma of the Prostate

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TESTICULAR CARCINOMAS

Incidence

Testicular neoplasms are relatively rare with approximately two new cases per 100,000 male population occurring per year. The peak occurrence is between the ages of 20 and 40. Because of their highly malignant characteristics testicular neoplasms must be treated aggressively if cure is to be achieved.

Etiology

The most significant etiologic factor is the predisposition for the occurrence of carcinoma in the cryptorchid or undescended testicle. The cryptorchid testis is at 40 to 50 times the risk of the normal scrotal testicle for developing a cancer; various theories for this predisposition to malignancy have been proposed. The most likely is that the cryptorchid testicle is inherently abnormal (a very strong argument also to explain its failure to descend) and therefore provides a fertile ground for neoplastic change.

Histology

Testicular tumors may be divided into neoplasms of germ cell origin (arising from the spermatogonia within the seminiferous tubules) and of non-germ cell origin (arising from the supporting Leydig and Sertoli cells). The latter constitute only 5% of all testicular tumors.

For purposes of histology and treatment regimens the germ cell tumors are divided into the semi-nomatous tumors which are most common, constituting approximately 60% of all testicular tumors, and the non-seminomatous tumors constituting the remaining 35% of tumors. The non-seminomatous tumors consist of embryonal carcinoma, teratocarcinoma, teratoma, or choriocarcinoma. Rarely do each of these types exist in absolutely pure form; most nonseminomatous tumors combine the elements of embryonal and teratomatous carcinomas and these may have elements of choriocarcinoma as well. With the exception of pure choriocarcinoma, a distinctly rare entity comprising less than 1% of tumors, the treatment regimen for the nonseminomatous tumors is identical to and independent of the percentage of each histologic type that constitutes the mixed tumor.

Diagnosis:

All testicular masses must arouse suspicion of carcinoma and some swellings such as testicular hematomas, orchitis, and epididymitis may cause induration difficult to distinguish from a tumor diagnosed only by inguinal exploration and biopsy.

Treatment

When a testicular mass is suspect of carcinoma, it must be explored through an inguinal incision. A rubbershod or umbilical tape is used to obstruct the venous return and therefore reduce or eliminate embolic dissemination during manipulation of the testicle. If there is some doubt about the diagnosis, the testicle is isolated with towels, and a biopsy and a frozen section are performed prior to orchiectomy and removal of the cord. The testicle must never be biopsied through the scrotum, either by incision or by needle aspiration; by doing so an entirely new nodal

chain for metastases is established. The testicle drains to the para-aortic nodes, the scrotum to the inguinal nodes. If the tumor cells seed in the scrotal incision, which can easily occur, then the entire inguinal chain is at risk for embolic metastases.

The diagnosis of testes tumors is too often delayed for a number of reasons. Routine and careful bimanual examination of the testes is often omitted in routine examinations. Furthermore, patients who note testicular masses are often reticent to present their complaints to a physician because of embarrassment, or fear of association with venereal disease.

Metastatic evaluation. Once a diagnosis is made a number of radiologic studies, serum studies, and urine studies are warranted to stage the neoplasm and identify areas of metastases. The chest represents a common area of distant metastases and should be evaluated not only by anteroposterior and lateral x-ray, but by pulmonary tomograms. Lesions are frequently bilateral and multiple. The primary route of drainage of the testicular lymphatics is to the para-aortic and paracaval nodes between the superior mesenteric and the inferior mesenteric arteries. Crossover drainage does occur and is most frequent from the right side to the left. Bipedal lymphangiography is of importance in identifying spread to the retroperitoneal nodes. Para-aortic and paracaval nodes are well visualized as is, frequently, the supraclavicular node. Intravenous pyelogram also assesses the retroperitoneum by evaluation of renal and/or ureteral deviation, compression, and deformity. Computerized axial tomography (CT) scanning and ultrasound studies can be used to delineate retroperitoneal masses precisely and may be used as noninvasive techniques to follow these masses periodically during the course of chemotherapy or radiotherapy to evaluate treatment.

Staging of testes tumors is as follows:

Stage A: Tumor limited to testes, that is, no metastases.

Stage B: Tumor present in testes with metastases limited to regional nodes, that is, para-aortic nodes below diaphragm.

Stage C: Tumor present in testes with metastases beyond regional nodes, that is, metastases to scalene node, lung, bone, liver, and so forth.

Seminomatous tumors. These neoplasms are characteristically very radiosensitive. Radiotherapy constitutes the main method of treatment and rarely, if ever, is surgery indicated. If the tumor is Stage A

(negative lymphangiogram and pulmonary tomograms), radiation is given in the dose of 2,500 R to the ipsilateral-iliac nodes and to the para-aortic nodes bilaterally to the level of the diaphragm.

If the tumor is Stage B (evidence of nodal involvement on lymphangiogram), the fields are extended so as to include the mediastinum and both supraclavicular areas, and the infradiaphragmatic area is treated to 3,000 R. The 5-year survival rate for patients with Stage A tumors, so treated, ranges around 95%. If the tumor is Stage B (evidence of positive para-aortic nodes), the 5-year survival rate will range around 80%.

If the tumor is Stage C (evidence of pulmonary visceral or osseous metastases), radiation therapy may be given to these areas of metastatic involvement if they are relatively isolated, that is, one or two pulmonary nodules in one lung lobe. If disease is more diffuse, however, a radiomimetic chemotherapeutic agent, either chlorambucil (Leukeran) or cyclophosphamide (Cytoxan) is used. Five-year survival rates for Stage C tumors range between 40% and 50%.

The only indication for surgery for seminomatous tumors arises with the failure of what has been diagnosed as seminoma to respond satisfactorily to radiotherapy. In such a case one must suspect the presence of non-seminomatous elements, and surgery with excisional biopsy will eliminate the lesion, confirm a change in histology, and dictate a change in treatment to that used for non-seminomatous neoplasms.

Non-seminomatous tumors. There is significant controversy as to the optimal management of non-seminomatous tumors with North American urologic centers applying surgery, and European centers employing radiation therapy as the primary modes of treatment of the retroperitoneal area. Non-seminomatous tumors are much more difficult to control with radiation than the seminoma and therefore radiation failures are more common.

In the United States a non-seminomatous neoplasm is approached as follows: if the tumor is Stage A, a retroperitoneal node dissection is undertaken; if lymph node dissection reveals no evidence of histologic metastases to the nodes, no further treatment is undertaken; and if the nodes are positive, chemotherapy is administered as the tumor is pathologically Stage B.

If the tumor is Stage B, a node dissection is again performed and chemotherapy instituted postopera-

tively. If nodal dissection is incomplete or there is tumor spillage, radiotherapy postoperatively to the retroperitoneal area is recommended. Chemotherapy is administered for two years after the last evidence of clinical disease is noted.

If the tumor is Stage C, chemotherapy is instituted and if clinically measurable metastatic disease regresses, a node dissection is then considered.

Five-year survival rates for Stage A, non-seminomatous tumors range from 85% to 90% (the pathologist is not always 100% accurate and may have missed microfoci in the excised lymph nodes and/or metastases may have skipped the retroperitoneal nodes and disseminated distantly without nodal involvement). Five-year survival rates for Stage B disease are 60% to 70% and for Stage C, 25% to 30%.

Tumor markers. Until recently, 24-hour urinary choriogonadotropin was measured in patients with testicular tumor in an effort to identify those with choriocarcinoma which as a functioning cell would produce choriogonadotropins detectable in the urine. The assay used is a biological one and has all the inherent difficulties of bioassays.

A serum radioimmunoassay has been developed to overcome this difficulty. It measures the B chain of human choriogonadotropin (termed Beta sub unit) and is very sensitive and specific. Any elevation in the male is abnormal and indicates the presence of functioning tumor cells.

Alpha-fetoprotein is a protein produced by the fetus, but its production ceases and levels fall to nanogram marks soon after birth. Testis carcinoma cells may revert to the metabolic machinery of the fetal cell and produce alpha-fetoprotein, causing increased serum levels. Like the Beta sub unit, elevated alpha-fetoprotein identifies the presence of active tumor.

Tumor markers are sensitive indicators of residual microfoci of disease long before any evidence of clinical or radiologic disease may appear. Active chemotherapy must continue until tumor markers are reduced to and remain within normal levels.

CARCINOMA OF THE PROSTATE

Incidence

The incidence of carcinoma of the prostate is steadily increasing; at the present time it is the most common genitourinary malignancy and the second leading cause of death from cancer among males in the United States. Its incidence of 60 new cases/ 100,000 population and 20 deaths/100,000 population per annum is exceeded only by carcinoma of the lung. The incidence of carcinoma of the prostate increases with age, and autopsy studies have revealed it in 50% to 80% of males who have survived to age 80. Thus, we can anticipate that with greater longevity the diagnosis of prostatic carcinoma will be made more frequently and the problems of treatment of a malignancy in an aged population will be of increasing concern.

Etiology

No specific carcinogen has been identified as the cause of prostate cancer. The most likely inciting event at present is a change in the hormonal milieu which occurs as a natural consequence of aging. The nature of the change and the hormone fluctuations involved are as yet unidentified.

Anatomy and Histology

The prostatic glandular elements can be divided into two major sectors—the inner periurethral glands and the peripheral tuboalveolar glands which are connected by long ducts to the prostatic urethra. The periurethral glands are those which most frequently give rise to benign hypertrophy and the peripheral tuboalveolar glands to adenocarcinoma of the prostate.

Natural History

Carcinoma of the prostate is a neoplasm with varied growth characteristics and degrees of malignancy. The tumor may be rapidly metastatic and cause death within one to two years or it may be slowly growing, metastasizing only five to ten, or even fifteen, years after discovery of the primary lesion; another five or more years may pass before the metastases become life-threatening. This variability makes it difficult to assess the efficacy of therapy, and makes it necessary to follow patients for ten to fifteen years after initiating treatment in order to judge its value. The reason for this is that, given a tumor with a relatively slow-growing and benign course, one cannot state whether prolonged survival is based on the treatment administered or the low biologic potential of that tumor. Unfortunately, at the present time there are few characteristics, other than the grade of anaplasia, that can be measured to identify at the time of diagnosis which tumors will follow a benign course from those which will not.

Diagnosis

While a high index of suspicion may be generated by induration felt on digital rectal examination, carcinoma of the prostate must be ultimately diagnosed by histologic proof of malignancy. A number of other causes for induration of the prostate include prostatic calculi, granulomatous prostatitis, nodular prostatic hypertrophy and, more rarely, tuberculous granulomas. Once a suspicious area of induration or nodularity is identified a transperineal or transrectal needle biopsy employing the Vim-Silverman needle is used to obtain tissue for histologic examination.

Other warning signals in the elderly male of prostatic cancer include the onset or recent exacerbation of low back pain, possibly a reflection of osseous metastases; the presence of sciatic pain, possibly a reflection of sciatic nerve impingement by massive retroperitoneal lymphadenopathy secondary to metastases; and the rapid progression of bladder outlet obstruction which can be identical to that seen with benign prostatic hypertrophy (BPH).

Radiographic identification of carcinoma of the prostate is facilitated by the characteristic radiodense or osteoblastic lesions most frequently found in the pelvic bones and the lumbosacral spine. These may be identified on routine skeletal survey, but more early identification is provided by the technetium 99 phosphorous bone scan which identifies metastases prior to radiographic skeletal changes. (It has been shown that more than 50% of the bone must be destroyed or replaced by malignancy before a routine skeletal survey becomes positive). Intravenous pyelography may demonstrate obstruction at the ureterovesical junction secondary to prostatic malignant growth and, specifically, involvement of the seminal vesicles. Also the ureters may be displaced by retroperitoneal metastatic adenopathy.

Biochemical or serum abnormalities occur with prostatic carcinoma. Serum acid phosphatase represents the most characteristic and distinct abnormality; in essence, it is a tumor marker. It can frequently be used to identify the presence of metastatic disease, and its levels may be followed as a means of monitoring treatment; however, it is not a specific test as acid phosphatase may be elevated in a number of other diseases such as pulmonary embolism, muscle necrosis, Gaucher disease, and osteosarcoma, to mention a few. It is also not a very sensitive marker as diffuse metastases may be present in the face of a normal acid phosphatase. The recent development of a radioimmunoassay for measurement of prostatic acid phosphatase offers significant advantages for tumor staging, and follow-up. The immune assay is *specific* for the *prostatic fraction* of acid phosphatase and is *sensitive* to extremely minor changes in serum levels of the enzyme. Elevation of alkaline phosphatase is a reflection of bony destruction and repair. Serum calcium may be elevated as a result of extensive osseous metastases.

Treatment

Many methods of treatment are used either individually or in combination. Transurethral resection of the prostate is used to relieve obstruction. This is obviously palliative and relieves symptoms but does nothing to stem or alter the growth of the neoplasm. Radical prostatectomy, namely the total removal of the prostate gland and the seminal vesicles, is performed with the intent to cure by removal of all neoplasm. Curative radiation therapy delivered from a linear accelerator or cobalt source is directed at the prostate and often the pelvic lymph nodes as well. Interstitial implantation of radioactive seeds is used in an effort to deliver high local doses.

Treatment is based on the staging of the disease at the time of presentation: Stage A—carcinoma entirely unsuspected on physical examination, or on serum chemical or radiographic examination but which is found incidentally on pathologic examination of the prostate excised for presumed BPH, that is, in the transurethrally resected prostatic chips or the prostate enucleated by an open technique. Stage B—tumor confined to the prostate gland on physical examination specifically without lateral or seminal vesicle extension; Stage C—tumor locally confined to the pelvis but demonstrating lateral extension and seminal vesicle invasion; Stage D—metastases to lymph nodes, bone, lung, and so forth.

Management of Stage A depends to a large extent on the patient's age, the grade of lesion, and the extent of the involvement. When only microfoci of well differentiated neoplasm are present, it is reasonable to pursue no further treatment. If the tumor is more extensive or poorly differentiated, treatment is as outlined for Stage B.

For Stage B, either radical excision of the prostate and seminal vesicles (radical prostatectomy) or treatment with external beam radiotherapy or interstitial implantation of radioactive sources (I-125 seeds) may be employed. The advantages of radiotherapy are the inclusion of the periprostatic tissue (and thereby hoped-for sterilization of microscopic

extensions outside the prostate) and avoidance of the side effects of surgery, namely universal impotence and a 10% to 20% incidence of incontinence.

The survival rates for Stage B carcinoma of the prostate are approximately 75% at five years, 45% to 50% at ten years, and 25% to 35% at fifteen years.

In Stage C carcinoma of the prostate, extension beyond the confines of the prostate and seminal vesicles usually makes cure by radical prostatectomy highly unlikely; therefore, radiation therapy, either external beam or interstitial seeds, constitutes the mainstay of treatment. Occasionally it is also necessary to relieve prostatic obstruction by transurethral prostatectomy either before treatment or immediately afterwards. Five- and ten-year survival rates for Stage C are approximately 45% and 30% respectively.

The philosophy for treatment of Stage D carcinoma of the prostate varies throughout the country. It is our policy to await the appearance of symptoms prior to the institution of therapy. Cure of Stage D prostatic neoplasm has not been documented, and therefore palliation of symptoms, and prolongation of survival remain the primary objectives of treatment. Conditions warranting treatment include systemic symptoms such as weight loss, fatigue, weakness, bone pain, ureteral obstruction, and bone marrow replacement as evidenced by anemia.

Hormonal manipulation (estrogen or orchiectomy) is the mainstay of treatment for metastatic carcinoma of the prostate. Dramatic relief from pain and regression of metastases, and at times complete disappearance of the primary prostatic lesion, follow the administration of hormones, or castration. The administration of estrogens works via the negative feedback system whereby high-estrogen doses suppress luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are pituitary trophic hormones stimulating the testes to produce testosterone. Orchiectomy removes the source of androgen production. It is felt at the present time that either one of these modes is equally effective and can be expected to produce regression in approximately 80% of patients with prostate carcinoma. There is no documented advantage from using both methods, that is, estrogen plus orchiectomy as opposed to either one or the other alone, nor unfortunately is a second regression seen with any frequency by applying one of these modes when a relapse occurs after the institution of the other.

Estrogens have certain distinct disadvantages; an orally ingested pill is required daily, nausea can occur, as can gynecomastia and other secondary sex changes. Of greater significance is data demonstrating an increased incidence of death from cardiovascular disease, namely fluid retention, pulmonary edema, and congestive heart failure in patients receiving estrogen therapy. Orchiectomy, a simple surgical procedure that can be performed under local anesthesia, avoids these secondary effects of estrogen treatment.

Other forms of hormonal ablation include adrenalectomy and hypophysectomy, but these are rarely used and have not been consistently successful in offering extended palliation.

Local radiation therapy to painful osseous lesions may significantly relieve discomfort. Radiation is reserved for treatment of well-localized areas of painful metastases.

Cytotoxic agents have just come under investigation in clinical trials and hold some promise for treatment of estrogen failures. Investigation of certain cytotoxic agents linked to hormones (Estracyst = estrogen + nitrogen mustard; Leo = prednisone + chlorambucil) suggests that cytotoxic agents may be delivered within the prostatic cancer cell by steroid carriers which attach to hormone receptors. Other agents which depend on the acid phosphatase enzyme for cleavage to the active form are also in developmental stages.

REFERENCE

Cancer 32:1017–1286, 1973