



# The seventieth anniversary of the hormonal treatment of prostatic carcinoma

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## SUMMARY

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*Hormonal treatment of prostatic carcinoma was initiated in the first half of twentieth century. Theoretical basis of hormonal treatment was established with the work of Charles Brenton Huggins published in 1941. Initial results were encouraging, but fatal outcome occurred anyway. There are four directions of hormonal treatment of pancreatic cancer: orchiectomy, estrogens, LHRH agonists, or antiandrogens. Refinements of hormonal therapy were constant and resulted in prolonged survival time and fairly improved quality of life. These results rank hormonal therapy of pancreatic cancer as the most successful systemic treatment of metastatic disease.*

**Key words:** Prostatic Neoplasms; Carcinoma; Antineoplastic Agents, Hormonal; History of Medicine

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## INTRODUCTION

Prostatic carcinoma (PCa) was a well recognized medical entity during the eighteen and nineteenth century, with a little knowledge about its biological behavior and a small number of patients who could be cured by radical surgery. Estimated number of PCa suitable for radical curative surgery was about 7% even until the seventies of the last century (1). In majority of cases disease was considered as aggressive and self-perpetuating, with the final stage characterized by incurable and painful bone metastasis. Metastatic stage of the disease was sometimes considerably long, so the quality of life was severely diminished (2, 3).

One of the most important inventions in 20<sup>th</sup> century medicine was a discovery of external endocrine manipulation over the PCa. It gave the possibility for the treatment of advanced disease stages especially the patients with metastatic disease in whom no other treatment modality was left. The discovery of endocrine dependence of PCa was published seventy years ago (1941) by Huggins and Hodges, and revolutionized the treatment especially of advanced PCa (4). However, constant changes and permanent refinements occurred during the time, and resulted in extended life expectancy, from average twenty four months to the average four year survival, diminished side effects of therapy, and improved quality of life (5).

It seems worthy to remind of the development of this revolutionary idea and the most important steps in the evolution of endocrine therapy of prostatic cancer during the past seven decades.

### The period before Huggins

The first description of hormonal dependence of the prostate was published in the eighteenth century. The work of John Hunter (1728-1793) described endocrine dependence of prostatic tissue from the circulating testosterone (5). Orchiectomy was advised as a treatment of benign prostatic hyperplasia by the famous authors like Cabot who reported a cure of prostatic hyperplasia in 83.6% of 203 patients (6). Symptomatic improvements were reported in more than half of the patients but the final results were not promising. Soon after the beginning of primary enthusiasm, it became apparent that more effective treatments of benign prostatic hyperplasia were necessary. There were numerous variations in obtaining hormonal ablation at that time, some

of them completely erroneous, like bilateral vasectomy, with final results under the expectations (3, 7).

Thomas Beatson, a cancer surgeon from Glasgow Cancer Hospital, performed a treatment of the recurrent breast carcinoma with bilateral ovariectomy. Contrary to the general opinion, he believed that the breast cancer was under the hormonal control and that complete involution of the tumor would occur after the hormonal ablation. His observations were published in *Lancet* in 1895. (8). Although PCa and breast cancer are sharing endocrine dependence in many ways, and his observations were clear, he was not loud enough, so, nothing important happened regarding the endocrine therapy during next forty years.

### Endocrine therapy of the PCa

First experimental studies about hormonal control over the PCa were started by Charles Brenton Huggins (1901-1997). He was a Canadian born American surgeon and a graduate from the Harvard Medical School. He published the results of the experiments upon dogs and observed the effect of testosterone in the improvement of secretory activity of the prostatic cells (9). His epic work with his student Hodges resulted in publication *The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate* (1941), which became a cornerstone and theoretical basis of endocrine therapy for PCa (10). The most important conclusions of the paper were: (1) PCa is controlled by the endocrine system; (2) Metastatic disease is inhibited by eliminating androgens either by orchiectomy or injection of estrogens and (3) Disseminated prostate disease is activated by androgen injections (10).

First encouraging results in 70% of patients with metastatic PCa were published about one year after these theoretical conclusions (11). In 1966, Huggins became a laureate of the Nobel Prize for medicine together with the virologist Peyton Rous (1879-1970).



Figure 1. Facsimile of the original paper of Huggins and Hodges which became a cornerstone of hormonal therapy of prostatic carcinoma

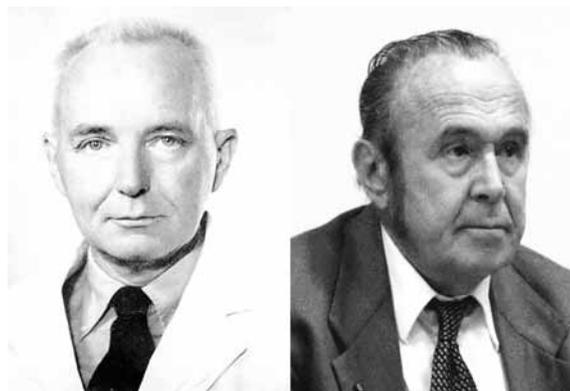


Figure 2. Charles Huggins (left) who received Nobel Prize for the establishing of hormonal therapy and Andrew Schelly (right) who received Nobel Prize for invention of GnRH, the base for use LHRH agonists

There were initial reports with the use of estrogen in patients with PCa in early forties (12).

Although the first results of endocrine therapy of PCa were very promising, even in a way that problem of PCa was solved, it became evident two or three years later, that initial improvements were temporary and fatal outcome of the disease occurred anyway (3).

### Modalities of endocrine therapy

Four principal directions were the mainstream of endocrine therapy of PCa during different periods.

Bilateral orchiectomy was efficient, cheap, and frequently used method of hormonal ablation before the era of LHRH analogs but it had high

influence on patient's psychology. It is almost abandoned now and used only in cases with low availability of medical services and in patients with imminent pathologic fractures in whom a prompt testosterone decrease is mandatory. There are no other medical reasons for the particular preference of orchiectomy now (12).

Estrogen - diethylstilbestrol was frequently used in USA until seventies and became a classical endocrine therapy especially in this country and a reference point for the evaluation of other treatments by Food and Drug Administration (FDA). Veterans Administration Research Cooperative Urology Research Group (VACURG) study and other study groups proved numerous cardiovascular side effects of diethylstilbestrol with the high influence on noncancerous related PCa mortality (13, 14). Dose reduction from 3mg to 1mg daily decreased the efficiency of the drug and doses  $\geq 3$ mg daily were proved to be harmful (12).

Roger Gulleman and Andrew Shelly from New Orleans discovered structure and synthesis of Gonadotropine Releasing Hormone (LHRH) (1971). It has cleared the path for the discovery of medication that can affect relationship between hypophysis and effectors (testicles). Both of them became laureates of the Nobel Prize for Medicine in 1977. LHRH agonists, which mimic the effect of high dose GnRH and make permanent hypophysis exhaustion, are in clinical use for more than 30 years. The problems like histamine release, etc. were overcome in the clinical use (12).

Extragenital androgens as an additional resource to testosterone were well known during forties, but adrenalectomy, which was advised at that time, has never been widely accepted. Antiandrogens, medications that can interfere with the binding of testosterone to the androgen receptor were developed during 1970-80. Antiandrogens have never been advised as a single therapy of PCa (12).

Total (or maximal) androgen blockade (TAB) was established as a concept during nineties because the first results were encouraging with the longer survival time; but nowadays, it is considered as an hormonal *overmanipulation* that exhausts hormonal treatment tools too early and potentiates side effects of therapy. Benefits regarding the survival have become less clear during the time (13-16).

### Challenges of the Hormonal Treatment in 21<sup>st</sup> Century

Wide use of prostate specific antigen (PSA) during nineties contributed to the downstage migration of PCa. There is a majority (or significant number at least) of patients with organ confined disease, and lower number of patients with metastatic disease (12-15%) (17). However, new challenges in front of endocrine therapy arise in order to minimize side effects (that cannot be neglected during the long lasting hormonal therapy) and optimize effects of the treatment.

### Standard treatment

Prostate Cancer Trialist Cooperative Group summarized data about the use of TAB. There was a minimal difference in 5-year survival in patients with PCa that favors TAB treatment over LHRH agonists alone, which is difficult to achieve in real conditions. Steroidal peripheral antiandrogens are not recommended due to increased mortality risk. Monotherapy with LHRH agonist is now considered as a first line treatment in metastatic disease (15-17). Another option, still without clear suggestion, is peripheral

antiandrogen and 5-alpha reductase inhibitor that improves maintenance of sexual function and decrease values of serum PSA (18).

### Early versus delayed hormonal treatment

There were a lot of conflicting data about the time of initiation of hormone therapy in metastatic disease. Two EORTC trials favored early hormonal treatment with the slightly better results. There is also a problem of patients with only elevated level of PSA that occurs in at least 20% of patients after the attempt of radical cure. Although it is difficult to uniform the approach, immediate treatment is usually advised in cases with high PSA doubling time, high grade and Gleason score (18).

### Continuous versus intermittent androgen blockade

Androgen blockade has significant side effects so it seems useful to make an intermittent pattern of the blockade to minimize them without affecting effects of the treatment. The most important is measurement of the effects of therapy. In cases with the prompt decrease of the levels of PSA  $\leq$  0.2 ng/ml cancer specific mortality is low (4%) and intermittent androgen therapy seems to be an affective option in a selected group of patients after seven months of initiation (16, 18).

### CONCLUSION

Hormonal therapy is the most effective systemic therapy and the most effective palliative treatment of the metastatic PCa that has been based on the same concept for seventy years. Single use of antiandrogens has never been proved as equally effective as orchiectomy, TAB or LHRH agonists alone. Although hormonal therapy is usually considered as a palliative treatment in some cases its use is closer to the radical treatment, due to long life expectancy. Initial concept of maximal hormonal blockade is now balanced – effective hormonal manipulation designed to minimize side effects of therapy.

### Conflict of interest

We declare no conflict of interest.

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