

## Bölüm 13

# NÖROENDOKRİN TÜMÖRLER VE NÜKLEER TIP

Burçak YILMAZ<sup>14</sup>

### GİRİŞ

Nöroendokrin tümörler (NET) vücudumuzda dağınık yerleşimli nöroendokrin hücrelerden kaynaklanan ve oldukça nadir görülen tümörlerdir (1). ‘Nöroendokrin’ terimi bu hücrelerin nörohormon, nörotransmitter veya nöromodülatör sentezlemesi, depolaması ve salgılamasını ifade etmektedir (2). Nöroendokrin sistem üç ana bölümden oluşmaktadır: (i) Santral veya periferel sinir sistemindeki nöronlar, (ii) Epitelial endokrin hücreler (Gastrointestinal ve solunum sisteminde, tiroid glandında, timusta, deride, meme dokusunda, larenks, böbrek, mesane, prostat glandı ve pankreasta yerleşimli), (iii) hipofiz bezi, paratiroid glandı ve sürrenal glandlar gibi endokrin organlar (3). Nöroendokrin hücreler özelliklerine göre gastrin, insulin, serotonin, glukagon, pankreatik polipeptid, prolaktin, TSH ve hatta FSH gibi pek çok spesifik hormon salgılamaktadır. NET hücrelerinden özel ve genel belirteçler salgılabilmektedir. Nöron spesifik enolaz (NSE), kromogranin ve sinaptofizin genel belirteçlere örnek olup hemen tüm nöroendokrin hücrelerde bulunmaktadır. Tümör hücreleri tarafından üretilen amin veya hormonlar da özel belirteçlerdir ve bu hastalarda görülebilen paraneoplastik sendromlardan sorumludurlar (4).

NET insidansı yıllık yaklaşık 1-2 vaka/100000 olarak bildirilmektedir. NET’ler çoğunlukla sporadik görülür fakat nadiren multipl endokrin neoplazi tip 1 ve tip 2 (MEN1 ve MEN2) gibi herediter sendromlarla da görülebirlirler. En sık görülen grup solunum sistemi kaynaklı NET’ler ve bunlar arasında da küçük hücreli akciğer kanseri (KHAK)’ dir. Bu grubu gastrointestinal sistem ve sonrasında da diğer sistemler takip etmektedir. NET’ler hormonal sekresyon durumuna göre fonksiyone ve non-fonksiyone olarak gruplandırılmaktadır (1).

<sup>14</sup> Uzm. Dr., Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi, Nükleer Tıp Kliniği, İstanbul, Türkiye; drburcak@gmail.com

sintigrafisi pozitif metastatik NET'li hastalarda da I-131 MIBG tedavi seçeneği akılda tutulmalıdır. Bunlar dışında NET'lerin karaciğer metastazlarında lokal tedavi seçeneği olan TARE de önemli bir güncel tedavi seçeneğidir.

## KAYNAKLAR

1. Bodei L, Boni G, Paganelli G, Volterrani D. (2013). Neuroendocrine Tumors. Strauss HW, Mariani G, Volterrani D, Larson SM (Eds.), *Nuclear Oncology* (pp.491-520). London: Springer.
2. Langley K. The neuroendocrine concept today. *Ann N Y Acad Sci.* 1994;733:1-17.
3. Polak JM, Bloom SR. The diffuse neuroendocrine system. Studies of this newly discovered controlling system in health and disease. *J Histochem Cytochem.* 1979;27:1398-400.
4. Day R, Salzet M. The neuroendocrine phenotype, cellular plasticity, and the search for genetic switches: redefining the diffuse neuroendocrine system. *Neuro Endocrinol Lett.* 2002;23:447-51
5. DeLellis R, Lloyd R, Heitz P, et al. (2004). World Health Organization classification of tumours, pathology and genetics of tumours of endocrine organs. Lyon: IARC Press.
6. Rindi G. The ENETs guidelines: the new TNM classification system. *Tumori.* 2010;96:806-9.
7. Kloppel G, Couvelard A, Perren A, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology.* 2009;90:162-6.
8. Turner GB, Johnston BT, McCance DR, et al. Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut.* 2006;55:1586-91.
9. Giovanella L, Ceriani L, Lumastro C, et al. False-positive serum chromogranin A assay due to heterophile antibody interference. *Clin Chim Acta.* 2007;379:171-2.
10. Grossman A, Pacak K, Sawka A, et al. Biochemical diagnosis and localization of pheochromocytoma: can we reach a consensus? *Ann N Y Acad Sci.* 2006;1073:332-47.
11. Ozkan E, Soydal Ç. Theranostics in Neuroendocrine Tumors. *Nükleer Tıp Sem.* 2015;2:103-8
12. Panagiotidis E, Alshammari A, Michopoulou S, et al. Comparison of the Impact of 68Ga-DOTATATE and 18F-FDG PET/CT on Clinical Management in Patients with Neuroendocrine Tumors. *J Nucl Med.* 2017;58:91-96.
13. Wong F, Kim E. (2001). Peptide receptor imaging. Kim E, Yang D (Eds.), *Targeted molecular imaging in oncology* (pp. 102-10). New York: Springer.
14. Buchmann I, Henze M, Engelbrecht S, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2007;34:1617-26
15. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging.* 2007;34:982-93
16. Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: somatostatin receptor imaging with 111In-pentetreotide. *Neuroendocrinology.* 2009;90:184-9.
17. Schillaci O, Spanu A, Scopinaro F, et al. Somatostatin receptor scintigraphy in liver metastasis detection from gastroenteropancreatic neuroendocrine tumors. *J Nucl Med.* 2003;44:359-68.
18. Perri M, Erba P, Volterrani D, et al. Octreo-SPECT/CT imaging for accurate detection and localization of suspected neuroendocrine tumors. *Q J Nucl Med Mol Imaging.* 2008;52:323-33.
19. Krenning EP, Kooij PP, Bakker WH, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. *Ann N Y Acad Sci.* 1994;733:496-506.

20. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2013;40:800-816.
21. Reubi JC, Schar JC, Waser B, et al. Afinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotacers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med* 2000;27:273-282.
22. Viola KV, Sosa JA. Current advances in the diagnosis and treatment of pancreatic endocrine tumors. *Curr Opin Oncol*. 2005;17:24-7.
23. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The role of 68Ga-DOTATATE PET/CT in suspected neuroendocrine tumors. *J Nucl Med* 2012;53:1686-1692.
24. Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med* 2010;51:669-673.
25. Baum RP, Kulkarni HR. Theranostic: From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radionuclide therapy-The Bad Berka experience. *Theranostic* 2012;5:437-447.
26. Gabriel M, Deristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3- octreotide PET in neuroendocrine tumors : comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med* 2007;48:508-518
27. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med*. 2009;50:1214-21.
28. Kwekkeboom DJ, Kam BL, van Essen M, et al. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2010;17:R53-73.
29. Ambrosini V, Tomassetti P, Castellucci P, et al. Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. *Eur J Nucl Med Mol Imaging*. 2008;35:1431-8.
30. Haug A, Auernhammer CJ, Wangler B, et al. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2009;36:765-70.
31. Garin E, Le Jeune F, Devillers A, et al. Predictive value of 18F FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. *J Nucl Med*. 2009;50:858-64.
32. Tsagarakis S, Christoforaki M, Giannopoulou H, et al. A reappraisal of the utility of somatostatin receptor scintigraphy in patients with ectopic adrenocorticotropin Cushing's syndrome. *J Clin Endocrinol Metab*. 2003;88:4754-8.
33. Rodriguez JA, Meyers MO, Jacome TH, et al. Intraoperative detection of a bronchial carcinoid with a radiolabeled somatostatin analog. *Chest*. 2002;121:985-8
34. Chong S, Lee KS, Chung MJ, et al. Neuroendocrine tumors of the lung: clinical, pathologic, and imaging findings. *Radiographics*. 2006;26:41-57. discussion 57-8.
35. Pandit N, Gonen M, Krug L, et al. Prognostic value of [18F]FDGPET imaging in small cell lung cancer. *Eur J Nucl Med Mol Imaging*. 2003;30:78-84.
36. Cecchin D, Lumachi F, Marzola MC, et al. A meta-iodobenzylguanidine scintigraphic scoring system increases accuracy in the diagnostic management of pheochromocytoma. *Endocr Relat Cancer*. 2006;13:525-33
37. Guller U, Turek J, Eubanks S, et al. Detecting pheochromocytoma: de fi ning the most sensitive test. *Ann Surg*. 2006;243: 102-7.
38. Giammarile F, Chiti A, Lassmann M, et al. EANM. EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy. *Eur J Nucl Med Mol Imaging*. 2008;35:1039-47.
39. Bhatia KS, Ismail MM, Sahdev A, et al. 123I-metaiodobenzylguanidine (MIBG) scintigraphy for the detection of adrenal and extraadrenal phaeochromocytomas: CT and MRI correlation. *Clin Endocrinol*. 2008;69:181-8

40. Rozovsky K, Koplewitz BZ, Krausz Y, et al. Added value of SPECT/CT for correlation of MIBG scintigraphy and diagnostic CT in neuroblastoma and pheochromocytoma. *AJR Am J Roentgenol.* 2008;190:1085–90.
41. Ilias I, Chen CC, Carrasquillo JA, et al. Comparison of 6-18F- fl uorodopamine PET with 123I-metaiodobenzylguanidine and 111In-pentetreotide scintigraphy in localization of non-metastatic and metastatic pheochromocytoma. *J Nucl Med.* 2008;49:1613–9.
42. Modlin IM, Latich I, Kidd M, et al. Therapeutic options for gastrointestinal carcinoids. *Clin Gastroenterol Hepatol.* 2006;4:526–47.
43. O’Toole D, Hentic O, Corcos O, et al. Chemotherapy for gastroenteropancreatic endocrine tumours. *Neuroendocrinology.*2004;80 Suppl 1:79–84.
44. Reubi JC, Schar JC, Waser B, et al. Af fi nity pro fi les for human somatostatin receptor subtypes SST1–SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med.* 2000;27:273–82.
45. Hofland LJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocr Rev.* 2003;24:28–47.
46. Bozkurt MF, Özcan Z. The Evolving Role of Nuclear Medicine and Molecular Imaging: Theragnostics and Personalized Therapeutic Applications. *Mol Imaging Radionucl Ther.* 2018;27:1-2.
47. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol.* 2008;31:271–9.
48. Tomozawa Y, Jahangiri Y, Pathak P, et al. Long-Term Toxicity after Transarterial Radioembolization with Yttrium-90 Using Resin Microspheres for Neuroendocrine Tumor Liver Metastases. *J Vasc Interv Radiol.* 2018;29:858-865.
49. Gray JA, Roth BL. Cell biology. A last GASP for GPCRs? *Science.* 2002;297:529–31.
50. Jamar F, Barone R, Mathieu I, et al. 86Y-DOTA0-D-Phe1-Tyr3- octreotide (SMT487)—a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *Eur J Nucl Med Mol Imaging.* 2003;30:510–8.
51. Valkema R, Pauwels SA, Kvols LK, et al. Long-term follow-up of renal function after peptide receptor radiation therapy with 90 Y-DOTA 0 , Tyr 3 -octreotide and 177 Lu-DOTA 0 , Tyr 3 -octreotate. *J Nucl Med.* 2005;46:83–91.
52. Brans B, Bodei L, Giammarile F, et al. Clinical radionuclide therapy dosimetry: the quest for the “Holy Gray”. *Eur J Nucl Med ol Imaging.* 2007;34:772–86.
53. Bodei L, Cremonesi M, Zoboli S, et al. Receptor-mediated radionuclide therapy with 90Y-DO-TATOC in association with amino acid infusion: a phase I study. *Eur J Nucl Med Mol Imaging.* 2003;30:207–16.
54. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med.* 2006;36:147–56.
55. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA0, Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol.* 2008;26:2124–30.
56. Gosewisch A, Delker A, Tattenberg S, et al. Patient-specific image-based bone marrow dosimetry in Lu-177-[DOTA(0),Tyr(3)]-Octreotate and Lu-177-DKFZ-PSMA-617 therapy: investigation of a new hybrid image approach. *EJNMMI Res.* 2018;3;8:76.
57. Cremonesi M, Botta F, Di Dia A, et al. Dosimetry for treatment with radiolabelled somatostatin analogues. A review. *Q J Nucl Med Mol Imaging.* 2010;54:37–51.
58. Van Essen M, Krenning EP, De Jong M, et al. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. *Acta Oncol.* 2007;46:723–34.

59. Bushnell Jr DL, O'Dorisio TM, et al. 90 Y-edotreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol.* 2010; 28:1652–9.
60. Imhof A, Brunner P, Marinček N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [ 90 Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol.* 2011;29:2416–23.
61. de Jong M, Kwekkeboom D, Valkema R, et al. Radiolabelled peptides for tumour therapy: current status and future directions. Plenary lecture at the EANM 2002. *Eur J Nucl Med Mol Imaging.* 2003;30:463–9.
62. Teunissen JJ, Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0, Tyr3]octreotate. *J Clin Oncol.* 2004;22: 2724–9.
63. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177 Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2011;38:302–11.
64. Strosberg J, El-Haddad G, Wolin E, et al. NETTER-1 Trial Investigators. Phase 3 Trial of (177) Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017;12;376:125-135.
65. Strosberg J, Wolin E, Chasen B, et al. 6LBA 177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: results of the phase III NETTER-1 trial. *Eur J Cancer* 2015; 51:710.
66. Nayak T, Norenberg J, Anderson T, et al. A comparison of high- versus low-linear energy transfer somatostatin receptor targeted radionuclide therapy in vitro. *Cancer Biother Radiopharm* 2005;20:52–7.
67. Nayak TK, Norenberg JP, Anderson TL, et al. Somatostatin-receptor-targeted alpha-emitting 213Bi is therapeutically more effective than beta(-)-emitting 177Lu in human pancreatic adenocarcinoma cells. *Nucl Med Biol* 2007;34: 185–93.
68. Carrasquillo JA, Pandit-Taskar N, Chen CC. I-131 Metaiodobenzylguanidine Therapy of Pheochromocytoma and Paraganglioma. *Semin Nucl Med.* 2016;46:203-14.
69. Noto RB, Pryma DA, Jensen J, et al. Phase 1 Study of High-Specific-Activity I-131 MIBG for Metastatic and/or Recurrent Pheochromocytoma or Paraganglioma. *J Clin Endocrinol Metab.* 2018;103:213-220.
70. Krempf M, Lumbroso J, Mornex R, et al: Use of m-[I-131]iodobenzyl- guanidine in the treatment of malignant pheochromocytoma. *J Clin Endocrinol Metab* 1991;72:455-461.
71. Goncalves E, Ninane J, Wese FX, et al: Familial pheochromocytoma— Successful treatment with I-131 MIBG. *Med Pediatr Oncol.* 1990;18:126-130.