Management of Hormone Refractory Prostate Cancer

Essay

Submitted for partial fulfillment of The Master Degree

In Radiation Oncology and Nuclear Medicine

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Introduction

Prostate cancer is a significant health issue. One in six American men will develop prostate cancer during his lifetime. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program estimated that prostate cancer accounted for ٣٣٪ of all newly diagnosed cancers in ٢٠٠٦ **[Kuban. et al, ٢٠٠٧].**

Although it is the second leading cause of cancer death for men in the United States, only a handful of men diagnosed with prostate cancer will actually die of disease. **[Coen. et al, ٢٠٠٨].**

Considerable changes have occurred in the incidence of prostate cancer since the widespread availability of PSA in the early ١٩٩٠s. As increasingly prostate tissue has been biopsied in men without symptoms **[Attard. et al, ٢٠٠٩].**

Prostate cancer screening with PSA and digital rectal examination (DRE) has resulted in not only an increase in prostate cancer detection but also a stage shift. More cancers are now being detected at earlier stages, when they are potentially curable. However, Prostate cancer is diagnosed exclusively by the use of a transrectal ultrasound guided needle biopsy **[Moul. et al, ٢٠٠٩].**

Most men presenting with prostate cancer are asymptomatic and diagnosed only because of an elevated PSA or an abnormal digital rectal examination. Occasionally a diagnosis is made

following a transurethral resection of the prostate (TURP) for obstructive symptoms caused by BPH. Rarely patients present with obstructive symptoms or urinary retention caused by tumor bulk, and some develop metastatic disease without ever manifesting obstructive symptoms **[Andriole. et al, ٢٠٠٩].**

Prostate cancer preferentially spreads to regional lymph nodes and bone. Clinically significant metastases to liver, lung or other visceral organs are less common. Androgen deprivation therapy (ADT), by chemical or surgical castration, has become the mainstay for the treatment of metastatic prostate cancer since the observations of Huggins and Hodges in ١٩٤١ **[Brantley. et al, ٢٠٠٨].**

Historically, all patients with metastatic prostate cancer who are on hormone therapy develop hormone refractoriness (HRPC) after an average of ١٨ to ٢٤ months and their prognosis has been stated to be dismal with a median survival of ١٢ to ١٨ months **[Singh. et al, ٢٠٠٧] .**

The mechanism of progression from androgen dependent to independent disease remains poorly understood. It is thought that tumor cells either bypass or alter the androgen receptor (AR) activation pathway to allow continued growth, e.g., by AR amplification, mutation or modification or that hormone refractory cells may express aberrant levels of cofactors or activate the AR via alternative signaling pathways. This review examines the current knowledge of the molecular biology of prostate cancer and hormone-resistant prostate cancer focusing on the putative pathways involved in the progression to hormone refractory disease **[Kasper. et al, ٢٠٠٧].**

Newer chemotherapy regimens, such as docetaxel which now is the standard drug used to treat men with advanced HRPC, showed a PSA response rate of ٤٦٪ and an objective response rate of ٤٠٪. Moreover, its combination with estramustine demonstrated a very promising activity with manageable toxicity **[Eymard JC et al, ٢٠١٠].**

Until few years ago, chemotherapy for hormonal refractory prostate cancer (HRPC) showed modest activity and no survival benefits and mitoxantrone plus prednisone was approved only for its palliative activity **[Rosenberg et al, ٢٠٠٩].**

New trial using a novel oral platin (satraplatin), which could offer a new option to men with HRPC, and the result is ongoing **[Buratovich. et al, ٢٠٠٩].**

Immunotherapy with dendritic cells loaded with specific tumor antigens ex vivo has been studied extensively in animals, all of these studies found dendritic cells to be effective in treating or preventing tumors in experimental animals in an antigen-specific fashion. Several pilot clinical studies using dendritic cells to deliver antigen for immunotherapy of human malignancies have also shown promise and demonstrate that dendritic-cell therapy can elicit a beneficial immune response **[Beer. et al ٢٠٠٧].**

Chapter ١: Epidemiology of prostate cancer:

Incidence:

There are substantial worldwide variations in the incidence of carcinoma of the prostate, which is among the most common cancer in men. It was estimated that ١٨٦،٣٢٠ men would be diagnosed as having prostate cancer in ٢٠٠٨. It is also estimated that approximately ٢٨،٦٦٠ men would die of prostate cancer, making prostate cancer the number two cause of cancer death in men. There is no question that prostate cancer and its management is a significant public health issue **(Jemal A. et al, ٢٠٠٨)**.

The annual age-adjusted cancer incidence lifetime risk of a man developing prostate cancer appeared to peak between ١٩٩١ and ١٩٩٣, reflecting the initial "harvesting effect" from widespread screening in the early to mid ١٩٩٠s **(Pierorazio P. et al, ٢٠١٠)**.

Considerable changes have occurred in the epidemiology of prostate cancer since the widespread availability of PSA in the early ١٩٩٠s. A thorough understanding of these PSA-induced changes is necessary to understand current epidemiologic data, both nationally and internationally, as PSA-driven biopsies constitute one of the most important risk factors for the clinical diagnosis of prostate cancer **(Siegel R. et al, ٢٠٠٧).**

The National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program, has recently estimated that the current risk of prostate cancer in U.S. men during their lifetime is nearly ١٧٪ **(Akazaki K. et al, ٢٠٠٨).**

Prostate cancer currently has an exceptionally high incidence/mortality ratio in the United States. The current incidence/mortality ratio is ٨.١. In contrast, the other leading causes of cancer death in the United States (lung, female breast, and colon cancer) have an incidence/mortality ratio of approximately ١.٣, ٤.٤, and ٢.٩… respectively **(Ward E. et al, ٢٠٠٧).**

It should be emphasized, however, that the number of men dying from this disease is substantial and that a subset of men have a prostate cancer that can neither be ignored nor trivialized **(Akazaki K. et al, ٢٠٠٨).**

Unlike other common malignancies, aging men have a high rate of asymptomatic prostate cancer. In the pre-PSA era, autopsy studies indicated a cancer prevalence rate quite distinct from that of living men. This gap is now closing in populations in which PSA testing is widespread. Careful international studies in the pre-PSA era indicate that prostate cancer is present in a considerable number of asymptomatic men **(Yatani et al, ٢٠٠٧).**

Ascertainment biases are often incompletely acknowledged in the literature and data from international comparisons in particular have potential for misinterpretation. Given that the rate of prostate biopsy varies from country to country, comparison of international incidence rates should be cautiously interpreted. Further, comparison of rates among migrant populations should be cautiously interpreted unless PSA and prostate biopsy rates are understood and comparable between the populations of interest **(Siegel R. et al, ٢٠٠٧).**

Etiology of prostate cancer:

١. Environmental factors:

We are gradually learning more about the etiology of prostatic carcinoma. Its incidence increases in first generation males after migration from a less prevalent to a more prevalent (and usually more socially affluent) area. This might suggest that change of diet could be an important potential culprit, particularly the intake of animal fats and red meat. Other potential etiological factors such as smoking, alcohol intake, vasectomy and physical activity have now all been excluded **(Dagnelie P. Et al ٢٠٠٨).**

Another small study suggests that pomegranate juice may have a modest effect on PSA in patient failing therapy (**Pantuck A. et al ٢٠٠٦).**

Early epidemiologic and in vitro studies suggest a possible role of vitamin D and calcium, but larger and more recent studies do not. Early studies also suggested that a high intake of vitamin E was associated with a lower incidence of prostate cancer in one prospective randomized trial, but more recent large prospective studies have shown that vitamin E does not protect against prostate cancer, but increased consumption of gamma-tocopherol (which is present in walnuts, pecans, sesame seed oil and corn oil) is associated with a reduced risk of clinically relevant disease **(Lippman S. et al ٢٠٠٩)**.

The number of sexual partners, venereal disease, dietary fat, alcohol, cadmium, and exercise has inconsistently been supported by studies as risk factors. Consumption of high doses of multivitamins and supplements is associated with an increased risk of advanced and fatal prostate cancer **(Lawson K. et al ٢٠٠٧).**

٢. Genetic predisposition:

A genetic predisposition may profoundly affect the risk of developing prostate cancer **(Lange E. et al ٢٠٠٩).**

Recent studies have identified a number of genes that seem to correlate with susceptibility for prostate cancer in different populations. For example, single-nucleotide polymorphism–based, genome-wide linkage scans performed on ١٣١ white families with a history of prostate cancer found the strongest evidence for linkage at ١٦q٢٣ (LOD = ٢,٧٠). Prostate cancer linkage to the same region of ١٦q٢٣ has been observed by others, but was not detected in other prior linkage studies **(Beebe-Dimmer et al ٢٠٠٩).**

Genome-wide linkage analysis performed on another large prostate cancer pedigree from a population of cases and first-degree relatives identified a ١٤ Mb haplotype on chromosome ٥ (٥p١٣-q١٢) **(FitzGerald et al ٢٠٠٩).**

Screening first-degree relatives of prostate cancer patients may improve the cost-effectiveness of this practice. Thus the precise cause of prostate cancer is unknown, but it is likely to be multifactorial. **(Patterson B. et al ٢٠٠٩).**

٣. Non-steroidal anti-inflammatory drugs:

The possible role of non-steroidal anti-inflammatory drugs has suggested a possible protective effect. A recent paper from Canada showed a clear negative trend between cumulative duration of aspirin use and prostate cancer risk with an ١٨٪ reduction over ٨ years, using a case-controlled study design with over ٢٠٠٠ prostate cancer cases **(Morgentaler A. et al, ٢٠٠٦).**

٤. Testosterone levels:

The role of serum testosterone levels in the development of prostate cancer remains controversial. However, one recent study suggests that higher levels of serum-free testosterone are associated with an increased risk of aggressive prostate cancer among older men **(Pierorazio P. et al, ٢٠١٠)**.

Histopathology of prostate:

Normal prostatic epithelium contains a heterogeneous group of cells representing several distinct levels of differentiation. Epithelial layers are more readily observed in organs such as the skin or colon but are nevertheless present in the normal prostate as well. Secretory luminal cells are well-differentiated epithelial cells that are PSA-producing and androgen receptor (AR)-positive **(Signoretti S. et al, ٢٠٠٦).**

The secretory cells are derived from basal cells through an intermediate proliferating group of cells that are variable in AR and PSA expression. More mature cells in the intermediate pool are positive for AR and PSA, whereas less mature cells in this pool are not. The PSA-producing secretory luminal cells are terminally differentiated and incapable of proliferation **(Loda M. et al, ٢٠٠٦)**.

Rare neuroendocrine cells are also present in normal prostatic epithelium. Studies indicate a critical role for the stroma in supporting the growth of epithelial cancer cells and the complex relationship between cancer and stroma is an area of active investigation **(Chung L. et al, ٢٠٠٥)**.

More than ٩٥٪ of malignancies in the prostate are adenocarcinomas that arise in acinar and proximal ductal epithelium. Most tumors arise in the peripheral zone of the prostate but transitional zone tumors are well described and occur in about ١٠٪ to ٢٠٪ of patients **(Briganti A. et al, ٢٠٠٧)**.

Other tumors developing in the prostate include intralobular acinar carcinomas, ductal carcinomas, small cell or scirrhous pattern tumors, a rare clear cell variant resembling renal cell carcinomas, and mucinous carcinoma. Small cell tumors of the prostate have neuroendocrine

features and are composed of small, round, undifferentiated cells **(Jeldres C. et al, ٢٠٠٧)**.

Ductal and small cell tumors are prone to early metastases. Urothelial and rectal cancers may invade the prostate from adjacent organs and are occasionally diagnosed during a prostate biopsy as a consequence of DRE abnormalities and/or elevations in PSA **(De Marzo et al, ٢٠٠٧)**.

The typical adenocarcinoma of the prostate can be distinguished from other neoplasms using PSA immune-histochemistry. Neuroendocrine differentiation can be assessed by markers such as neuron-specific enolase, synaptophysin, and chromogranin A **(Sutcliffe S et al, ٢٠٠٧)**.

Intraductal proliferation, termed prostatic intraepithelial neoplasia (PIN), is generally agreed on as a histologic precursor of invasive malignancy. However, an atrophic but highly proliferative condition associated with chronic inflammation, proliferative inflammatory atrophy (PIA), may in fact be the first histologic step in the carcinogenic process **(Platz E. et al, ٢٠٠٧)**.

Prostatic adenocarcinomas are often multifocal and heterogeneous, a factor that complicates both prognostication and attempts to develop focal therapies. Studies of step-sectioned radical prostatectomy (RP) specimens indicate that most cancers contain multiple grades arranged in heterogeneous and unpredictable interrelationships **(Nelson W. et al, ٢٠٠٥)** .

Patients not only have multifocal tumors but also an average of ٢.٧ different grades of cancer in each specimen. Only ١٠٪ of index cancers in RP specimens are comprised of a single histologic grade **(Isaacs W. et al, ٢٠٠٥).**

Thus, any diagnostic method short of whole gland sampling is inevitably subject to sampling error. Careful genetic studies indicate that multifocality is typically a function of separately arising tumors rather than intraprostatic tumor spread **(De Marzo et al, ٢٠٠٥).**

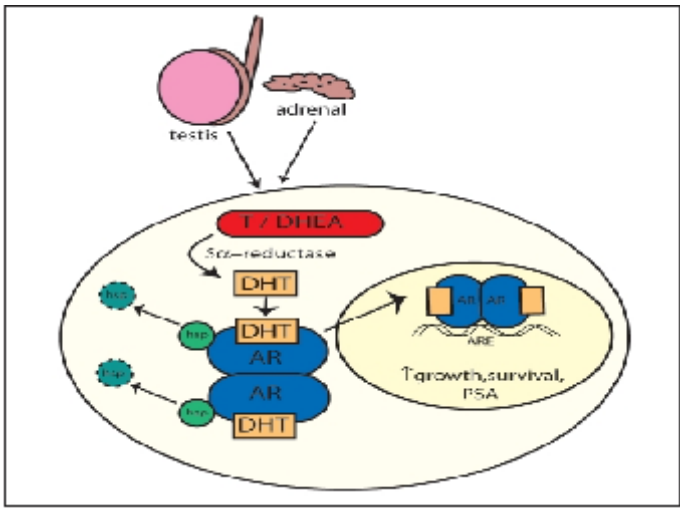
Chapter ٢: Pathogenesis of prostate cancer and hormone refractory prostate cancer

Hormone-refractory prostate cancer (HRPC) is an inevitable evolution of prostate carcinogenesis, through which the normal dependence on hormones for growth and survival is bypassed **(Papatsoris a. et al, ٢٠٠٥).**

The Androgen Receptor (AR):

Androgens are essential to the normal development and biology of the prostate. The majority of testosterone is produced by the testes, with a smaller contribution of androgens (٥٪) from the adrenal glands. These androgens are metabolized by ٥α-reductase to dihydrotestosterone (DHT) which binds to the androgen receptor (AR) **(Whitaker H. et al, ٢٠٠٧)**.

Ligand binding initiates phosphorylation, homodimerisation of the AR and dissociation of heat-shock proteins, allowing translocation of the AR complex to the nucleus. Here the AR binds to specific DNA sequences called androgen response elements (ARE) promoting transcription of androgen-responsive genes. Such genes control a range of cellular events such as growth, differentiation and apoptosis **(Mills I. et al, ٢٠٠٧)**.



[Fig ١] Intracellular metabolism of androgens.

AR - androgen receptor,

T - Testosterone,

DHEA – Dehydro epiandro sterone,

DHT - Dihydrotestosterone,

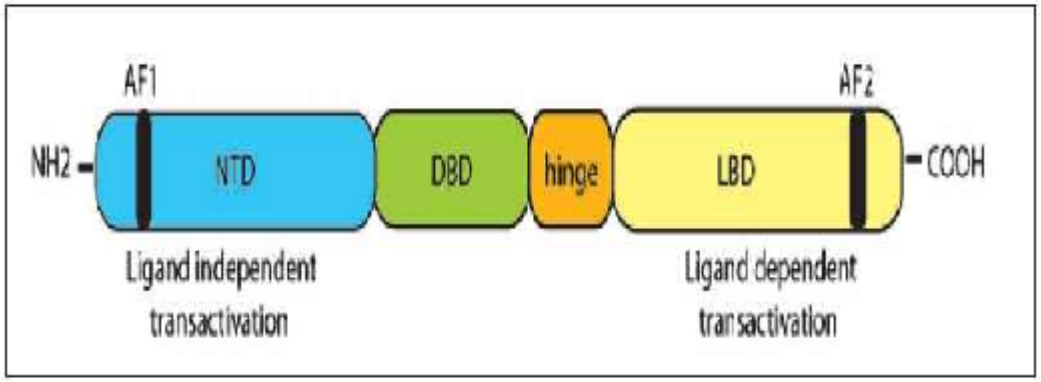
HSP - heat shock protein,

ARE - Androgen response elements.

Quoted from (Whitaker H. et al, ٢٠٠٧).

the steroid receptor superfamily and functions as a ligand-dependent transcription factor. The majority of the nuclear receptors, including the AR, share a common structure composed of four domains: an N-terminal domain (NTD), central DNA-binding domain (DBD), hinge region and C-terminal ligand-binding domain (LBD) **(Girling J. et al, ٢٠٠٧)**.

Transcription is mediated by two activation function domains (AF-١ and AF٢). The AF٢ is contained within the LBD and the binding of the hormone induces the conformational changes necessary for its activation. However, unlike other steroid receptors the AF-١ region of the AR has been shown to be most important for transactivation and can be activated even in the absence of hormone **(Neal D. et al, ٢٠٠٧).**



[Fig ٢] Schematic representation of androgen receptor. Showing the NTD - N-terminal domain, DBD - DNA-binding domain, LBD – legend binding domain, AF - activation function domains ١ in N-terminus and ٢ in LBD. **Quoted from (Neal D. et al, ٢٠٠٧).**

This is supported by recent data demonstrating that activation of AF-١ alone is responsible for AR activation in hormone refractory cells, even in the presence of antiandrogens. This would clearly be possible if the ligand binding does not effect conformational changes in the NTD **(Dehm S. et al, ٢٠٠٦)**.

As hormone refractory prostate cancer continues to grow in the presence of anti-androgens the term hormone independence may be misleading as it implies that the AR is no longer required for growth. However, the AR is expressed throughout the progression of prostate cancer, including more than ٨٠٪ of hormone refractory tumors, suggesting that AR signaling remains essential **(Tomlins S. et al, ٢٠٠٧)**.

It has also been shown that over-expression of the AR alone is sufficient to promote hormone refractory disease. Indeed, the persistence of AR in the metastatic LNCaP cell line and continued nuclear expression of hormone refractory tumor samples is indicative of continued AR involvement **(Mehra R. et al, ٢٠٠٧).**

Amplification of the AR gene is rarely identified in untreated cases of prostate cancer. Using comparative genome hybridization (CGH) and fluorescent in-situ hybridization (FISH), ٣٠٪ of treated cases exhibited AR amplification. Patients exhibiting amplification have been shown to have an improved response to hormone manipulation with a relapse-free time of more than ١٢ months **(Rhodes D. et al, ٢٠٠٧)**.

Identical techniques were also used to identify chromosomal aberrations, among which ٨q amplification was the most consistent finding in up to ٩٠٪ of locally advanced and metastatic tumors. Amplification of the AR gene does not always result in over-expression of AR mRNA or protein **(Mills IG. et al, ٢٠٠٧)**.

However, several studies have shown a correlation between AR amplification and AR protein expression. Conversely, AR over-expression does occur in the absence of AR amplification and there is growing evidence that in all except the small minority of small cell prostate tumors AR is ubiquitously expressed **(De Marzo. et al, ٢٠٠٧).**

In particular, AR expression is known to be increased in hormone refractory disease allowing activation by adrenal androgens. Using micro-array genome-wide profiling of xeno-graft models comparing androgen ablation in treated and untreated prostate cancer, Chen et al demonstrated that over-expression of AR cDNA, mRNA and protein levels were the only consistent and significant differences **(Platz E. et al, ٢٠٠٧)**.

In patients, AR over-expression conferred a better response to combined androgen blockade but despite this it also correlates with poorer outcome. Despite medical or surgical castration, tumor levels of androgens in human prostate samples, in particular DHT, have been shown to remain at levels sufficient to Trans-activate the AR in cell line studies **(Sutcliffe S. et al, ٢٠٠٧)**.

Although serum testosterone is reduced by ٩٥٪ following castration, tissue levels of DHT remain as high as ٤٠٪ suggesting that through intracrine processing within the prostate, adrenal androgens are transformed into the ١٠ times more potent DHT. Following studies in androgen-regulated cell lines which indicated an increase in apoptosis and reduction in proliferation, use of ٥a-reductase inhibitors are currently being assessed as a potential adjuvant agent **(Schell M. et al, ٢٠٠٥)**.

Mutations in the AR are uncommon (٠-٤٪) in untreated prostate cancer and those treated with surgical castration. However, in hormone refractory tumors the incidence of mutations increases by up to ٥٠٪. Over ٧٠ AR mutations have been found in association with prostate cancer with the majority being point mutations resulting in a single amino acid substitution **(Liu W. et al, ٢٠٠٦).**