



Bölüm 15

Küçük Hücre Dışı Akciğer Kanseri

Güler YAVAŞ¹

Epidemiyoloji, Risk faktörleri

Akciğer kanseri ülkemizde ve dünyada en sık görülen kanserler arasında olup, her iki cinsiyette de kansere bağlı ölümlerde ilk sırada yer almaktadır. Epidemiyolojik verilere göre 2021 yılında Amerika'da beklenen akciğer kanseri insidansı her iki cinsiyet için toplam 235.760 (erkek: 119.100 ve kadın: 116.660)'tır. Yine Amerika'da 2021 yılında beklenen akciğer kanserine bağlı mortalite her iki cinsiyet için toplam 131.880'dir (erkek: 69.410 ve kadın: 62.470) (1). Türkiye'de akciğer kanseri, Sağlık Bakanlığı 2016 verilerine göre erkeklerde en sık, kadınlarda is beşinci sıklıkta görülen kanser türüdür. Ülkemizde her yıl yaklaşık olarak 30.000 yeni vakanın teşhis edildiği tahmin edilmektedir. Tüm dünyada olduğu gibi ülkemizde de akciğer kanseri, hem erkekler hem de kadınlar arasında kanserden ölümlerin en sık nedenidir ve tüm kanser ölümlerinin neredeyse %25'ini oluşturmaktadır (2).

Akciğer kanserinin risk faktörünü araştıran çalışmaların çoğu gelişmiş ülkelerden yayınlanmaktadır ve bu ülkelerde tütün ve tütün ürünleri kullanımı akciğer kanseri için en önemli risk

faktörüdür. Tüm akciğer kanserlerinin yaklaşık olarak %90'ının sigara kullanımı sonucunda geliştiği tahmin edilmektedir (3). Pasif içicilik de yine önemli bir risk faktörüdür. Tütün ve tütün ürünü kullanımının azaltılmasına yönelik çalışmalar akciğer kanseri insidansını azaltacak gibi görünmektedir. Tütün ve tütün ürünlerine ek olarak asbestos, radon, silika, arsenik, formaldehit, ağır metaller (nikel, kadmiyum, krom), polisiklik aromatik hidrokarbonlar, iyonizan radyasyon ve vinil kloridin de akciğer kanseri için birer risk faktörü oldukları bilinmektedir (4). Akciğer kanserinde genetik faktörlerin de rol oynadığı bilinmektedir.

KHDAK tüm akciğer kanserlerinin yaklaşık %85'ini oluşturmaktadır. En sık görülen histolojik subtipleri adenokarsinom, yassı hücreli ve büyük hücreli karsinomdur. Son yıllarda en sık rastlanan subtip adenokarsinomdur.

Evreleme

Akciğer kanseri tanısı konulduktan sonra tedavi planını ve prognozu belirlemek amacı ile hastalığın evresini belirlemek oldukça önemlidir. Küçük

¹ Prof. Dr. Güler YAVAŞ, Başkent Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi AD., guler.aydinyavas@gmail.com

KHDAK için de kardiyak toksisitenin önemli akılda bulundurulmalı ve doz sınırlamalarına özen gösterilmelidir. RTOG 0617 çalışması akciğer kanserinde kardiyak toksisitenin önemini gösteren önemli çalışmalardan biridir. Bu çalışmada yüksek doz grubundaki düşük sağ kalımların (28.7 vs. 20.3 ay) bir nedenin de kardiyak toksite olabileceği vurgulanmış ve 3-boyutlu konformal RT yerine YART gibi daha teknolojik tedavilerin kullanılması gerektiği vurgulanmıştır(47, 48).

Özellikle SVRT uygulamalarında RT'ye bağlı göğüs duvarı ağrısı ve kosta kırıkları gözlemlenebilir. Bu nedenle SVRT uygulamalarında göğüs duvarı kritik bir organ olarak kontrolmalıdır ve doz sınırlamalarına özen gösterilmelidir. Yine treakea ve ana bronşlarda radyasyona bağlı fibrozis ve nekroza bağlı hemoptizi, darlıklar, fistüller, perforasyon ve artmış enfeksiyon riski görülebilir. Özellikle santral yerleşimli tümörlerde SVRT uygulamalarında bu riskler dikkate alınmalı ve uzun fraksinizasyonlu şemalar tercih edilmelidir.

Kaynaklar

1. Siegel RL, Miller KD, Fuchs HE ve ark. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021 Jan;71(1):7-33.
2. Şencan İ, Keskinlik B (eds). Türkiye Kanser İstatistikleri. T.C. Sağlık Bakanlığı, Türkiye Halk Sağlığı Kurumu, 2015, Ankara.
3. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest* 2003; 123:21S.
4. Coultas DB, Samet JM. Occupational lung cancer. *Clin Chest Med* 1992; 13:341.
5. Goldstraw P, Chansky K, Crowley J ve ark. The IAS-LC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016; 11:39.
6. Paesmans M, Garcia C, Wong CY ve ark. Primary tumour standardised uptake value is prognostic in nonsmall cell lung cancer: a multivariate pooled analysis of individual data. *Eur Respir J* 2015; 46:1751.
7. Nestle U, De Ruyscher D, Ricardi U ve ark. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. *Radiother Oncol.* 2018 Apr;127(1):1-5.
8. Rivera MP, Mehta AC, Wahidi MW. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013 May;143(5 Suppl):e142S-e165S.
9. Bovio S, Cataldi A, Reimondo G ve ark. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J Endocrinol Invest* 2006; 29:298.
10. Groome PA, Bolejack V, Crowley JJ ve ark. The IAS-LC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2007; 2:694.
11. Pisters KM, Evans WK, Azzoli CG ve ark. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non-small-cell lung cancer guideline. *Journal of Clin Oncol* 2007;25(34):5506.
12. Pignon JP, Tribodet H, Scagliotti GV ve ark. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008;26(21):3552.
13. Wu YL, Tsuboi M, He J ve ark. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med.* 2020;383(18):1711.
14. Wang EH, Corso CD, Rutter CE ve ark. Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2015;33(25):2727.
15. Buderer SI, Shackcloth M, Woolley S. Does induction chemoradiotherapy increase survival in patients with Pancoast tumour? *Interact Cardiovasc Thorac Surg.* 2016 Nov;23(5):821-825.
16. Selek U, Chang JY. Optimal sequencing of postoperative radiotherapy and chemotherapy in IIIA-N2 non-small cell lung cancer. *J Thorac Dis* 2016 Jul;8(7):1394-7.
17. Le Pechoux C, Pourel N, Barlesi F ve ark. An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-

- 0503, UK NCRI, SAKK) NCT00410683. *Ann Oncol* 2020;31S:ESMO #LBA3_PR.
18. Albain KS, Swann RS, Rusch V ve ark. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009; 374:379.
 19. Antonia SJ, Villegas A, Daniel D ve ark. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342.
 20. Antonia SJ, Villegas A, Daniel D ve ark. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919.
 21. Faivre-Finn C, Vicente D, Kurata T, ve ark. Durvalumab after chemoradiotherapy in stage III NSCLC: 4-year survival update from the phase III PACIFIC trial. *Ann Oncol* 2020; 31S: ESMO #LBA49.
 22. Hanna N, Johnson D, Temin S ve ark. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017;35:3484-3515.
 23. Gomez DR, Tang C, Zhang J ve ark. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol*. 2019 Jun 20;37(18):1558-156.
 24. Palma DA, Olson RA, Harrow S ve ark. Stereotactic ablative radiotherapy versus standard-of-care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomized, phase II, open-label trial. *Lancet*. 2019;393(10185):2051–8.
 25. Sibley GS. Radiotherapy for patients with medically inoperable stage I nonsmall cell lung carcinoma smaller volumes and higher doses – a review. *Cancer* 1998;82:433–8.
 26. Jeremic B, Classen J, Bamberg M. Radiotherapy alone in technically operable medically inoperable, early-stage (I/ II) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:119–30.
 27. Ou SH, Zell JA, Ziogas A ve ark. Prognostic factors for survival of stage I nonsmall cell lung cancer patients : a populationbased analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. *Cancer*. 2007 Oct. 1;110(7):1532-41.
 28. Fowler JF, Tomé WA, Fenwick JD ve ark. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004;60:1241–56.
 29. Bradley JD, leumwananonthachai N, Purdy JA, ve ark. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2002;52:49–57.
 30. Kong FM, Ten Haken RK, Schipper MJ, ve ark. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324–33.
 31. Onishi H, Araki T, Shirato H ve ark. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004; 101:1623–1631.
 32. Timmerman R, Paulus R, Galvin J ve ark. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA*. 2010 Mar 17;303(11):1070-6.
 33. Nyman J, Hallqvist A, Lund JÅ ve ark. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016; 121:1.
 34. Senti S, Lagerwaard FJ, Haasbeek CJ ve ark. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; 13:802.
 35. Hobbs CJ, Ko SJ, Paryani NN ve ark. Stereotactic Body Radiotherapy for Medically Inoperable Stage I-II Non-Small Cell Lung Cancer: The Mayo Clinic Experience. *Mayo Clin Proc Innov Qual Outcomes* 2018; 2:40.
 36. Chang JY, Senan S, Paul MA ve ark. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; 16:630.
 37. Rusch VW, Giroux DJ, Kraut MJ, ve ark. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg* 2001; 121:472.
 38. Rusch VW, Giroux DJ, Kraut MJ, ve ark. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol* 2007; 25:313.
 39. Kunitoh H, Kato H, Tsuboi M, ve ark. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical On-

- cology Group trial 9806. *J Clin Oncol* 2008; 26:644.
40. Pourel N, Santelmo N, Naafa N, ve ark. Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response. *Eur J Cardiothorac Surg* 2008; 33:829.
 41. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998; 352:257.
 42. Douillard JY, Rosell R, De Lena M, ve ark. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006; 7:719.
 43. Lally BE, Zelterman D, Colasanto JM ve ark. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2006 Jul 1;24(19):2998-3006.
 44. Jumeau R, Vilotte , Durham AD ve ark. Current landscape of palliative radiotherapy for non-small-cell lung cancer. *Transl Lung Cancer Res*. 2019 Sep; 8(Suppl 2): S192–S201.
 45. Fairchild A, Harris K, Barnes E, ve ark. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol* 2008;26:4001-11.
 46. Socinski MA, Blackstock AW, Bogart JA, ve ark. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008; 26: 2457–63.
 47. Bradley JD, Bae K, Graham MV ve ark. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010 May 10;28(14):2475-80.
 48. Bradley JD, Paulus R, Komak R ve ark. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015 Feb; 16(2): 187–199.
 49. Bradley JD, Hu C, Komak R ve ark. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2020 Mar 1;38(7):706-714.
 50. Kong FM, Ritter T, Quint DJ, ve ark. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys* 2011;81:1442–57.
 51. De Ruyscher D, Faivre-Finn C, Moeller D ve ark. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol*. 2017 Jul;124(1):1-10.
 52. NCCN guideline. Non-small cell lung cancer. Version 3.2021. Available: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
 53. Guckenberger M, Andratschke N, Dieckmann K ve ark. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. *Radiother Oncol*. 2017 Jul;124(1):11-17.
 54. Jing X, Meng X, Sun X ve ark. Delineation of clinical target volume for postoperative radiotherapy in stage IIIA-pN2 non-small-cell lung cancer. *Onco Targets Ther*. 2016 Feb 19;9:823-31.
 55. Spoelstra FO, Senan S, Le Pechoux C ve ark. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. *Int J Radiat Oncol Biol Phys*. 2010;76(4):1106–1113.
 56. Hanania AN, Mainwaring W, Ghebre YT ve ark. Radiation-induced lung injury: assessment and management. *Chest*. 2019;156(1):150–62.
 57. Bar-Ad V, Ohri N, Werner-Wasik M. Esophagitis, treatment-related toxicity in non-small cell lung cancer. *Rev Recent Clin Trials*. 2012;7(1):31–5.