

# BÖLÜM 21

## Lokalize ve Metastatik Prostat Kanserinde Morfolojik ve Fonksiyonel Sınıflandırma

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### GİRİŞ

Lokalize ve metastatik prostat kanserinde risk sınıflaması hastaların hangilerinde aktif izlem, küratif tedavi veya palyatif tedavi yaklaşımlarını belirleyebilmemiz açısından önem taşır. Risk sınıflamasında tümörün evrelemesini belirleme amaçlı kullandığımız TNM sınıflamasının yanında, PSA düzeyleri, Gleason skoru, doku biyopsisi verileri, gen mutasyonları ve ileri düzey görüntüleme tekniklerinden faydalanılmaktadır. Bu tetkiklerin sonuçları doğrultusunda hastaya ait risk grubu belirlenir ve böylece gereksiz tetkik ve tedavilerin önüne geçilmiş olur.

**PSA Düzeyleri:** PSA (Prostat Spesifik Antijen) düzeyleri, prostat kanserinin teşhisinde ve izlenmesinde kritik bir rol oynar. PSA düzeyleri, tedavi sürecinde düzenli aralıklarla ölçülür.

**DRM (Dijital Rektal Muayene):** DRM, prostatın fiziksel olarak muayene edilmesini içerir. Bu muayene, prostat kanserinin erken aşamalarında bile anormallikleri tespit edebilir. Hastalığın T evrelemesini belirlemede yardımcı olabilmektedir.

**Genetik Testler:** BRCA 1-2 gen mutasyonları prostat ca tanımlı hastalarda yaklaşık %6 oranında görülür ve BRCA-2 gen mutasyonu hastalığın agresif gidişatının göstergesidir bu nedenle her hastada rutin test bakılması önerilir.(1) Ayrıca HOXB13 veya ATM gen mutasyonları aile bireylerinde yüksek risk olduğunu göstermesi nedeni ile bakılması tavsiye edilir.(2)

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## KAYNAKLAR

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *Ca Cancer J Clin*; 2021;71(1): 7-33.
2. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. International Agency for Research on Cancer. France: Lyon; 2020. Available online: <https://gco.iarc.fr/today/homescreening> (accessed on 29 December 2020).
3. Patel AR, Klein EA. Risk factors for prostate cancer. *Nature clinical practice Urology*; 2009; 6(2):87-95.
4. EAU Guidelines; European Association of Urology: Arnhem, The Netherlands, 2020; ISBN 978-94-92671-07-3.
5. Messina C, Cattrini C, Soldato D, et al. BRCA Mutations in Prostate Cancer: Prognostic and Predictive Implications. *Journal of oncology*; 2020:2020.
6. Breslow N, Chan CW, Dhom G, et al. Latent carcinoma of prostate at autopsy in seven areas. Collaborative study organized by the International Agency for Research on Cancer, Lyons, France. *International journal of cancer. International journal of cancer*; 1977; (20):680-688.
7. Karr JP. Prostate cancer in the United States and Japan. *Adv Exp Med Biol* (1992); 324:17-28.
8. Aly M, Leval A, Schain F, et al. Survival in patients diagnosed with castration-resistant prostate cancer: A population-based observational study in Sweden. *Scand. J. Urol*; 2020; 54:115-121.
9. Tangen CM, Hussain MH, Higano CS et al. Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). *J Urol*; 2012; 188: 1164.
10. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med*; 2000; 132: 566-77.
11. Tsushima T, Nasu Y, Saika T, et al. Optimal starting time for flutamide to prevent disease flare in prostate cancer patients treated with a gonadotropin-releasing hormone agonist. *Urol Int*; 2001; 66:135-9.
12. Sciarra A, Fasulo A, Ciardi A, et al. A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer. *Medicine*; 2016; 95:e3845.
13. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*; 2015; 373: 737-46.
14. Fizazi K, Tran N, Fein L et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*; 2017; 377: 352-60.
15. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*; 2019; 381(2):121-31.
16. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*; 2019; 37(32):2974-86.
17. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N. Engl. J. Med*; 2019; 381:13-24.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*; 2009; 45:228-47.
19. Schwartz LH, Seymour L, Litiere S, et al. RECIST 1.1 - Standardisation and disease-specific adaptations: perspectives from the RECIST Working Group. *Eur J Cancer*; 2016; 62:138-45.
20. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med*; 1998; 339:1036-1042.
21. Sizar O, Schwartz J. Hypogonadism. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK532933/>

22. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. *The Journal of urology*; 2007; 178(4):1290-1295.
23. Perachino M, Cavalli V. Testosterone (t) level correlates with survival in pts with advanced prostate cancer (apc): the lower is really the better. *J Urol*; 2008; 179(4S):179-180.
24. Cassileth BR, Soloway MS, Vogelzang NJ, et al. Patients' choice of treatment in stage D prostate cancer. *Urology*; 1989; 33(Suppl. 5):57-62.
25. Schally AV, Coy DH, Arimura A. LH-RH agonists and antagonists. *International Journal of Gynecology & Obstetrics*; 1980; 18(5):318-324.
26. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12 month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*; 2008; 102(11):1531-1538.
27. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*; 2020; 382(23):2187-2196.
28. United States Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. 06/23/2020; Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications> Retrieved December 26, 2020
29. James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). *Eur Urol*; 2015; 67(6):1028-1038.
30. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*; 2013; 368(14):1314-1325.
31. Sountoulides P, Rountos T. Adverse Effects of Androgen Deprivation Therapy for Prostate Cancer: Prevention and Management. *ISRN Urol*; 2013; 2013:240108.
32. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2021). Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Retrieved February 23, 2021.
33. Millikan RE, Wen S, Pagliaro LC, et al. Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. *J Clin Oncol*; 2008; 26:5936.
34. Schweizer MT and Antonarakis ES: Chemotherapy and its evolving role in the management of advanced prostate cancer. *Asian J Androl*; 2014; 16:334.
35. Tannock IF, De Wit R, Berry WR, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *N. Engl. J. Med*; 2004; 351:1502-1512.
36. Petrylak DP, Tangen CM, Hussain MHA, et al. Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer. *N. Engl. J. Med*; 2004; 351:1513-1520.
37. Sekino Y and Teishima J. Molecular mechanisms of docetaxel resistance in prostate cancer. *Cancer Drug Res*; 2020; 3:676-685.
38. Gan L, Chen S, Wang Y, et al. Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. *Cancer Res*; 2009; 69:8386-8394.
39. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*; 2016; 387:1163-1177.
40. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in noncastrate metastatic prostate cancer (GETUG-AFU 15): A randomised, open-label, phase 3 trial. *Lancet Oncol*; 2013; 14:149-158.

41. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol*; 2018; 36:1080–1087.
42. Vale C, Burdett S, Rydzewska L, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *The lancet oncology*; 2016; 17(2):243–256.
43. Sathianathen NJ, Philippou YA, Kuntz GM, et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. *Cochrane Database Syst Rev*; 2018; Oct 15; 10(10):CD012816.
44. Gravis G, Boher J-M, Chen Y-H, et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. *Eur Urol*; 2018; 73:847–855.
45. Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J. Clin. Oncol*; 2008; 26:4563–4571.
46. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. *N. Engl. J. Med*; 2011; 364: 1995–2005.
47. Fizazi K, Scher HI, Molina A, et al. 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.
48. Hoyle AP, Ali A, James ND, et al. Abiraterone in “High-” and “Low-risk” Metastatic Hormone-sensitive Prostate Cancer. *Eur. Urol*; 2019; 76:719–728.
49. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*; 2019; 20(5):686–700.
50. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: Directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann. Oncol*; 2018; 29:1235–1248.
51. Sartor O, De Bono JS. *Metastatic Prostate Cancer. N. Engl. J. Med*; 2018; 378:645–657.
52. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*; 2015; 16:152–160.
53. Tran C, Ouk S, Clegg NJ, et al. Development of a second generation antiandrogen for treatment of advanced prostate cancer. *Science*; 2009; 324:787–790.
54. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*; 2021; 39:2294– 2303.
55. Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. *Lancet Oncol*; 2019; 20(11):1518–30.
56. Zurth C, Sandman S, Trummel D, et al. Higher blood brain barrier penetration of [14C] apalutamide and [14C] enzalutamide compared to [14C] darolutamide in rats using whole-body autoradiography. *J Clin Oncol*; 2019; 37(Suppl.7):156.
57. Fizazi K, Albiges L, Loriot Y, et al. ODM-201: a new-generation androgen receptor inhibitor in castration-resistant prostate cancer. *Expert Rev Anticancer Ther*; 2015; 15(9):1007–1017.
58. ODM-201 in addition to standard ADT and docetaxel in metastatic castration sensitive prostate cancer. *ClinicalTrials.gov*. <https://clinicaltrials.gov/ct2/show/NCT02799602>. Accessed August 13, 2020.

59. Fizazi K, Maldonado X, Foulon S, et al. A phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. *J. Clin. Oncol*; 2021; 39: 5000.
60. Fizazi K, Foulon S, Carles J, et al. "Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2x 2 factorial design. *The Lancet*; 399; 10336 (2022):1695-1707.
61. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med*; 2022; 386:1132-1142.
62. Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol Off J Am Soc Clin Oncol*; 2016; 34(24):2835–2842.
63. Boeve LMS, Hulshof M, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the horrad trial. *Eur Urol*; 2019; 75(3):410–8.
64. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*; 2018; 392(10162):2353–66.
65. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol*; 2019; 76(1):115–24.
66. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*; 2020; 38(25):2830–8.
67. Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the advanced prostate cancer consensus conference APCCC 2017. *Eur Urol*; 2018; 73(2):178–211.
68. D'Angelillo RM, Francolini G, Ingrosso G, et al. Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: a position paper of Italian association of radiotherapy and clinical oncology (AIRO). *Crit Rev Oncol Hematol*; 2019; 138:24–8.