

# BÖLÜM 28

## MEDÜLLER TİROİD KANSERİNE YAKLAŞIM



Derya CEBECİ<sup>1</sup>

### GİRİŞ

Medüller tiroid kanseri (MTK), tiroid parafoliküler C hücrelerinden köken alan bir nöroendokrin tümördür. Medüller tiroid kanseri gerek klinik gerekse tanı-te-davi açısından, iyi diferansiye (folliküler hücrelerden köken alan) tiroid kanserle-rinden farklı özelliklere sahiptir.

MTK yönetimi, endokrinoloji, onkoloji, patoloji, kulak burun boğaz uzmanı ya da endokrin cerrahi uzmanının yer aldığı bir ekiple, multidisipliner yaklaşım gerektirir.

Bu bölümde en güncel kaynaklar eşliğinde medüller tiroid karsinomu hakkın-da bilgi aktarımı yapılacaktır.

### EPİDEMİYOLOJİ

Parafoliküler C hücrelerinden köken alan medüller tiroid karsinomu, tüm tiroid karsinomlarının %5'inden daha az kısmını oluşturur (1). Sporadik ve herediter olmak üzere iki farklı şekilde görülebilir. Herediter grupta yer alanlar Multiple Endokrin Neoplazi Tip 2 (MEN 2) veya Ailesel Medüller Tiroid karsinomu ile ilişkilidir ve otozomal dominant geçişlidir.

<sup>1</sup> Op. Dr., İstanbul Gaziosmanpaşa Eğitim ve Araştırma Hastanesi, Kulak Burun ve Boğaz Hastalıkları Kliniği, drderyacebeci@gmail.com



ve tedavi süreci multidisipliner yaklaşım gerektirir. Görülme sıklığı az olduğu için yapılan çalışma sayısı ve yapılmış çalışmalardaki hasta sayıları sınırlı sayıdadır. Herediter olan MTK hastalarında aile bireylerinin de takibi önemlidir ve kılavuzlar ışığında periyodik takipler ve gerekli ise cerrahi müdahaleler planlanmalıdır.

## KAYNAKLAR

1. Siegel RL, Miller KD, Jemal A. Cancerstatistics, 2018. *CA Cancer J Clin.* 2018; 68 (1):7-30. DOI: 10.3322/caac.21442.
2. Leboulleux S, Baudin E, Travaglini JP, et al. Medullary thyroid carcinoma. *Clin Endocrinol* 2004; 61: 299–310.
3. Dabelić N, Nukić T, Fröbe. A Medullary Thyroid Cancer – Feature Review and Update on Systemic Treatment. *Acta Clin Croat (Suppl. 1)* 2020; 59:50-59. doi: 10.20471/acc.2020.59.s1.06
4. Filetti S, Durante C, Hartl D, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019; 30 (12):1856-83. DOI: 10.1093/annonc/mdz400.
5. Kuo EJ, Sho S, Li N, et al. Risk Factors Associated With Reoperation and Disease-Specific Mortality in Patients With Medullary Thyroid Carcinoma. *JAMA Surg.* 2018; 153 (1):52-9. DOI: 10.1001/jamasurg.2017.3555
6. Meijer JA, le Cessie S, van den Hout WB, et al. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis. *Clin Endocrinol (Oxf).* 2010;72 (4):534-42. DOI: 10.1111/j.1365-2265.2009.03666.x.
7. Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. *Cell* 1985; 42:581–588.
- 8- Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet* 1993;2:851–856.
9. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA* 1996;276:1575e1579.
10. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009;19:565e612.
11. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015;25:567-610.
12. Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. *Nature Reviews: Endocrinology* 2016;12 192–202. (<https://doi.org/10.1038/nrendo.2016.11>)
13. Hedinger C, Williams ED, Sobin LH. (1988). Histological typing of thyroid tumours. In: International classification of tumours (2nd ed.) Berlin: Springer-Verlag.
14. LiVolsi VA. C cell hyperplasia/neoplasia. *J Clin Endocrinol Metab* 1997;82:39e41.
15. Khurana R, Agarwal A, Bajpai VK, et al. Unraveling the amyloid associated with human medullary thyroid carcinoma. *Endocrinology* 2004;145:5465–5470.
16. Boerner SL AS. (2017) *Biopsy Interpretation of the Thyroid* (2nd ed.). Philadelphia, PA: Wolters Kluwer.



17. Nangue C, Bron L, Portmann L, et al. Mixed medullarypapillary carcinoma of the thyroid: report of a case and review of the literature. *Head Neck* 2009; 31:968–974.
18. Ljungberg O, Ericsson UB, Bondeson L, et al. A compound follicularparafollicular cell carcinoma of the thyroid: a new tumor entity? *Cancer* 1983; 52:1053–1061.
19. Gagel RF, Jackson CE, Block MA, et al. Age-related probability of development of hereditary medullary thyroid carcinoma. *J Pediatr* 1982; 101:941e946.
20. Leboulleux S, Travagli JP, Caillou B, et al. Medullary thyroid carcinoma as part of a multiple endocrine neoplasia type 2B syndrome: influence of the stage on the clinical course. *Cancer* 2002; 94:44e50.
21. Alcantara F, Feido M, Albizuri F. Notalgia Paresthetica and Multiple Endocrine Neoplasia Syndrome 2A: A Case Report *Pediatric Dermatology* 2016; Vol. 33 No. 5 e303–e305.
22. Makri A, Akshintala S, Derse-Anthony C, et al. Multiple endocrine neoplasia type 2B presents early in childhood but often is undiagnosed for years. *Journal of Pediatrics* 2018; 203 447–449. (<https://doi.org/10.1016/j.jpeds.2018.08.022>)
23. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J Clin Endocrinol Metab.* 2010; 95 (6):2655–63. DOI: 10.1210/jc.2009-2368.
24. Rosario PW, Calsolari MR. Usefulness of serum calcitonin in patients without a suspicious history of medullary thyroid carcinoma and with thyroid nodules without an indication for fine needle aspiration or with benign cytology. *Hormone and Metabolic Research.* 2016; 48 372–276. (<https://doi.org/10.1055/s-0042-107246>)
25. Baloch Z, Carayon P, Conte-Devolx B, et al. Guidelines Committee, National Academy of Clinical Biochemistry Laboratory medicine practice guidelines. Calcitonin and RET proto-oncogene mesaurements. *Thyroid* 2003;13:68e79.
26. Turk Y, Makay O, Ozdemir M, et al. Routine calcitonin measurement in nodular thyroid disease management: is it worthwhile? *Annals of Surgical Treatment and Research* 2017; 92 173–178. (<https://doi.org/10.4174/astr.2017.92.4.173>)
27. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: thyroid carcinoma [Internet]. Plymouth Meeting: NCCN; c2021 [http://www.nccn.org/professionals/physician\\_gls/pdf/thyroid.pdf](http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf). adresinden ulaşılmıştır.
28. Adam MA, Thomas S, Roman SA, et al. Rethinking the current American Joint Committee on Cancer TNM staging system for medullary thyroid cancer. *JAMA Surg* 2017; 152:869-76.
29. Zhang L, Wei WJ, Ji QH, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* 2012; 97:1250–1257.
30. Machens A, Holzhausen HJ, Dralle H. Contralateral cervical and mediastinal lymph node metastasis in medullary thyroid cancer: systemic disease? *Surgery* 2006; 139:28–32.
31. Stålberg P, Carling T. Familial parathyroid tumors: diagnosis and management. *World J Surg* 2009; 33:2234e2243.
32. Martinez SR, Beal SH, Chen A, et al. Adjuvant external beam radiation for medullary thyroid carcinoma. *J Surg Oncol* 2010; 102:175–178.
33. Call JA, Caudiill JS, McIver B, et al. A role for radiotherapy in the management of advanced medullary thyroid carcinoma: the mayo clinic experience. *Rare Tumors.* 2013; 5 (3):e37. DOI: 10.4081/rt.2013.e37.
34. Bhandare N, Mendenhall WM. A literature review of late complications of radiation therapy for head and neck cancers: incidence and dose response. *J Nucl Med Radiat Ther.* 2012; S2:009. DOI:10.4172/2155-9619.S2-009.
35. Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary th-



- roid cancer. *Best Pract Res Clin Endocrinol Metab.* 2017; 31 (3):335-47. DOI:10.1016/j.beem.2017.04.009.
36. Maia AL, Wajner SM, Vargas CV. Advances and controversies in the management of medullary thyroid carcinoma. *Curr Opin Oncol.* 2017; 29 (1):25-32. DOI : 10.1097/CCO.0000000000000340.
  37. Zatelli MC, Piccin D, Tagliati F, et al. Selective activation of somatostatin receptor subtypes differentially modulates secretion and viability in human medullary thyroid carcinoma primary cultures: potential clinical perspectives. *Journal of Clinical Endocrinology and Metabolism* 2006; 91 2218–2224. (<https://doi.org/10.1210/jc.2006-0334>)
  38. Fromigue J, De Baere T, Baudin E, et al. Chemoembolization for liver metastases from medullary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2006; 91 2496–2499. (<https://doi.org/10.1210/jc.2005-2401>)
  39. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, doubleblind phase III trial. *J Clin Oncol.* 2012; 30 (2):134-41. DOI: 10.1200/JCO.2011.35.5040.
  40. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol.* 2013;31 (29):3639-46. DOI : 10.1200/JCO.2012.48.4659.
  41. Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. *Ann Oncol.* 2018; 29 (8):1869-76. DOI: 10.1093/annonc/mdy137
  42. Subbiah V, Gainor JF, Rahal R, et al. Precision Targeted Therapy with BLU -667 for. *Cancer Discov.* 2018; 8 (7):836-49. DOI: 10.1158/2159-8290.CD-18-0338.
  43. Antonelli A, Ferrari SM, Fallahi P. Current and future immunotherapies for thyroid cancer. *Expert Rev Anticancer Ther.* 2018; 18 (2):149-59. DOI: 10.1080/14737140.2018.1417845.
  44. Beukhof CM, Brabander T, van Nederveen FH, et al. Peptide receptor radionuclide therapy in patients with medullary thyroid carcinoma: predictors and pitfalls. *BMC Cancer* 2019; 19:325.
  45. Papewalis C, Wuttke M, Jacobs B, et al. Dendritic cell vaccination induces tumor epitope-specific Th1 immune response in medullary thyroid carcinoma. *Horm Metab Res* 2008; 40:108-16.
  46. Kraeber- Bodere F, Rousseau C, Bodet- Milin C, et al. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and <sup>131</sup>I-labeled bivalent hapten in a phase I optimization clinical trial. *J Nucl Med.* 2006; 47:247-55.
  47. Fugazzola L, Pinchera A, Luchetti F, et al. Disappearance rate of serum calcitonin after total thyroidectomy for medullary thyroid carcinoma. *Int J Biol Markers* 1994; 9:21e24.
  48. Laure Giraudet A, Al Ghulzan A, Aupérin A, et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times. *Eur J Endocrinol.* 2008;158:239e246.
  49. Barbet J, Champion L, Kraeber-Bodéré F, et al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. *J Clin Endocrinol Metab.* 2005; 90:6077e6084.
  50. Elisei R, Lorusso L, Romei C, et al. Medullary thyroid cancer secreting carbohydrate antigen 19–9 (Ca 19–9): a fatal case report. *Journal of Clinical Endocrinology and Metabolism* 2013; 98 3550–3554. (<https://doi.org/10.1210/jc.2013-1940>)