

## Bölüm 15

# İNCE BAĞIRSAK NÖROENDOKRİN TÜMÖRLERİ

Sinan ÖMEROĞLU<sup>16</sup>

Emre BOZKURT<sup>17</sup>

### GİRİŞ

İnce bağırsak nöroendokrin tümörleri gastrointestinal sistemdeki nöroendokrin hücrelerden kaynaklanan nadir ve yavaş büyüyen tümörlerdir. Bu hücreler isimlerini sinir hücreleri ile ilişkili nöron spesifik enolaz, sinaptofizin gibi proteinleri ifade etmesinden ve somatostatin, substance P, vazoaaktif intestinal peptid gibi hormonları salgılamasından almıştır. Çeşitli klinik sendromlara yol açan peptid, nöroamin ve diğer vazoaaktif maddeleri üretme yeteneğine sahiptirler. Sindirim sistemi foregut, midgut ve hindgut'tan oluşur. Foregut bronş, mide, duodenum ve pankreas; midgut jejunum, ileum, apendiks ve asendan/transvers kolon; hindgut distal kolon ve rektum bölümlerini içerir. Nöroendokrin tümörler (NET) ince bağırsağın (SI) en sık görülen neoplazmidir. Sıklıkla distal ileumdan, ileoçekal valve 60 cm mesafeden kaynaklanır(1). Genellikle fokal lezyonlar olmakla birlikte vakaların üçte birinde multifokal hastalık görülür(2). SI-NET'ler, akciğer ve rektumdan sonra üçüncü en sık görülen ve uzak metastaz geliştiren en yaygın alt tiptir (2).

### Epidemiyoloji

Evreleme sistemleri, endoskopik incelemeler, görüntüleme yöntemleri ve patolojik inceleme yöntemlerindeki tıbbi gelişmelere bağlı olarak nöroendokrin tümörlerin yıllık insidansı giderek artmaktadır. ABD'de 0.67/100000 olarak görülmektedir(3). SEER (Surveillance Epidemiology and Ends Results) veri tabanından elde edilen veriler, SI-NET için tahmini yıllık % 3.5 artış olduğunu

<sup>16</sup> Genel cerrahi uzmanı, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi  
dr\_sinanomeroglu@hotmail.com

<sup>17</sup> Genel cerrahi uzmanı, Kelkit Devlet Hastanesi, dr.emrebozkurt@gmail.com

## **KAYNAKLAR**

1. Maggard MA, O'Connell JB and Ko CY: Updated populationbased review of carcinoid tumors. *Ann Surg* 240(1): 117-122, 2004
2. Kim JY and Hong SM: Recent updates on neuroendocrine tumors from the gastrointestinal and pancreatobiliary tracts. *Arch Pathol Lab Med* 140(5): 437-448, 2016
3. 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;26:3063–3372.
4. Haugvik SP, Basim Ibrahim I, Hedenstrom P, Valente R, Haye AJ, Siuka D, Gladhaug IP and Capurso G: Smoking, alcohol and family history of cancer as risk factors for small intestinal neuroendocrine tumors: A systematic review and meta-analysis. *Scand J Gastroenterol* 52(8): 797-802, 2017.
5. Norlen O, Stalberg P, Oberg K, Eriksson J, Hedberg J, Hessman O, Janson ET, Hellman P and Akerstrom G: Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 36(6): 1419-1431, 2012.
6. Current status of gastrointestinal carcinoids. *Gastroenterology* 128(6): 1717-1751, 2005.
7. Modlin IM, Gustafsson BI, Moss SF, et al. Chromogranin A biological function and clinical utility in neuroendocrine tumor disease. *Ann Surg Oncol.*2010;17:2427–2443.
8. Manfè AZ, Norberto L, Marchesini M, et al. Usefulness of chromogranin A, neuron-specific enolase and 5-hydroxyindolacetic acid measurements in patients with malignant carcinoids. *In Vivo.* 2011;25:1027–1029.
9. Modlin IM, Drozdov I, Kidd MS. A multitranscript blood neuroendocrine tumor molecular signature to identify treatment efficacy and disease progress. *ournal of Clinical Oncology* 2013 31:15\_suppl, 4137-4137
10. Rossi RE, Conte D, Elli L, Branchi F, Massironi S Endoscopic techniques to detect small-bowel neuroendocrine tumors: A literature review *United European Gastroenterology Journal* 2017, Vol. 5(1) 5–12
11. Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, Nieveen van Dijkum EJ, Pape UF, Pascher A, Ramage J, Reed N, Ruzsiewicz P, Scoazec JY, Toumpanakis C, Kianmanesh R, Falconi M and all other Antibes Consensus Conference participants: ENETs consensus guidelines for standard of care in neuroendocrine tumours: Surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology* 105(3): 255-265, 2017.
12. Schnirer, II, Yao JC and Ajani JA: Carcinoid--a comprehensive review. *Acta Oncol* 42(7): 672-692, 2003.
13. Woltering EA, Voros BA, Beyer DT, Wang YZ, Thiagarajan R, Ryan P, Wright A, Ramirez RA, Ricks MJ and Boudreaux JP: Aggressive surgical approach to the management of neuroendocrine tumors: A report of 1,000 surgical cytoreductions by a single institution. *J Am Coll Surg* 224(4): 434-447, 2017.
14. Farley HA and Pommier RF: Surgical treatment of small bowel neuroendocrine tumors. *Hematol Oncol Clin North Am* 30(1):49-61, 2016.
15. Farra CJ and Rodgers ES: Small bowel neuroendocrine tumors. In: *Surgical Endocrinopathies: Clinical Management and the Founding Figures.* Pasiaka LJ and Lee AJ (eds.). Springer International Publishing: Cham, pp. 323-331, 2015
16. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, Oberg K and Vienna Consensus Conference participants: ENETs consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 103(2): 172-185, 2016.

17. Landry CS, Lin HY, Phan A, Charnsangavej C, Abdalla EK, Aloia T, Nicolas Vauthey J, Katz MH, Yao JC and Fleming JB: Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. *World J Surg* 37(7): 1695-1700, 2013.
18. *Tnm classification of malignant tumours (ebook)*. WileyBlackwell (Verlag): 8. Auflage 272 Seiten, 2016.
19. Almond LM, Hodson J, Ford SJ, Gourevitch D, Roberts KJ Shah T, Isaac J and Desai A: Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis. *Eur J Surg Oncol* 43(10): 1808-1815, 2017.
20. Pasquer A, Walter T, Rousset P, Hervieu V, Forestier J, LombardBohas C and Poncet G: Lymphadenectomy during small bowel neuroendocrine tumor surgery: The concept of skip metastases. *Ann Surg Oncol* 23(Suppl 5):804-808, 2016.
21. Pasquer A, Walter T, Hervieu V, Forestier J, Scoazec JY, Lombard-Bohas C and Poncet G: Surgical management of small bowel neuroendocrine tumors: Specific requirements and their impact on staging and prognosis. *Ann Surg Oncol* 22 Suppl 3(3):S742-749, 2015.
22. Lardiere-Deguelte S, de Mestier L, Appere F, Vullierme MP, Zappa M, Hoeffel C, Noaves M, Brixi H, Hentic O, Ruszniewski P, Cadiot G, Panis Y and Kianmanesh R: Toward a preoperative classification of lymph node metastases in patients with small intestinal neuroendocrine tumors in the era of intestinal-sparing surgery. *Neuroendocrinology* 103(5): 552-559, 2016.
23. Pasquer A and Poncet G: Small bowel neuroendocrine tumors surgery: Technical point - with video. *J Visc Surg* 154(1): 61-62, 2017.
24. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao JC and North American Neuroendocrine Tumor S: The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas*39(6): 753-766, 2010.
25. Boudreaux JP: Surgery for gastroenteropancreatic neuroendocrine tumors (gepnets). *Endocrinol Metab Clin North Am* 40(1): 163-171, ix, 2011.
26. Wang YZ, Carrasquillo JP, McCord E, et al. Reappraisal of lymphatic mapping for midgut neuroendocrine patients undergoing cytoreductive surgery. *Surgery*. 2014;156:1498-1502; discussion 1502 1503
27. Wang YZ, Chauhan A, Rau J, Diebold AE, Opoku-Boateng A, Ramcharan T, Boudreaux JP and Woltering EA: Neuroendocrine tumors (nets) of unknown primary: Is early surgical exploration and aggressive debulking justifiable? *Chin Clin Oncol*5(1): 4, 2016.
28. Modlin IM, Shapiro MD and Kidd M: Carcinoid tumors and fibrosis: An association with no explanation. *Am J Gastroenterol* 99(12): 2466-2478, 2004.
29. Ethun CG, Postlewait LM, Baptiste GG, McInnis MR, Cardona K, Russell MC, Kooby DA, Staley CA and Maithel SK: Small bowel neuroendocrine tumors: A critical analysis of diagnostic work-up and operative approach. *J Surg Oncol* 114(6): 671-676, 2016.
30. Hughes MS, Azoury SC, Assadipour Y, Straughan DM, Trivedi AN, Lim RM, Joy G, Voellinger MT, Tang DM, Venkatesan AM, Chen CC, Louie A, Quezado MM, Forbes J and Wank SA: Prospective evaluation and treatment of familial carcinoid small intestine neuroendocrine tumors (si-NETs). *Surgery* 159(1): 350-356, 2016.
31. Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V, Tamburrino D, Keck T, Caplin ME, Bartsch D, Thirlwell C, Fusai G and Falconi M: Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. *Neuroendocrinology*102(1-2): 68-76, 2015.
32. Graff-Baker AN, Sauer DA, Pommier SJ, et al. Expanded criteria for carcinoid liver debulking: maintaining survival and increasing the number of eligible patients. *Surgery* 2014;156:1369-77.

33. Moris D, Dimitroulis D, Vernadakis S, Papalampros A, Spartalis E, Petrou A, Pawlik TM and Felekouras E: Parenchymal-sparing hepatectomy as the new doctrine in the treatment of liver metastatic colorectal disease: Beyond oncological outcomes. *Anticancer Res* 37(1): 9-14, 2017.
34. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM and Howe JR: Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery* 159(1): 320-333, 2016.
35. Farley HA and Pommier RF: Treatment of neuroendocrine liver metastases. *Surg Oncol Clin N Am* 25(1): 217-225, 2016.
36. Glazer ES, Tseng JF, Al-Refaie W, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)* 2010;12:
37. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, Kwekkeboom D, Lau WY, Klersy C, Vilgrain V, Davidson B, Siegler M, Caplin M, Solcia E, Schilsky R and Working Group on Neuroendocrine Liver M: Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 15(1): e8-21, 2014.
38. Kianmanesh R, Sauvanet A, Hentic O, Couvelard A, Levy P, Vilgrain V, Ruszniewski P and Belghiti J: Two-step surgery for synchronous bilobar liver metastases from digestive endocrine tumors: A safe approach for radical resection. *Ann Surg* 247(4):659-665, 2008.
39. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinksi SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferrero A, Schulick RD, Choti MA, Mentha G, Strub J, Bauer TW, Adams RB, Aldrighetti L, Capussotti L and Pawlik TM: Surgical management of hepatic neuroendocrine tumor metastasis: Results from an international multiinstitutional analysis. *Ann Surg Oncol* 17(12): 3129-3136, 2010.
40. Vogl TJ, Straub R, Eichler K, Sollner O and Mack MG: Colorectal carcinoma metastases in liver: Laser-induced interstitial thermotherapy –local tumor control rate and survival data. *Radiology* 230(2): 450-458, 2004.
41. Vogl TJ, Naguib NN, Zangos S, Eichler K, Hedayati A and Nour-Eldin NE: Liver metastases of neuroendocrine carcinomas: Interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 72(3): 517-528, 2009.
42. Pavel M, Baudin E, Couvelard A, Krenning E, Oberg K, Steinmuller T, Anlauf M, Wiedenmann B, Salazar R and Barcelona Consensus Conference participants: 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* 95(2): 157-176, 2012.
43. Whitney R, Valek V, Fages JF, Garcia A, Narayanan G, Tatum C, Hahl M and Martin RC 2nd: Transarterial chemoembolization and selective internal radiation for the treatment of patients with metastatic neuroendocrine tumors: A comparison of efficacy and cost. *Oncologist* 16(5): 594-601, 2011
44. Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, Camerini T, Milione M, Regalia E, Spreafico C, Gangeri L, Buzzoni R, de Braud FG, De Feo T and Mariani L: The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant* 16(10): 2892-2902, 2016.
45. de Mestier L, Lardiere-Deguelte S, Brixi H, O'Toole D, Ruszniewski P, Cadiot G and Kianmanesh R: Updating the surgical management of peritoneal carcinomatosis in patients with neuroendocrine tumors. *Neuroendocrinology* 101(2): 105-111, 2015.
46. NCCN clinical practice guidelines in oncology. NCCN guidelines neuroendocrine tumors. Version 2.2017—March 29, 2017. [https://www.nccn.org/professionals/physician\\_gls/PDF/neuroendocrine.pdf](https://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf), 2017.
47. Kianmanesh R, Ruszniewski P, Rindi G, Kwekkeboom D, Pape UF, Kulke M, Sevilla Garcia I, Scoazec JY, Nilsson O, Fazio N, Lesurtel M, Chen YJ, Eriksson B, Cioppi F, O'Toole D and Palma de Mallorca Consensus Conference P: ENETs consensus guidelines for the management

- of peritoneal carcinomatosis from neuroendocrine tumors. *Neuroendocrinology* 91(4): 333-340,2010.
48. Elias D, David A, Sourrouille I, Honore C, Goere D, Dumont F, Stoclin A and Baudin E: Neuroendocrine carcinomas: Optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). *Surgery*155(1): 5-12, 2014.
  49. Chen JX, Rose S, White SB, El-Haddad G, Fidelman N, Yarmohammadi H, Hwang W, Sze DY, Kothary N, Stashek K, Wileyto EP, Salem R, Metz DC and Soulen MC: Embolotherapy for neuroendocrine tumor liver metastases: Prognostic factors for hepatic progression-free survival and overall survival. *Cardiovasc Intervent Radiol* 40(1): 69-80, 2017.
  50. Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: Classification, functional syndromes, diagnosis and medical treatment. *Best Pract Res Clin Gastroenterol*2005; 19: 675-697
  51. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 2004; 25: 458-511
  52. Soga J. Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. *J Exp Clin Cancer Res* 2003; 22: 349-363
  53. Kirshbom PM, Kherani AR, Onaitis MW, Hata A, Kehoe TE, Feldman C, Feldman JM, Tyler DS. Foregut carcinoids: a clinical and biochemical analysis. *Surgery*1999; 126: 1105-1110
  54. Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci*2004; 1014: 13-27
  55. Norheim I, Oberg K, Theodorsson-Norheim E, Lindgren PG, Lundqvist G, Magnusson A, Wide L, Wilander E. Malignant carcinoid tumors. An analysis of 103 patients with regard to tumor localization, hormone production, and survival. *Ann Surg*1987; 206: 115-125
  56. Vinik AI, Woltering EA, Warner RR, Caplin M, O'Dorisio TM, Wiseman GA, Coppola D, Go VL. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas*2010; 39: 713-734
  57. Jensen RT, Rindi G, Arnold R, Lopes JM, Brandi ML, Bechstein WO, Christ E, Taal BG, Knigge U, Ahlman H, Kwekkeboom DJ, O' Toole D. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). *Neuroendocrinology*2006; 84: 165-172