Prostate Cancer

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In 1974 an estimated 54,000 new cases of prostatic cancer will be diagnosed in the United States. Approximately 18,000 patients will die of this disease. Despite numerous clinical advances and innovations with hormonal palliation, age-adjusted death rates for prostatic cancer have not significantly changed in the past 40 years.

The probability of developing cancer of the prostate increases with age. Death rates appear to be higher in white married men aged 54-74 years than in single men. There is also some suggestion that in certain population groups, mortality rates are rising faster in nonwhite males than in white males. (Fig. 1.) Studies are currently being conducted by the National Prostatic Cancer Project to determine if a high-risk group can be further identified.

Morphology and Diagnosis

Clinical staging of prostatic cancer follows the system originally proposed by Whitmore. Stage A: Clinically inapparent prostatic cancer, found incidentally either at autopsy or during examination of removed prostatic tissue, without evidence of local extension beyond the prostatic capsule or of metastasis.

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Stage B: Clinically evident prostatic cancer, apparently confined within the prostatic capsule, without evidence of metastasis.

Stage C: Clinically evident lesion with apparent local extension beyond the prostatic capsule, without evidence of metastasis.

Stage D: Clinically metastatic prostatic cancer.

In addition to clinical stage, other factors must be considered in determining clinical response. For instance, variations in clinical course before and after endocrine therapy can be related to the histologic grade of the primary tumor. (Table 1.) Double-blind studies also show that the primary grade of the tumor correlates with the degree of elevated acid phosphatase and the presence of osseous metastases. (Table 2.) Further investigations have confirmed the relationship between clinical stage and primary grade of prostatic carcinoma and the survival of the patient.

Diagnostic techniques, other than intravenous pyelogram with roentgenographic evaluation, include 85 scintigraphic scanning which is of some value in detecting metastatic prostatic carcinoma. In some instances, a clinical lesion can be anticipated on the basis of the scan, but caution must be exercised in interpreting the results of this test.

Bone marrow aspiration, even of sternal bone marrow, in the absence of anemia is an important clinical adjuvant in the detection of unexpected tumor dissemination. Bone marrow acid phosphatase can also be helpful; its value will, of course, increase with the more frequent use of chemotherapy for advanced prostatic carcinoma. Serial evaluations in this instance may also be of value.

Staging by lymph node as well as pelvic node biopsies for unsuspected prostatic cancer is now being clinically eval-

| Grade of Primary Prostatic Carcinoma | Number of Patients | Survival In Years** |
|-------------------------------------|--------------------|---------------------|
| I                                   | 52                 | 3.21 (0.58)         |
| II                                  | 137                | 2.51 (0.26)         |
| III                                 | 54                 | 2.72 (0.41)         |
| IV                                  | 5                  | 1.80 (0.86)         |

*Based on all causes of death.14  **Mean ± 1 standard error.5

The lymphatic spread of prostatic cancer is still difficult to determine and may account for some of the discrepancy between the clinical stage of the disease and its apparent rapid progression and lack of response to either primary treatment or palliation.

Additional diagnostic tests involve the determination of LDH isoenzymes in prostatic tissue and sera, although it is doubtful that this test will soon receive widespread application or usage. The development of an effective radiomunoassay for carcinoembryonic antigen, however, may potentially have the ability to identify patients with unsuspected prostatic cancer and help fol-
low their clinical course. It is known, for example, that CEA can be assayed to a measurable degree in the urine, further increasing its screening ability. A fall in this tumor-associated antigen has been clinically associated with chemotherapeutic response in other advanced disease states. To be of more practical value further modifications of CEA related to prostatic cancer antigens are necessary and are being attempted.

**Primary Treatment**

A small number of patients with localized prostatic nodules or disease can be effectively managed by radical prostatectomy. The number of patients, however, is limited despite all attempts to increase general physical examinations and, particularly, rectal inspection and biopsy in the elderly male.

Some investigators feel that, on occasion, an inoperable prostatic carcinoma can be converted into an operable tumor by the concurrent or preoperative use of estrogens. Radiotherapy from external sources has generally proven less than satisfactory in patients with advanced prostatic carcinoma and has sometimes been associated with pathological evidence of tumor persistence in the primary or metastatic sites. However, Bag-

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**Fig. 2. Clinical Staging of Prostatic Cancer**

| STAGE A | Occult, incidental |
|---------|--------------------|
| STAGE B | Nodular or limited within the gland |
| STAGE C | Localized to the periprostatic area |
| STAGE D | Regional metastases |
|         | Distant metastases |

D1, D2
Shaw and associates have demonstrated that cure can be achieved by primary radiation therapy in selected patients with early disease. Others have combined interstitial radioactive gold and external sources; early results indicate possible primary therapeutic value and will obviously be closely followed with great interest. 10,11

**Palliation Therapy**

Our results with palliative therapy for patients with advanced prostatic carcinoma, regardless of the estrogen dosage or the presence or absence of orchiectomy, have not revealed a large number of cardiovascular deaths, contrary to other studies. (Table 3.) In our study, there were few dropouts or crossovers, and the patients were without a significant degree of prior liver disease. However, death from causes unrelated to prostatic carcinoma remains an important factor and on occasion can pose a significantly greater threat to patients with localized disease than to those with advanced prostatic carcinoma. (Table 3.) Our guidelines for conventional hormonal palliation in patients with advanced, untreated prostatic carcinoma are:

1. Withhold therapy until the patient’s symptoms or general condition warrant treatment;

### Table 2. Correlation of Primary Grade with Elevated Acid Phosphatase and Osseous Metastases

| Grades | Serum Acid Phosphatase | Osseous Metastases |
|--------|------------------------|--------------------|
| I      | 42.0%                  | 37.0%              |
| II     | 55.5%                  | 47.5%              |
| III    | 40.5%                  | 40.0%              |
| IV     | 48.0%                  | 49.0%              |

### Table 3. Cause of Death by Primary Treatment

| Cause of Death               | Orchietomy (69 Patients) | Estrogen + Orchietomy (256 Patients) |
|------------------------------|--------------------------|-------------------------------------|
| Prostatic carcinoma          | 47.4%                    | 64.7%                               |
| Other neoplasms              | 32.8%                    | 6.0%                                |
| Cardiovascular diseases      | 13.2%                    | 22.9%Δ                              |
| Other, mainly respiratory diseases | 6.6%                  | 6.4%                                |

*Excluding patients who are alive or have died from unknown causes. 14
ΔNot statistically significant.
2. Generally, use castration alone although many physicians also administer stilbestrol either with or without castration;

3. When stilbestrol is administered following symptomatic or clinical relapse after castration, limit the dose to 1 mg. daily. There is some suggestion, however, that 3 mg./day may provide better androgen suppression in certain patients;

4. High-dose estrogen therapy (natural or synthetic source) is not recommended except for selected use in short-term, acute situations.

Hypophysectomy is of significant palliative benefit in patients with relapsed advanced prostatic carcinoma, previously treated by conventional methods. 11 Studies by Scott have shown that hypophysectomy is also effective in terms of the ratio of response, relief of pain and survival of the patient. 11 Open hypophysectomy, however, is a hazardous procedure in many patients with advanced disease. The recently advocated trans-sphenoidal cryosurgical hypophysectomy has proven more satisfactory and less hazardous. In fact, this particular approach demonstrated that it is unnecessary to achieve complete and total ablation of the pituitary.

Results of adrenalectomy for prostatic carcinoma are reviewed in Table 4. 12 Patients who had a bilateral adrenalectomy performed soon after relapse from other forms of palliation generally exhibited a good response. The excretion of androgen metabolites as measured by the 11-deoxy-17-ketosteroids in the urine shows a sustained decrease following adrenalectomy or hypophysectomy and correlates well with a clinical remission. We are at present unable to predict which patients will respond to either adrenalectomy or hypophysectomy, although a previous response to estrogen and castration usually predicts response to this form of therapy as well. Younger patients generally do better than older patients. Unfortunately, with a limited degree of information, at present we cannot come to any conclusions about tumor differentiation, either of the primary or metastatic lesions.

Short-term palliation in patients with widespread bony metastases has also been achieved by the injection of radio-labeled phosphorus, but there are several limitations to this form of treatment. Initial priming with successive doses of testosterone can, on occasion, contribute to severe morbidity. Recent studies utilizing parathormone have exhibited less patient morbidity. Another limiting
feature is its associated anemia; a patient with pre-existent anemia is not a good candidate for this particular treatment. The injection of phosphorus usually results in only a few months of palliation, but can be repeated. L-DOPA has been found to afford some relief of bone pain in previously treated patients with relapsing Stage D prostatic carcinoma. The results cannot as yet be fully evaluated.

The place of palliative cryosurgery for patients with prostatic carcinoma must also be studied further. Repeat cryosurgery may have a possible influence on the presence of distant metastases. Some patients have undergone measured remission, but follow-up documentation and other immunologic testing is still necessary. Nevertheless, although multiple forms of palliative therapy can achieve some prolongation of life, the main benefit is relief of pain. This is true even when patients with advanced disease treated with estrogen and castration are compared to those treated at an institution where this therapy was not available.

Apparent discrepancies between the effects of estrogen or castration in the palliation of patients with prostatic cancer will likely be resolved with greater knowledge of prostatic cancer cell receptor sites or peripheral conversion of hormones. These factors are known to exist normally in man and indeed may be altered in patients with advanced prostatic cancer. At present a suitable animal model is lacking. Clinical controlled trials (Phase I, II) are being conducted to determine if available anti-androgens can be used as an alternative form of hormonal palliative therapy. Although results from early unrandomized cases are available, further testing and evaluation are necessary before widespread clinical use is possible. At present, BCG therapy is also limited to clinical trials, as are other immunological techniques.

**Future Prospects**

Estradiol mustard will likely be used in future chemotherapy of prostatic cancer. Phase I and II studies with the oral preparation are limited in this country; however, in Europe, chiefly under the leadership of Jönsson and Högborg, intravascular or parenteral Estracyt has produced a reasonable number of apparent clinical responses in patients with relapsed advanced prostatic disease following other forms of conventional palliation.13

Further results of chemotherapy in patients with prostatic carcinoma are awaited. Flocks and associates have followed a large number of patients receiving either 5-FU or Cytoxan with some apparently good results.5 A survey from the National Cancer Institute on a limited group of prostatic cancer patients that have received a diverse number of agents suggests benefit with a number of drugs, including 5-FU and Cytoxan. For this reason, a chemotherapy program currently under proposal at the National Prostate Project involves a crossover study with 5-FU and Cytoxan and an appropriate standard treatment. In vitro screening for chemotherapy models remains a persistent clinical problem. The ability of any compound to inhibit DNA synthesis in the central prostate tissue of the castrated rat may provide a suitable or predictable model.16 Additional models, such as those measuring alphareductase activity and arginase activity, may also help. Results obtained under experimental conditions are, however, incomplete and attention is now directed to studying the effects of chemotherapeutic agents on normal, hyperplastic and carcinomatous human prostatic tissue maintained in organ culture conditions. Long-term growth of prostatic carcinoma cells of human origin remains a problem, but would obviously represent a further significant extension of this field. Successful demonstration of therapeutic correlations between the
models and chemotherapy responses of some duration in patients with advanced disease may open new vistas for clinical use.

Prostatic carcinoma in man remains an enigma. The results of primary treatment, such as surgery or irradiation from an interstitial or external source, are at a clinical plateau. Further advances through cooperative, randomized clinical trials must be sought. Although new forms of palliation in man have been recently achieved, the results are still limited. One does not generally speak of "cures." The development of additional chemotherapeutic agents will doubtless expand our horizons. The problem, however, remains grave.

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