

Bölüm 16

TİROİD MEDÜLLER KANSERİ

Kadir ESER

GİRİŞ

Medüller tiroid kanseri (MTC), tiroid bezinin parafoliküler C hücrelerinin nöroendokrin tümörüdür. MTC, tiroid kanserlerinin yaklaşık yüzde 1-2'sini oluşturmaktadır [1]. Kalsitonin üretimi bu tümörün karakteristik bir özelliğidir. C hücreleri embriyonik nöral krestten kaynaklanır, bu nedenle medüller karsinomlar sıklıkla karsinoid ve adacık hücresi tümörleri gibi diğer nöroendokrin tümörlerin klinik ve histolojik özelliklerine sahiptir.

Medüller tiroid karsinomlarının çoğu sporadiktir. Bununla birlikte, yaklaşık yüzde 25'i multipl endokrin neoplazi tip 2 (MEN2) sendromunun bir parçası olarak aileseldir.

Klinik: Sporadik MTK Sporadik medüller tiroid kanseri (MTK) tüm hastalık vakalarının yaklaşık yüzde 75'ini oluşturur (Tablo 1). Tipik görülme yaşı yaşamın dördüncü ve altıncı dekattadır [1]

Tablo 1. MTK'nin Sınıflandırılması

Kalıtısal MTK (germline RET mutasyonu mevcut)	%25
Sporadik MTK (tanımlanmış germline RET mutasyonu yok)	%75
Sporadik MTK (tanımlanmış germline RET mutasyonu yok)	
• Somatik RET mutasyonu bulunamadı	%35
• Somatik RET mutasyonları bulundu	%65
- Ekson 16, kodon 918	%60
- Ekson 11, kodon 630, 634	%21
- Ekson 10, kodon 609, 620	%9
- Ekson 15, kodon 891	%9

Belirtiler ve bulgular

Sporadik MTC'nin en sık görülen bulgusu, hastaların yüzde 75-95'inde meydana gelen soliter tiroid nodülüdür [2-5]. C hücreleri baskın olarak her tiroid lobunun üst kısmında bulunur, bu nedenle çoğu tümör bu bölgede tespit

KAYNAKLAR

- Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015; 25:567.
- Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. *Medicine (Baltimore)* 1984; 63:319.
- Dottorini ME, Assi A, Sironi M, et al. Multivariate analysis of patients with medullary thyroid carcinoma. Prognostic significance and impact on treatment of clinical and pathologic variables. *Cancer* 1996; 77:1556.
- Gagel RF, Hoff AO, Cote GJ. Medullary thyroid carcinoma. In: Werner & Ingbar's *The Thyroid*, 9th, Braverman LE, Utiger RD (Eds), Lippincott Williams & Wilkins, Philadelphia 2005. p.967.
- Kebebew E, Ituarte PH, Siperstein AE, et al. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 2000; 88:1139.
- Pacini F, Castagna MG, Cipri C, Schlumberger M. Medullary thyroid carcinoma. *Clin Oncol (R Coll Radiol)* 2010; 22:475.
- Machens A, Hauptmann S, Dralle H. Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer. *World J Surg* 2007; 31:1960.
- Scheuba C, Kaserer K, Bieglmayer C, et al. Medullary thyroid microcarcinoma recommendations for treatment a single-center experience. *Surgery* 2007; 142:1003.
- Machens A, Dralle H. Surgical cure rates of sporadic medullary thyroid cancer in the era of calcitonin screening. *Eur J Endocrinol* 2016; 175:219.
- Kwon H, Kim WG, Sung TY, et al. Changing trends in the clinicopathological features and clinical outcomes of medullary thyroid carcinoma. *J Surg Oncol* 2016; 113:152.
- Machens A, Ukkat J, Hauptmann S, Dralle H. Abnormal carcinoembryonic antigen levels and medullary thyroid cancer progression: a multivariate analysis. *Arch Surg* 2007; 142:289.
- Busnardo B, Girelli ME, Simioni N, et al. Nonparallel patterns of calcitonin and carcinoembryonic antigen levels in the follow-up of medullary thyroid carcinoma. *Cancer* 1984; 53:278.
- Trimboli P, Nasrollah N, Amendola S, et al. Should we use ultrasound features associated with papillary thyroid cancer in diagnosing medullary thyroid cancer? *Endocr J* 2012; 59:503.
- Choi N, Moon WJ, Lee JH, et al. Ultrasonographic findings of medullary thyroid cancer: differences according to tumor size and correlation with fine needle aspiration results. *Acta Radiol* 2011; 52:312.
- Lee S, Shin JH, Han BK, Ko EY. Medullary thyroid carcinoma: comparison with papillary thyroid carcinoma and application of current sonographic criteria. *AJR Am J Roentgenol* 2010; 194:1090.
- Kim SH, Kim BS, Jung SL, et al. Ultrasonographic findings of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma. *Korean J Radiol* 2009; 10:101.
- Bugalho MJ, Santos JR, Sobrinho L. Preoperative diagnosis of medullary thyroid carcinoma: fine needle aspiration cytology as compared with serum calcitonin measurement. *J Surg Oncol* 2005; 91:56.
- Bhanot P, Yang J, Schnadig VJ, Logroño R. Role of FNA cytology and immunochemistry in the diagnosis and management of medullary thyroid carcinoma: report of six cases and review of the literature. *Diagn Cytopathol* 2007; 35:285.

- Kudo T, Miyauchi A, Ito Y, et al. Diagnosis of medullary thyroid carcinoma by calcitonin measurement in fine-needle aspiration biopsy specimens. *Thyroid* 2007; 17:635.
- Costante G, Filetti S. Early diagnosis of medullary thyroid carcinoma: is systematic calcitonin screening appropriate in patients with nodular thyroid disease? *Oncologist* 2011; 16:49.
- Toledo SP, Lourenço DM Jr, Santos MA, et al. Hypercalcitoninemia is not pathognomonic of medullary thyroid carcinoma. *Clinics (Sao Paulo)* 2009; 64:699.
- Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. *Ann Intern Med* 2005; 142:926.
- Erdogan MF, Gursoy A, Kulaksizoglu M. Long-term effects of elevated gastrin levels on calcitonin secretion. *J Endocrinol Invest* 2006; 29:771.
- Preissner CM, Dodge LA, O’Kane DJ, et al. Prevalence of heterophilic antibody interference in eight automated tumor marker immunoassays. *Clin Chem* 2005; 51:208. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (Accessed on August 20, 2012).
- Machens A, Hauptmann S, Dralle H. Medullary thyroid cancer responsiveness to pentagastrin stimulation: an early surrogate parameter of tumor dissemination? *J Clin Endocrinol Metab* 2008; 93:2234.
- Cohen R, Campos JM, Salaün C, et al. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d’Etudes des Tumeurs a Calcitonine (GETC). *J Clin Endocrinol Metab* 2000; 85:919.
- Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *J Clin Endocrinol Metab* 2005; 90:2029.
- Barbet J, Campion 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; 90:6077.
- 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; 158:239.
- Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J Clin Endocrinol Metab* 2010; 95:2655.
- Mirallié E, Vuillez JP, Bardet S, et al. High frequency of bone/bone marrow involvement in advanced medullary thyroid cancer. *J Clin Endocrinol Metab* 2005; 90:779.
- Oudoux A, Salaun PY, Bournaud C, et al. Sensitivity and prognostic value of positron emission tomography with F-18-fluorodeoxyglucose and sensitivity of immunoscintigraphy in patients with medullary thyroid carcinoma treated with anticarcinoembryonic antigen-targeted radioimmunotherapy. *J Clin Endocrinol Metab* 2007; 92:4590.
- Giraudet AL, Vanel D, Leboulleux S, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. *J Clin Endocrinol Metab* 2007; 92:4185.
- Ong SC, Schöder H, Patel SG, et al. Diagnostic accuracy of 18F-FDG PET in restaging patients with medullary thyroid carcinoma and elevated calcitonin levels. *J Nucl Med* 2007; 48:501.
- Berná L, Cabezas R, Mora J, et al. 111In-octreotide and 99mTc(V)-dimercaptosuccinic acid studies in the imaging of recurrent medullary thyroid carcinoma. *J Endocrinol* 1995; 144:339.

- Udelsman R, Ball D, Baylin SB, et al. Preoperative localization of occult medullary carcinoma of the thyroid gland with single-photon emission tomography dimercaptosuccinic acid. *Surgery* 1993; 114:1083.
- American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19:565.
- Krausz Y, Rosler A, Guttmann H, et al. Somatostatin receptor scintigraphy for early detection of regional and distant metastases of medullary carcinoma of the thyroid. *Clin Nucl Med* 1999; 24:256.
- Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med* 2011; 13:755.
- Eng C, Mulligan LM, Smith DP, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 1995; 43:123.
- Zedenius J, Wallin G, Hamberger B, et al. Somatic and MEN 2A de novo mutations identified in the RET proto-oncogene by screening of sporadic MTC:s. *Hum Mol Genet* 1994; 3:1259.
- Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1996; 81:3740.
- Decker RA, Peacock ML, Borst MJ, et al. Progress in genetic screening of multiple endocrine neoplasia type 2A: is calcitonin testing obsolete? *Surgery* 1995; 118:257.
- Elisei R, Romei C, Cosci B, et al. RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. *J Clin Endocrinol Metab* 2007; 92:4725.
- Romei C, Elisei R, Pinchera A, et al. Somatic mutations of the ret protooncogene in sporadic medullary thyroid carcinoma are not restricted to exon 16 and are associated with tumor recurrence. *J Clin Endocrinol Metab* 1996; 81:1619.
- Marsh DJ, Learoyd DL, Andrew SD, et al. Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 1996; 44:249.
- Moura MM, Cavaco BM, Pinto AE, et al. Correlation of RET somatic mutations with clinicopathological features in sporadic medullary thyroid carcinomas. *Br J Cancer* 2009; 100:1777.
- Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. *J Clin Endocrinol Metab* 2011; 96:E863.
- Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab* 2008; 93:682.
- Rosen JE, Lloyd RV, Brierly JD, et al. Thyroid Medullary. In: *AJCC Cancer Staging Manual*, 8th, Amid AB (Ed), Springer, New York 2017. p.891. Corrected at 4th printing, 2018.
- 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.
- Tuttle RM, Ganly I. Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging. *Oral Oncol* 2013; 49:695.
- Yang JH, Lindsey SC, Camacho CP, et al. Integration of a postoperative calcitonin measurement into an anatomical staging system improves initial risk stratification in medullary thyroid cancer. *Clin Endocrinol (Oxf)* 2015; 83:938.

- Lindsey SC, Ganly I, Palmer F, Tuttle RM. Response to initial therapy predicts clinical outcomes in medullary thyroid cancer. *Thyroid* 2015; 25:242.
- Kwon H, Kim WG, Jeon MJ, et al. Dynamic risk stratification for medullary thyroid cancer according to the response to initial therapy. *Endocrine* 2016; 53:174.
- National Comprehensive Cancer Network (NCCN) Guidelines http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (Accessed on July 26, 2012).
- Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015; 25:567.
- Cohen R, Campos JM, Salaün C, et al. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). *J Clin Endocrinol Metab* 2000; 85:919.
- Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J Clin Endocrinol Metab* 2010; 95:2655.
- Scollo C, Baudin E, Travagli JP, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. *J Clin Endocrinol Metab* 2003; 88:2070.
- Kebebew E, Ituarte PH, Siperstein AE, et al. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 2000; 88:1139.
- Duh QY, Sancho JJ, Greenspan FS, et al. Medullary thyroid carcinoma. The need for early diagnosis and total thyroidectomy. *Arch Surg* 1989; 124:1206.
- Fleming JB, Lee JE, Bouvet M, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. *Ann Surg* 1999; 230:697.
- Machens A, Hauptmann S, Dralle H. Prediction of lateral lymph node metastases in medullary thyroid cancer. *Br J Surg* 2008; 95:586.
- Lindsey SC, Ganly I, Palmer F, Tuttle RM. Response to initial therapy predicts clinical outcomes in medullary thyroid cancer. *Thyroid* 2015; 25:242.
- Tuttle RM, Ganly I. Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging. *Oral Oncol* 2013; 49:695.
- Saad MF, Guido JJ, Samaan NA. Radioactive iodine in the treatment of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1983; 57:124.
- Engelbach M, Gorges R, Forst T, et al. Improved diagnostic methods in the follow-up of medullary thyroid carcinoma by highly specific calcitonin measurements. *J Clin Endocrinol Metab* 2000; 85:1890.
- Yang JH, Lindsey SC, Camacho CP, et al. Integration of a postoperative calcitonin measurement into an anatomical staging system improves initial risk stratification in medullary thyroid cancer. *Clin Endocrinol (Oxf)* 2015; 83:938.
- 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; 158:239.
- Ong SC, Schöder H, Patel SG, et al. Diagnostic accuracy of 18F-FDG PET in restaging patients with medullary thyroid carcinoma and elevated calcitonin levels. *J Nucl Med* 2007; 48:501.
- Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: implications for diagnosis, treatment and prognosis. *Expert Rev Mol Diagn* 2008; 8:83.
- Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 2009; 9:28.

- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205.
- Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 2002; 62:7284.
5. Wells SA Jr, Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol* 2010; 28:767.
- Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Endocrinol Metab* 2010; 95:2664.
- <http://www1.astrazeneca-us.com/pi/vandetanib.pdf> (Accessed on April 13, 2011).
- Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30:134.
- http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022405s000lbl.pdf (Accessed on April 08, 2011).
- http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002315/WC500123533.pdf (Accessed on October 01, 2012).
- <http://www.medicines.org.uk/EMC/medicine/26040/SPC/Caprelsa+100+mg+%26+300+mg+film+coated+tablets/> (Accessed on October 01, 2012).
- US Food and Drug Administration. FDA approves Cometriq to treat rare type of thyroid cancer. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm330143.htm> (Accessed on December 03, 2012).
- Cui JJ. Inhibitors targeting hepatocyte growth factor receptor and their potential therapeutic applications. *Expert Opin Ther Pat* 2007; 17:1035.
- Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011; 29:2660.
- Schoffski P, Elisei R, Muller S, et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. *J Clin Oncol* 2012; 30 (suppl):5508. http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/5508 (Accessed on January 25, 2013).
- Schlumberger M, Elisei R, Muller S, et al. Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib (Cabo) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline. *J Clin Oncol* 2015; 33 (suppl): abstr 6012. <http://meetinglibrary.asco.org/content/147994-156> (Accessed on October 11, 2016).
- Sherman SI, Clary DO, Elisei R, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. *Cancer* 2016; 122:3856.
- Schlumberger M, Elisei R, Muller S, et al. Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib (Cabo) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline. *J Clin Oncol* 2015; 33 (suppl): abstr 6012. <http://meetinglibrary.asco.org/content/147994-156> (Accessed on October 11, 2016).

- 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.
- Kober F, Hermann M, Handler A, Krotla G. Effect of sorafenib in symptomatic metastatic medullary thyroid cancer. *J Clin Oncol* 2007; 25:14065.
- Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol* 2010; 28:2323.
- Hong DS, Sebti SM, Newman RA, et al. Phase I trial of a combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in advanced malignancies. *Clin Cancer Res* 2009; 15:7061.
- Kim DW, Jo YS, Jung HS, et al. An orally administered multitarget tyrosine kinase inhibitor, SU11248, is a novel potent inhibitor of thyroid oncogenic RET/papillary thyroid cancer kinases. *J Clin Endocrinol Metab* 2006; 91:4070.
- Kelleher FC, McDermott R. Response to sunitinib in medullary thyroid cancer. *Ann Intern Med* 2008; 148:567.
- 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.
- Ravaud A, de la Fouchardière F, Courbon F, et al. Sunitinib in patients with refractory advanced thyroid cancer: The THYSU phase II trial. *J Clin Onc* 2008; 26:6058.
- 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.
- Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007; 6:2012.
- Bible KC, Suman VJ, Molina JR, et al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab* 2014; 99:1687.
- Ball DW. Medullary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am* 2007; 36:823.
- Wu LT, Averbuch SD, Ball DW, et al. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. *Cancer* 1994; 73:432.
- Nocera M, Baudin E, Pellegriti G, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs à Calcitonine (GETC). *Br J Cancer* 2000; 83:715.
- Shimaoka K, Schoenfeld DA, DeWys WD, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer* 1985; 56:2155.
- Porter AT, Ostrowski MJ. Medullary carcinoma of the thyroid treated by low-dose adriamycin. *Br J Clin Pract* 1990; 44:517.
- Schott M, Seissler J, Lettmann M, et al. Immunotherapy for medullary thyroid carcinoma by dendritic cell vaccination. *J Clin Endocrinol Metab* 2001; 86:4965.
- Stift A, Sachet M, Yagubian R, et al. Dendritic cell vaccination in medullary thyroid carcinoma. *Clin Cancer Res* 2004; 10:2944.

- 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.
- Bachleitner-Hofmann T, Friedl J, Hassler M, et al. Pilot trial of autologous dendritic cells loaded with tumor lysate(s) from allogeneic tumor cell lines in patients with metastatic medullary thyroid carcinoma. *Oncol Rep* 2009; 21:1585.
- Kraeber-Bodéré F, Rousseau C, Bodet-Milin C, et al. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and ¹³¹I-labeled bivalent hapten in a phase I optimization clinical trial. *J Nucl Med* 2006; 47:247.
- Chatal JF, Champion L, Kraeber-Bodéré F, et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. *J Clin Oncol* 2006; 24:1705.
- Iten F, Müller B, Schindler C, et al. Response to [⁹⁰Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. *Clin Cancer Res* 2007; 13:6696.
- National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf (Accessed on February 20, 2018).
- American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19:565.
- Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. *J Clin Endocrinol Metab* 2009; 94:1493.
- Tsimberidou AM, Vaklavas C, Wen S, et al. Phase I clinical trials in 56 patients with thyroid cancer: the M. D. Anderson Cancer Center experience. *J Clin Endocrinol Metab* 2009; 94:4423.
- Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; 8:592.