

TREATMENT OF METASTATIC PROSTATE CANCER

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ABSTRACT

The traditional definition of “metastatic” prostate cancer refers to disease stage and traditionally has included only patients with widespread osteoblastic or soft tissue metastases (clinical or pathologic stage Tany Nany M1, D2); it does not take into account the pathogenicity of the cancer or the risk of metastasis. Current evidence indicates that this definition should be broadened to include patients with a substantial risk of disease progression and death from prostate cancer, as well as those with traditional stage D-2 disease.

Because many patients with T-3 disease or local lymph node metastases progress to distant metastases, the concept of metastatic or advanced prostate cancer should also include stages C and D-1 (Tany N-1 to N-3, T-3 and T-4). Furthermore, based on the widespread use of prostate-specific antigen (PSA) level as an early indicator of treatment outcome, many men treated for clinically localized disease will progress i.e. “PSA-only recurrence” and, depending on their age and general health, should be included in the advanced stage category. Furthermore, using prognostic marker modeling with PSA, tumor grade and other factors, recurrences can be predicted even earlier in many cases. This is particularly significant in light of recent clinical data indicating that early androgen ablation therapy in patients with advanced (M-0, N-1 or M-1) prostate cancer delays disease progression and improves survival relative to outcomes seen with delayed therapy.

The luteinizing hormone-releasing hormone (LH-RH) agonists have become the preferred method of androgen ablation in patients with advanced prostate cancer. The use of a LH-RH agonist, alone or combined with an antiandrogen, is more acceptable to many patients than orchiectomy and lacks the potential cardiotoxicity associated with the use of estrogens. Combined hormonal therapy (CHT) remains controversial but may provide a modest survival benefit, especially for men with minimal metastatic disease. Intermittent hormonal therapy (IHT) has great appeal, particularly because of the potentially deleterious effects of long-term (CHT), including the possibility of osteoporosis; however, its long-term efficacy has yet to be proven. Antiandrogens alone to treat metastatic or advanced disease is also under intense study. An overview of the changing definition and management of metastatic prostate cancer follows.

Key words: prostate, prostate carcinoma, metastatic prostate cancer, management, hormonal therapy
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INTRODUCTION

The diagnosis, staging and management of prostate cancer has changed dramatically in much of the world since the introduction of prostate specific antigen (PSA) in the late 1980's (1-3). The overall incidence has increased and a stage-migration to ear-

lier stage presentation has occurred (Figures-1 and 2). At the same time, the average age at diagnosis has declined in many countries while the average life expectancy has increased. The “typical” patient with “metastatic” prostate cancer has changed during this “PSA-era”. Specifically, a decade ago the average patient had traditional stage D-2 disease, whereas,

now the presentation may be more likely to be a younger, healthier man with a rising PSA after prior radical prostatectomy and “occult” metastatic disease suspected.

Since its introduction in 1941 (4), endocrine manipulation by means of orchiectomy or medical hormonal therapy remains the mainstay of treatment for metastatic adenocarcinoma of the prostate. New options for hormonal therapy have been accompanied by controversies regarding not only the preferable forms and timing of treatment, but also the very definition of what is considered “advanced” prostatic cancer. A revised definition of metastatic prostate cancer incorporates recently acquired knowledge of the disease and can influence the treatment and monitoring of various manifestations of advanced disease.

CONTEMPORARY DEFINITION OF METASTATIC PROSTATE CANCER

The term “metastatic prostate cancer” is synonymous with “incurable” to most patients and clinicians (5). Traditionally, the definition of advanced disease has referred only to disease stage and has included only symptomatic stage D-2 dis-

ease with bony or soft tissue metastases. However, patients with extra-prostatic disease have an increased risk of dying from prostatic cancer compared with patients with localized disease. Because a majority of these contemporary patients are otherwise healthy with no competing morbidity, stages D-1 (regional lymph node involvement), T-4 (tumor is fixed or invades adjacent structures other than the seminal vesicles), and T-3 (tumor has extended through the prostatic capsule) should be included in the revised definition of advanced or metastatic prostate cancer in the new millennium for most men (6-8). When both clinical and pathologic staging are assessed, T-3 disease, in particular, represents a large percentage of the prostate cancers being treated. Approximately half of patients with clinically confined T-2 cancers are found on pathologic assessment to have T-3 cancers. Moreover, a 34% incidence of extracapsular extension is noted, even in tumors identified because of elevated prostate-specific antigen (PSA) levels, which characterize so-called stage T-1c disease (9).

Patients with a persistent elevation in PSA after prostatectomy or radiation therapy, as well as those with rising PSA levels without evidence of metastases, should also be included in the definition

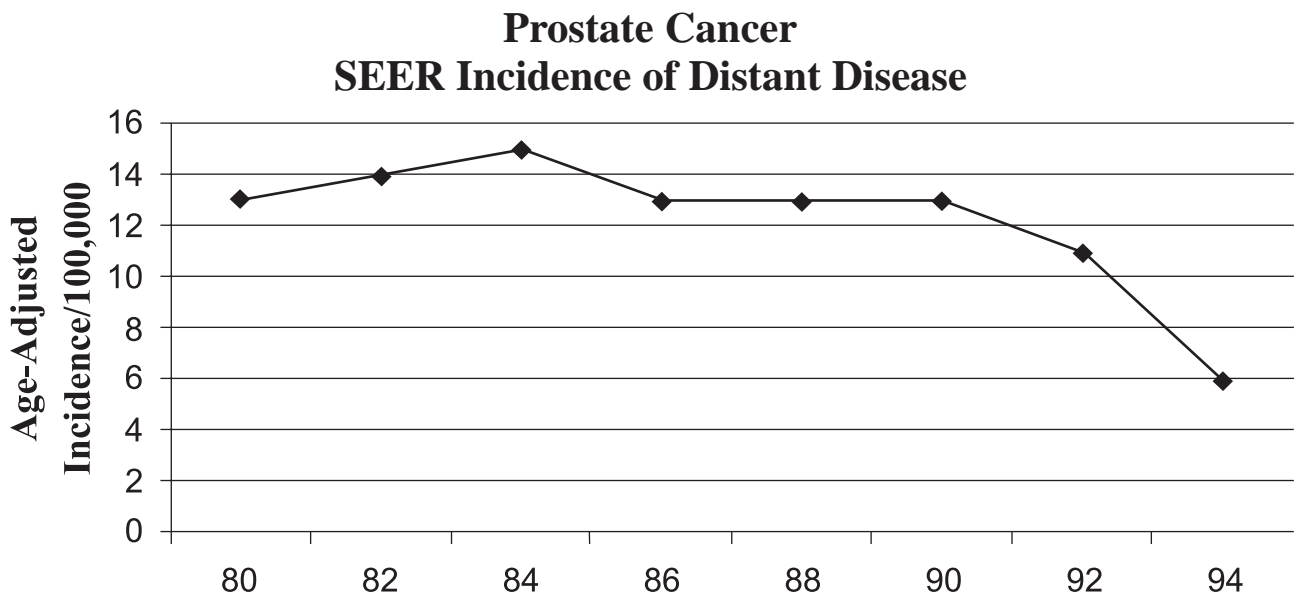


Figure 1 - Illustration graph of the declining incidence of traditional metastatic (distant disease) prostate cancer in the United States from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) national prostate cancer database.

**Center of Prostate Disease Research
Prostate Cancer Database: WRAMC 1988-1996
Stage Migration**

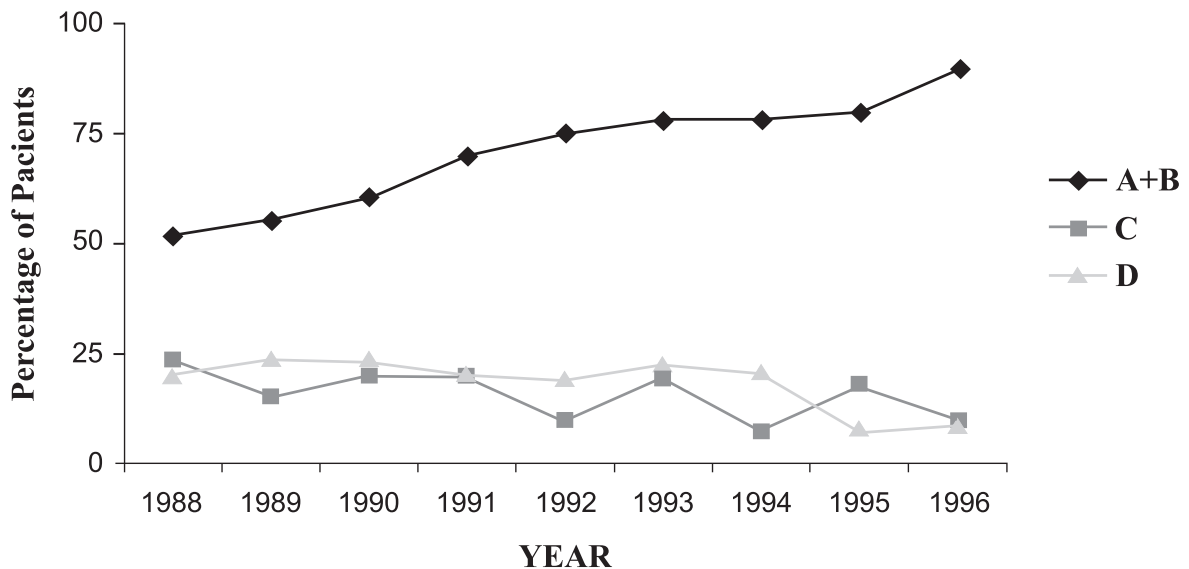


Figure 2 - Illustration graph of the stage migration in prostate cancer initial presentation from 1988 to 1996 from the authors' institution, Walter Reed Army Medical Center (WRAMC). The Center for Prostate Disease Research cancer research program at Walter Reed. Note that the incidence of localized disease (A & B) has increased while the rate of advanced disease (C & D) has decreased over the years of study as PSA became widely used.

of advanced disease in most cases (10). PSA is a sensitive marker for monitoring response to therapy (11). After radical prostatectomy, PSA should fall to undetectable levels; a postoperative rise in PSA indicates the presence of residual tumor (12,13). PSA testing is also the best method available for monitoring patients after external beam radiation or brachytherapy; after radiation, a post-treatment nadir value lower than 0.5 ng/ml indicates a good prognosis (14,15) and three consecutive rises in PSA level after the post-treatment nadir indicates disease recurrence (16).

The prognostic significance of a rising PSA level after radical prostatectomy has recently been clarified. In a study of approximately 2,000 radical prostatectomies performed at Johns Hopkins Hospital in Baltimore, between 1982 and 1997, 304 men who experienced PSA rise were studied (17). None of these men were treated with hormonal therapy or radiation until they experienced clinical evidence of

metastatic disease. To date, the authors found that the mean time from first PSA elevation to clinical metastatic disease was 8 years with another 5 years elapsing until death from prostate cancer. For many younger, healthier men, the 8 year "window" is not reassuring and clinicians are considering the "PSA-only recurrence" as evidence of advanced or metastatic disease prior to documented metastases (18).

Recent work with prognostic markers has enabled the selection of men at high risk for disease recurrence after treatment for clinically localized prostate cancer. Partin et al. (19) studied clinical stage B-2 patients undergoing radical prostatectomy and was able to select a subgroup of men at very high risk of recurrence using an equation based on pretreatment PSA, surgical Gleason sum, and organ-confinement status. Our Department of Defense Center for Prostate Disease Research (CPDR) group has also created and validated a radical prostatectomy recurrence model that is useful for all stages of patients (20).

The equation available on the Internet (www.cpd.org) uses four prognostic factors: 1)- PSA, 2)- Gleason sum, 3)- pathologic stage, and 4)- race, to derive a risk of recurrence. In our CPDR study, the high-risk group had a 55.5% chance of recurrence at 3 years and an 84.8% chance at 5 years. In my opinion, at least this high-risk group may be considered to have advanced prostate cancer and we can determine this in the immediate postoperative period. Aside from these equations using traditional prognostic markers, our group and others are using newer markers such as molecular biomarkers to establish risk of recurrence and progression to advanced disease. For example, in our hands, when the p53 tumor suppressor gene protein and the bcl-2 oncogene protein were overexpressed in radical prostatectomy specimens, all patients had disease recurrence within 5 years of surgery (21). Similar prognostic models have been developed by the Baylor University group for surgery patients' (22) and by the Harvard and University of Pennsylvania groups for radiation patients' (23).

To summarize, the current definition for metastatic prostate cancer should include not only cases with widespread osteoblastic metastases, weight loss, and urinary obstruction, but also those with a substantial risk of disease progression and death from prostate cancer, even those without symptoms (Table-1).

Table 1 - Clinical and pathologic findings included in the contemporary definition of advanced prostatic cancer

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- **Stage D-2** disease (distant metastases)
 - **Stage D-1** disease (regional lymph node involvement)
 - **Stage C** disease:
 - **T-3** (tumor extends through the prostatic capsule, with or without seminal vesical invasion)
 - **T-4** (tumor is fixed to pelvic wall or invades adjacent structures other than seminal vesicles)
 - High risk of disease recurrence after local therapy*
 - PSA-recurrence after local therapy*
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* in selected individuals with otherwise long natural-life expectancy

TREATMENT OF METASTATIC PROSTATE CANCER (OPTIONS)

Androgen ablation therapy has been the mainstay of treatment for stage D-2 metastatic prostate cancer for over 50 years (4). Treatment options

include orchiectomy, LH-RH agents, and combination hormonal therapy (CHT), which add an oral non-steroidal antiandrogen to the testicular ablation. Estrogens are currently rarely used because they may cause cardiovascular toxicity (24).

LH-RH Agonists

The use of LH-RH agonists has become the preferred method of androgen ablation. In their depot formulations, LH-RH analogues are easily administered, produce castrate serum levels of testosterone in a short time, and are associated with no increased cardiovascular risk. Although the prospect of a cure is not offered by any of the currently available hormonal therapies for advanced prostate cancer, all symptomatic patients with stage D disease should receive hormonal therapy to improve quality of life and relieve symptoms (25). Open multicenter studies in patients with stage D-2 prostate cancer have demonstrated that treatment with depot formulations of the LH-RH agonist were associated with an objective tumor response (no progression), normalization of, or at least a 50% decrease in PSA, and improvement or stabilization of both local disease status and overall performance status in nearly all patients (26,27).

In the United States, as of 1999, there were two LH-RH agonist approved by the Food and Drug

Administration (FDA), namely leuprolide acetate (Lupron®) and goserelin acetate (Zoladex®). Leuprolide acetate is currently available as 1, 3 and 4-month depot formulations and goserelin is available as 1 and 3 month depot pellet. A recent study found equal efficacy between the two LH-RH ago-

nists (28). Leuprolide is administered as a standard intra-muscular injection and has been the more widely prescribed LH-RH agent over the last decade in the U.S. In the late 1990's many health plans in the United States, including the government provider (Medicare), for persons 65 years of age or older, have mandated "Least costly alternative" for the LH-RH agents. Intense price competition has resulted in a somewhat more balanced market share for the two available LH-RH agents.

There are a number of products on the horizon which may have a practice - impact on medical hormonal therapy. A titanium implant containing leuprolide acetate that will provide sustained release over 12 months will likely be released in 2000. The implant, called Duros™, is a human implantable, osmotically driven, therapeutic system to deliver leuprolide at a nominal of 120 mg/day over a period of 1-year (29). Another agent under development is a pure LH-RH antagonist, which does not produce the flare of testosterone release seen in the first few weeks of LH-RH agonist administration. The agent is called Abarelix® and in multicenter phase II study, it rapidly induced medical castration without the initial androgen surge characteristic of LH-RH agonists (30). It is unknown what impact these new agents will have on the broad medical hormonal therapy marketplace in the U.S. and worldwide.

Aside from these new agents, use of LH-RH agents may change for other reasons. A recent study by Oefelein (31) found that the average patient maintains a castrate testosterone level beyond the typical 3-month dosing schedule of a LH-RH agonist. To save money, clinicians may start monitoring serum testosterone and provide custom dosing rather than providing the injection at standard quarterly intervals.

Orchiectomy vs. Medical Hormonal Therapy

Although the outcome of orchiectomy is equivalent to that of LH-RH agents, most patients now prefer depot LH-RH injections to the prospect of castration. Past study has showed that patients prefer LH-RH to orchiectomy because of the psychological implications of loss of the testicles (32).

In the late 1990's, an additional concern for patients is that hormonal therapy should be reversible. With the prospect of effective intermittent hormonal therapy (see later), even as yet unproven, patients have expressed the desire for this approach, should it be proven efficacious, or should hormonal therapy side effects become troublesome.

Combined Hormonal Therapy

Cancer progression during androgen deprivation therapy may be explained by inadequate suppression of adrenal androgens or by development of androgen-independent tumor cell subpopulations. It appears that the new millennium will bring continued debate regarding the clinical value of combined hormonal therapy (CHT). Since initial reports appeared in the mid 1980s (33), the value of adding an antiandrogen to testicular androgen deprivation has been debated. Because low levels of dihydroxytestosterone produced by the adrenals may continue to stimulate androgen-sensitive cells, the use of an antiandrogen, either in addition to a LH-RH agonist or after bilateral orchiectomy, may offer an advantage over monotherapy. There is some evidence that combination therapy results in improved response and survival rates (34-38). The National Cancer Institute (NCI)-0036 (38), EORTC-30853 (37), Canadian Anandron Study, and Multinational Nilutamide Study (34) all showed a survival benefit of 7 to 15 months with CHT; however, the recently reported intergroup #0105 NCI trial of orchiectomy and flutamide versus orchiectomy and placebo showed no statistically significant survival benefit from addition of an antiandrogen to the treatment of patients undergoing orchiectomy (39). Furthermore, four meta-analyses of CHT studies came to different conclusions (40-43). The first meta-analysis published in *The Lancet* (41) found minimal benefit from the use of CHT (2-3 month survival advantage); yet three other published meta-analyses found benefits to CHT (7.3-7.6 month survival benefit) (40,42,43). Most of the patients in all of these studies were men with significantly advanced metastatic disease, and the benefit of CHT in earlier advanced disease (so called, minimal disease) may be more significant. For example, in minimal metastatic disease both the NCI-0036 and EORTC-

30853 showed a more pronounced survival advantage for CHT (35-37). However, the minimal disease subgroup in NCI 0105 did not show a survival benefit for CHT with orchiectomy (39).

There are currently three pure non-steroidal antiandrogens in clinical use: flutamide, bicalutamide, and nilutamide. All three are generally well tolerated, however, the side-effect profile differs somewhat between agents and all are rarely associated with hepatotoxicity. Flutamide is associated with diarrhea in 10-15% of patients while nilutamide is associated with delayed adaptation to light change in approximately 15% of men and a reversible pulmonary fibrosis in 1-2% of patients. A recent study found that there is equal efficacy between flutamide and bicalutamide (44). To my knowledge, no direct clinical trial comparison between nilutamide and the other two agents have been performed. In patients who are experiencing rising PSA levels on CHT, the initial treatment is to withdraw the antiandrogen to assess for an "antiandrogen withdrawal" response (45). This intervention alone may result in a several month PSA decline and is considered the first standard treatment in early hormone refractory prostate cancer. From a practical standpoint, it will take longer (4-6 weeks) to assess response for bicalutamide due to the longer half-life and time required for clearance.

External Beam Radiation for Locally Advanced (Metastatic?) Disease

While treatment of clinical stage T-3 and T-4 disease remains controversial, external beam radiation remains the mainstay of treatment. Although observation, transurethral resection, or hormonal therapy in patients with low-grade stage T-3 tumors is sometimes used (46), none of these methods offers a significant chance for long-term disease control because most patients have occult metastases. Surgical treatment of clinical stage T-3 disease has not been widely advocated because of the potential for incomplete excision of local tumor and the high incidence of lymph node metastases; however, survival rates with radical prostatectomy are comparable to those achieved with radiation therapy (47).

Neoadjuvant androgen deprivation therapy using a LH-RH agonist can shrink the prostate gland

by as much as 40% to 50% depending on the duration of therapy (48,49) and often results in the normalization of PSA levels (50). In a recent Phase III Radiation Therapy Oncology Group (RTOG) trial involving 456 evaluable patients, short-term androgen deprivation with radiation therapy resulted in a cumulative incidence of local progression at 5 years of 46% compared with 71% for radiation therapy alone ($p < 0.001$); progression-free survival rates, including normal PSA levels for 396 patients with at least one PSA recorded, were 36% for patients treated with androgen deprivation plus radiation therapy compared with 15% for patients treated with radiation therapy alone ($p < 0.001$) (51).

Additional data from the Radiation Therapy Oncology Group (RTOG) regarding hormonal therapy and external beam radiation have been published (52). Patients with clinical stage C (T3N0M0) or D-1 (Tany N1 – 3M0) prostate cancer were randomized to radiation and immediate adjuvant LH-RH agent therapy indefinitely versus radiation and observation with LH-RH only given at the time of relapse. Of 488 patients entered on the immediate LH-RH arm, 477 were analyzable at 5 years, including 438 by PSA criteria. Similarly, for the delayed LH-RH arm, the numbers were 489, 468, and 429, making this a large and valuable addition to the literature. There was a statistically significant improvement in 5-year failure rates for local failure, distant metastases, and disease-free survival for the patients in the immediate LH-RH group (it started immediately after radiation therapy and continues indefinitely). Perhaps, because only one fourth of the patients have died thus far, an overall survival benefit for immediate LH-RH therapy is not yet evident. However, even at this modest follow-up of 5 years, a survival advantage for immediate hormonal therapy is seen for high-grade (Gleason 8-10) patients. With these two published RTOG trials: 86-10 (32) and 85-31 (33), the value of both neoadjuvant hormonal therapy (NHT) and adjuvant hormonal therapy (HT) in patients receiving external beam radiation is becoming clear. Most recently, a study from Europe confirmed the clinical value of long-term adjuvant LH-RH agonist with external beam radiotherapy for locally advanced prostate cancer. Bolla et al. (53) randomized 415 patients with locally ad-

vanced stage prostate cancer to external beam radiation alone versus radiation plus adjuvant LH-RH agonist therapy for three years starting at the beginning of the radiation course. This study was the first to confirm a survival benefit to adjuvant LH-RH agonist treatment. The 5 year survival was 79% in those men randomized to adjuvant hormones versus 62% in those receiving radiation alone ($p=0.001$). Furthermore, the disease-free survival was 85% and 45% in the two arms, respectively ($p<0.001$). Further study will be necessary to determine the optimum duration of NHT and adjuvant HT (i.e. 4 month vs. 3 years vs. indefinite or other duration) the value in lower stage (T-1c, T-2) disease, and the value and duration of antiandrogens (CHT) in this setting. Furthermore, although these studies with external beam radiation look very appealing, the value of NHT and adjuvant HT in surgically treated, brachytherapy-treated, and cryotherapy-treated patients is less well established.

Discussion of Early versus Delayed Hormonal Therapy

In 1997, the Medical Research Council (MRC) in Great Britain has published an important paper suggesting that early hormonal therapy (HT) prolongs survival over delayed treatment for advanced non-metastatic (M-0) and traditional D-2 patients (54). This large study included 938 patients with M-0, M-X, or M-1 prostate cancer, 469 of whom received hormonal therapy immediately versus 465 men who received hormones only when they became symptomatic. By stage, in approximately 55% in both treatment arms patients had non-metastatic (M-O) disease, about 20% were staged as M-X because they did not have a bone scan but had other suggestion of metastatic disease and approximately 25% had traditional (D-2) metastatic disease.

It is interesting that for the deferred hormonal therapy patients, although 181 (39%) were treated for bone pain progression, 159 (34%) men were treated for local progression. The impact of immediate versus delayed HT on morbidity is striking. Patients who received delayed HT had higher rates of pathologic fracture, cord compression, ureteral obstruction, extraskelatal metastases, and need for TURP, all of which are very clinically relevant.

Regarding the death rate from prostate cancer, 67% of the patients who died, died of prostate cancer. Interestingly, this compares to only 41% of men who died of prostate cancer in the Veterans Administration Cooperative Urological Research Group (VACURG) studies (55) and illustrates that as men are remaining healthier longer, the impact of prostate cancer death in the current era is greater. Cancer-specific survival was superior ($p=0.02$) in the immediate HT arm for all patients and there was even a more pronounced benefit for immediate HT in the subset of patients with M0 disease ($p<0.001$), which may be somewhat analogous to many current patients with PSA recurrence after prior local therapy. Aside from this extrapolation, this study provides fairly compelling evidence in favor of early hormonal therapy for true metastatic disease. The authors conclude by stating, "The survival data are perhaps the first clear evidence from a comparative study that early hormone treatment has an effect on mortality." Aside from this landmark finding, the benefits of immediate HT regarding major morbidity such as cord compression cannot be overemphasized.

Aside from these Medical Research Council data regarding the value of early hormonal therapy, there is other supporting evidence. A reanalysis of the VACURG data suggests a survival advantage for younger patients with stage D disease and high-grade (Gleason score 7-10) tumors who undergo androgen ablation therapy at the time of diagnosis (56). Furthermore, in a retrospective review of 68 patients with stage D disease, delayed treatment resulted in a significantly ($p=0.0087$) shorter median interval to the appearance of bone metastases than did early intervention with orchiectomy or exogenous antiandrogen therapy (43 months versus 100 months). The median period from diagnosis to death was 90 months in the delayed treatment group and 150 months in the immediate treatment group (57). Another study of patients with stage D-1 prostate cancer who had undergone bilateral pelvic lymphadenectomy and radical retropubic prostatectomy demonstrated a disease progression rate of only 10% in 162 patients who underwent immediate orchiectomy, compared with 50% in 104 patients who received delayed orchiectomy or other forms of adjuvant treatment ($p<0.0001$). Five

and 10-year nonprogression rates for patients who underwent immediate orchiectomy were 84% and 80%, respectively, compared with 48% and 38%, respectively, for patients who did not undergo immediate orchiectomy (58).

Most recently, Messing et al. (59), from the Eastern Cooperative Oncology Group (ECOG) reported a multicenter, randomized trial of immediate versus delayed hormonal therapy in patients who had stage D-1 (Tany N1-3, M0) prostate cancer after radical prostatectomy. In 98 men who were randomized between 1988 and 1992, the progression rates and cancer-specific survival strongly favored immediate hormonal therapy. Specifically, the cancer-specific death rate was 4.3% in the immediate group vs. 30.8% in the delayed group at the 7.2 year mean follow-up. Corresponding progression rates were 8.7% and 55.8%, respectively.

Despite this encouraging news that early hormonal therapy prolongs survival, the concern is the unknown effect of years of hormonal therapy use. One recent concern is that osteoporosis may result, as well as the more well established hot flashes, sexual dysfunction, and loss of muscle mass. Although one study has suggested that osteoporosis does result from long-term androgen withdrawal (60), our group and others are studying this in a prospective manner, and early results suggest that hormonal therapy patients do not have significantly lower bone mineral densities than age-matched control patients (61).

NEW TREATMENT CONCEPTS - ANTIANDROGENS ALONE

The concept of using oral-only antiandrogen therapy to treat metastatic or advanced prostate cancer is not new (64). The classic teaching over the last decade has been that monotherapy with antiandrogens alone provide an inferior survival compared to traditional hormonal therapy for men with traditional (D-2) metastatic prostate cancer (64). With the stage migration to fewer cases of traditional D-2 disease and the emergence to use of hormonal therapy for nontraditional "less" advanced metastatic disease (i.e. D-1, T-3, T-4) and PSA-only recurrence, this oral-only monotherapy is being revisited (65,66).

Bicalutamide and flutamide have been more widely studied in this regard (64). Bicalutamide has typically been used at a dose of 150 mg daily (64) while flutamide has been used at varying doses and has commonly been combined with finasteride (65). More study with longer follow-up is necessary to determine the efficacy of these approaches.

Survival in Metastatic Prostate Cancer and Hormone Refractory Disease

The median survival of patients with traditional metastatic prostate cancer treated with androgen ablation is approximately 3 years, although there is wide variation depending on the severity of metastatic disease (67). Furthermore, in the late 1990's many more patients have very early or occult metastatic disease with fewer metastases and survival of 5 to 15 years is common.

A decline in PSA level indicates a response to hormonal therapy. In patients who had bone pain at the start of hormonal therapy, the vast majority will have dramatic, rapid, complete relief of this pain. Patients who do not respond to initial hormonal therapy should have the level of serum testosterone measured to ensure that it is indeed at castrate level (67). A subsequent increase in PSA level or return of symptoms, including bone pain, is an indicator of tumor progression. At the point, the patients have hormone refractory prostate cancer (HRPC) or what some clinicians also call stage D3 disease. This is the stage of prostate cancer most commonly associated with painful bone metastases. Treatment of HRPC includes withdrawal of antiandrogens for those patients on combination hormonal therapy (45), a different antiandrogen or other second line hormonal therapy, cytotoxic chemotherapy, and/or radiopharmaceutical agents to treat symptomatic bone pain.

Adenocarcinoma of the prostate is resistant to most chemotherapeutic regimens, but trials of single-and multiple-agent chemotherapy for HRPC are ongoing (67). The evaluation of chemotherapy treatment response in HRPC has been a major problem both for investigators and clinicians. The majority of patients have disease confined to bone, a site not readily amenable to objective response assessment. Bone scan response assessment is complicated

by the slow improvements in true responders and the difficulty in distinguishing improvement from progression, both of which may appear as an increase in signal intensity. Similarly, evaluation of soft-tissue disease, which may comprise only a minority of patients, is also difficult. Biochemical responses may be inferred from declines in PSA; however, it is difficult to know whether PSA response reflects true reduction in tumor bulk or some direct effect of treatment on the production of this serum marker. In addition, there have been attempts to quantify disease-related symptomatology using symptom score tools and quality-of-life (QOL) scales, although these instruments are still being validated.

Survival and progression-free survival remain important endpoints in the setting of randomized, controlled studies. However, there is no accepted standard therapy for HRPC and no drug to date has demonstrated a survival advantage over other acceptable therapies. Objective responses occur infrequently and are difficult to define given the heterogeneity of tissue involved by the disease. For these reasons, disease palliation and pain control are now accepted endpoints and are recognized by the FDA with regard to prostate cancer treatments. Mitoxantrone, a chemotherapeutic agent similar to adriamycin, was FDA-approved in the late 1990's for HRPC in combination with prednisone or hydrocortisone and is effective in palliation of bone pain, although a survival benefit has not been demonstrated (68,69). Aside from mitoxantrone and glucocorticoids, current trials are focusing on ketoconazole, estramustine, vinblastine, and suramin (67). The combination of etoposide and estramustine is an active but fairly toxic regimen (70). These other chemotherapies may also have some effect on bone pain in patients who respond.

To treat painful bone metastases, there are also now two FDA-approved radioactive pharmaceuticals: strontium-89 and samarium-153-lexidronam. Strontium-89 is a beta-radiation emitting medication that is injected intravenously and follows the same biologic pathway as the mineral calcium (71). It is taken up by the body's skeletal system, to a greater degree by the cancerous areas in the bone than by normal areas. This absorption of the radioactive agent may kill some cancerous cells, but it specifically

works to reduce bone pain, although the mechanism of action is unclear. Patients usually begin to notice a reduction in pain between 10 and 20 days after the injection. Pain reduction lasts from 4 to 15 months, but on average about 6 months. If the pain returns, the patient can get another injection as often as every 3 months. Multiple clinical trials involving more than 500 patients found about 10% to 50% had complete or dramatic response, with bone pain completely or virtually eliminated (71). A partial or complete response was reported by 20% to 97% of patients in the different studies. On average, 80% of the men reported a partial or complete response rate. In other words, most of the men got some relief.

Samarium-153-lexidronam has also undergone large-scale controlled testing in the United States and Europe (72). Like strontium-89, there was improvement of pain in the majority of patients and relatively rapid onset of action, specifically within one week for many patients. The duration of pain control is variable, but a single samarium-153-lexidronam injection typically was effective for 3 to 4 months. Both strontium-89 and samarium-153-lexidronam may affect bone marrow function principally in the form of decreased platelet counts, but this side effect is relatively mild and reversible.

CONCLUSIONS

The paradigm of advanced or metastatic prostate cancer should include not only those patients with widely disseminated metastatic disease but also those with a significant chance of progression and risk of death from prostate cancer, including those with stage D-1 (N-1 to N-3), T-4, and T-3 disease and those with less clearly demarcated stages (MX and M-0) at which primary treatment has failed. Increasing numbers of patients diagnosed with advanced prostate cancer enter treatment long before the development of bony metastases.

It is now recognized that early androgen ablation has the potential to markedly delay the onset of disease progression in patients with advanced prostate cancer, thereby allowing a longer symptom-free interval and a potentially better quality of life. The use of a LH-RH agonist, alone or combined with an

antiandrogen, is more acceptable to patients than is orchiectomy; it also is not associated with cardiotoxicity, and, therefore, has become the preferred method of androgen ablation in patients with advanced prostate cancer.

Debate continues regarding the clinical value of CHT; there is conflicting evidence that combination therapy results in improved response and survival rate. There is also concern about the known and unknown effects of years of hormonal therapy use, including the potential for resultant osteoporosis. Thus, intermittent hormonal therapy and other nontraditional approaches such as antiandrogens alone has become an area of research focus in recent years. Hormone refractory prostate cancer

(HRPC) remains a challenge. No agent has been proven to prolong survival although, mitoxantrone chemotherapy and the radiopharmaceuticals strontium-89 and samarium-153 have proven palliative benefit. Goals of future study must include a determination of the most effective treatment approaches using hormonal and other therapies that demonstrate the greatest efficacy and the least detriment for the patient.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the U.S. Army or the Department of Defense.

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