

BÖLÜM 36

Radyodermatit



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GİRİŞ

Radyodermatit, radyoterapi (RT)'nin en sık görülen yan etkilerinden bir tanesidir. RT alan hastaların yaklaşık olarak %95'ini etkilemektedir (1-5). RT; radyasyon dozu, uygulanan alan, uygulama süresi, uygulama tekniği ve uygulanan bireye ait özelliklere göre değişen derecelerde istenmeyen reaksiyonlara yol açabilmektedir. Kronolojik oluşum sürecine göre ikiye ayrılabilir. Akut radyodermatit, tedavinin başlamasından hemen sonra ortaya çıkan 90 gün içinde devam edebilen eritem, ödem, pigment değişiklikleri, saç dökülmesi ve deskuamasyonla karakterize akut bir reaksiyondur. Kronik radyodermatit ise radyasyon tedavisi tamamlandıktan aylar ya da yıllar sonra ortaya çıkan ülser, nekroz, fibrozis ve telenjektazilerle karakterize kronik bir süreçtir (6).

Akut reaksiyonlar, yaşam kalitesini de etkileyecek ciddi sekellere yol açabilir. Bu akut reaksiyonları önlemek için uygun deri bakımı sağlanmalıdır. Semptomları azaltmak amacıyla topikal kortikosteroidler kullanılabilir. Akut kutanöz reak-

siyonların tedavisi öncelikle yara bakımı yönetimini içerir. Kronik değişiklikler, tedaviden aylar veya yıllar sonra gelişebilir. Kronik radyasyon dermatiti genellikle kalıcı ve ilerleyicidir.

Kitabın bu bölümünde radyodermatitin epidemiyolojisini, gelişmesi için risk faktörlerini, patogenezini, klinik özellikleri ve klinik derecelendirilmesini, klinik seyir ve komplikasyonlarını, teşhis ve ayırıcı tanısı ile radyodermatit gelişiminin önlenmesini ve tedavi stratejilerini tartışmayı planladık.

EPİDEMİYOLOJİ

Radyasyon dermatiti, özellikle deri kanseri, meme kanseri ve baş-boyun kanseri olan hastalar olmak üzere, RT alan hastaların yaklaşık % 95'inde görülmektedir (1, 7, 8). Bu hasta popülasyonlarında radyodermatitin daha yüksek oranda görülmesinin sebebi yüzey dozunun, yani derinin maruz kaldığı radyasyon miktarının daha yüksek olmasındandır. Genellikle deri reaksiyonu hafif veya orta düzeydedir. Hastaların yaklaşık %20-45'inde nemli deskuamasyon ve ülserasyon izlenir (5, 8).

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- Meme kanseri, baş-boyun kanseri, akciğer kanseri veya sarkomu olan hastalarda daha sık görülür.
- İleri yaş, kadın cinsiyet ve obezite radyasyon dermatiti gelişimi için bireysel risk faktörleridir.
- Eş zamanlı alınan kemoterapiler radyasyon dermatiti gelişimine eğilim yaratabilir.
- Radyasyon dermatiti gelişimini azaltmak için RT döneminde uygun deri bakımına dikkat edilmelidir.
- Radyasyon dermatiti oluşan deri hasarının şiddetine göre tedavi edilir.
- IMRT ve VMAT gibi modern radyasyon tedavisi teknikleri ile hedef dışındaki normal dokuya radyasyon maruziyeti en aza indirilerek odaklanılan tedavi alanına uygun radyasyon verilmesi sağlanır. Modern teknikler ile radyodermatit gelişim riski daha düşüktür.

KAYNAKLAR

1. Hickok JT, Morrow GR, Roscoe JA, et al. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. *J Pain Symptom Manage*. 2005; 30:433.
2. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006; 54:28-46.
3. Brown KR, Rzcudlo E. Acute and chronic radiation injury. *J Vasc Surg*. 2011; 53:15S.
4. Singh M, Alavi A, Wong R, Akita S. Radiodermatitis: A Review of Our Current Understanding. *Am J Clin Dermatol*. 2016; 17:277.
5. Leventhal J, Young MR. Radiation Dermatitis: Recognition, Prevention, and Management. *Oncology (Williston Park)*. 2017; 31:885.
6. Jensen JM, Gau T, Schultze J, et al. Treatment of acute radiodermatitis with an oil-in-water emulsion following radiation therapy for breast cancer: a controlled, randomized trial. *Strahlenther Onkol*. 2011; 187:378.
7. McQuestion M. Evidence-based skin care management in radiation therapy: clinical update. *Semin Oncol Nurs*. 2011; 27:e1.
8. Salvo N, Barnes E, van Draanen J, et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Curr Oncol*. 2010; 17:94.
9. Vuong T, Franco E, Lehnert S, et al. Silver leaf nylon dressing to prevent radiation dermatitis in patients undergoing chemotherapy and external beam radiotherapy to the perineum. *Int J Radiat Oncol Biol Phys*. 2004 Jul 1;59(3):809-14.
10. Delfino S, Brunetti B, Toto V, Persichetti P. Burn after breast reconstruction. *Burns*. 2008; 34:873.
11. Vandeweyer E, Deraemaeker R. Radiation therapy after immediate breast reconstruction with implants. *Plast Reconstr Surg*. 2000; 106:56.
12. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. *J Invest Dermatol*. 2012; 132:985.
13. Housri N, Yarchoan R, Kaushal A. Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary? *Cancer*. 2010;116(2):273-83.
14. Meyer F, Fortin A, Wang CS, et al. Predictors of severe acute and late toxicities in patients with localized head-and-neck cancer treated with radiation therapy. *Int J Radiat Oncol Biol Phys*. 2012; 82:1454.
15. Swift M, Morrell D, Cromartie E, et al. The incidence and gene frequency of ataxia-telangiectasia in the United States. *Am J Hum Genet*. 1986;39(5):573-83.
16. Iannuzzi CM, Atencio DP, Green S, et al. ATM mutations in female breast cancer patients predict for an increase in radiation-induced late effects. *Int J Radiat Oncol Biol Phys*. 2002;52(3):606-13
17. Ambrosone CB, Tian C, Ahn J, et al. Genetic predictors of acute toxicities related to radiation therapy following lumpectomy for breast cancer: a case-series study. *Breast Cancer Res*. 2006; 8:R40.
18. Terrazzino S, La Mattina P, Masini L, et al. Common variants of eNOS and XRCC1 genes may predict acute skin toxicity in breast cancer patients receiving radiotherapy after breast conserving surgery. *Radiother Oncol*. 2012;103(2):199-205.
19. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA Oncol*. 2015; 1:931.
20. Jagsi R, Griffith KA, Boike TP, et al. Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule: Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort. *JAMA Oncol*. 2015; 1:918.
21. Tejwani A, Wu S, Jia Y, et al. Increased risk of high-grade dermatologic toxicities with radiation plus epidermal growth factor receptor inhibitor therapy. *Cancer*. 2009 Mar 15;115(6):1286-99.
22. O'Rourke ME. Enhanced cutaneous effects in combined modality therapy. *Oncol Nurs Forum*. 1987;14(6):31-5.
23. Wallach JB, Rietschel P, Kalnicki S, Fox JL. BRAF inhibitor (vemurafenib) concurrent with radiation



- therapy for metastatic melanoma producing severe skin and oral cavity reactions. *Pract Radiat Oncol*. 2014;4(5):e213–6.
24. Coleman CN, Turrisi AT. Radiation and chemotherapy sensitizers and protectors. *Crit Rev Oncol Hematol*. 1990;10(3):225–52.
 25. Toledano A, Garaud P, Serin D, et al. Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study. *Int J Radiat Oncol Biol Phys*. 2006;65(2):324–32.
 26. Azria D, Gourgou S, Sozzi WJ, et al. Concomitant use of tamoxifen with radiotherapy enhances subcutaneous breast fibrosis in hypersensitive patients. *Br J Cancer*. 2004;91(7):1251–60.
 27. Lopez E, Guerrero R, Nunez MI, et al. Early and late skin reactions to radiotherapy for breast cancer and their correlation with radiation-induced DNA damage in lymphocytes. *Breast Cancer Res*. 2005;7(5):R690–8.
 28. Denham JW, Hauer-Jensen M. The radiotherapeutic injury—a complex ‘wound’. *Radiother Oncol*. 2002;63(2):129–45.
 29. Müller K, Meineke V. Radiation-induced alterations in cytokine production by skin cells. *Exp Hematol*. 2007; 35:96.
 30. Müller K, Meineke V. Radiation-induced mast cell mediators differentially modulate chemokine release from dermal fibroblasts. *J Dermatol Sci*. 2011; 61:199.
 31. Haase O, Rodemann HP. Fibrosis and cytokine mechanisms: relevant in hadron therapy? *Radiother Oncol*. 2004;73(Suppl 2):S144–7.
 32. Martin M, Lefaix J, Delanian S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? *Int J Radiat Oncol Biol Phys*. 2000; 47:277.
 33. Canney PA, Dean S. Transforming growth factor beta: a promotor of late connective tissue injury following radiotherapy? *Br J Radiol*. 1990;63(752):620–3.
 34. Abdollahi A, Li M, Ping G, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. *J Exp Med*. 2005;201(6):925–35.
 35. Quarmby S, Kumar P, Kumar S. Radiation-induced normal tissue injury: role of adhesion molecules in leukocyte-endothelial cell interactions. *Int J Cancer*. 1999;82(3):385–95.
 36. Bernier J, Bonner J, Vermorken JB, et al. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. *Ann Oncol*. 2008; 19:142.
 37. He Y, Guo T, Guan H, et al. Concurrent chemoradiotherapy versus radiotherapy alone for locoregionally advanced nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy: a meta-analysis. *Cancer Manag Res*. 2018; 10:1419.
 38. Bonomo P, Desideri I, Loi M, et al. Management of severe bio-radiation dermatitis induced by radiotherapy and cetuximab in patients with head and neck cancer: emphasizing the role of calcium alginate dressings. *Support Care Cancer*. 2019; 27:2957
 39. Bernier J, Russi EG, Homey B, et al. Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines. *Ann Oncol*. 2011; 22:2191.
 40. Budach W, Bölke E, Homey B. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med*. 2007; 357:514.
 41. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed on March 09, 2018).
 42. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995 Mar 30;31(5):1341–6.
 43. González Sanchis A, Brualla González L, Sánchez Carazo JL, et al. Evaluation of acute skin toxicity in breast radiotherapy with a new quantitative approach. *Radiother Oncol*. 2017 Jan;122(1):54–59.
 44. Shore RE. Overview of radiation-induced skin cancer in humans. *Int J Radiat Biol*. 1990 Apr;57(4):809–27..
 45. Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol*. 2001;36(5):549–54.
 46. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2005;23(16):3733–41.
 47. Shore RE, Moseson M, Xue X, et al. Skin cancer after X-ray treatment for scalp ringworm. *Radiat Res*. 2002;157(4):410–8.
 48. Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. *J Natl Cancer Inst*. 1996;88(24):1848–53.
 49. Casamiquela KM, Cohen PR. Radiation port dermatophytosis: tinea corporis occurring at the site of irradiated skin. *Dermatol Online J*. 2012; 18:5.
 50. Mendelsohn FA, Divino CM, Reis ED, Kerstein MD. Wound care after radiation therapy. *Adv Skin Wound Care*. 2002; 15:216.
 51. Campbell IR, Illingworth MH. Can patients wash during radiotherapy to the breast or chest wall? A randomized controlled trial. *Clin Oncol*. 1992;4(2):78–82.



52. Roy I, Fortin A, Larochelle M. The impact of skin washing with water and soap during breast irradiation: a randomized study. *Radiother Oncol.* 2001;58(3):333–9.
53. Baumann BC, Verginadis II, Zeng C, et al. Assessing the Validity of Clinician Advice That Patients Avoid Use of Topical Agents Before Daily Radiotherapy Treatments. *JAMA Oncol.* 2018; 4:1742
54. Wong RK, Bensadoun RJ, Boers-Doets CB, et al. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group. *Support Care Cancer.* 2013; 21:2933
55. Santa Cruz O, Tsoutsou P, Castella C, et al. Loco-regional Control and Toxicity in Head and Neck Carcinoma Patients following Helical Tomotherapy-Delivered Intensity-Modulated Radiation Therapy Compared with 3D-CRT Data. *Oncology.* 2018; 95:61.
56. Meghrajani CF, Co HS, Arcillas JG, et al. A randomized, double-blind trial on the use of 1% hydrocortisone cream for the prevention of acute radiation dermatitis. *Expert Rev Clin Pharmacol.* 2016; 9:483.
57. Ulf E, Maroti M, Serup J, et al. Prophylactic treatment with a potent corticosteroid cream ameliorates radiodermatitis, independent of radiation schedule: A randomized double blinded study. *Radiother Oncol.* 2017; 122:50.
58. Miller RC, Schwartz DJ, Sloan JA, et al. Mometasone furoate effect on acute skin toxicity in breast cancer patients receiving radiotherapy: a phase III double-blind, randomized trial from the North Central Cancer Treatment Group N06C4. *Int J Radiat Oncol Biol Phys.* 2011; 79:1460.
59. Hindley A, Zain Z, Wood L, et al. Mometasone furoate cream reduces acute radiation dermatitis in patients receiving breast radiation therapy: results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2014; 90:748.
60. Ho AY, Olm-Shipman M, Zhang Z, et al. A Randomized Trial of Mometasone Furoate 0.1% to Reduce High-Grade Acute Radiation Dermatitis in Breast Cancer Patients Receiving Postmastectomy Radiation. *Int J Radiat Oncol Biol Phys.* 2018; 101:325.
61. Chan RJ, Webster J, Chung B, et al. Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer.* 2014; 14:53.
62. Dörr W, Herrmann T; Study Group. Efficacy of Wobe-Mugos E for reduction of oral mucositis after radiotherapy : results of a prospective, randomized, placebo-controlled, triple-blind phase III multicenter study. *Strahlenther Onkol.* 2007 Mar;183(3):121-7
63. Rosenthal A, Israilevich R, Moy R. Management of acute radiation dermatitis: A review of the literature and proposal for treatment algorithm. *J Am Acad Dermatol.* 2019; 81:558.
64. Yang X, Ren H, Guo X, et al. Radiation-induced skin injury: pathogenesis, treatment, and management. *Aging (Albany NY).* 2020 Nov 16;12(22):23379-23393.
65. Hegedus F, Mathew LM, Schwartz RA. Radiation dermatitis: an overview. *Int J Dermatol.* 2017 Sep;56(9):909-914.
66. Gosselin T, Ginex PK, Backler C, et al. ONS Guidelines™ for Cancer Treatment-Related Radiodermatitis. *Oncol Nurs Forum.* 2020 Nov 1;47(6):654-670.
67. Villavicencio M, Granados-García M, Vilajosana E, Domínguez-Cherit J. Management of radiodermatitis associated with cetuximab in squamous cell carcinomas of the head and neck. *Int J Dermatol.* 2017; 56:602.
68. Zhu G, Lin JC, Kim SB, et al. Asian expert recommendation on management of skin and mucosal effects of radiation, with or without the addition of cetuximab or chemotherapy, in treatment of head and neck squamous cell carcinoma. *BMC Cancer.* 2016; 16:42.
69. Pinto C, Barone CA, Girolomoni G, et al. Management of Skin Reactions During Cetuximab Treatment in Association With Chemotherapy or Radiotherapy: Update of the Italian Expert Recommendations. *Am J Clin Oncol* 2016; 39:407.
70. Koutcher LD, Wolden S, Lee N. Severe radiation dermatitis in patients with locally advanced head and neck cancer treated with concurrent radiation and cetuximab. *Am J Clin Oncol.* 2009; 32:472.
71. Waghmare CM. Radiation burn—from mechanism to management. *Burns.* 2013; 39:212.
72. Bey E, Prat M, Duhamel P, et al. Emerging therapy for improving wound repair of severe radiation burns using local bone marrow-derived stem cell administrations. *Wound Repair Regen.* 2010; 18:50.
73. Lataillade JJ, Doucet C, Bey E, et al. New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. *Regen Med.* 2007; 2:785.
74. Wolbarst AB, Wiley AL Jr, Nemhauser JB, et al. Medical response to a major radiologic emergency: a primer for medical and public health practitioners. *Radiology.* 2010; 254:660.
75. Burris HA 3rd, Hurtig J. Radiation recall with anti-cancer agents. *Oncologist.* 2010; 15:1227.
76. Kodym E, Kalinska R, Ehringfeld C, et al. Frequency of radiation recall dermatitis in adult cancer patients. *Onkologie.* 2005; 28:18.
77. Boussemart L, Boivin C, Claveau J, et al. Vemurafenib and radiosensitization. *JAMA Dermatol.* 2013; 149:855.
78. Levy A, Hollebecque A, Bourcier C, et al. Targeted therapy-induced radiation recall. *Eur J Cancer.* 2013; 49:1662.



79. Forschner A, Zips D, Schraml C, et al. Radiation recall dermatitis and radiation pneumonitis during treatment with vemurafenib. *Melanoma Res.* 2014; 24:512.
80. Anker CJ, Grossmann KF, Atkins MB, et al. Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG). *Int J Radiat Oncol Biol Phys.* 2016; 95:632.
81. Korman AM, Tyler KH, Kaffenberger BH. Radiation recall dermatitis associated with nivolumab for metastatic malignant melanoma. *Int J Dermatol.* 2017; 56:e75.
82. Rueda RA, Valencia IC, Covelli C, et al. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. *Arch Dermatol.* 1999; 135:804.
83. Bourgeois JF, Gourgou S, Kramar A, et al. A randomized, prospective study using the LPG technique in treating radiation-induced skin fibrosis: clinical and profilometric analysis. *Skin Res Technol.* 2008;14(1):71–6.
84. Delanian S, Balla-Mekias S, Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J Clin Oncol.* 1999;17(10):3283–90.
85. Lefaix JL, Delanian S, Vozenin MC, et al. Striking regression of subcutaneous fibrosis induced by high doses of gamma rays using a combination of pentoxifylline and alpha-tocopherol: an experimental study. *Int J Radiat Oncol Biol Phys.* 1999;43(4):839–47.
86. Lefaix JL, Delanian S, Leplat JJ, et al. Successful treatment of radiation-induced fibrosis using Cu/Zn-SOD and Mn-SOD: an experimental study. *Int J Radiat Oncol Biol Phys.* 1996;35(2):305–12.
87. Tran TN, Hoang MV, Phan QA, et al. Fractional epidermal grafting in combination with laser therapy as a novel approach in treating radiation dermatitis. *Semin Cutan Med Surg.* 2015;34(1):42–7.
88. Delanian S, Baillet F, Huart J, et al. Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: clinical trial. *Radiother Oncol.* 1994;32(1):12–20.
89. Gottlobber P, Steinert M, Bahren W, et al. Interferon-gamma in 5 patients with cutaneous radiation syndrome after radiation therapy. *Int J Radiat Oncol Biol Phys.* 2001;50(1):159–66.
90. Gothard L, Stanton A, MacLaren J, et al. Non-randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema and tissue fibrosis after radiotherapy for early breast cancer. *Radiother Oncol.* 2004;70(3):217–24.
91. Teas J, Cunningham JE, Cone L, et al. Can hyperbaric oxygen therapy reduce breast cancer treatment-related lymphedema? A pilot study. *J Women's Health.* 2004;13(9):1008–18.
92. Pritchard J, Anand P, Broome J, et al. Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiother Oncol.* 2001;58(3):279–86.
93. Carl UM, Feldmeier JJ, Schmitt G, Hartmann KA. Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. *Int J Radiat Oncol Biol Phys.* 2001;49(4):1029–31.
94. Magnusson M, Höglund P, Johansson K, et al. Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: a phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). *Eur J Cancer.* 2009; 45:2488.
95. Jacobson G, Bhatia S, Smith BJ, et al. Randomized trial of pentoxifylline and vitamin E vs standard follow-up after breast irradiation to prevent breast fibrosis, evaluated by tissue compliance meter. *Int J Radiat Oncol Biol Phys.* 2013; 85:604.
96. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol.* 2005; 23:8570.
97. MacarRossi AM, Nehal KS, Lee EH. Radiation-induced Breast Telangiectasias Treated with the Pulsed Dye Laser. *J Clin Aesthet Dermatol.* 2014; 7:34.
98. Santos-Juanes J, Coto-Segura P, Galache Osuna C, et al. Treatment of hyperpigmentation component in chronic radiodermatitis with alexandrite epilator laser. *Br J Dermatol.* 2009; 160:210.