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Prostate Cancer
Old Problems and New Approaches*

Part III. Prevention and Treatment

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In Part Three of this review, we begin with an analysis of prevention strategies for prostate cancer followed by a discussion of the clinical use of molecular techniques for the evaluation and treatment of patients with clinically localized prostate cancer. New developments in neutron and photon therapy of prostate cancer are addressed as well as the use of systemic radiotherapy for the treatment of bone metastases. Finally, we conclude with the role of hormonal therapy in the treatment of prostate cancer and the current status of development of chemo therapeutic regimens for the treatment of prostate cancer. (Pathology Oncology Research Vol 2, No 4, 276–292, 1996)

Key words: prostate cancer, prevention, radiotherapy, chemotherapy

7. PREVENTION AND TREATMENT OF PROSTATE CANCER

7.1. Prevention Strategies for Prostate Cancer

In general, cancer prevention strategies can be defined as primary, secondary, and tertiary prevention. The target populations for primary and secondary prevention are subjects at normal or high risk. Unlike primary and secondary prevention, which are aimed at uninitiated and already initiated cells during the promotional phase of tumorigenesis, tertiary prevention is aimed to reverse precancerous lesions or to prevent the precancerous lesions from developing into cancer. Therefore, individuals with precancerous conditions are the target for tertiary prevention. As the incidence and mortality of PCa rise at alarming rates, PCa has become an important public health problem. Accumulating studies on risk factors (both environmental and genetic) and the biology of the PCa allow the development of potential preventional strategies for PCa. Risk factors for PCa such as age, race, and family history do not lend themselves well to prevention efforts. There are, however, life-style and dietary factors that if modified, may lead to a lower PCa risk. Earlier sections have extensively discussed the risk factors for PCa. Here we choose to focus on chemoprevention.

Chemoprevention is defined as the administration of natural or synthetic agents to prevent the initiation and/or promotion of events during tumorigenesis.[1] Preventional intervention should decrease the incidence of PCa or suppress or reverse precursor lesions. Any agent that can successfully inhibit the progression of indolent localized disease also would be valuable. However, in order to be practical, the intervention must be safe and easily tolerated. So far, a variety of potential chemoprevention agents have been investigated in *in vitro* and *in vivo* PCa models.

Difluoromethylornithine (DFMO) is a suicide inhibitor of ornithine decarboxylase (ODC), a key enzyme that catalyzes ornithine to polyamines which are important in the synthesis and stabilization of DNA and thus cell proliferation.[2] Since the prostate has very high concentrations of

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polyamines and of polyamine synthetic enzymes including ODC. DFMO has been investigated for its potential role in the chemoprevention of PCa.[3,4] It was found that the ODC activity of the Dunning R3327 rat prostatic carcinomas is as sensitive to inhibition by DFMO as the normal rat prostate. It also has been demonstrated that DFMO is inhibitory to the growth of PCa both *in vitro* and *in vivo*.[3,4] Several human phase I trials of DFMO showed that the dose-limiting toxicity was thrombocytopenia and reversible ototoxicity at 9 g/m^2/day. Mild leukopenia and anemia were also noted with DFMO.[5] In a phase II study, Meyskens et al[6] found that reversible sensorineural hearing loss occurred in 30-70% of patients with long-term, high-dose therapy. For chemoprevention, the optimal oral dose has yet to be identified. Due to its toxicity, DFMO is currently unacceptable for use in the chemoprevention target population which are healthy individuals.

An accumulating body of evidence support the concept that androgens stimulate cell proliferation and inhibit prostate cell death and suggest that androgenic stimulation promotes prostate carcinogenesis.[7] Since the side effects associated with LHRH agonists and antiandrogens in therapeutic regimens are unacceptable among healthy populations, widespread chemoprevention usage of these agents is very unlikely.

Testosterone is the dominant stimulus for prostatic growth and dihydrotestosterone (DHT), which is a metabolic product of testosterone catalyzed by 5α-reductase, is the most active intracellular androgen. Inhibitors of 5α-reductase may inhibit PCa occurrence and growth while causing very few side effects.[8] The potential utility of 5α-reductase inhibitors as chemoprevention agents came from the study of an inherited deficiency of 5α-reductase, a form of male pseudohermaphroditism characterized by mild external secondary sexual anomalies and an underdeveloped prostate. It was found that individuals with 5α-reductase deficiency do not develop BPH or PCa.[9,10] A number of 5α-reductase inhibitors have been synthesized. Finasteride (Proscar, 5 mg/day, orally) was the first 5α-reductase inhibitor to enter clinical trials. Finasteride selectively inhibits 5α-reductase, thereby blocking the metabolism of testosterone to DHT. It has been investigated extensively for the management of BPH[11] and it was approved by the FDA in 1992 for that indication. In October 1993, the PCa prevention trial (PCPT) was designed to determine whether finasteride reduces PCa incidence. In the PCPT, 18,000 healthy men ages 55 and older, with no evidence of PCa, will be enrolled. The participants will be randomized to receive either finasteride (5 mg/day, orally) or placebo and evaluated for seven years. The primary objective is to demonstrate a decreased incidence of PCa in the treatment group compared to the placebo group. The secondary objectives include evaluating the side effects and toxicities of finasteride, the grade and stage of prostate and other diagnosed cancers, cancer mortality rates, incidence of BPH, effectiveness of PSA and digital rectal examination (DRE) screening, and quality-of-life issues. This large randomized trial is expected to yield valuable information on: i) the epidemiology, risk factors for, and natural history of PCa; ii) the screening and diagnosis of PCa; iii) finasteride's ability to prevent BPH and PCa.

A number of chemotherapeutic agents, such as estramustine, etoposide, vinblastine, tamoxifen, and colchicine, have been shown to inhibit the growth of the established PCa and of the cultured PCa cells.[12,13,14] Phase I and II clinical trials have been carried out to examine the effect of chemotherapeutic agents in patients with metastatic hormone-refractory PCa.[12,13,14] However, the potential value of these agents in PCa chemoprevention in the general population is yet to be elucidated. Pentosan polysulfate, a highly negatively charged polysaccharide, has been demonstrated to inhibit angiogenesis *in vitro* and suppress prostate tumor growth *in vivo*.[15] Recently, it has been shown that oral administration of modified citrus pectin, a soluble component of plant fiber derived from citrus fruit, can inhibit spontaneous metastasis in a rat PCa model. Since citrus pectin has no effects on primary tumor growth or blood vessel endothelial cell growth, it seems to act as an antiadhesive agent in the early stages of metastasis. Citrus pectin is thought to interfere with cell-cell interaction mediated by cell surface carbohydrate-binding galectin-3 molecules.[16] Studies of the toxicity, dose, and efficacy of modified citrus pectin in preventing metastasis of human PCa are warranted.

In summary, although a large number of agents show activity against tumor cell growth or progression/metastasis, none of them has been proven to prevent tumor initiation or to reverse the process of prostate carcinogenesis. Finasteride has a demonstrable role in management of BPH. Its role in prevention of BPH and PCa is currently being investigated in the PCPT trial. Due to its low toxicity, finasteride may prove to be the first agent to be used for prevention of PCa in general as well as in high risk populations.

7.2. Clinical Use Of Molecular Techniques In The Evaluation And Treatment Of Patients With Clinically Localized Prostate Cancer

Complete surgical removal of the prostate has been an option for the treatment of clinically localized PCa for over 70 years. Beginning in 1980, improvements in surgical technique and a better understanding of the anatomical relationship of the prostate to the dorsal venous complex and the corpora cavernosal nerves have elevated radical prostatectomy to become the treatment of choice for men with clinically localized PCa who have a life expectancy of greater than ten years. The best surgical candidates are those that have pathologically organ-confined disease. Unfortunately, currently available staging techniques

understage approximately 30% of patients with clinically localized PCa.[17,18]

Although many patients with extraprostatic disease can be effectively treated by a combination of radical prostatectomy, hormonal therapy and radiation therapy, the percentage of patients in this group who are cured is much lower than for those with pathologically organ-confined disease. As discussed above, novel methods are needed to determine the biological aggressiveness of PCa and identify new staging techniques to decide which patient will benefit from definitive local therapy.

In this section we will discuss the role of surgery in the treatment of PCa, the use of PCR amplification of the PSA mRNA sequence (RTPCR) in bone marrow aspirates to better stage patients with clinically localized PCa, and how comparative genomic hybridization (CGH) can determine the biological aggressiveness of PCa.

Contemporary methods of staging PCa involve radiologic techniques, biochemical assays, clinical examination of the prostate, and histological evaluation of PCa biopsy specimens (see above). The serum prostatic specific antigen (PSA) value increases proportionally with the clinical and pathologic stages of the disease. However, the overlap between stages is too great for PSA to accurately stage PCa. Even for PCa patients with a PSA in the normal range (less than 4.0 ng/ml) 25% will have extraprostatic disease.[19]

As discussed above, the Gleason score from the pathological specimen is a powerful predictor of disease-free survival in patients with PCa.[20] However, the significance of the Gleason score in the needle biopsy specimen is less clear. This is because 42% of Gleason scores from the needle biopsy specimen will be under- or overstaged, when compared with the pathologic specimen.[21] Most of the grading differences between the needle biopsy and the pathologic specimen are within one point. Despite this limitation, patients with a Gleason score of less than 7 and 7 or greater have a 63%, and 26% incidence of organ-confined disease, respectively.[19]

The Digital Rectal Examination (DRE) and transrectal ultrasonography of the prostate are poor determinants of extraprostatic disease. This is because these modalities cannot detect microscopic tumor extension. Through the widespread use of the PSA blood test in the screening for PCa, 40 to 50% of newly diagnosed PCa are stage T1c (PSA elevation only). By definition, these tumors are impalpable and cannot be imaged, therefore the DRE and transrectal ultrasonography have assumed a lesser role in the staging of the disease.

None of the above tests can accurately identify the individual patient that will ultimately relapse after definitive local therapy. For patients that have pathologically organ-confined disease, a radical prostatectomy can be curative in upwards of 90% of patients. We are using molecular biology techniques to better select those patients who will benefit from local tumor treatment.

The rationale for complete surgical removal of the prostate in the treatment of localized PCa are multifaceted. Clearly a radical prostatectomy and bilateral pelvic lymph node dissection provides the most complete tumor staging. By accurately identifying the full extent of the patient's disease, a more accurate determination of the patient's long-term risk for disease recurrence as well as the possible need for adjuvant therapy can be determined. Identification of minimal residual disease early in a patient's treatment course may allow less toxic systemic therapies to be instituted with the goal of curing the disease.

We have recently analyzed our radical prostatectomy data for years 1991 and 1992. A total of 307 patients are evaluable that had a three month or longer follow-up (range 4 to 56 months, mean 30.8 months). There were a total of 10 deaths in this series, 2 from PCa and the other 8 from unrelated illnesses. Of the 307 patients, 37% had pathologically organ-confined disease and 63% had extraprostatic disease *(Table 1)*. Twenty-eight percent of the patients have a detectable serum PSA level and 2.3% have clinical evidence of metastatic disease.

Table 1. **Pathological stage of 307 consecutive radical prostatectomy speciemens from 1991-1992**

Pathologic stage	*Number of patients*	*Percent of Patients*
Organ confined	114/307	37
Extraprostatic extension only	16/307	5
Positive surgical margins	89/307	29
Seminal vesicle invasion	53/307	17
Positive nodes	35/307	11

Only 6 out of 114 (5%) patients with organ confined PCa had a detectable PSA. This compares to 41% of patients with extraprostatic disease. To further refine the pathologic stages that are most predictive of disease recurrence, we subdivided our patients with positive surgical margins or extraprostatic disease *(Table 2)*. Patients with positive nodes or seminal vesicle invasion have a 58 and 69% risk of disease recurrence, respectively. For patients with extraprostatic extension and positive margins 39% of these patients will eventually fail. Most interestingly, patients with extraprostatic extension alone with negative margins or those patients with positive margins and no evidence of extraprostatic extension have only a 13% chance of disease recurrence. This latter group of patients have disease at the apex or anteriorly where there is no extraprostatic tissue. For these patients all tumor may have been resected despite the presence of a positive surgical margin.

At our institution, 75% of patients undergoing radical prostatectomy for clinically localized disease are disease-free three to five years after surgery. Although this is an excellent disease-free survival rate for patients with clini-

cally localized PCa, it is our goal that through better patient selection, earlier diagnosis, and a better understanding of the biological aggressiveness of the disease, we will be able to decrease the morbidity and mortality from PCa even further.

Table 2. **Number of patients with recurrent disease after radical prostatectomy according to the pathologic stage of disease**

Pathologic stage	*Number of patients*	*Patients with PSA>0.4*	*PSA<0.4*
Organ confined	114	6 (5%)	108 (95%)
Extraprostatic extension only	16	2 (13%)	14 (87%)
Positive surgical without extraprostatic extension	48	6 (13%)	42 (87%)
Positive margins with extraprostatic extension	41	16 (%)	25 (61%)
Seminal vesicle invasion	53	31 (%)	22 (42%)
Positive nodes	35	24 (%)	11 (31%)

To accomplish this goal we are utilizing PCR amplification of the PSA mRNA sequence (RTPCR) to identify PCa cells in the bone marrow of patients with PCa. We have shown that this technique can identify one PCa cell in a background of 10^6 lymphocytes.[22] The presence of circulating PCa cells in the bone marrow is strongly correlated with the pathologic stage of disease.[23] We have evaluated the bone marrow of 79 patients with clinically localized PCa undergoing radical prostatectomy for the presence of circulating prostate cells. None of these patients had previously been treated with hormonal or radiation therapy. Fifty-two percent of patients had pT1-2 and 48% had pT3-4/N+ tumors. The follow-up ranged from 1 to 43 months (median 12 months). Ten of the 79 patients had recurrent disease (defined as a serum PSA >0.4). RTPCR for the PSA and actin mRNA was performed on all samples. The actin RTPCR, which served as a positive control, was positive for all of these samples.

Thirty-eight of 79 (48%) patients were RTPCR PSA positive: 32% of the pT1-2 and 66% of the pT3-4/N+ were RTPCR PSA positive (p=0.01) *(Table 3)*. Two of the 41 (5%) RTPCR PSA negative and 8 of the 38 (21%) RTPCR PSA positive patients have recurred. Patients who were RTPCR PSA positive had a significantly shorter disease-free survival than those patients that were RTPCR PSA negative (p=0.0126). The median disease-free survival for RTPCR PSA negative patients has not been reached compared to 19.1 months for RTPCR PSA positive patients.

Because RTPCR detection of circulating PCa cells appears to be an excellent predictor of disease-free survival in patients with clinically localized PCa undergoing radical prostatectomy we are investigating the presence of circulating prostate cells in patients treated with definitive radiation therapy, hormonal therapy, or watchful waiting. We are now evaluating individual metastatic PCa cells for phenotypic and genotypic properties that may help determine their clinical significance.

To determine the biological aggressiveness of PCa, we are screening individual tumors for the extent and pattern of chromosomal alterations. This information can be used to compare the unique genetic alterations in PCa between African-American and Caucasian men. Comparative genomic hybridization (CGH) is a new and powerful methodology for mapping DNA sequence deletions and amplifications throughout the genome of a tumor in a single experiment.[24] This procedure involves simultaneous, dual color fluorescence in situ hybridization of tumor genomic DNA and normal genomic DNA to normal human metaphase chromosome spreads. The ratio of the intensities of the two colors along the metaphase chromosomes gives the relative copy number of tumor DNA to normal DNA at each location. Thus deletions and amplification are simultaneously detected and mapped along all chromosome arms. Analysis of a series of tumors reveals genomic regions of recurrent or consistent deletions or amplifications. These regions likely harbor tumor suppressor gene(s) (deletions) or oncogene(s) (amplifications) important to the development and progression of that type of tumor. This technique is unbiased in that it does not rely on previous knowledge of genes important to the development and progression of particular types of cancer--there are no specific probes, and the entire genome is screened. Further, this technique is likely to yield prognostic information superior to that achieved by DNA content ploidy analysis for two reasons. First, tumors may actually have large portions of the genome deleted and gained but if the overall DNA content is balanced, the ploidy result will be normal. Second, the biological aggressiveness of a tumor is likely to be related to gain or loss of specific chromosomal regions detectable only by CGH.

To date, we have used CGH in two PCa studies. In the first study, we assessed the ability of CGH to detect alterations in clinically localized PCa and found it to be highly sensitive and specific in comparison with PCR-based loss of heterozygosity measurements on chromosome 8p. We created the first genome-wide map of regional chromosomal alterations in PCa.[25] In the second study, we studied tumors from 31 patients with metastatic disease. Five of the 31 men were African-American. Overall, the frequency and pattern of genetic alterations was similar between African-Americans and Caucasians. Importantly, we found preliminary evidence of more frequent gains in the region of 4q25-q30 in tumors from African Americans.

We were also able to improve the technique of CGH significantly. A new statistical analysis was developed to allow for the objective and standardized interpretation of fluorescence intensity ratios both within the genome of individual tumors and between the genomes of several

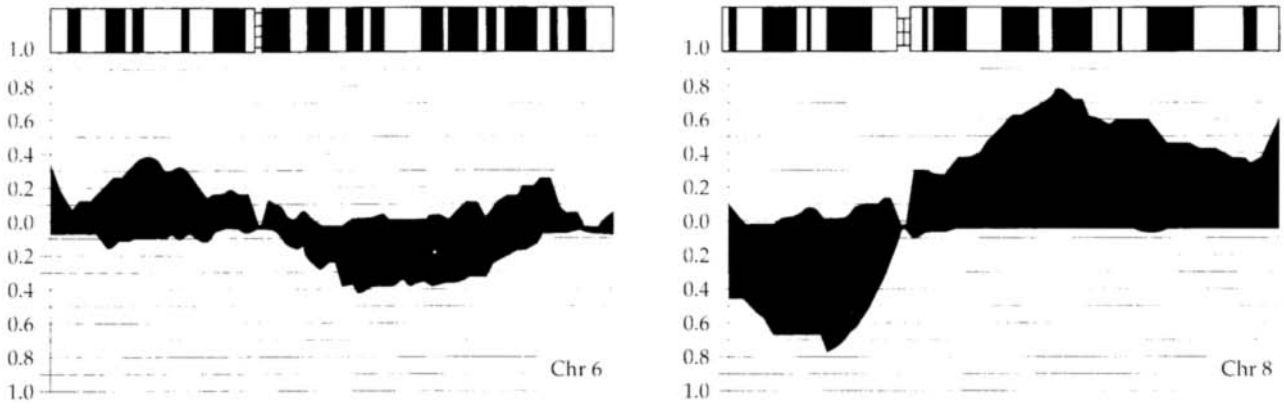

Figure 1. *Region specific frequency of gains (above central axis) and delations (below central axis) on chromosomes 6 (left) and 8 (right) in 31 metastatic prostate cancers. For example, the 8p22 region was deleted in 19/31 (61%) of tumors.*

tumors. Summary data obtained in this study for chromosomes 6 and 8 are shown in *Fig.9*.

In addition to the genetic analysis of tumors, we examined the tumor cellular proliferative fraction. We and others have shown that tumor cellular proliferative fraction, as determined by any of several immunocytochemical techniques, shows excellent promise as a marker of prognosis in PCa.[26] Recently, we have measured the cellular proliferative fraction within a single pathologic stage of PCa using an antibody to the Ki67 antigen. We found that the proliferative fraction predicted survival better than the histological grade. Thus, we believe that measurement of cellular kinetics provides information on the biological aggressiveness of tumors beyond that achieved by standard clinicopathological parameters. By combining molecular techniques with earlier diagnosis of PCa, we hopefully will be able to identify patients who have PCa at a curable stage. If PCa can be identified before it has grown outside the prostate, radical prostatectomy is potentially curable.

7.3. Conformal Neutron and Photon Irradiation in Non-metastatic Prostate Cancer

In the management of locally advanced PCa fast neutron irradiation has demonstrated a statistically significant improvement in local tumor control and disease-free survival compared with conventional photon radiotherapy.[27,28] At 10 years follow-up, there was a significant improvement in clinically assessed local control (70 vs. 58%) and survival (53 vs. 29%) in favor of the neutron arm.[27]

In 1986, this trial was retested using the newer neutron therapy facilities that had been sponsored by the National Cancer Institute. The rate of biochemical relapse (elevation of the serum PSA levels) was significantly lower in the neutron treated patients (17 vs. 45%).[28] However, the rate of severe complications was significantly higher for the neutron-treated patients. In total, 24% of neutron-treated patients experienced Grade 3 or 4 chronic toxicity compared to 8% of photon-treated patients.[28] Analysis of these complications suggested that differences in the capability of beam collimation among different neutron facilities were responsible for the observed differences in late rectal and bladder complication rates.[29]

In view of the benefits of neutron irradiation for local control in PCA, a series of three Phase II studies were conducted at Wayne State University to study whether the use of 3 Dimensional conformal neutron irradiation would allow for the safe delivery of fast-neutron irradiation in patients with localized and locally advanced adenocarcinoma of the prostate.

Table 3. **Presence of circulating prostate cells according to pathologic stage**

Stage	*Number of patients*	*Circulating cells present*	*Percent*
Organ confined	41	13	32
Capsular penetration	10	5	50
Positive margins	12	7	58
Seminal vesicle invasion	6	5	83
Bladder neck invasion	1	1	100
Positive pelvic nodes	9	7	77
Total	79	38	48

Forty-seven patients with locally advanced disease (Stage $\geq$ T3 and/or Gleason Score $\geq$ 8) received 15 NGy + 18 PhGy. One hundred four patients with localized PCA (Stage $\leq$ T2C and Gleason Score $\leq$ 7) received either 9 NGy + 38 PhGy (51 patients) or 10 NGy + 38 PhGy (53 patients). Prior to treatment, patients either underwent conventional x-ray simulation followed by treatment-planning CT or virtual CT simulation, alone. All patients were immobilized in the supine position with a custom-made alpha cradle cast. Simulation included oral, intravesicle and urethral contrast according to a previously reported technique.[30]

The outline of the prostate, seminal vesicles, pelvic lymph nodes, pelvic bones, femoral heads, urethra,

Table 4. **Summary of radiation fields and doses**

Photon component	*Localized Prostate Cancer*		*Locally Advanced PCa*
Daily dose PSV*	2 Gy	2 Gy	1.8 Gy
PLN	–	–	1.8 Gy
Total dose PSV	38 Gy	38 Gy	18 Gy
PLN	–	–	9Gy#
Field arrangement	Ap/PA/ RL/LL	Ap/PA/ RL/LL	Ap/PA/ RL/LL
Neutron component			
Daily dose PSV	0.9 N Gy	1.0 N Gy	1.0 N Gy
PLN	–	–	0.6 N Gy
Total dose PSV	9 N Gy	10 N Gy	15 N Gy
PLN	–	–	9 N Gy
Fields	RL/LL RAISO/ LAISO	RL/LL RAISO/ LAISO	AP/PA RL/LL
Neutron Schedule	10 consecutive days (M–F)	10 consecutive days (M–F)	every other day alternate with photon
Total dose	9 N + 38 Ph Gy	9 N + 38 Ph Gy	15 N + 18 Ph Gy

* PSV prostate and seminal vesicles
+ PSA + PLN prostate, seminal vesicles and pelvic lymph nodes
# using partial transmission through multirod collimator

bladder, rectum, and skin were digitized into the 3D planning system. The tumor volume, normal tissues and block outline were displayed with the beam's eye view (BEV) technique. The BEVs were registered to the simulation films by aligning the bony pelvic anatomy. These films served as templates for the cerrobend block fabrication and port film verification for the photon treatment. For neutron field shaping of patients undergoing virtual simulation, block fabrication was directly accomplished using the BEV and digitally reconstructed radiographs.

The neutrons were produced by using a superconducting cyclotron with a 48.5 MeV deuteron beam incident on an internal beryllium target[31] resulting in depth dose characteristics similar to that of a 4MV photon beam.[32] The multirod collimating system[33] of the cyclotron produced irregularly shaped and partial transmission fields. A summary of the doses, fields and volumes irradiated is shown in *Table 4*. Dose volume histograms comparing the neutron and photon dose distribution to the prostate, seminal vesicles, rectum, and bladder demonstrated no significant differences.[30,33] An isodose curve for the non-neutron beam is shown in *Fig.2*. At each follow-up visit, there was a symptom assessment, physical exam including digital rectal examination (DRE), complete blood count, blood chemistries, serum PAP and PSA levels.

Biopsies were obtained at 6 and 18, or 12 and 24 months posttreatment. Toxicity was graded according to the RTOG morbidity grading system. *(Table 5).*[35] A complete biochemical response was scored if a patient without hormone therapy reached a PSA level ≤ 1ng/ml. Whereas a biochemical failure if the PSA level rose on two successive follow-up visits. Postradiation biopsies were performed with transrectal ultrasound guidance. Six 18-gauge cores were obtained from the dominant hypochoic or color Doppler regions of suspicion in each sextant. All postradiation biopsies were reviewed by a single pathologist. Biopsies were scored as negative, marked, moderate, minimal therapeutic effect, or positive.

The times to last follow-up, to recurrence, to development of a radiation complication, or to death were calculated from the date of last treatment. Estimates of survival probabilities were derived by the Kaplan-Meier method.[36] Estimates of cumulative incidence probabilities were done for complete biochemical responses and complication, and comparisons for categorical variables used the Fisher's exact test.[37] The median follow-up was 16 months (range: 3-30 months).

1. *Toxicity* – Two patients (1%) reported acute Grade 3 GU (genitourinary) toxicity during radiation treatment. Both experienced bladder spasms requiring brief hospitalization for narcotics and antispasmodic medication. One patient was in the 9 NGy arm and 1 received 15 NGy. No other Grade 3-5 acute toxicity was recorded.

No chronic Grade 3-5 GI or GU (gastrointestinal) complications have been reported. The actuarial rates of Grade 2 GI morbidity at 20 months were 6% for the low dose and 29% for the high dose neutron arm (P=0.07). The actuarial rates of Grade 2 GU morbidity were 4 and 16% for the low and high neutron dose arms, respectively (P=0.08).

Stiffness in flexing or abducting the hips was seen in 20 and 42% of the patients receiving 9-10 NGy and 15 NGy, respectively (P=0.01). Severe Grade 3 or 4 hip stiffness

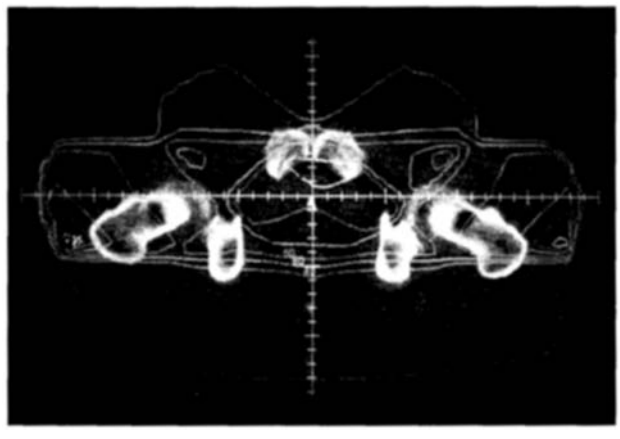

Figure 2. *Axial computed tomography view at the level of the prostate gland showing the isodose distribution of the nonaxial neutron beams (RL/LL/RAISO/LAISO).*

Table 5. **RTOG Chronic morbidity grading scale**

Grade 0	none
Grade 1	minor symptoms, no treatment required
Grade 2	symptoms responding to outpatient treatment no change in performance status
Grade 3	distressing symptoms altering a patient's lifestyle and/or requiring hospitalization for minor surgical intervention
Grade 4	major surgical intervention or prolonged hospitalization
Grade 5	fatal complications

was seen in 0 and 26% of patients, respectively ($P<0.05$). Three high dose (15 NGy) patients had painful pelvic bone necrosis identified on magnetic resonance imaging. Potency was maintained in 65% of patients with no significant effect secondary to neutron dose or the use of neoadjuvant hormones. Chronic complications as a function of dose are listed in *Table 6*. No Grade 3-5 skin or subcutaneous tissue toxicity has been reported.

Table 6. **Grade 2 late treatment complications following conformal mixed neutron and photon irradiation**

	9-10 N Gy + 38 Ph Gy	*15 N Gy + 18 Ph Gy*	*p value*
rectal	6 %	29 %	0.07
bladder	4 %	16 %	0.08
potency	67 %	60 %	NS
hip stiffness (moderate to severe)	20 %	42 %	0.01

NS = not significant ($p>0.05$)

2. *Efficacy* – At 12 months, 91% of all patients had a serum PSA < 4, 78% < 2, and 57% < 1ng/ml. Among patients with an initial pretreatment PSA level < 10 ng/ml, 100% had a 12-month PSA ≤ 2 ng/ml and 80% ≤ 1 ng/ml. By 18 months, the cumulative probability of achieving a PSA ≤ 4 ng/ml was 95% for the low-dose, localized patients and 93% for the high dose, locally advanced patients ($P = .81$). The actuarial probability of reaching a PSA ≤ 1 ng/ml was 81 and 57%, for localized and locally advanced patients, respectively ($P = 0.001$).

Local control at the histological level was assessed by postradiation biopsies in 73 patients. Overall, 63% of patients (46) were negative, 3% (2) showed a marked therapeutic response, 4% (3) a moderate response, and 30% (22) were positive. At six months, 20% of biopsies were negative, 70% at 12 months, and 85% at 18 months. The negative biopsy rate was not affected by clinical stage, Gleason score, pretreatment PSA volume or neutron dose.

The data from these three prospective studies of different neutron-photon dose combinations confirm that conformally designed fast-neutron irradiation can be delivered with acceptable levels of chronic toxicity. The rates of complete response at the biochemical and histological levels also suggest that the previously demonstrated superiority of neutron irradiation has been maintained with these mixtures of neutron and photon irradiation.[27,28]

The use of neutron irradiation in patients with localized PCa (low stage, low to intermediate grade) was justified based on lower than expected rates of complete response at the histological and biochemical levels reported in patients with Stage T1 or T2 disease treated with photons alone.[38] In this group of patients, high rates of chronic morbidity would not be acceptable and often therapeutic decisions are based on quality of life considerations.[39] The rates of chronic GI and GU morbidity seen in the low neutron dose arms are not statistically different than those achieved using 3D conformal photon irradiation alone.[40] Because of the enhanced rate of chronic toxicity seen with 15NGy, the current dose level for locally advanced PCa is 11 NGy + 46 PhGy twice daily with equates to 2 Gy/fraction photon equivalent dose of 82 Gy.

Based on the preliminary observations that neoadjuvant hormonal therapy increased the complete histological response rate, the role of neoadjuvant hormonal therapy in conjunction with conformal neutron-photon irradiation is being assessed. In addition, the optimal sequence of mixed neutron-photon irradiation is unknown and this is being assessed in an ongoing randomized trial at Wayne State University.

7.4. Palliative Radiation Therapy for Bone Metastasis Secondary to Prostate Cancer

Despite some dramatic improvements in the treatment of cancer in young people, the overall mortality and curability of solid tumors has changed little in the past half century.[41] The majority of cancer patients will eventually succumb to their cancer, and more than half of these patients will require some form of palliative therapy during their lifetime. Thus, the indications, techniques, and results of non-curative, but symptom relieving therapy is becoming increasingly important.

In the United States, despite improvements in radical surgery, radiation, and chemotherapy, the PCa death rates have not decreased. The fact remains that a substantial number of patients will eventually fail definitive therapy.

Palliation simply defined is the alleviation of symptoms in a patient usually with active, progressive disease for whom the prognosis is limited and the focus of care is to preserve quality of life. The basic tenets of palliation is to do good, minimize harm, and foster patient autonomy. Due consideration is given to the condition of the patient, to the chances of effecting palliation, and, of course, to the patient's wishes. Palliative radiotherapy can be highly effective, delivered in a relatively short time frame, and cause few side effects when the tolerance of normal tissues are respected. The ability of radiation to decrease pain,

prevent hemorrhage and obstruction, and to improve organ function has been well documented. Treatment can usually be completed in 1-3 weeks or less.

7.4.1. Natural History

To administer effective palliation, a thorough understanding of the cancer is required. At diagnosis, 50% of PCa patients have disease confined to the prostate gland or vicinity (T1-4), 20% have lymph node metastasis and 30% have distant metastasis.[42]

Regional lymph node involvement follows a predetermined pattern. Periprostatic and obturator nodes are involved first, followed by external iliac, hypogastric, common iliac, and periaortic nodes.[43] The number and magnitude of lymph node involvement correlates well with prognosis. Prout et al. has demonstrated that patients with solitary lymph node involvement developed progression of their disease in 20% of cases as compared to 75% for patients with multiple lymph node involvement.[44]

Of all patients diagnosed with PCa, more than 50% will die from their disease and more than two-thirds will suffer local and/or systemic progression prior to their terminal event. Prostate carcinoma metastasizes distantly to skeleton, liver, lungs, and occasionally to the brain and other sites. About 50% of the patients will experience bone metastases at some time during their lifetime. The mechanism of preferential dissemination to the spine and pelvic bones by the vertebral veins was initially proposed by Batson.[45] Recently, this concept has been disputed and an equal distribution of skeletal metastases from PCa as compared to nonprostatic cancers was described. The mechanism of dissemination to spine, pelvic bone, and long bones is a function of the regional arterial blood supply rather than the venous drainage.[46]

7.4.2. Bone Metastases

Bone metastases represents a common problem. 50-70% of PCa patients are estimated to develop osseous metastases.[47] Many therapies are available for bone metastases, including surgery, medical management, and radiation. Radiation therapy can treat most patients with highly effective symptom relief.

The hallmark of osseous metastases is localized pain which is many times continuous and unrelenting regardless of the site. The pain caused by bone metastases is not well understood. Some investigators have hypothesized that irritation of the periosteal membrane or the release of biologic mediators is responsible for bony pain. The most serious complication of osseous metastases is spinal cord compression which is discussed in the next section.

Most bony metastases can be diagnosed by physical exam, plain radiographs, and a bone scan. Plain radiographs are highly accurate in detecting metastatic lesions particularly when associated with pain, however the sensitivity is poor. The radiographic pattern is typically blastic for PCa and almost always lytic for renal cancer. Bone scanning is a useful adjunct to plain films. 99mTc-disphosphonate is taken up in areas of bone production and can be used be used for detection of bony metastases and following response to therapy. Bone scintigraphy is approximately 50-80% more sensitive than plain radiographs.[48] It can frequently show metastatic lesions long before changes on plain films are appreciated. Several investigators have estimated that this may be 2-6 months.[49,50] Plain films and bone scans are frequently used to plan radiation fields and define technique. CT and MRI are sometimes required if there is suspicion of bone involvement, but x-ray and bone scan are negative, or if there is soft tissue involvement.

Most clinical situations including pain management and preservation of bone integrity can be managed by the judicious use of radiation therapy. Planning radiation requires a clear understanding of the patient's disease and the intent of treatment. Although radiation has been shown to be highly effective, actual treatment delivery, dose, fractionation, and volume can vary greatly from center to center. Therefore, treatment can be customized to the patients needs. Certainly, patients with a painful bony lesion and a poor prognosis will most likely have a different treatment regimen than a patient with a good prognosis. In GU cancer patients, it is not unlikely for patients with bone metastases, especially prostate, to have many useful years of life.

The most widely quoted bone metastases study utilizing radiation is the RTOG trial 74-02 reported by Tong et al.[51] This study analyzed 1016 patients. All patients had at least one painful bony site, most required narcotic medications, and 56% described their pain as being constant and severe. These patients were randomized to receive several different radiation therapy regimens. There were 83% of patients who received a partial response and 54% obtained a complete response usually within 2-4 weeks of treatment. Pain relief was influenced by the site and pain status prior to irradiation. More than 70% of patients who experienced some pain relief did not relapse before death. There were no significant differences in the frequency of pain relief among the various treatment arms. A reanalysis of this RTOG study however, concluded that the two high dose protracted programs (270 cGy x 15 and 300 cGy x 10) had significantly better complete responses and decreased narcotic use, and patients treated to higher doses required fewer retreatments.[52] Reviewing the data from currently available prospective studies has shown overall response rates ranging from 85-100% using various treatment schedules.[53,54] Single fraction regimens (800 cGy x 1) appears to be as effective as the other more protracted regimens, but is also associated with increased acute morbidity particularly to the abdominal organs. A frequently used regimen in the U.S. is 3000 cGy

given in 10 divided fractions. This dose is adequate for most GU cancers including prostate.

A metastasis to a weight bearing region raises many concerns. A pathologic fracture can be painful and disabling both functionally and psychologically. Certain radiographic and clinical factors that warrant consideration of prophylactic surgical fixation include:

1. An intramedullary lytic lesion equal to or greater than 50% of the cross sectional diameter of the bone.
2. A lytic lesion involving a length of cortex equal to or greater than the cross sectional diameter of the bone or greater than 2.5 cm in axial length.[55]

These patients should be evaluated by an orthopedic surgeon. If a pathologic fracture has occurred in a weight bearing region, surgical fixation is required for pain control and to promote adequate healing. In all situations, postoperative radiation is required. Since PCa produces primarily blastic metastases, pathologic fracture is correspondingly infrequent.

7.4.3. Spinal Cord Compression

Spinal cord compression is a medical emergency. Failure to diagnose and promptly treat can lead to significant morbidity including paraplegia and autonomic dysfunction. In general, GU tumors, especially prostate and kidney, account for 13% of spinal cord compressions.[56] Approximately 18,000 cases of spinal cord compression occur in the United States every year.[57]

The predominant symptom of cord compression is that of pain in about 95% of patients.[58] Pain usually precedes a diagnosis of spinal cord compression by about 4 months. Symptoms however can progress rapidly to neurological dysfunction in a matter of hours to days. When a patient has progressed to paraplegia, return of function is infrequent. Therefore, early diagnosis and therapy are critical.

Diagnostic tools include x-rays, bone scan, CT, MRI, and myelogram. Plain films are positive in about 80% of patients with epidural compression, but is neither specific or sensitive.[59] A major limitation of plain films is that the bone requires at least 50% decalcification before radiologic changes can be appreciated. Bone scans as mentioned earlier are more sensitive but not specific. Plain films and bone scans with physical examination can detect most spinal cord compressions (85-90%).[60] The gold standard for diagnosis has traditionally been the myelogram. The sensitivity and specificity are approximately 95% and 88%.[61] However, this test is invasive and several investigators have shown MRI to be of similar if not superior accuracy.[62,63] MRI has the added benefit of imaging the entire spine.

Once the diagnosis of spinal cord compression is made, treatment can include surgery, radiation, or both. In most instances, radiation therapy suffices and obviates the need for surgery. Several retrospective series have shown equivalent results between radiation alone and laminectomy, plus radiation in terms of pain control, and functional improvement.

The most widely quoted study evaluating this issue is that of Gilbert et al.[58] In general, despite the therapy instituted, if a patient is ambulatory, there is an 85% chance that he will remain ambulatory. If nonambulatory, there is less than a 50% chance of regaining ambulation, and if paraplegic, less than 5% of becoming ambulatory. Again, this emphasizes the need for early diagnosis and treatment. Improvement of pain is similar to those results obtained with radiotherapy for other bone metastases.[58]

Radiation therapy can be instituted quickly and efficiently. Results of MRI or other diagnostic tests together with physical examination can help determine the appropriate treatment volume. Multiple epidural lesions can be treated in one continuous field or by multiple treatment fields. The volume treated is usually the level of cord involvement together with two vertebral bodies above and two below the epidural lesion. With the accuracy of MRI, many centers use one vertebral body above and one below the area of cord compression. The optimal radiation dose and fractionation scheme has not been firmly established. However, different from the treatment of other bony metastases, the goal is not only pain relief but also tumor reduction. It is for this reason that protracted fractionation for spinal cord compression is recommended.

Friedman et al demonstrated a good response in 71% of patients who received more than 2500 cGy for epidural compression versus 34% for patients receiving less than 2500 cGy.[64] The patients in this study had the diagnosis of lymphoma which is usually more radiosensitive than other tumor histologies. Commonly employed doses are 3000-4000 cGy over 2-4 weeks. In all cases, spinal cord tolerance to radiation should be respected. Often, initial doses of 300-500 cGy are given for the first two to three treatments to attempt quicker symptom palliation, but there is no firm data to support this.

There are a few instances where surgery should be considered as an option before radiation. They include pathologic fracture with spine instability or compression of the spinal cord by bone, unknown tissue diagnosis, a history of previous radiation to the same area, and a radiation resistant tumor with neurological deficits.

Once the diagnosis of cord compression is made or even suspected, all patients should be placed on steroid therapy. Steroids can decrease vasogenic edema and provide striking analgesic benefit. The loading dose of Decadron is 4-100 mg followed by maintenance dose of 4-24 mg q 6 hours.

4. Palliative Systemic Radiotherapy

Hemibody Irradiation – The concept of palliative systemic radiation therapy has interested physicians since 1905.[65] Over the years, the techniques and applications of

this form of treatment has continued to progress. Prior to the 1970's, experience in systemic radiotherapy was primarily in the form of total body irradiation (TBI). Its use was mostly in the treatment of hematologic diseases. The main limitations of this form of treatment was bone marrow organ toxicity which limited the maximal dose which can be given, 225-300 cGy.

Fitzpatrick and Rider began using hemibody irradiation (HBI) to circumvent the shortcomings associated with TBI in the early 1970's. In 1976, they published a landmark paper on their experiences with HBI.[66] Using single fractions of 500-1000 cGy, they treated 140 patients with symptomatic bone metastases and reported the results of 82 patients. HBI was tolerable and effective in achieving palliation of pain, in many cases within 48 hours of treatment. Deaths from radiation pneumonitis and hematopoietic failure were few. The study also showed that systemic radiotherapy can be effective in treating solid tumors. Following this publication, several articles evaluating their retrospective data on HBI for palliation of bony metastases were reported.[67,68] Results were encouraging and prompted the RTOG to evaluate this modality.

The final analysis of RTOG 78-10 was published in 1986 by Salazar et al.[69] The protocol explored increasing single doses of half body irradiation in patients with multiple symptomatic osseous metastases. The doses used were 600-800 cGy in the upper hemibody and 800-1000 cGy in the lower or middle hemibody. The most common histologies treated were prostate (40%), breast (29%), and lung (18%). Pain relief was experienced in 73% of patients. Fifty percent of patients achieved pain relief within 48 hours and 80% within one week. There were no fatalities and treatment was considered tolerable. Most effective and safest dosages were 600 cGy for the upper hemibody and 800 cGy for the lower and middle hemibody. When compared to RTOG 74-02, (local irradiation for palliation of bone metastases), HBI achieved similar number of patients experiencing pain relief, however, local irradiation achieved twice the number of complete responses. Another important finding was that recurrences of pain within irradiated field were four times lower with HBI than with local irradiation. This indicated that prophylactic irradiation to bones can decrease the rate of disease involvement. Studies by Jacobsson and Kaplan showed that PCa patients who received periaortic irradiation developed significantly less lumbar metastases than those who had whole pelvis irradiation alone.[70,71]

Based on the results of RTOG 78-10 and on the preliminary data on prophylactic irradiation, RTOG 82-06 was designed. This prospective randomized study evaluated at the effect of adjuvant systemic radiotherapy (HBI) in delaying the onset of bony metastases.[72] A total of 499 patients with painful bony metastases were randomized to either local radiation or local radiating and HBI 800 cGy. Those patients who received HBI had an increased progression free survival, 12.6 mo vs. 6.3 mo, and fewer retreatments. Overall, the incidence of toxicities were 5-15%. There were no fatalities or radiating pneumonitis since lung shields were used. The authors of the study concluded that 800 cGy of HBI can cause micrometastases to regress and that HBI has the potential to be used to treat systemic and occult metastases and improve quality of life for these patients.

HBI is delivered by external beam irradiation. The field arrangements have changed little since the conception of this treatment. Because of the long treatment fields, the source to skin distance is usually > 180 cm. Shielding is used for the oral cavity and all sites of previous irradiation. Lung blocks are used to reduce lung dose to 600 cGy corrected for lung transmission. The typical dose is 600 cGy to upper hemibody and 800 cGy to the middle and lower hemibody given in a single fraction.

The major chronic toxicity associated with HBI is radiation pneumonitis. Without lung correction, the incidence of radiation pneumonitis is estimated to be 18-35% for doses of 600-1000 cGy, and less than 10% if corrected for lung transmission.[73] Approximately 50% of patients will have depression of their hematological profile and 10% of patients may require transient hematological support. Irradiation of the head can cause xerostomia and cataract formation. If the head and brain has a low incidence of metastatic involvement, then exclusion of the head from the upper hemibody is acceptable. The most troublesome acute complication is nausea and vomiting that occurs in 80% of patients particularly with upper and middle hemibody irradiation. With the use of premedication programs using prednisone, odansetron, and hydration, the incidence of emesis is less than 5%.[74] HBI should be considered in any patient with multiple bony disease sites that are not responsive to hormone or chemotherapy maneuvers and have adequate bone marrow function.

Strontium-89 – In 1941, a new tool in the treatment of skeletal metastases was introduced: the radionuclide, Strontium-89. Strontium-89 is a calcium analog that emits beta irradiation. It has a half life of 50.6 days and the average beta energy is 1.46 Mev. Because of strontium's physical and chemical characteristics, it has the following advantages:

1. It selectively uptakes in areas of active bone formation.
2. Irradiation of normal tissues is limited and therefore tolerance is high.
3. Strontium-89 can be administered quickly and easily.
4. The patient is not a radiation hazard to family members or hospital staff.

Strontium-89 has several advantages over hemibody irradiation including better patient tolerance and ease of administration, with similar efficacy at least for PCa.

Pecher was first to demonstrate the effectiveness of Strontium-89 for the palliation of painful bone metastases in the early 1940's.[75] Over the proceeding years, numerous studies have confirmed the efficacy and safety of this form of treatment in palliating painful bony metastases particularly blastic metastases.[76,77] Several phase II trials have shown complete pain relief in 6-50% of patients and a reduction of analgesic use by 50%. Overall response rates in prostate patients is approximately 80%. Prospective randomized studies looking at this issue have also been completed.

Porter et al reported the findings of a phase III (TransCanadian) trial evaluating the efficacy of palliative Strontium-89 therapy in the management of hormone resistant metastatic PCa.[78] There were 126 patients randomized to strontium therapy versus placebo after local field radiation for symptomatic lesions. Those patients who received Strontium had significant reduction in analgesic intake at 3 months, (17% vs. 2.4% not requiring analgesics), progression of new painful sites (58.7% vs. 34% free of new painful sites at 3 months), and need for retreatment (51 weeks vs. 23 weeks time to retreatment). The levels of PSA were also significantly reduced with Strontium-89 therapy. The results of this study are provocative.

The UK Metastron Investigators' Group Study is another prospective study evaluating the efficacy of Strontium-89 after external beam radiotherapy.[79] Entry criteria were similar to the TransCanadian Study. External beam irradiation consisted of either local field or hemibody irradiation. The dose of Strontium-89 was 5.4 mCi. A total of 284 patients were treated according to protocol. Median follow up was 12 weeks. There were no significant differences in survival or overall pain relief with Strontium-89, local field, or hemibody therapy. However, patients receiving Strontium-89 were significantly less likely to develop new sites of pain or require retreatment.

Pain relief with Strontium-89 usually begins at 10-20 days after treatment, and the response lasts about 4-15 months. Some patients experience a pain flare 1-2 weeks after Strontium injection, and this usually indicates a better outcome. The recommended dosage of Strontium-89 is 4 mCi or 40-60 mCi/kg. The drug is administered by slow IV injection. Strontium-89 is cleared by the kidneys (two-thirds) and by the GI tract (one-third). All patient excretions can be flushed away without special monitoring. Strontium therapy is well tolerated. The major toxicity is hematological, especially thrombocytopenic. Most patients show a 24-50% decrease in platelet count from pretreatment levels.[80] The platelet nadir occurs 4-8 weeks after therapy, however medical intervention or hematological support is rarely needed. Platelet recovery is gradual and expected. Strontium should be used with caution in patients with platelets <100,000 and WBC <2400. Repeated administrations of strontium is possible based on individual patient response, but are generally not recommended at intervals of less than 90 days.

In conclusion, while it is important to continue to develop and refine our curative strategies in the management of patients with PCa it is also necessary to focus on effective management options for that subset of patients in whom cure is not possible but where the rapid and sustained reduction of symptoms is our goal.

7.5. The Evolving Role Of Hormonal Therapy In The Treatment Of Prostate Cancer

In 1941, Charles Huggins showed that surgical castration dramatically improved the condition of patients with metastatic PCa, alleviating their bone pain and reducing serum acid phosphatase levels.[81] Synthetic estrogen therapy subsequently achieved similar results. Since then, androgen deprivation therapy has been the mainstay of treatment for metastatic adenocarcinoma of the prostate. Despite an initial favorable response of about 80%, most patients will develop predictable and irreversible resistance to androgen deprivation.[82] The basic therapeutic approach for metastatic PCa is focused on suppression of testicular function, either medically or surgically. These therapies have resulted in a median progression-free survival time of 12 to 18 months and an overall survival time of 24 to 30 months.[83,84]

The recognition of the role of adrenal androgens in the formation of prostatic dihydrotestosterone led to the development of the concept of combined androgen blockade, accomplished by using an antiandrogen, flutamide, in combination with primary gonadal suppression to treat patients with newly diagnosed metastatic prostatic cancer.[86] Several randomized, double-blind studies have shown that the progression-free and overall survival rates for patients with metastatic PCa treated with combined androgen blockade are longer than those achieved by leuprolide treatment or orchidectomy alone.[84,85] However, hormonal therapy for metastatic PCa is not curative, and newer methods of treating metastatic PCa are required.

New basic science research has centered on understanding how androgen deprivation results in PCa cell death and on preventing the development of cellular mechanisms that render the cell resistant to androgen-deprivation therapy. Recent studies have shown that androgen-receptor mutations and alterations in the apoptosis pathway occur in hormonally insensitive PCa cells (see Part II).[87,88] Exploitation of these genetic events in the formation and progression of hormone-insensitive PCa may lead to novel methods for treating this disease. Until these newer therapies are available, emphasis is being placed on the combination of hormonal therapy and chemotherapy, as well as on intermittent androgen blockade.

One persistent fact about hormonal therapy for metastatic PCa is that such therapy is not curative. Because 80% of patients respond either completely or partially to this therapy, many clinicians are tempted to use hormonal

therapy as a first-line treatment. However, because most men who develop metastatic PCa are relatively old by the time the disease becomes refractory to hormone treatment, they often cannot tolerate treatment with investigational chemotherapeutic agents. Nevertheless, several treatments are being investigated, including the withdrawal of flutamide, the use of a combination of Estramustine and Vinblastine or VP-16, and the administration of intermittent androgen therapy (see below).

Paradoxically, approximately 20% of patients who have been treated with maximal androgen deprivation will experience a decrease in PSA levels and a partial resolution of bony and soft-tissue disease when flutamide treatment is withdrawn after the PCa becomes refractory to hormone therapy.[89] This response is not durable; the median response time is six months. The mechanism of this phenomenon may be related to alterations in the androgen receptor, which can be stimulated by flutamide instead of being blocked by flutamide. Current studies suggest that androgen receptor mutations occur in more than 30% of hormone-refractory PCa (see above).[87] Whether such mutations are the reason for the flutamide withdrawal effect is unknown.

Finally, several groups of researchers are investigating intermittent androgen deprivation. The theory behind this treatment method was pioneered by Bruchovsky and his colleagues from Canada,[90] who studied androgen-sensitive mammary tumors in male Shionogi nude mice. After the tumors had grown to approximately 1 cm in size, the animals were castrated and more than 90% of the tumor cells were eradicated. However, androgen-unresponsive tumors eventually began to grow. By transplanting the tumor to another male nude mouse before androgen-unresponsive tumors began to grow, the investigators were able to provide circulating serum androgens and to reinstate an androgen-responsive cell type. This cycle of androgen addition followed by deprivation could continue for a total of six cycles before the growth of an androgen-unresponsive tumor occurred. Clinically intermittent androgen suppression has been used successfully to treat a small group of patients.[91] This method is being investigated clinically by the Southwest Oncology Group, although no findings will be available for several years.

The greatest advance in the treatment of PCa was the identification of androgen responsiveness by Huggins et Hodges.[81] However, androgen responsiveness may also present the greatest problem in the treatment of PCa. Although a large percentage of patients will experience a partial response to androgen deprivation treatment, none will experience a complete response. The presence of good palliative treatment has inhibited the search for curative therapy. Novel therapeutic measures, including combinations of hormonal therapy with chemotherapy or gene therapy, will be required if the treatment of metastatic PCa is to be significantly improved.

7.6. Chemotherapy and Prostate Cancer

As discussed above, suppression of androgenic stimuli has been the main therapeutic strategy for patients with newly diagnosed systemic metastases. Despite an initial significant response rate and palliation, virtually all patients progress in a predictable and irreversible manner to androgen independence/hormone refractory status reflecting the inability of androgen deprivation to eradicate all cancer cell populations.[92]

Biologically, androgen-independent PCa patients are a heterogeneous group with a relatively variable clinical course. Clinical observations would suggest that progression following first-line androgen deprivation therapy does not universally mean androgen independence as some of these patients may still respond to second line hormonal therapy indicating some level of androgen sensitivity. However, these responses are short lived and virtually all patients will ultimately progress.

7.6.1. Chemotherapy of androgen-independent PCa

The conventional approach to treating androgen-independent PCa has been palliative owing to the frequently poor general condition of these patients, presence of comorbid diseases, and the lack of "effective systemic" therapy. Chemotherapy trials have been conducted mostly in patients with end-stage hormone refractory PCa with multiple prior hormonal manipulations with less than a 10% objective response rates and a median survival of 6-9 months.[93] Despite the current lack of standard chemotherapy, advances in systemic therapy have occurred as a result of the translational application of basic science observation.

Suramin – A polysulphonated naphthylurea that has multiple effects including the induction of transforming growth factor-alpha, the ability to block receptor binding of platelet-derived growth factor, transforming growth factor-beta, and insulin-like growth factor. The interest in evaluating suramin in PCa stems from its ability to inhibit responses to a variety of growth factors which have been isolated from prostatic tissues as well as its growth inhibitory effect on PCa cell lines *in vitro*.[94] Suramin has a long half life (30-50 days) and a wide spectrum of toxicities including a syndrome of malaise and fatigue, neurological abnormalities, adrenal insufficiency requiring hydrocortisone replacement, coagulopathy, renal dysfunction and multiple metabolic disturbances. These toxicities, especially the neurological symptoms, appear to be related to drug concentration and duration of therapy since the drug possesses a narrow therapeutic window. While the appropriate dose/schedule of suramin continues to be explored, current data would indicate that suramin can be safely administered on an outpatient basis using an intermittent intravenous schedule with either limited or no pharmaco-

kinetic monitoring.[95] Since the initial NCI trial reporting a 35% objective response rate,[94] several investigators evaluated suramin in phase I/II trials primarily in hormone refractory PCa using a variety of doses and schedules *(Table 7)*.[96,97] Although most of the studies indicate significant response rates in measurable disease sites ranging from 18-50% and a ≥ 50% drop in PSA in approximately half the patients, suramins' efficacy has been questioned. This relates to the possible role of flutamide withdrawal and the potential contribution of co-administered hydrocortisone required to negate the adrenal inhibitory effects of suramin.[98]

Table 7. **Suramin in hormone refractory prostate cancer**

Author (ref)	*Patients*	*>50% PSA fall*	*Response*
Myers et al[94]	38	21/38 (55%)	6/17 (35%)
Eisenberger et al[96]	67	40/67 (60%)	7/18 (40%)
Mendoza et al[113]	21	9/21 (43 %)	2/11 (18%)
Petrylak et al[97]	28	13/28 (46%)	2/11 (18%)

Estramustine phosphate combinations – Estramustine phosphate is a nitrogen mustard derivative of estradiol-17-B- phosphate that has only modest activity in hormone refractory PCa. Recently the in vitro additive effect/synergy of estramustine and a variety of microtubule and topoisomerase II inhibitory agents has been investigated clinically in patients hormone refractory PCa. Three such combinations have been reported as single institutional trials and include:

i. Estramustine + vinblastine The first of the estramustine combinations to be evaluated in three separate trials *(Table 8)*.[99,100,101] The response, based on ≥ 50% decrease in PSA, was similar in the three trials and was approximately 50%. This trial used relatively stringent criteria for a partial remission requiring a ≥50% PSA decline sustained for 6 weeks, an improved or stable performance status and pain score, and measurable soft tissue response if applicable. Their overall response rate based on these criteria was 30%. Overall this combination is well tolerated. In the study that used a higher vinblastine dose, hematological toxicities were more frequently observed.

ii. Oral etoposide, estramustine + oral etoposide (VP-16) (Table 8) – Recent results were reported using oral VP-16 only and a combination of estramustine and oral VP-16. Oral VP-16 alone had minimal activity.[102] The rationale for the combination of estramustine and oral VP-16 is based on the in vitro and *in vivo* synergistic action between the two agents to inhibit PCa cell growth by interacting at the level of the nuclear matrix.[103] Forty two patients (18 with measurable disease and 24 with bone-only disease) were treated.[103] Using standard solid tumor response criteria, 9/18 measurable disease patients achieved a response (3 complete, 6 partial). All of the responders had a PSA decline, but only 6/9 had a >50% drop in PSA. Approximately 50% (5/9) of the patients with a measurable disease response also had a response by bone scan. Of the 24 patients with bone-only disease, 6 had improvement on bone scan and 14 (58%) had a >50% decline in PSA. The overall response rate was 36%. The primary toxicity was myelosuppression. This protocol was extended to a series of 95 patients with similar results.

iii. Taxol, estramustine + taxol (Table 8) Taxol induces of tubulin polymerization resulting in the formation of excessive and dysfunctional microtubules. Taxol has gained a great deal of interest due to its activity in a variety of solid tumors. Clinically, the most appropriate taxol dose and schedule for PCa is still evolving. Given as a 24 hour infusion every 21 days, taxol as a single agent had minimal activity in 23 patients with hormone refractory PCa.[104] At our institution taxol was investigated in the LNCaP tumor model in SCID mice. Given in multiple doses over a 9 day period significant antitumor activity was demonstrated.[105] The difference in schedule of administration may explain the apparent lack of activity clinically. Taxol and estramustine, however produced synergistic cytotoxicity in estramustine-sensitive and resistant DU145 (androgen independent PCa cell line).[106] Preliminary clinical evaluation of this combination suggests an encouraging level of activity with both objective responses seen in measurable disease sites (3/6) and significant PSA reductions (≥ 50% and ≥ 80% in 58.8% and 35% of patients, respectively).[106]

Mitoxantrone + prednisone – Mitoxantrone is a semisynthetic anthracenedione with some structural similarities to doxorubicin. Symptomatic improvement using single agent mitoxantrone has been reported.[107] Prednisone has been combined with mitoxantrone since the former agent has demonstrated a palliative effect. This combination was found to be well tolerated and resulted in a palliative response in 9/25 (36%) assessable patients (response assessment is based on analgesic requirement, present pain intensity record, and visual analog scale).[107] Mitoxantrone + prednisone were the subject of a recently reported phase III study and a recently closed phase III trial conducted by CALGB. The first trial randomized symptomatic hormone

Table 8. **Estramustine combination therapy**

Agents	*Dose*	*Patients*	*>50% PSA fall*	*Response*	*Ref*
Estramustine Vinblastine	10mg/kg 4 mg/m^2	25	54%	2/5	99
Estramustine Vinblastine	600 mg/m^2 4 mg/m^2	36	61%	1/7	100
Estramustine Vinblastine	420 mg/day 6 mg/m^2	29	50%	3/7	101
Estramustine oral VP-16	15 mg/kg 50 mg/m^2	42	54%	9/18	102
Estramustine Taxol	600 mg/m^2 120-140 mg/m^2	17	59%	3/6	104

refractory PCa patients to receive 10 mg of prednisone/day or prednisone + mitoxantrone at 12 mg/m^2 intravenously every 3 weeks.[108] The primary end point was a 2 point decrease in pain assessed by a validated 6-point pain scale without increase in analgesic medication maintained for 6 weeks. A total of 161 patients were randomized. The response by these criteria was 27.5% vs. 13.6%, in favor of the combination arm (p=0.033). Longer palliation was observed in the combination arm, 43+ weeks vs. 19 weeks, (p<0.0001). There were no differences in the overall survival. The treatment was well tolerated with 9 episodes of neutropenic sepsis and three episodes of possible cardiac toxicity in the mitoxantrone arm.

7.6.4. Other considerations and controversies

Response Assessment – Due to the nature of the metastases of PCa, optimal assessment of response to therapy has been difficult. Historically, the National Prostatic Cancer Project (NPCP) criteria were used but abandoned as they included non-objective response criteria. Standard solid tumor criteria are useful in the presence of bidimensionaly measurable disease which is only present in 10-15% of metastatic PCa patients. In oncology, tumor markers have long been used as indicators of the diseases' response to therapy and recurrence. Normalization of PSA has been a powerful tool to predict response and survival in hormonally treated metastatic PCa. In the hormone refractory setting, PSA normalization is not a frequent occurrence. A ≥ 50% reduction in response to therapy has been reported to correlate with a longer median survival.[109] Although the concept of using PSA to gauge responsiveness to chemotherapy is attractive, there are several concerns in this regard including: 1) uncertainty as to the extent and the duration of a meaningful decrease 2) the heterogeneous nature of PSA expression, 3) the possibility of drug effects on PSA levels without significant cell death, 4) no consistent relationship exists between the extent of PSA reduction and response in measurable/evaluable disease and 5) validated data from trials controlling for other prognostically significant variables are lacking. A recent report on 103 hormone refractory PCa patients treated with suramin demonstrated no differences in survival when using PSA decreases of less than 50% or ≥ 50% and less than 75% or ≥75% illustrating the reason for caution in interpreting PSA reductions.[110]

While improvement in survival is clearly the most desired objective of therapy, its absence must not be equated with lack of benefit. In line with this thinking is the use of improvements in quality of life (QOL) and pain score as primary end points of therapy. Although QOL improvements are extremely important in a disease that has not been significantly improved by current treatments, it remains to be seen whether "soft" endpoints will play a role as a measure of therapeutic response in the development of new treatment strategies for this disease.

Value of Continued Androgen Deprivation – Continued androgen deprivation therapy for patients with hormone refractory PCa has been advocated, however, no prospective data is available to justify it. We analyzed data on patients with hormone refractory PCa enrolled on several phase II Southwest Oncology Group (SWOG) studies.[93] No response or survival differences were observed between orchidectomized and non-orchidectomized patients who were required to discontinue exogenous androgen deprivation. This is in contrast to the experiences of the Eastern Cooperative Oncology Group (ECOG).[93] The SWOG analysis indicated an association between longer duration of response to primary endocrine therapy and ultimate overall survival implying the possibility of a more indolent disease process. This factor was not evaluated in the ECOG review.

7.6.5. Future Directions

Conventional cytotoxic chemotherapy has been disappointing though recently developed combination therapy give reason for optimism. The complexity of PCa biology is just now unfolding, as interest in this disease is increasing.[111] Of particular clinical significance is the evidence that progression to androgen-independence results in part from the lack of androgen-induced differentiation of the tumorigenic stem cells, thus resulting in an inability to undergo apoptosis.[111] Progression to androgen independence is also associated with the expression of previously androgen-repressed genes some of which are apoptosis inhibitors and some of which code for autocrine/paracrine growth factors that substitute for androgens in maintaining the viability of the cancer cells.[111,112] Moreover, PCa is recognized for it's low proliferative fraction. This together with the documented expression of apoptosis inhibiting genes such as bcl2 (which has also been associated with chemoresistance in other tumor cell lines) may explain the apparent failure of conventional cytotoxic chemotherapy in inducing significant responses. Therefore, as discussed above, alternative, biologically based, therapies must be pursued. Novel agents, growth factors inhibitors, antiangiogenic agents, immunotherapy and gene therapy are examples of current and future treatment strategies.

CONCLUSION

PCa, like most other solid tumors such as colon and lung cancers is a multistep disease that progresses from a preneoplastic lesion to a metastatic stage. Although a multistep tumorigenesis model has not been proposed for human PCa, as it has for colon cancer, the complex nature of the disease warrants a multifaceted approach encompassing

developmental, translational, and clinical research. The accomplishment of this research will deepen our understanding of the molecular mechanisms of PCa tumorigenesis, result in the identification of better diagnostic and prognostic markers and lead to preclinical and clinical trials of novel therapeutic regimens.

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