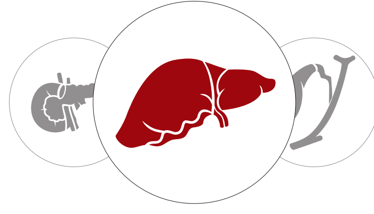


BÖLÜM 16

Nöroendokrin Tümör Karaciğer Metastazları

Serdar ŞENOL [1]

ÖZET

Nöroendokrin tümörler (NET), değişken klinik davranışlar gösterebilen heterojen bir tümör grubunu kapsar. Sıklıkla köken aldıkları bölgeye göre, ön barsaktan köken alanlar: bronşial, gastrik, duodenal, pankreas; orta barsaktan köken alanlar: ince barsak, apendiks, proksimal kolon; son barsaktan köken alanlar: distal barsak ve rektum olarak sınıflandırılır. En sık akciğerlerde gözlenirken azalan sıklıkta ince barsak, rektum ve pankreasta görülür.

NET karaciğer metastazlarının (NETLM) prevalansı %27 ile %60 arasında değişmektedir. Hastaların yaklaşık %12-74'ü tanı anında karaciğer metastazları (LM) ile başvurmaktadır. Hepatik metastaz izlenme oranları bazı hasta alt gruplarında daha yaygın olarak izlenir. İnce barsak NEN'larında 67-91%, pankreatik NEN'larında 27-77%'sinde izlenirken mide, apendiks NEN'larında nadir olarak bildirilmiştir. Hastaların 5% ile 10%'unda ise primeri tespit edilemeyen karaciğer metastazları görülür.

NEN'lar diferansiyasyon ve derecesine göre histolojik olarak sınıflandırılır: düşük dereceli, iyi diferansiye (G_1) NET; orta dereceli, iyi diferansiye (G_2) NET; yüksek dereceli, iyi diferansiye (G_3) NET ve yüksek dereceli, kötü diferansiye (NEC) nöroendokrin karsinom. Çoğu NEN'ler G_1 ve G_2 olarak sınıflandırılır. G_3 NEN'ler nadirdir ve kötü seyirli hastalık alt grubudur.

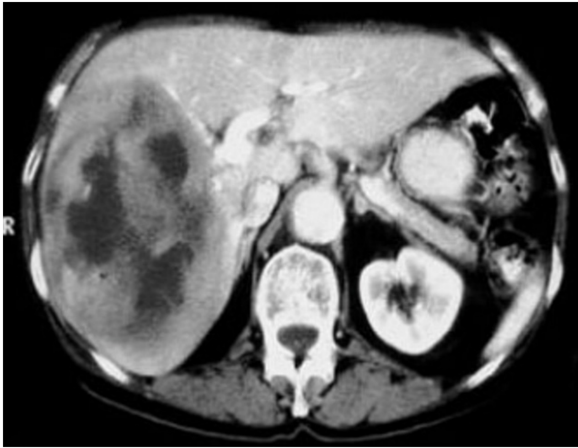
Nöroendokrin karaciğer metastazları (NELM) tedavisi, cerrahi, sistemik tedaviler, girişimsel yöntemler gibi çok çeşitli seçeneklerin kullanılmasını gerektirebilir. Primer tümör lokalizasyonu, metastazın sayı, büyüklüğü, tümör grade göre endikasyonlar belirlenir. Cerrahi tek küratif tedavi seçeneğidir. Ancak medikal tedaviye dirençli fonksiyonel tümörlerde semptomların palyasyonu için de kullanılabilir.

NEN'ların çoğunluğu asemptomatiktir. Ancak hastaların 20% ile 30%'unda farklı klinik sendromlara yol açan biyolojik olarak aktif bileşiklerin sekresyonuna bağlı semptomatiktir. NEN'ların çoğunluğu asempto-

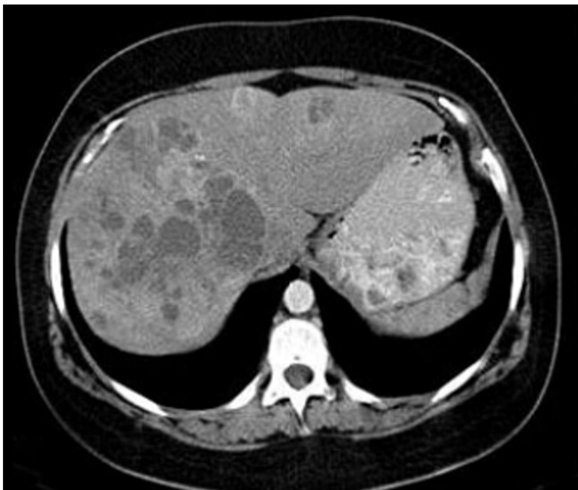
[1] Uzm. Dr. Serdar ŞENOL, SBÜ Samsun Eğitim ve Araşatırma Hastanesi, Gastroenteroloji Cerrahisi
serdarardaduru@gmail.com

rinde randomize kontrollü çalışmalar olmasa da retrospektif özellikte çalışmalarda PRRT'in etkinliği gösterilmiştir (109,111). Unrezektable yaygın karaciğer metastazları olan G1-2 pankreas NEN'lerinin tedavisinde PPRT'ye yanıtın artması ve PFS'ın uzaması nedeniyle upfront cerrahi yaklaşımı önerilmektedir (70). PPRT'nin miliyer tarzdaki karaciğer metastazlarında daha etkili olması nedeniyle ekstrahepatik hastalığın eşlik ettiği, büyük karaciğer tümörlerinde radyoembolizasyonla kombine edilerek kullanılması önerilmiştir (71).

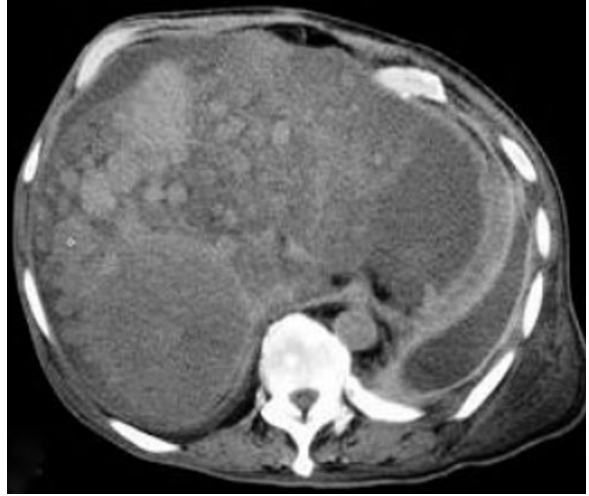
Kullanılan radyonüklit ajanların toksisitesine bağlı sık olmamak kaydıyla myelotoksisite, böbrek ve karaciğer yetmezliği gelişebileceği bildirilmiştir (68,72).



Resim IA



Resim IB



Resim IC

Resim I; Nöroendokrin karaciğer metastazlarının dağılımına göre hastalık yükünün sınıflandırılması: IA: tek bir metastaz (boyuttan bağımsız) (tip I); IB: küçük metastazların eşlik ettiği metastatik hastalık (her iki karaciğer lobu her zaman etkilenir) (tip II); IC: dissemine metastatik yayılma (her iki karaciğer lobu her zaman tutulmuş, değişen boyutta lezyonlar, hemen hemen hiç normal karaciğer parankimi yok) (tip III)
(Frilling ve arkadaşları'nın (12) yaptıkları çalışmadan altıntı yapılmıştır.)

KAYNAKLAR

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–1342.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–959.
3. Chamberlain RS, Canes D, Brown KT, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg. 2000;190(4):432-45.
4. 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(18):3063–72.
5. Niederle B, Pape U-F, Costa F, et al. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. Neuroendocrinology. 2016;103(2):125–38
6. 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(2):157–76.
7. Pawa N, Clift AK, Osmani H, et al. Surgical management of patients with neuroendocrine neoplasms of the appendix: appendectomy or more? Neuroendocrinology. 2018;106(3):242-251.

8. Frilling A, Clift AK. Therapeutic strategies for neuroendocrine liver metastases. Cancer. 2015;121(8):1172-86.
9. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. J Clin Oncol. 2011;29(17):2372-77.
10. Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. Endocr Rev. 2020;41(2):371-403.
11. Pavel M, O'Toole D, Costa F, et al; 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. 2016;103(2):172-85.
12. Frilling A, Li J, Malamutmann E, et al. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg. 2009;96(2):175-84.
13. Nigri G, Petrucciani N, Debs T, et al. Treatment options for PNET liver metastases: a systematic review. World J Surg Oncol. 2018;16(1):142.
14. Frilling A, Modlin IM, Kidd M, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15(1):e8-21.
15. Saxena A, Chua TC, Perera M, et al. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. Surg Oncol. 2012;21(3):e131-41.
16. Kaçmaz E, Heidsma CM, Besselink MGH, et al. Treatment of liver metastases from midgut neuroendocrine tumours: a systematic review and meta-analysis. J Clin Med. 2019;8(3):403.
17. Yu X, Gu J, Wu H, et al. Resection of liver metastases: a treatment provides a long-term survival benefit for patients with advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. J Oncol. 2018;2018:6273947.
18. Kianmanesh R, Sauvanet A, Hentic O, et al. Two-step surgery for synchronous bilobar liver metastases from digestive endocrine tumors: a safe approach for radical resection. Ann Surg. 2008;247(4):659-65.
19. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405-14.
20. Jaeck D, Oussoultzoglou E, Bachellier P, et al. Hepatic metastases of gastroenteropancreatic neuroendocrine tumors: safe hepatic surgery. World J Surg. 2012;255(3):405-14.
21. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013;59(5):1029-36.
22. Linecker M, Kambakamba P, Raptis DA, et al. ALPPS in neuroendocrine liver metastases not amenable for conventional resection - lessons learned from an interim analysis of the International ALPPS Registry. HPB (Oxford). 2020;22(4):537-44.
23. Baili E, Tsilimigras DI, Filippou D, et al. Associating liver partition and portal vein ligation for staged hepatectomy in patients with primary liver malignancies: A systematic review of the literature. J BUON. 2019;24(4):1371-81.
24. Addeo P, Bertin JB, Imperiale A, et al. Outcomes of simultaneous resection of small bowel neuroendocrine tumors with synchronous liver metastases. World J Surg. 2020;44(7):2377-84
25. Gaujoux S, Gonen M, Tang L, et al. Synchronous resection of primary and liver metastases for neuroendocrine tumors. Ann Surg Oncol. 2012;19(13):4270-7.
26. Schurr PG, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. Ann Surg. 2007;245(2):273-81.
27. Adam R, de Gramont A, Figueras J, et al; of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015;41(9):729-41.
28. Gurusamy KS, Pamecha V, Sharma D, et al. Palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. Cochrane Database Syst Rev. 2009;2009(1):CD007118.
29. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery. 1990;108(6):1091-6.
30. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg. 1995;169(1):36-42; discussion 42-3.
31. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197(1):29-37.
32. Chambers AJ, Pasieka JL, Dixon E, et al. The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. Surgery. 2008;144(4):645-51;
33. 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(6):1369-76; discussion 1376-7.
34. Morgan RE, Pommier SJ, Pommier RF. Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. Surgery. 2018;163(1):218-25.
35. Maxwell JE, Sherman SK, O'Dorisio TM, et al. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? Surgery. 2016;159(1):320-33.
36. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol. 2010;17(12):3129-36.
37. Boudreaux JP, Wang Y-Z, Diebold AE, et al. A single institution's experience with surgical cytoreduction of stage IV, well differentiated, small bowel neuroendocrine tumors. J Am Coll Surg. 2014;218(4):837-44.
38. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. Endocr Relat Cancer. 2009;16(3):885-94.

39. Howe JR, Cardona K, Fraker DL, et al. The surgical management of small bowel neuroendocrine tumors: Consensus guidelines of the North American Neuroendocrine Tumor Society. Pancreas. 2017;46(6):715-731.
40. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society Consensus paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas. 2020;49(1):1-33.
41. Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. Surgery. 2017;162(3):525-36.
42. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol. 2007;47(4):460-6.
43. Mazzaferro V, Sposito C, Coppa J, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant. 2016;16(10):2892-902.
44. Chan MY, Ma KW, Chan A. Surgical management of neuroendocrine tumor-associated liver metastases: a review. Gland Surg. 2018;7(1):28-35.
45. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. HPB. 2015;17(1):23–28.
46. Gamblin TC, Christians K, Pappas SG. Radiofrequency ablation of neuroendocrine hepatic metastasis. Surg Oncol Clin N Am. 2011;20(2):273-9, vii-viii.
47. Scott AT, Breheny PJ, Keck KJ, et al. Effective cytoreduction can be achieved in patients with numerous neuroendocrine tumor liver metastases (NETLMs). Surgery. 2019;165(1):166-75.
48. Mayo SC, de Jong MC, Bloomston M, et al. Surgery versus intraarterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol. 2011;18(13):3657-65.
49. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery. 2007;142(1):10-9.
50. Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. Ann Surg Oncol2008 Oct;15(10):2757-64
51. Rhim H, Lim HK. Radiofrequency ablation of hepatocellular carcinoma: pros and cons. Gut Liver. 2010;4 Suppl 1(Suppl 1):S113-8
52. Minami Y, Kudo M. Radiofrequency ablation of hepatocellular carcinoma: Current status. World J Radiol. 2010 Nov 28;2(11):417-24.
53. Berber E, Tsinberg M, Tellioglu G, et al. Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. J Gastrointest Surg. 2008;12(11):1967-72.
54. Landry CS, Scoggins CR, McMasters KM, et al. Management of hepatic metastasis of gastrointestinal carcinoid tumors. J Surg Oncol. 2008;97(3):253-8.
55. Akyildiz HY, Mitchell J, Milas M, et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. Surgery. 2010;148(6):1288-93
56. Urbonas T, Anderson EM, Gordon-Weeks AN, et al. Factors predicting ablation site recurrence following percutaneous microwave ablation of colorectal hepatic metastases. HPB (Oxford). 2019;21(9):1175-1184.
57. Perrodin SF, Renzulli MM, Maurer MH, et al. Can microwave ablation be an alternative to resection for the treatment of neuroendocrine liver metastases? Endocr Pract. 2020;26(4):378-387.
58. Cannon R, Ellis S, Hayes D, Narayanan G, Martin RCG. Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. J Surg Oncol.?????????
59. Kennedy A, Bester L, Salem R, et al. NET-Liver-Metastases Consensus Conference. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver- Metastases Consensus Conference. HPB (Oxford). 2015;17(1):29-37.
60. Bhagat N, Reyes DK, Lin M, et al. Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. Cardiovasc Intervent Radiol. 2013;36(2):449-59.
61. de Baere T, Deschamps F, Tselikas L, et al. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETs. Eur J Endocrinol. 2015;172(4):R151-66.
62. Zappa M, Abdel-Rehim M, Hentic O, et al. Liver-directed therapies in liver metastases from neuroendocrine tumors of the gastrointestinal tract. Target Oncol. 2012;7(2):107-16.
63. Del Prete M, Fiore F, Modica R, et al; Multidisciplinary Group for NeuroEndocrine Tumors of Naples. Hepatic arterial embolization in patients with neuroendocrine tumors. J Exp Clin Cancer Res. 2014;33(1):43.
64. Dong XD, Carr BI. Hepatic artery chemoembolization for the treatment of liver metastases from neuroendocrine tumors: a long-term follow-up in 123 patients. Med Oncol Northwood Lond Engl. 2011;28 Suppl 1:S286-90.
65. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. AJR Am J Roentgenol. 2007;188(5):1201-7.
66. Mayo SC, de Jong MC, Bloomston M, et al. Surgery versus intraarterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol. 2011;18(13):3657-65.
67. van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETs update: Radionuclide therapy in neuroendocrine tumors. Eur J Endocrinol. 20015;172(1):R1-8.
68. Hicks RJ, Kwekkeboom DJ, Krenning E, et al; Antibes Consensus Conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology. 2017;105:295-309.
69. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125-135.

70. Bertani E, Fazio N, Radice D, et al. Resection of the primary tumor followed by peptide receptor radionuclide therapy as upfront strategy for the treatment of G1-G2 pancreatic neuroendocrine tumors with unresectable liver metastases. Ann Surg Oncol. 2016;23:981-989.
71. Ezziddin S, Meyer C, Kahancova S, et al. 90Y Radioembolization after radiation exposure from peptide receptor radionuclide therapy. J Nucl Med. 2012;53:1663-1669.
72. Kesavan M, Turner JH. Myelotoxicity of peptide receptor radionuclide therapy of neuroendocrine tumors: a decade of experience. Cancer Biother Radiopharm 2016;31:189-198.