Bölüm
24

PRİMER GASTROİNTESTİNAL DIŞI NÖROENDOKRİN TÜMÖRLERDE MEDİKAL YAKLAŞIM

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GİRİŞ

Nöroendokrin tümörler(NET) vücudun çeşitli yerlerine dağılmış endokrin ve nörolojik fonksiyonları olan dokulardan kaynaklanan neoplazilerdir. Nöroendokrin tümörler biyolojik davranış, histolojik görünüm ve tedaviye yanıt açısından farklılıklar gösteren heterojen bir tümör grubudur. Bu neoplazilerin çeşitli tipleri, yavaş/hızlı büyüme özelliği ve hormonların veya vazoaktif maddelerin sık salgılanmasıyla karakterizedir. NET'ler nadir görülen neoplaziler olup insidansı 100.000 kişide 2,5 ila 5 vaka arasında değişmektedir. Son yıllarda görüntüleme tekniklerinin gelişmesiyle insidansı artmaktadır. Vücudun herhangi bir yerinden oluşabilirler ancak en sık gastrointestinal sistemden kaynaklanırlar. NET'in diğer en sık görüldüğü yer bronşial kaynaklı tümörler olup ayrıca timus, adrenal bez, tiroid, cilt ve ürogenital gibi yerlerden de kaynaklanabilir. Hastaların yaklaşık % 15'inde ise primer organ tutulumu belirlenememektedir. Hastaların yaklaşık % 30 ila% 40'ında hastalık süresince vazomotor değişiklikler (kızarıklık ve hipotansiyon), ishal ve bronkospazm atakları gibi karsinoid sendromun özellikleri ile ortaya çıkar. NET'ler multipl endokrin neoplazi (MEN) tip-1 ve tip-2 sendromunun bir bileşeni olarak ortaya çıkabilirler. Günümüzde standart görüntülemeler dışında NET'lerin fonksiyonel açıdan değerlendirilmesi için moleküler görüntüleme metotlarına ihtiyaç duyulmaktadır. Bu amaçla radyoaktif işaretli somatostatin analogları ile somatostatin reseptör görüntüleme yöntemleri sıklıkla kullanılmaktadır. NET'lerde cerrahi rezeksiyon yanı sıra sistemik kemoterapiler, radyoterapi, uzun etkili somatostatin analogları, hedefe yönelik tedaviler ve radyonükleotid tedavi gibi tedavi seçenekleri mevcuttur. Bu bölümde gastrointestinal dışı tü-

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gittikçe önemi artmaktadır. Özellikle TKİ'ler(kabazantinib,vandetanib) ile yapılan çalışmalarda medüller tiroid karsinomunda sağ kalımı önemli ölçüde artırdığı kanıtlanmıştır. Son dönemlerde NET'lerde radyonükleotid tedavilere olan ilgi arttı ve giderek artan bir şekilde tedavide yer almaya başladı. Birden fazla tedavi seçeneği bulunan bu tümör grubunda her seçeneğin tartışılması için tümör konseylerine sunulmalı ve tedaviler bireyselleştirmelidir. Moleküler genetik çalışmaların ilerlemesi ile NET'lerde yeni tedavi hedefleri belirlenecektir.

KAYNAKLAR

1. Galvan JA, Astudillo A, Vallina A, et al. Prognosticanddiagnosticvalue of epithelial to mesenchymal transition markers in pulmonary neuroendocrine tumors. BMC Cancer 2014;14:855.
2. Fasano M, Corte CMD, Papaccio F, et al. Pulmonary large cell neuroendocrine carcinoma From epidemiology to therapy. J ThorOncol 2015;10:1133-41.
3. Skuladottir H, Hirsch FR, Hansen HH, et al. Pulmonary neuroendocrine tumors: incidence and prognosis of histological subtypes. A population-basedstudy in Denmark. LungCancer. 2002;37(2):127–135.
4. Cooper WA, Thourani VH, Gal AA, et al. The surgical spectrum of pulmonary neuroendocrine neoplasms. Chest. 2001;119(1):14–18.
5. Granberg D, Eriksson B, Wilander E, et al. Experience in treatment of metastatic pulmonary carcinoid tumors. AnnOncol. 2001;12(10):1383–1391. doi: 10.1023/A:1012569909313. [PubMed] [CrossRef] [Google Scholar]
6. Crona J, Fanola I, Lindholm DP, et al. Effect of temozolomide in patients with metastatic bronchial carcinoids. Neuroendocrinology. 2013;98(2):151–155. doi: 10.1159/000354760. [PubMed] [CrossRef] [Google Scholar]
7. Mills S.E., Cooper P.H., Walker A.N., et al. Atypicalcarcinoidtumor of thelung. A clinicopathologicstudy of 17 cases. Am J SurgPathol 1982; 6: pp. 643-654 ViewInArticle | Cross Ref
8. National Comprehensive Cancer Network NCCN. Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. 2019. Available online: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf [PubMed]
9. Fernandez FG, Battafarano RJ. Large cell neuroendocrine carcinoma of the lung. Cancer Control 2006;13:270-5.
10. Takei H, Asamura H, Maeshima A, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 2002;124:285-92.
11. Varlotto JM, Medford-Davis LN, Recht A, et al. Should large cell neuroendocrine lung carcinoma be classified and treated as a small cell lung cancer or with other large cell carcinomas? J Thorac Oncol. 2011;6(6):1050–1058.
12. Korse CM, Taal BG, van Velthuysen ML, et al. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer. 2013;49(8):1975–1983.
13. Gu J, Gong D, Wang Y, et al. The demographic and treatment options for patients with large cell neuroendocrine carcinoma of the lung. Cancer Medicine. 2019 May 14; 8(6): 2979-2993.
14. Matsuura N, Nakashima N, Igai H, et al. Prognosis of surgically treated large cell neuroendocrine carcinoma. KyobuGeka. 2011;64:187-190. [PubMed] [Google Scholar]
15. Iyoda A, Hiroshima K, Moriya Y, et al. Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. Ann Thorac Surg. 2006;82(5):1802–1807.

16. Iyoda A, Hiroshima K, Moriya Y, et al. Postoperative recurrence and the role of adjuvant chemotherapy in patients with pulmonary large-cell neuroendocrine carcinoma. J Thorac Cardiovasc Surg. 2009;138(2):446–453
17. Derks JL, Suylen RJV, Thunnissen E, et al. Chemotherapy for pulmonary large cell neuroendocrine carcinomas: does the regimen matter? Eur Respir J 2017;49(6). pii: 1601838. doi: 10.1183/13993003.01838-2016.
18. Rossi A, Di Maio M, Chiodini P et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. J Clin Oncol2012;30:1692–1698. [PubMed] [Google Scholar]
19. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018; 379:2220.
20. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-72. 10.1200/JCO.2007.15.4377 [PubMed] [CrossRef] [Google Scholar]
21. Wick MR, Carney JA, Bernatz PE, et al. Primary mediastinal carcinoid tumors. Am J Surg Pathol1982;6:195-205. 10.1097/00000478-198204000-00001 [PubMed] [CrossRef] [Google Scholar]
22. Chaer R, Massad MG, Evans A, et al. Primary neuroendocrine tumors of the thymus. Ann Thorac Surg 2002; 74:1733.
23. Dusmet ME, McKneally MF. Pulmonary and thymic carcinoid tumors. World J Surg 1996;20:189-95. 10.1007/s002689900029 [PubMed] [CrossRef] [Google Scholar]
24. Phan AT, Oberg K, Choi J, et al. North American Neuroendocrine Tumor Society (NANETS): NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the thorax (includes lung and thymus). Pancreas 2010;39:784-98. 10.1097/MPA.0b013e3181ec1380 [PubMed] [CrossRef] [Google Scholar]
25. Travis WD, Brambilla E, Burke AP, et al. WHO classification of tumours of the lung, pleura, thymus and heart, Fourth edition. France: International Agency for Research on Cancer 2015;234-42. [Google Scholar]
26. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg 2007;134:1477-83. 10.1016/j.jtcvs.2007.07.049 [PubMed] [CrossRef] [Google Scholar]
27. Huang J, Riely GJ, Rosenzweig KE, et al. Multimodality therapy for locally advanced thymomas: state of the art or investigational therapy? Ann Thorac Surg 2008;85:365-7. 10.1016/j.athoracsur.2007.10.098 [PubMed] [CrossRef] [Google Scholar]
28. Asbun HJ, Calabria RP, Calmes S, et al. Thymic carcinoid. Am Surg 1991; 57:442.
29. Filosso PL, Actis Dato GM, Ruffini E, et al. Multidisciplinary treatment of advanced thymic neuroendocrine carcinoma (carcinoid): report of a successful case and review of the literature. J Thorac Cardiovasc Surg. 2004;127(4):1215–1219.
30. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg. 2010;251(6):1117–1121.
31. Öberg K, Hellman P, Ferolla P, Papotti M. ESMO Guidelines Working Group. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(suppl 7):vii120–vii123.
32. Chaer R, Massad MG, Evans A, et al. Primary neuroendocrine tumors of the thymus. Ann Thorac Surg. 2002;74(5):1733– 1740.
33. Marsh DJ Clinical characteristics, treatment, prognostic factors and a comparison of staging systems. Cancer 2000; 88(5): 1139-48., Learoyd DL, Robinson BG. MedullaryThyroidCarcinoma: Recentadvancesandmanagementupdate. Thyroid 1995; 5(5): 407-24.
34. Kebebew E, Ituarte PH, Siperstein AE, et al. Medullarythyroidcarcinoma:
35. Machens A, Schneyer U, Holzhausen HJ et al. Prospects of remission in medullary Thyroid carcinoma according to basal calcitonin level. J ClinEndocrinolMetab 2005; 90: 2029–2034.

36. American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, Evans DB et al. Medullary Thyroid cancer: management guidelines of theAmerican Thyroid Association. Thyroid 2009; 19: 565–612.
37. Thyroid cancer: ESMO ClinicalPracticeGuidelinesPublished in 2012 – AnnOncol 2012; 23 (Suppl 7): vii110-vii119. Authors: *F. Pacini, M. G. Castagna, L. Brilli, et al.*
38. Petursson SR. 1988. Metastatic medullary thyroid carcinoma. Complete response to combination chemotherapy with dacarbazine and 5-fluorouracil. Cancer 62:1899–1903 [PubMed] [Google Scholar]
39. Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma: The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma Thyroid. 2015 Jun 1; 25(6)567
40. Capp C, Wajner SM, Siqueira DR, et al. 2010. Increased expression of vascular endothelial growth factor and its receptors, VEGFR-1 and VEGFR-2, in medullary thyroid carcinoma. Thyroid 20:863–871 [PubMed] [Google Scholar]
41. SA Wells Jr, BG Robinson, RF Gagel, et al: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial J Clin Oncol 30: 134– 141,2012 Link, Google Scholar
42. R Elisei, MJ Schlumberger, SP Müller , etal: Cabozantinib in progressive medullary thyroid cancer J Clin Oncol 31: 3639– 3646,2013 Link, Google Scholar
43. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004; 64:7099.
44. Kober F, Hermann M, İşleyici A, et al. Semptomatik metastatik medüller tiroid kanserinde sorafenibin etkisi. J Clin Oncol 2007; 25: 14.065.
45. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res 2010; 16:5260.
46. Schlumberger M, Jarzab B, Cabanillas ME, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. Clin Cancer Res 2016; 22:44.
47. Martucci, V.L, Pacak, K. Pheochromocytoma and paraganglioma: Diagnosis, genetics, management, and treatment. Curr. Probl. Cancer 2014, 38, 7–41. [Google Scholar] [CrossRef] [PubMed]
48. Pacak, K. Preoperative management of the pheochromocytoma patient. J. Clin. Endocrinol. Metab. 2007, 92, 4069–4079. [Google Scholar] [CrossRef] [PubMed]
49. Eisenhofer, G, Peitzsch, M. Laboratory evaluation of pheochromocytoma and paraganglioma. Clin. Chem. 2014, 60, 1486–1499. [Google Scholar] [CrossRef] [PubMed]
50. Andersen KF, Altaf R, Krarup-Hansen A, et al. Malignant pheochromocytomas and paragangliomas - the importance of a multidisciplinary approach. Cancer Treat Rev 2011; 37:111.
51. Noda T, Nagano H, Miyamoto A, et al. Successful outcome after resection of liver metastasis arising from an extraadrenal retroperitoneal paraganglioma that appeared 9 years after surgical excision of the primary lesion. Int J Clin Oncol 2009; 14:473.
52. Strajina V, Dy BM, Farley DR, et al. Surgical Treatment of Malignant Pheochromocytoma and Paraganglioma: Retrospective Case Series. Ann Surg Oncol 2017; 24:1546.
53. Young WF, Nieman LK, Martin KA. Clinical presentation and diagnosis of pheochromocytoma. UpToDate; [cited 2015 Jul]. Available from: http://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-pheochromocytoma.
54. 54- Erickson D, Kudva YC, Ebersold MJ, et al. Benign paragangliomas: Clinical presentation and treatment outcomes in 236 patients. J Clin Endocrinol Metab. 2001;86(11):5210–16.[PubMed] [CrossRef]

55. Gonias S, Goldsby R, Matthay KK, et al. Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. J Clin Oncol 2009; 27:4162.
56. Niemeijer ND, Alblas G, van Hulsteijn LT, et al. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. Clin Endocrinol (2014) 81:642–51.10.1111/cen.12542 [PubMed] [CrossRef] [Google Scholar]
57. Tenenbaum F, Schlumberger M, Lumbroso J, et al. Beneficial effects of octreotide in a patient with a metastatic paraganglioma. Eur J Cancer 1996; 32A:737.
58. Kau R, Arnold W. Somatostatin receptor scintigraphy and therapy of neuroendocrine (APUD) tumors of the head and neck. Acta Otolaryngol 1996; 116:345.
59. Koriyama N, Kakei M, Yaekura K, et al. Control of catecholamine release and blood pressure with octreotide in a patient with pheochromocytoma: a case report with in vitro studies. Horm Res 2000; 53:46.
60. Santarpia L, Habra MA, Jimenez C. Malignant pheochromocytomas and paragangliomas: molecular signaling pathways and emerging therapies. Horm Metab Res (2009) 41:680–6.10.1055/s-0029-1214381 [PubMed] [CrossRef] [Google Scholar]
61. Ayala-Ramirez M, Chougnet CN, Habra MA, et al.Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. J Clin Endocrinol Metab (2012) 97:4040–50.10.1210/jc.2012-2356 [PMC free article][PubMed] [CrossRef] [Google Scholar]
62. Drasin H. Treatment of malignant pheochromocytoma. West J Med 1978; 128:106.
63. Fishbein L, Bonner L, Torigian DA, et al. External beam radiation therapy (EBRT) for patients with malignant pheochromocytoma and non-head and -neck paraganglioma: combination with 131I-MIBG. Horm Metab Res 2012; 44:405.
64. Teno S, Tanabe A, Nomura K, et al. Acutely exacerbated hypertension and increased inflammatory signs due to radiation treatment for metastatic pheochromocytoma. Endocr J 1996; 43:511.
65. McBride JF, Atwell TD, Charboneau WJ, et al. Minimally invasive treatment of metastatic pheochromocytoma and paraganglioma: efficacy and safety of radiofrequency ablation and cryoablation therapy. J Vasc Interv Radiol 2011; 22:1263.
66. Cozzi PJ, Englund R, Morris DL. Cryotherapy treatment of patients with hepatic metastases from neuroendocrine tumors. Cancer 1995; 76:501.
67. Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. Semin Oncol 2009; 36:52.
68. Moertel CG. Karnofskymemoriallecture. An odyssey in theland of small tumors. J ClinOncol 1987; 5:1502.
69. Yao JC, Buzzoni R, Carnaghi C, et al. Baseline demographics of the randomized, placebo-controlled, double-blind, phase III RADIANT-4 study of everolimus in nonfunctional gastrointestinal (GI) or lung neuroendocrine tumors (NET) (abstr) J Clinoncol 33, 2015 (suppl 3; abstr 276). Abstract Available online at http://meetinglibrary.asco.org/content/140092-158 (Accessed on September 04, 2015).
70. Yao JC, et al. Everolimus in advanced nonfunctional neuroendocrine tumors of lung or gastrointestinal origin: efficacyandsafetyresultsfromtheplacebo-controlleddouble-blindedmulticenter, phase III RADIANT-4 study. Data presented at 2015 European Cancer Congress, Vienna Austria (LBA 5) September 27. 2015. Abstract Available online at http://www.europeancancercongress.org/Scientific-Programme/Searchable-Programme#anchorScpr (Accessed on September 30, 2015).
71. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: Progression-freesurvival, radiographicresponse, and preliminary overall survival results in patients with midgut neuroen-

docrine tumors treated with 177-Lu-Dotatate (abstract). J ClinOncol 34, 2016 (suppl 4S; abstr 194). http://meetinglibrary.asco.org/content/160126-173 (Accessed on February 03, 2016).

72. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012; 95:157.
73. Hainsworth JD, Spigel DR, Litchy S, at al. Phase II trial of paclitaxel, carboplatin, andetoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J ClinOncol 2006; 24:3548.