

ERKEN VE LOKAL İLERİ EVRE HASTALIKTA ANDROJEN DEPRİVASYON TEDAVİSİ

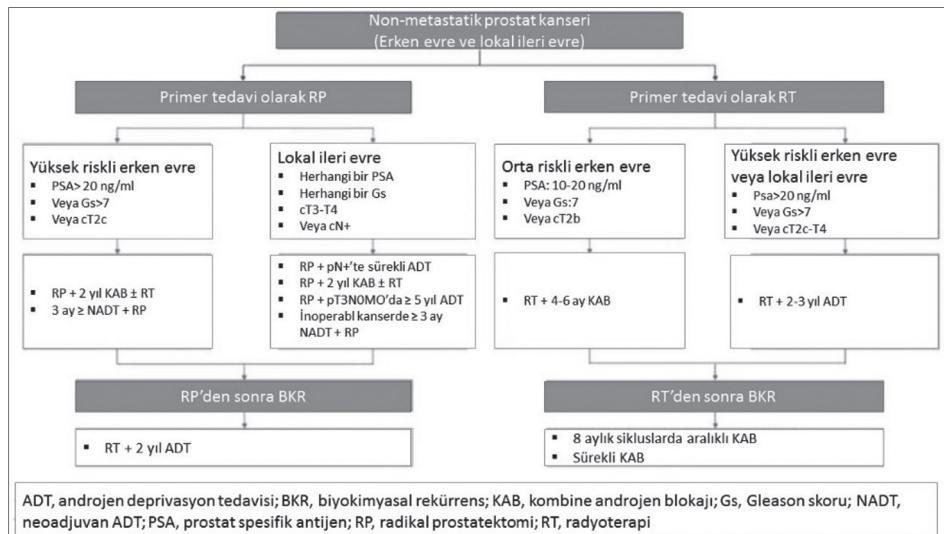
Selamettin DEMİR¹

GİRİŞ

Prostat kanserinin (PCa) 2012'de dünya çapında tahmini 1.1 milyon yeni vaka ile erkekleri etkileyen en sık ikinci kanser olduğu belirtilmiştir.^(1,2) PCa'da primer tedaviyi radikal prostatektomi veya radyoterapi oluşturmaktır fakat pozitif cerrahi sınırlı, ekstraprostatik yayılmış, lenf nodu tutulumlu, yüksek prostat spesifik antijenli (PSA) ve yüksek gleason skorlu hastaların primer tedaviden sonra yüksek rekürrens riskine sahip vakalar olduğu bilinmektedir. Bu hastalarda medikal ve cerrahi kastrasyonu içeren androjen deprivasyon tedavisi (ADT) tümör yükünü küçültmek, cerrahi sınır pozitifliğini ve rekürrens riskini azaltmak için primer tedaviden önce neoadjuvan tedavi olarak ve ayrıca ADT, radyoterapi veya bu ikisinin kombinasyonu da rekürrens riskini azaltmak için primer tedaviden sonra adjuvan tedavi olarak verilebilmektedir. Testiküler androjen seviyelerini baskılama veya androjen reseptörlerini hedefleme ile dolaşımındaki androjenleri inhibe ederek androjen seviyelerini tüketmeyi amaçlayan birkaç farklı ADT modalitesi mevcuttur. Sonuç olarak ADT'nin medikal veya cerrahi kastrasyon, antiandrojen tedavi ve bu ikisinin kombinasyonu olan maksimal androjen blokajı (MAB) ile verilmesi yaygın olarak kullanılmaktadır.^(3,4)

ADT monoterapisi erken evre PCa'da uygun olmamasına rağmen primer tedaviye ADT'nin eklenmesi orta veya yüksek riskli hastalarda anlamlı bir şekilde sonuçları iyileştirdiği gösterilmiştir.⁽⁴⁾ Ancak ideal hasta popülasyonu, tedavi için en uygun zaman ve süre gibi PCa tedavisinde ADT uygulamasını en iyi şekilde kullanmak konusunda birçok problemler hala devam etmektedir. Bu problemleri araştırmak, ideal randomize klinik çalışmaları yapma konusunda zorluklara yol açan uzun hayatı kalma ve uzun gözlem zamanı ile karmaşıklaşmaktadır. Ayrıca

¹ Üroloji uzmanı, S.B.Ü Van Eğitim ve Araştırma Hastanesi, drselami1978@hotmail.com



Şekil-1. ADT tedavi şeması. Alıntı: Fang D, et al.(84)

Anahtar Kelimeler: Androjen deprivasyon tedavisi, prostat kanseri, radikal prostatektomi, rayoterapi

KAYNAKÇA

- Howlader N, Noone A. M., & Krapcho, M. (eds.) (2015). SEER Cancer Statistics Review, 1975–2013. Bethesda, MD: National Cancer Institute; 2015. http://seer.cancer.gov/csr/1975_2013/
- Berglund RK, Tangen CM, Powell IJ, et al. Ten-year follow-up of neoadjuvant therapy with goserelin acetate and flutamide before radical prostatectomy for clinical T3 and T4 prostate cancer: update on southwest oncology group study 9109. Urology. 2012;79:633–637.
- Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–629.
- Mohler JL, Armstrong AJ, Bahnsen RR, et al. Prostate cancer, version 1.2016. J Natl Compr Canc Netw. 2016;14:19–30.
- Huggins C, Hodges CV. Studies on prostatic cancer, I: the effect of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res. 1941;1:293–297.
- Barry MJ, Delorenzo MA, Walker Corkery ES, et al. The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. BJU Int. 2006;98:973–8.
- Cooperberg MR, Grossfeld GD, Lubeck DP, et al. National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst. 2003;95:981–9.
- Loblaw DA, Mendelson DS, Talcott JA, et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol. 2004;22:2927–2941.
- McLeod DG. Hormonal therapy: historical perspective to future directions. Urology. 2003;61(1):3–7.
- Tolis G, Ackman D, Stellos A, et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci U S A. 1982;79:1658–1662.

11. Limonta P, Montagnani M, Moretti M, et al. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. *Expert Opin Investig Drugs.* 2001;10:709-720.
12. Kuhn JM, Billebaud T, Navratil H, et al. Prevention Of the transient adverse effects of a gonadotropin-releasing Hormone analogue (Buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (Nilutamide). *N Engl J Med.* 1989;321:413-418.
13. Scardino PT, et al. National Comprehensive CancerNetwork (NCCN) Practice Guidelines version 1.2004. Available at: http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Accessed March 1, 2005.
14. Abarelix package insert. Available at: <http://www.fda.gov/cder/foi/label/2003/021320lbl.pdf>. Accessed May 25, 2005.
15. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 1999;17:3461-3467.
16. Ofelelein MG, Feng A, Scolieri MJ, et al. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. *Urology.* 2000;56:1021-1024.
17. Thompson IM, Pauker DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med.* 2004;350:2239-2246.
18. Chodak GW, Keane T, Klotz L. Critical evaluation of hormonal therapy for carcinoma of the prostate. *Urology.* 2002;60:201-8.
19. Iversen P, Johansson JE, Lodding P, et al. Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol.* 2004;172:1871-6.
20. Wirth M, Tyrrell C, Delaere K, et al. Bicalutamide (Casodex) 150 mg plus standard care in early non-metastatic prostate cancer: results from Early Prostate Cancer Trial 24 at a median 7 years' follow-up. *Prostate Cancer Prostatic Dis.* 2007;10:87-93.
21. Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. *Eur Urol.* 2008;53:68-80.
22. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol.* 2007;177:2106-31.
23. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *Br J Urol.* 1997;79:235-46.
24. Kirk D. Timing and choice of androgen ablation. *Prostate Cancer Prostatic Dis.* 2004;7:217-22.
25. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol.* 2006;24:1868-76.
26. Studer UE, Collette L, Whelan P, et al. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). *Eur Urol.* 2008;53:941-9.
27. Wirth MP, See WA, McLeod DG, et al. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol.* 2004;172:1865-70.
28. Tyrrell CJ, Kaisary AV, Iversen P, et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg mono-therapy versus castration in the treatment of metastatic and locally advanced prostate cancer. *Eur Urol.* 1998;33:447-56.
29. Tyrrell CJ, Iversen P, Tammela T, et al. Tolerability, efficacy and pharmacokinetics of bicalutamide 300 mg, 450 mg or 600 mg as monotherapy for patients with locally advanced or metastatic prostate cancer, compared with castration. *BJU Int.* 2006; 98:563-72.
30. Kumar S, Shelley M, Harrison C, et al. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev.* 2006; CD006019.

31. Koie T, Ohyama C, Yamamoto H, et al. Both radical prostatectomy following treatment with neoadjuvant LHRH agonist and estramustine and radiotherapy following treatment with neoadjuvant hormonal therapy achieved favorable oncological outcome in high-risk prostate cancer: a propensity-score matching analysis. *World J Surg Oncol.* 2014;12:134.
32. Narita T, Koie T, Ookubo T, et al. The impact of extended lymph node dissection versus neoadjuvant therapy with limited lymph node dissection on biochemical recurrence in high-risk prostate cancer patients treated with radical prostatectomy: a multi-institutional analysis. *Med Oncol.* 2017;34:543.
33. Joung JY, Kim JE, Kim SH, et al. The prevalence and outcomes of pT0 disease after neoadjuvant hormonal therapy and radical prostatectomy in high-risk prostate cancer. *BMC Urol.* 2015;15:82.
34. Hajili T, Ohlmann C, Linxweiler J, et al. Neoadjuvant androgen deprivation in primarily inoperable prostate cancer: consecutive assessment of peri- and postoperative outcomes. *J Urol.* 2016;195:50-04.
35. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol.* 2001;166:500–506.
36. Gleave ME, La Bianca SE, Goldenberg SL, et al. Long-term neoadjuvant hormone therapy prior to radical prostatectomy: evaluation of risk for biochemical recurrence at 5-year follow-up. *Urology* 2000;56:289–294.
37. Naiki T, Kawai N, Okamura T, et al. Neoadjuvant hormonal therapy is a feasible option in laparoscopic radical prostatectomy. *BMC Urol.* 2012;12:36.
38. Selli C, Montironi R, Bono A, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. *J Clin Pathol.* 2002;55:508–513.
39. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol.* 2006;7:472–479.
40. Dorff TB, Flraig TW, Tangen CM, et al. Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: sWOG S9921 study. *J Clin Oncol.* 2011;29:2040–2045.
41. Tsurumaki Sato Y, Fukuhara H, Suzuki M, et al. Long-term results of radical prostatectomy with immediate adjuvant androgen deprivation therapy for pT3N0 prostate cancer. *BMC Urol.* 2014;14:13.
42. Siddiqui SA, Boorjian SA, Inman B, et al. Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. *J Urol.* 2008;179:1830–1837.
43. Glode L, Tangen C, Hussain M, et al. Adjuvant androgen deprivation (ADT) versus mitoxantrone plus prednisone (MP) plus ADT in high risk prostate cancer (PCa) patients following radical prostatectomy: A phase III intergroup trial (SWOG S9921). Paper presented at 2017 Genitourinary Cancers Symposium February 16–18, 2017; Orlando, FL.
44. Spahn M, Weiss C, Bader P, et al. Long-term outcome of patients with high-risk prostate cancer following radical prostatectomy and stage-dependent adjuvant androgen deprivation. *Urol Int.* 2010;84:164–173.
45. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait- and-see after radical prostatectomy: 10-year follow-up of the ARO96-02/AUOAP 09/95 trial. *Eur Urol.* 2014;66:243–250.
46. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* 2012;380:2018–2027.
47. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: aRO 96-02/AUO AP 09/95. *J Clin Oncol.* 2009;27:2924–2930.

48. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181:956–962.
49. Omrcen T, Hrepic D, Boraska Jelavic T, et al. Combination of adjuvant radiotherapy and androgen deprivation therapy after radical prostatectomy in high risk prostate cancer patients—results from retrospective analysis. *J BUON.* 2015;20:1061–1067.
50. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01–03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol.* 2016;17:727–737.
51. Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol.* 2016;17:747–756.
52. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med.* 2017;376:417–428.
53. Critz FA, Benton JB, Shrake P, et al. 25-year disease-free survival rate after irradiation for prostate cancer calculated with the prostate specific antigen definition of recurrence used for radical prostatectomy. *J Urol.* 2013;189:878–883.
54. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA.* 2008;299:289–295.
55. Bolla M, Maingon P, Carrie C, et al. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC trial 22991. *J Clin Oncol.* 2016;34:1748–1756.
56. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and shortterm androgen deprivation for localized prostate cancer. *N Engl J Med.* 2011;365:107–118.
57. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. *J Clin Oncol.* 2015;33:332–339.
58. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer:10-year data from the TROG 96.01 randomised trial. *Lancet Oncol.* 2011;12:451–459.
59. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2015;16:320–327.
60. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol.* 2010;11:1066–1073.
61. Roach M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol.* 2008;26:585–591.
62. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med.* 2009;360:2516–2527.
63. Iversen P, McLeod DG, See WA, et al. Casodex Early Prostate Cancer Trialists' Group. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide early prostate cancer programme at a median follow-up of 9.7 years. *BJU Int.* 2010;105:1074–1081.
64. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys.* 2005;61:1285–1290.
65. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol.* 2008;26:2497–2504.

66. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med.* 2012;367:895–903.
67. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European organisation for research and treatment of cancer (EORTC) trial 30891. *J Clin Oncol.* 2006;24:1868–1876.
68. Wang A, Karunasinghe N, Plank L, et al. Effect of androgen deprivation therapy on bone mineral density in a prostate cancer cohort in New Zealand: a pilot study. *Clin Med Insights Oncol.* 2017;11: 1179554917733449.
69. Smith MR, Egerdie B, Toriz NH, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009;361:745–755.
70. Smith MR, Morton RA, Barnette KG, et al. Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. *J Urol.* 2010;184:1316–1321.
71. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 2006;24:4448–4456.
72. Galvão DA, Spry N, Taaffe DR, et al. A randomized controlled trial of an exercise intervention targeting cardiovascular and metabolic risk factors for prostate cancer patients from the RADAR trial. *BMC Cancer.* 2009;9:419.
73. Newton RU, Taaffe DR, Spry N, et al. Can exercise ameliorate treatment toxicity during the initial phase of testosterone deprivation in prostate cancer patients? Is this more effective than delayed rehabilitation? *BMC Cancer.* 2012;12:432.
74. Chen D, See L, Liu J, et al. Risk of cardiovascular ischemic events after surgical castration and gonadotropin-releasing hormone agonist therapy for prostate cancer: a nationwide cohort study. *J Clin Oncol.* 2017;35:3697–3705.
75. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol.* 2015;67:825–836.
76. Chen AC, Petrylak DP. Complications of androgen deprivation therapy in men with prostate cancer. *Curr Oncol Rep.* 2004;6:209–215.
77. Strum SB, McDermid JE, Scholz MC, et al. Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormonal blockade. *Br J Urol.* 1997;79:933–941.
78. Green HJ, Pakenham KI, Headley BC, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. *BJU Int.* 2002;90:427–432.
79. Salminen E, Portin R, Korppela J, et al. Androgen deprivation and cognition in prostate cancer. *Br J Cancer.* 2003;89:971–976.
80. Salminen EK, Portin RI, Koskinen AI, et al. Estradiol and cognition during androgen deprivation in men with prostate carcinoma. *Cancer.* 2005; 103:1381–1387.
81. Herr HW, O'Sullivan M. Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol.* 2000;163:1743–1746.
82. Pirl WF, Siegel GI, Goode MJ, et al. Depression in men receiving androgen deprivation therapy for prostate cancer: a pilot study. *Psychooncology.* 2002;11:518–523.
83. Hong J, Liao C, Huang C, Lu Y. Chemical castration decreased the risk of dementia in patients with prostate cancer from 13368 patients, taiwan national health insurance research database. *Eur Urol Suppl.* 2017;16:86.
84. Fang D, Zhou L. Androgen deprivation therapy in nonmetastatic prostate cancer patients: Indications, treatment effects, and new predictive biomarkers. *Asia Pac J Clin Oncol.* 2019;15(3):108–120.