SMGroup

Insights into the Definition, Prognosis and Mechanisms of Development of Castrate Resistant Prostate Cancer

Javier C Angulo[1]* and José I López[2]

[1]Departamento Clínico, Universidad Europea de Madrid, Servicio de Urología, Hospital Universitario de Getafe, Spain

[2]Servicio de Anatomía Patológica, Hospital de Cruces, Universidad del País Vasco/Euskal Herriko Unibersitatea, Barakaldo, Vizcaya, Spain.

***Corresponding author:** Javier C Angulo, Departamento Clínico, Universidad Europea de Madrid, Servicio de Urología,, Hospital Universitario de Getafe, Crta. De Toledo km 12,500, 28905 Getafe, Madrid, Spain, Email: jangulo@futurnet.es

Published Date: June 20, 2016

ABSTRACT

The chapter reviews the fundamentals of Castrate Resistant Prostate Cancer **(CRPC)**, the final-end evolution of prostate cancer, focusing on its natural history and the physiological mechanisms and pathological features that impact in its clinical management and prognosis. Treatment of CRPC is currently evolving, as new elements of hormone therapy (abiraterone acetate and enzalutamide) and chemotherapy (cabazitaxel) have been incorporated in chemoresistant disease and also because abiraterone acetate and prednisone and enzalutamide alone are new effective options in chemotherapy-naïve patients. Histophatological features of CRPC that include neuroendocrine differentiation do not appear good tools to predict prognosis and new markers predictive of clinical response are desirable. A better knowledge of Androgen Receptor **(AR)** and its epigenetic regulation could be a starting point to develop new biomarkers of the disease.

Keywords: Castrate resistant prostate cancer; Histopathology; Treatment; Prognosis; Tumor markers

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

INTRODUCTION

Prostate cancer is the most common malignancy in men with over 26,000 deaths expected in USA in 2016 [1]. Despite the efforts of early detection campaigns, still approximately 10-20% of patients present with metastatic disease and many others develop metastases although having been treated with surgery or radiotherapy. We know that prostate cancer is an androgen-dependent tumor. Numerous clinical trials have shown a decrease in cancer-specific mortality in patients treated with orchiectomy or various therapeutic maneuvers that lead to androgen suppression. However, this state is transient in all advanced cancers, since inevitably androgen resistant cell clones are selected throughout the treatment. In fact, any therapy for metastatic prostate cancer is palliative.

About 80% of cases androgen ablation involves a significant symptomatic improvement and a reduction in levels of Prostate Specific Antigen **(PSA)**, but invariably the disease becomes refractory to hormonal treatment [2].

CASTRATE RESISTANT PROSTATE CANCER

Since the early 1940s when Huggins and Hodges described the effects of castration on metastatic prostate cancer [3], androgenic deprivation has been a fundamental resource in the urological armamentarium for treating the disease. Hormone therapy is used initially in a restricted manner for advanced inoperable disease; however, in the era of PSA, the early detection of the disease has led to a migration to earlier stages and has resulted in a greater diversity of treatments. Therefore, patients with this disease can be treated with a hormonal blockade earlier, generally combined with other therapies, although it is assumed that the value of androgen deprivation is greater in advanced disease [3,4].

Patients with locally advanced or metastatic prostate cancer who cannot be healed with local treatments and who undergo medical or surgical castration often have complete disease remission for a period varying between 14-30 months [5]. Nevertheless, these patients invariably progress and once again express active Androgen Receptor **(AR)** signaling despite very low androgen levels. The return of androgenic signaling occurs due to the confluence of various mechanisms, some AR dependent (such as the local production of androgens in the tumor environment and AR gene amplification) and some non-AR dependent, such as co-activation and transactivation mechanisms [6]. In fact, during the independent progression to androgens, the tumor cells develop different mechanisms that enable them to survive and replicate: AR gene mutations, promoter gene silencing by abnormal methylation, AR ligand independent activation and the intervention of cancer stem cells [7-9]. The result is the development of a disease completely refractory to androgen deprivation [7], a condition that we know today as Castration-Resistant Prostate Cancer **(CRPC)**.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

Metastatic prostate cancer is an incurable disease and development of CRPC anticipates death from prostate cancer. In some patients hormone resistance is incomplete, since cancer can continue to show signs of certain hormone dependence. CRPC is a fatal disease that follows an aggressive course, although it follows a variable progression, with some patients dying quickly and others with lesser metastatic potential who can live with the disease for a period that very rarely exceeds 40 months [10]. The various systemic chemotherapy regimens had achieved very little improvement in the survival of these patients until the discovery of the Bcl-2 molecule/microtubule complex as a therapeutic target. Docetaxel (75 mg/m2 every 3 weeks) combined with prednisone has in recent years achieved a modest survival benefit (18.9 months vs. 16.4 months for mitoxantrone and prednisone) and improved analgesic control in the final phase of the disease [11,12]. Docetaxel based systemic chemotherapy can reduce serum PSA levels and even improve pain, but the main concern is its tolerance; especially as most patients are elderly and have other medical problems. Low dose steroids can be palliative in some patients. Other therapeutic options in the refractory phase include not only palliative analgesia, but also therapies that reduce the rate of skeletal complications, such as strontium-89 or bisphosphonates. Also second-line hormonal treatments allow achievement of partial remission, objective symptomatic improvement and increased radiological progression-free survival.

At present, the comprehensive treatment of CRPC is continuously evolving [13,14], having incorporated new elements of hormone therapy (abiraterone acetate and enzalutamide) and chemotherapy (cabazitaxel). The use of oral abiraterone acetate, selective inhibitor of 17α-hidroxilase/17,20 liase (CYP17), in association with prednisone was introduced for patients in which chemotherapy was unsuccessful. More recently, chemotherapy naïve has revolutionized the concept of second-line hormone therapy and the expectations of comprehensive survival improvements in these patients. Also enzalutamide, an inhibitor of Androgen Receptor **(AR)** signaling, nuclear translocation of the receptor and its union and activation of DNA has demonstrated clinical efficacy. The affinity for enzalutamide to AR is 5-8 times that of the antiandrogen bicalutamide. Pivotal clinical trial for enzalutamide has confirmed increased survival rates than placebo (18.4 months versus 13.6 months) in metastatic CRPC that progressed after docetaxel [15]. Abiraterone acetate plus prednisone and enzalutamide are useful second-line hormone therapy for CRPC, both to delay use of chemotherapy and also for patients who have already undergone cytotoxic therapy, and are clinically indicated to improve the care in the final phase of the disease [16-19].

NEW TREATMENTS IMPROVE PROGNOSIS OF CRPC

To evaluate the prognosis of CRPC and also how combined new therapies including systemic chemotherapy (docetaxel and/or cabazitaxel) and second-line hormone therapy (abiraterone acetate plus prednisone and/or enzalutamide) globally improve life expectancy of these patientswe retrospectively analyzed our experience with CRPC. A series of consecutive patients

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

with actively treated CRPC (n=33) including systemic chemotherapy and second-line hormone therapy (either before or after docetaxel use) treated between 2011 and 2014 was reviewed. This group was compared with a historical group of patients with CRPC (n=31) treated before the regular use of docetaxel. This control group was exclusively managed with antiandrogen withdrawal and palliative measures, that generally included analgesic control and 10mg oral prednisone in the final phase of the disease.

In every case the definition of CRPC was equivalent: recurring disease despite appropriate castration (serum testosterone <50 mg/mL) and confirmed biochemical progression (3 consecutive increases in PSA levels, separated by at least 1 week, which produced two 50% increases over nadir, with PSA levels >2 ng/mL) or radiological progression (emergence of 2 or more bone lesions in scintigraphy or a soft-tissue lesion using the Response Evaluation Criteria In Solid Tumors criteria) during follow-up [20]. The primary diagnosis and initiation of androgen ablation was established during the period 2000-2013. At the time of initial diagnosis median patient age was 68(63-65 IQR) years, and median PSA 44.7(14.4-101.4 IQR) ng/mL. Regarding clinical stage at the time initial diagnosis, 79.7% manifested as locally advanced and 40.6% metastatic disease. Fifty percent of the cases had Gleason 5 pattern in the initial prostate biopsy (total Gleason score >9). There were no statistically significant differences in age, PSA level at diagnosis, Gleason score and Tumor extent **(T)** or Metastasis **(M)** category at diagnosis (p>.05) between the actively treated group and the historical group treated merely with palliation.

Cancer-specific survival of the actively treated patients has been compared to that of the control group using Kaplan-Meier and log-rank tests. In the context of clinical practice, we confirm the survival advantage for patients with CRPC who are actively treated with second-line hormone therapy combined or not with chemotherapy with taxanes (docetaxel and sometimes cabazitaxel). Disease specific survival of the full patient series with CRPC was 68.5%, 48.6%, 35.5% and 20.6% at 1, 2, 3 and 4 years, respectively (Figure 1). Disease specific survival from the diagnosis of CRPC was significantly greater for the patients actively treated than for the historical control group (log-rank, p<.0001) (Figure2). One-year survival was 93.5% for patients actively treated and 41.5% for those that received palliation exclusively. Similarly, 3-year survival was 65.5% versus 5.7%. Cost-effectiveness studies are needed, but the introduction of docetaxel and cabacitaxel in the last decade, and also abiraterone acetate and enzalutamide more recently, has broaden considerably the therapeutic possibilities of this patients.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

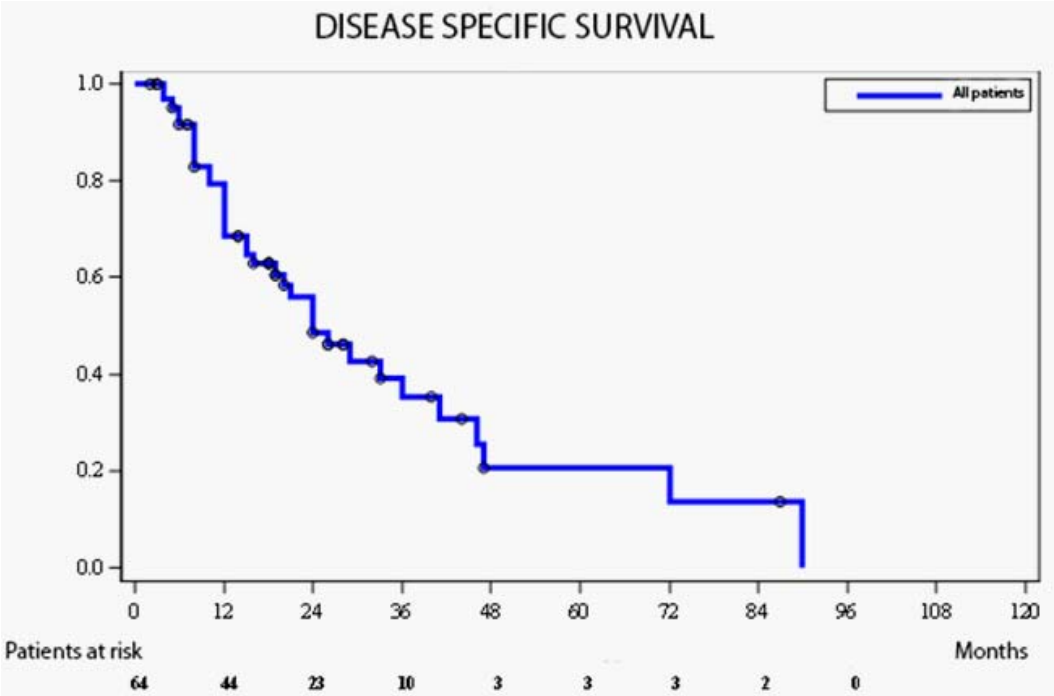


Figure 1: Disease-free survival in the total series of castrate-resistant prostate cancer.

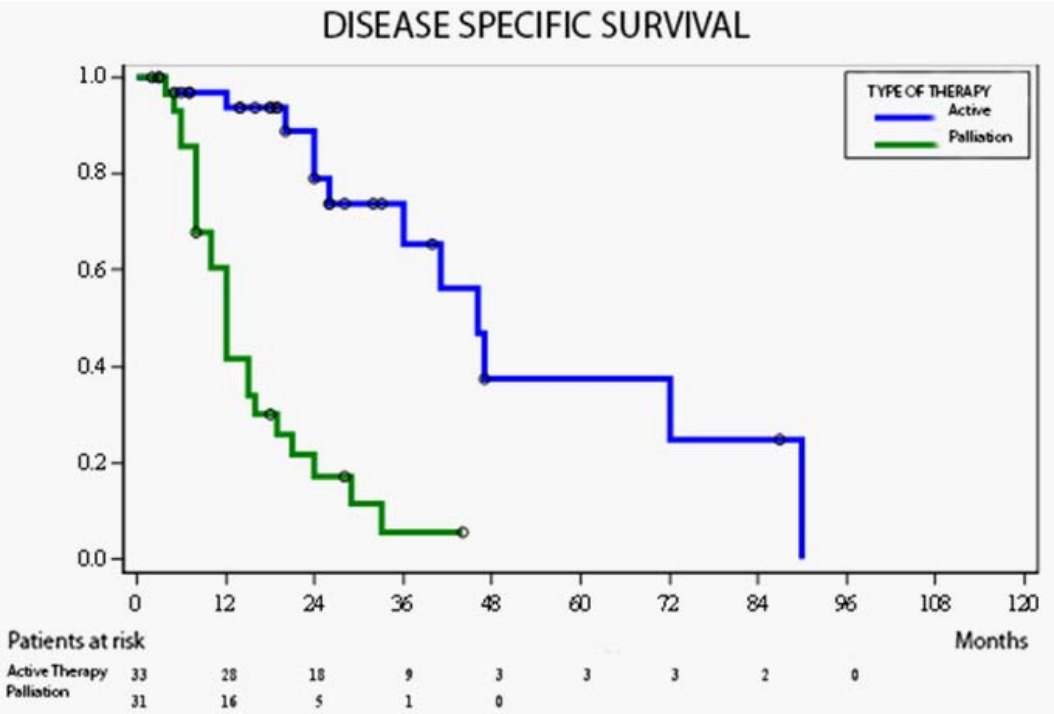


Figure 2: Disease-specific survival comparing patients actively treated versus the control group.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

HISTOPATHOLOGY OF CRPC

CRPC histopathology is comparable to androgen-sensitive cancer. Adenocarcinoma, often highly undifferentiated (high Gleason score), is strictly indistinguishable from the point of view of the histopathological undifferentiated forms that respond to androgen blockade (castration, LH-RH, antiandrogen) [21]. The only distinction that can be found based on morphology is the tendency to show pure patterns of undifferentiated cells and increased expression of neuroendocrine phenotype. Hormone deprivation accelerates programmed cell death. Prostate tumors on androgen deprivation also tend to a reduction in acinar size and density, and an increase in the Gleason score, a reduction in nuclear size with chromatin condensation and disappearance of nucleoli, and also prominent cytoplasmic clearance leading to vacuolization [22].

At the cellular level androgen deprivation causes inhibition of cell growth, tumor DNA fragmentation and appearance of apoptotic bodies. At the genetic level, deprivation stimulates the expression of several genes including transforming growth factor-β, c-myc, c-fos, and glutathione S-transferase Xb1among others.The immunohistochemical expression of PSA and prostatic acid phosphatase remains positive while expression of high molecular weight cytokeratin (34b-E12) continues absent. The expression of neuroendocrine differentiation markers themselves as chromogranin, neuron-specific enolase, synaptophysin, serotonin and somatostatin is sometimes emphasized [23, 24].

Virtually all prostate adenocarcinomas have at least a small number of neuroendocrine cells, although special studies are needed to identify them. Today we know that neuroendocrine differentiation occurs in a high proportion of tumors, and not only in the rare cases of neuroendocrine carcinoma. Routine immunohistochemical studies with different antibodies (serotonin, chromogranin, synaptophysin and enolase) show that the neuroendocrine phenotype is present in many prostate adenocarcinomas [23,25,26] (Figures 3 to 7). Although the real role of these cells in both normal and neoplastic prostate is unknown, there is a substantial body of evidence to consider that this component of prostatic cancer is linked to resistance to hormone therapy. Actually, it is assumed that neuroendocrine cell activation may be one of the mechanisms of tumor progression during hormone treatment in androgen independent tumor [27]. Also chromogranin A serum and neuron-specific enolase have been used as markers for neuroendocrine activity with implications for prognosis thus reflecting the acquisition of a castration-resistant phenotype [28-30]. This fact is added to the experience that neuropeptide expression does not diminish androgen deprivation [25], and that typical acinar carcinomas with focal neuroendocrine differentiation and neuroendocrine carcinomas recur after hormone therapy [23,31].

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

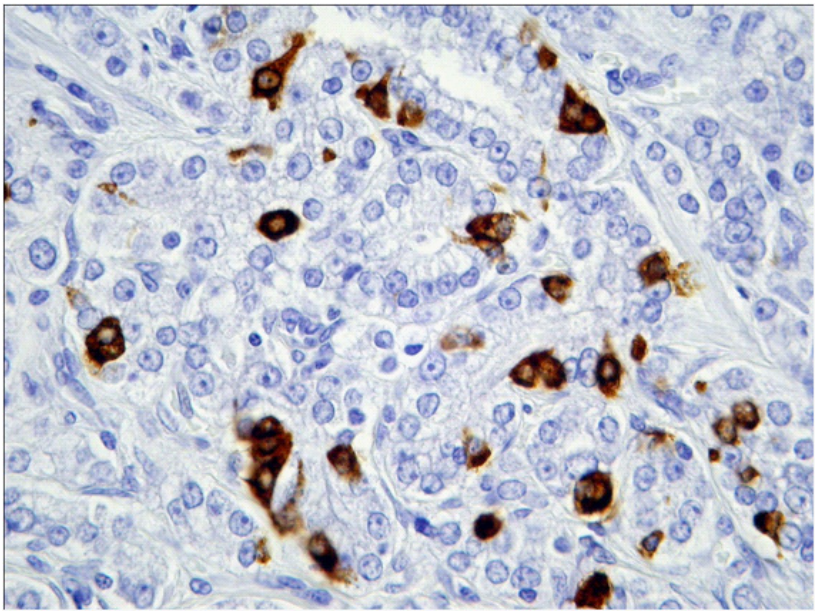


Figure 3: Focal immunohistochemical expression of chromogranin-A in prostate cancer cells.

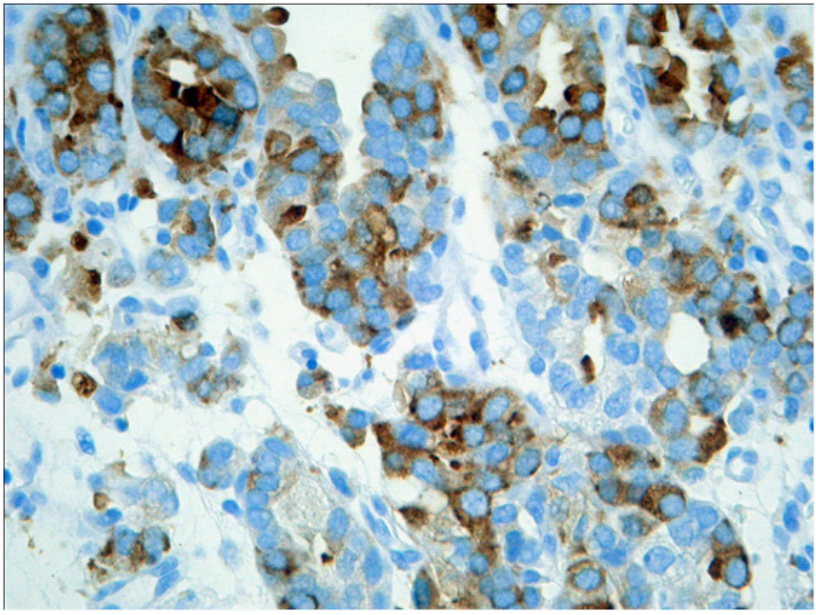


Figure 4: Diffuse neuron-specific enolase immunohistochemical expression in high grade prostate cancer cells.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

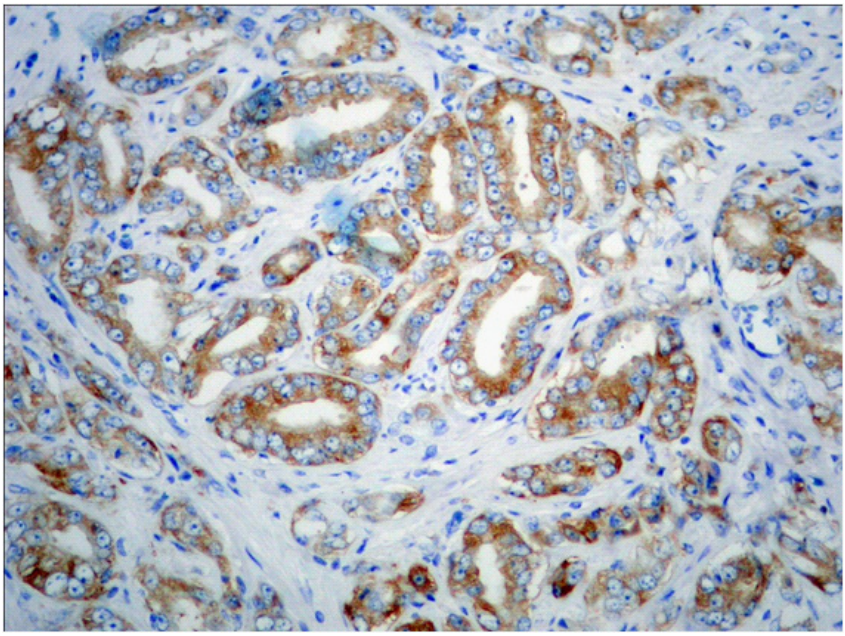


Figure 5: Diffuse synaptophysinimmunohistochemical expression in prostate cancer cells.

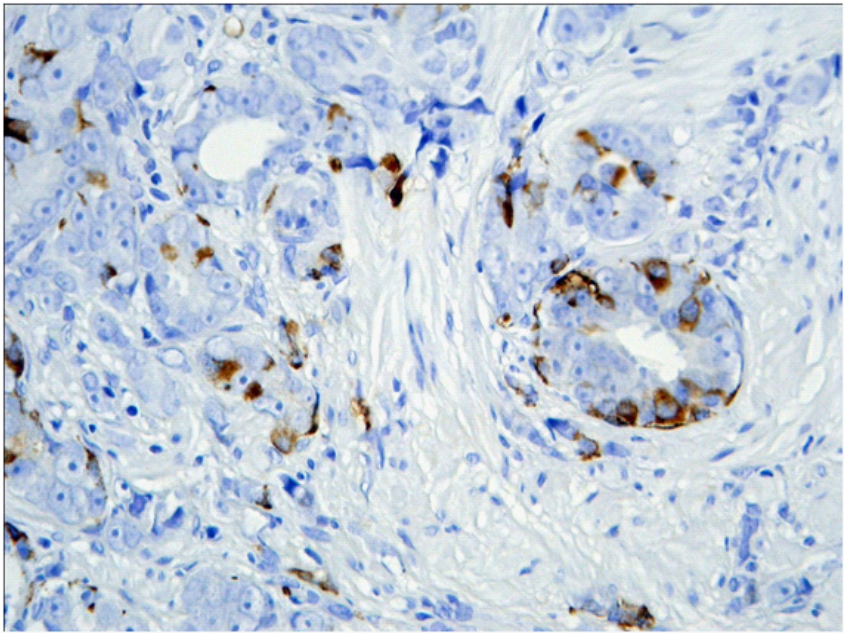


Figure 6: Focal serotonin immunohistochemical expression in prostate cancer cells.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

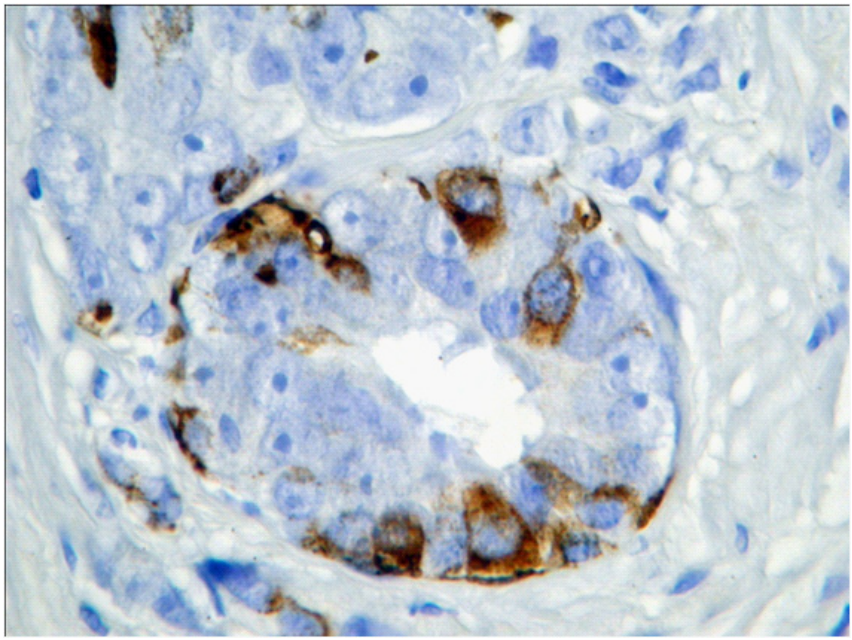


Figure 7: Focal somatostatin immunohistochemical expression in prostate cancer cells.

Although the current biological significance of neuroendocrine cells in prostate cancer is largely unknown, an endocrine/paracrine regulatory role in tumor growth and cell proliferation has been postulated. Neuroendocrine cells expressed in benign and premalignant epithelium are post-mitotic, but cell proliferation studies with Ki-67 show that the adjacent cells are generally proliferative (Figure 8). Furthermore, the proto-oncogene Bcl-2, which acts as anti-apoptotic factor, is also preferentially expressed in adenocarcinoma cells that are in vicinity of the foci of neuroendocrine differentiation [32].

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

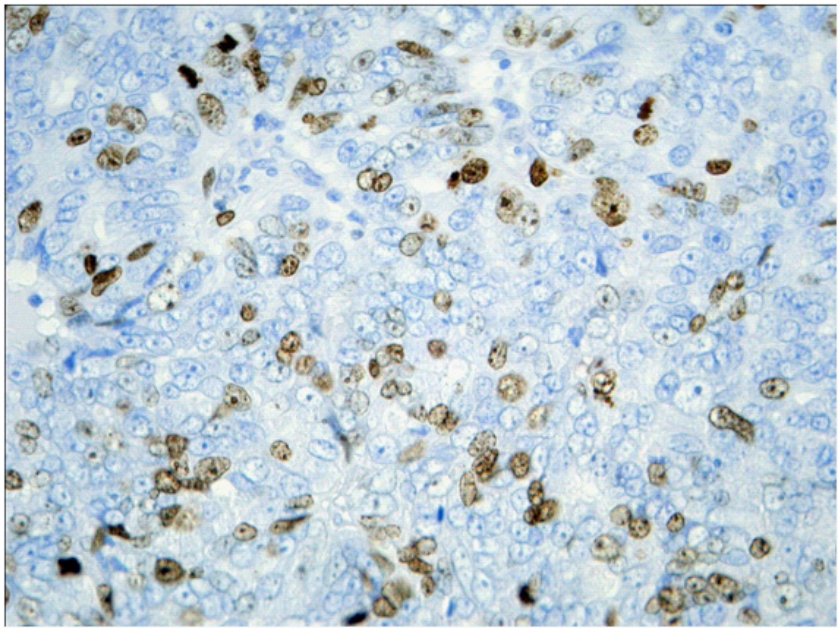


Figure 8: Nuclear immunostaining with Ki-67 in 30% of prostate cancer cells.

We know that some neuropeptides such as somatostatin inhibit tumor growth of androgen-dependent tumors [33]. But this modulation of growth is not entirely independent of androgen control, because it is known that the Androgen Receptor **(AR)** is also expressed in neuroendocrine cells [34]. In fact the AR is present in both, androgen sensitive and androgen refractory tumors. The percentage of adenocarcinoma cells expressing AR does not predict the time to progression in patients treated with hormone deprivation [35].

THE ANDROGEN RECEPTOR IN CRPC

The AR belongs to a family of steroid hormone receptor that acts as a transcription factor [36]. After binding to the ligand receptor is phosphorylated and homodimerizes, joining androgen response elements located in the 5 'regions of genes to form multiprotein complexes. It seems that mutations of AR are not too frequent [37] and presumably they play little role in the early stages of prostate carcinogenesis [38]. However, several studies conducted recently emphasize the role of AR in the emergence of the castration resistance [39]. AR amplification is selected after withdrawal of antiandrogen, and is associated with overexpression of the AR gene, although CRPC also expresses AR even in the absence of gene amplification [40].

Hormone therapy for prostate cancer is done using drugs that decrease serum testosterone levels, often in association with competitive antagonists of the androgen receptor, which it is called androgen blockade [41]. These therapies are initially effective in blocking tumor growth, but then fail to consistently control the disease and lead to the development of drug resistance. The postulated mechanisms for the development of CRPC include three different categories. The

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

first includes point mutations in AR gene that alter the response of the receptor, so that some ligands such as estrogen or hydrocortisone, or AR antagonists such as flutamide, can behave as agonists. The second category refers to most patients without AR mutation or amplification while maintain active AR signaling. Increased signaling activity mitogen-activated protein kinase, mediated by oncogenes such as ERBB2 or H-Ras activation may cause AR ligand independent activation. Altered balance between coactivators and corepressors may affect the activation of AR. The third category explaining development of CRPC is based on the concept that the growth and survival of AR promoter functions can be shorted by alternative signaling routes, such as upregulation of the antiapoptotic gene bcl-2.

Several explanations have very recently emerged to understand cancer resistance to abiraterone and enzalutamide, especially the AR-V7 splice variant [42], a potential target in advanced prostate cancer in the next future.

EPIGENETIC REGULATION OF AR GENE

We know that many genes can be methylated at different points during the histopathologic progression of prostate cancer [43]. DNA hypermethylation in the AR can be crucial in the loss of expression that occurs in this receptor in CRPC status. Twenty to thirty percent of CRPCs extensively lose expression of AR, and the loss seems to occur at the transcriptional level and not due to deletion or mutation mechanisms [44]. DNA hypermethylation is a well described mechanism involving the addition of methyl groups in CpG dinucleotides, known as "CpG islands" that typically accompany the transcriptional promoter sequence. Methylation of these islets plays a critical role in the repression of transcriptional level of certain genes. These epigenetic mechanisms are not due to genetic abnormalities but occur by changes in DNA methylation or acetylation mechanisms and deacetylation of histones [45]. Methylation of CpG islands or sites in the promoter of AR could reversibly inactivate transcription of AR [46], thus explaining how the selective pressure of androgen deprivation leads to CRPC.

A very interesting experience with human tissues showed that 4 out of 15 tumors obtained from men who die from CRPC lose the immunohistochemical expression of RA, being the gene methylated in two of them [47]. It is very likely that AR methylation plays a key role in the development of hormone resistance, especially in the group of advanced prostate cancer that has lost the expression of AR. Also, an altered methylation pattern may help to explain CRPC by defining an epigenetic profile associated to the development of CRPC [48].

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66: 7-30.
2. Chandrasekar T, Yang JC, Gao AC, Evans CP1. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol. 2015; 4: 365-380.
3. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst. 2003; 95: 981-989.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

4. Núñez C, Angulo J, Sánchez-Chapado M, Alonso S, Portillo JA. [Variability of the urological clinical practice in prostate cancer in Spain]. Actas Urol Esp. 2012; 36: 333-339.

5. Singer EA, Golijanin DJ, Miyamoto H, Messing EM. Androgen deprivation therapy for prostate cancer. Expert Opin Pharmacother. 2008; 9: 211-228.

6. Hoimes CJ, Kelly WK. Redefining hormone resistance in prostate cancer. Ther Adv Med Oncol. 2010; 2: 107-123.

7. Debes JD, Tindall DJ. Mechanisms of androgen-refractory prostate cancer. N Engl J Med. 2004; 351: 1488-1490.

8. Pienta KJ, Bradley D. Mechanisms underlying the development of androgen-independent prostate cancer. Clin Cancer Res. 2006; 12: 1665-1671.

9. Ashour N, Angulo JC, Andrés G, Alelú R, González-Corpas A. A DNA hypermethylation profile reveals new potential biomarkers for prostate cancer diagnosis and prognosis. Prostate. 2014; 74: 1171-1182.

10. Assikis VJ, Do KA, Wen S, Wang X, Cho-Vega JH. Clinical and biomarker correlates of androgen-independent, locally aggressive prostate cancer with limited metastatic potential. Clin Cancer Res. 2004; 10: 6770-6778.

11. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004; 351: 1502-1512.

12. Pienta KJ, Smith DC. Advances in prostate cancer chemotherapy: a new era begins. CA Cancer J Clin. 2005; 55: 300-318.

13. Lorente D, Mateo J, Perez-Lopez R, de Bono JS, Attard G (2015). Sequencing of agents in castration-resistant prostate cancer. Lancet Oncol 16: e279-292.

14. Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA. Prostate cancer. Lancet. 2016; 387: 70-82.

15. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367: 1187-1197.

16. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011; 364: 1995-2005.

17. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012; 13: 983-992.

18. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013; 368: 138-148.

19. Basch E, Autio K, Ryan CJ, Mulders P, Shore N. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol. 2013; 14: 1193-1199.

20. http://www.uroweb.org/gls/pdf/09%20Prostate%20Cancer_LRLV2.pdf

21. Miyamoto H, Messing EM, Chang C. Androgen deprivation therapy for prostate cancer: current status and future prospects. Prostate. 2004; 61: 332-353.

22. Smith DM, Murphy WM. Histologic changes in prostate carcinomas treated with leuprolide (luteinizing hormone-releasing hormone effect). Distinction from poor tumor differentiation. Cancer. 1994; 73: 1472-1477.

23. di Sant'Agnese PA1. Neuroendocrine differentiation in carcinoma of the prostate. Diagnostic, prognostic, and therapeutic implications. Cancer. 1992; 70: 254-268.

24. Zapata PD, Colas B, López-Ruiz P, Ropero RM, Martín RM. [Phosphotyrosine phosphatase SHP-, somatostatin and prostate cancer]. Actas Urol Esp. 2004; 28: 269-285.

25. Berner A, Nesland JM, Waehre H, Silde J, Fosså SD. Hormone resistant prostatic adenocarcinoma. An evaluation of prognostic factors in pre- and post-treatment specimens. Br J Cancer. 1993; 68: 380-384.

26. Cohen RJ, Glezerson G, Haffejee Z. Neuroendocrine cells. A new prognostic parameter in prostate cancer. Br J Urol, 1991; 68: 258-262.

27. Abrahamsson PA. Neuroendocrine differentiation and hormone-refractory prostate cancer. Prostate Suppl. 1996; 6: 3-8.

28. Jongsma J, Oomen MH, Noordzij MA et al. Androgen-independent growth is induced by neuropeptides in human prostate cancer cell lines. Prostate, 2000; 42: 34-39.

29. Hvamstad T, Jordal A, Hekmat N, Paus E, Fosså SD. Neuroendocrine serum tumour markers in hormone-resistant prostate cancer. Eur Urol. 2003; 44: 215-221.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

30. Kamiya N, Akakura K, Suzuki H, Isshiki S, Komiya A. Pretreatment serum level of neuron specific enolase (NSE) as a prognostic factor in metastatic prostate cancer patients treated with endocrine therapy. Eur Urol. 2003; 44: 309-314.

31. Hirano D, Okada Y, Minei S, Takimoto Y, Nemoto N. Neuroendocrine differentiation in hormone refractory prostate cancer following androgen deprivation therapy. Eur Urol. 2004; 45: 586-592.

32. Halmos G, Schally AV, Sun B, Davis R, Bostwick DG. High expression of somatostatin receptors and messenger ribonucleic acid for its receptor subtypes in organ-confined and locally advanced human prostate cancers. J Clin Endocrinol Metab. 2000; 85: 2564-2571.

33. Milovanovic SR, Radulovic S, Groot K, Schally AV. Inhibition of growth of PC-82 human prostate cancer line xenografts in nude mice by bombesin antagonist RC-3095 or combination of agonist [D-Trp6]-luteinizing hormone-releasing hormone and somatostatin analog RC-160. Prostate. 1992; 20: 269-280.

34. Abrahamsson PA, Ptak A, Nakada SY, et al. Immunohistochemical localization of the androgen receptor in neuroendocrine cells in human prostatic tissue and prostatic carcinoma. Mod Pathol, 1993; 6: 54.

35. Sadi MV, Barrack ER. Image analysis of androgen receptor immunostaining in metastatic prostate cancer. Heterogeneity as a predictor of response to hormonal therapy. Cancer. 1993; 71: 2574-2580.

36. Eder IE, Culig Z, Putz T, Nessler-Menardi C, Bartsch G. Molecular biology of the androgen receptor: from molecular understanding to the clinic. Eur Urol. 2001; 40: 241-251.

37. Sánchez Zalabardo D, Rosell Costa D, Honorato Cia B, Rioja Zuazu J, Regojo Balboa JM. [Mutations of the androgen receptor gene in patients with clinically localized adenocarcinoma of the prostate]. Actas Urol Esp. 2004; 28: 221-229.

38. Marcelli M, Ittmann M, Mariani S, Sutherland R, Nigam R. Androgen receptor mutations in prostate cancer. Cancer Res. 2000; 60: 944-949.

39. Shi XB, Ma AH, Xia L, Kung HJ, de Vere White RW. Functional analysis of 44 mutant androgen receptors from human prostate cancer. Cancer Res. 2002; 62: 1496-1502.

40. Linja MJ, Savinainen KJ, Saramäki OR, Tammela TL, Vessella RL. Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. Cancer Res. 2001; 61: 3550-3555.

41. Di Zazzo E, Galasso G, Giovannelli P, Di Donato M, Di Santi A1. Prostate cancer stem cells: the role of androgen and estrogen receptors. Oncotarget. 2016; 7: 193-208.

42. Ciccarese C, Santoni M, Brunelli M, Buti S, Modena A1. AR-V7 and prostate cancer: The watershed for treatment selection? Cancer Treat Rev. 2016; 43: 27-35.

43. Woodson K, Gillespie J, Hanson J, Emmert-Buck M, Phillips JM. Heterogeneous gene methylation patterns among pre-invasive and cancerous lesions of the prostate: a histopathologic study of whole mount prostate specimens. Prostate. 2004; 60: 25-31.

44. Wolf DA, Herzinger T, Hermeking H, Blaschke D, Hörz W. Transcriptional and posttranscriptional regulation of human androgen receptor expression by androgen. Mol Endocrinol. 1993; 7: 924-936.

45. Nakayama T, Watanabe M, Suzuki H, Toyota M, Sekita N. Epigenetic regulation of androgen receptor gene expression in human prostate cancers. Lab Invest. 2000; 80: 1789-1796.

46. Jarrard DF, Kinoshita H, Shi Y, Sandefur C, Hoff D. Methylation of the androgen receptor promoter CpG island is associated with loss of androgen receptor expression in prostate cancer cells. Cancer Res. 1998; 58: 5310-5314.

47. Kinoshita H, Shi Y, Sandefur C, Meisner LF, Chang C. Methylation of the androgen receptor minimal promoter silences transcription in human prostate cancer. Cancer Res. 2000; 60: 3623-3630.

48. Angulo JC, Andrés G, Ashour N, Sánchez-Chapado M, López JI, et al. Development of Castration Resistant Prostate Cancer can be Predicted by a DNA Hypermethylation Profile. J Urol. 2016; 195: 619-626.

Copyright © Angulo JC.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.