BÖLÜM
35

Medüller Tiroid Kanserinde Radyonüklid Görüntüleme ve Radyonüklid Tedaviler

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Özet

Medüller tiroid karsinomu, diferansiye tiroid kanserlerine göre çok daha nadiren görülen, ailesel ve sporadik formları olan bir kanser türüdür. Medüller tiroid kanserinde tümör henüz küçük ve tiroide sınırlıyken yapılan efektif bir cerrahi küratif olabilirken, ileri evrede teşhis konulan medüller tiroid kanserlerinde küratif bir tedavi seçeneği bulunmamaktadır. Dolayısıyla medüller tiroid kanserinde tanı ve takipte nüksün veya metastazın erken tanısının hayati önemi bulunmaktadır. Bu amaçla öncelikle konvansiyonel radyolojik görüntülemeler kullanılmakla birlikte, radyonüklid görüntüleme yöntemleri tümörün fonksiyonel davranışını hedefleyerek anatomik görüntülemeyle kıyaslandığında farklı avantajlar sağlamaktadır. Anatomik olarak saptanamayan veya önemsiz kabul edilen küçük lezyonların fonksiyonel olarak metastatik veya malign olup olmadığı saptanabilmekte, hedefe yönelik radyonüklid veya diğer medikal tedaviler için yol gösterici olabilmekte, tümörün diferansiyasyon derecesi hakkında fikir verebilmektedir. Medüller tiroid karsinomunda nükleer tıp görüntüleme yöntemlerinden ilk olarak sintigrafik görüntülemeler denenmiş, daha sonraki yıllarda ise pozitron emisyon tomogafisi (PET) sistemlerinin tüm dünyada yaygınlaşması, ve PET ajanlarının ulaşılabilir hale gelmesi ile sintigrafik ajanlara kıyasla çok daha başarılı tanısal görüntülemeler yapılabilir hale gelmiştir. Benzer şekilde, cerrahinin ve medikal tedavilerin yetersiz kaldığı durumlarda yine tümörün diferansiyasyon ve somatostatin reseptör ekspresyonu derecesinin sintigrafik ajanlar veya PET radyofarmasötikleri ile haritalandıktan sonra bu reseptörleri hedef alan radyonüklidler ile tedavi olanakları da gündeme gelmiştir. Bu bölümde, medüller tiroid kanserinin tanı ve takibinde Nükleer Tıp görüntüleme ve tedavi yöntemleri hakkında genel bir bakış açısı ve klinik yaklaşıma farklı bir perspektiften katkı sağlanması amaçlanmıştır.

Sonuç

Medüller tiroid kanseri, diferansiye tiroid kanserlerinden daha nadiren görülen bir tür olup, tanı ve takiplerinde Nükleer Tıp yöntemleri ile ilgili veri nispeten sınırlıdır. Fonksiyonel görüntüleme yöntemleri, konvansiyonel radyolojik anatomik görüntüleme metodlarından farklı olarak tümörün biyolojik davranışı, diferansiyasyonu ve reseptör ekspresyon durumu hakkında veri sağlaması nedeniyle klinik yaklaşımda tamamlayıcı bir rol üstlenmektedir. Medüller tiroid kanserinin ve nükslerinin erken tanı ve uygun cerrahi tedavisi sağkalımı etkileyen en önemli faktör olup, ileri evrede tanı konan hastalar ile metastatik vakalarda tedavi seçenekleri kısıtlıdır.

Medüller tiroid kanserinde sintigrafik görüntülemeler, radyolojik görüntüleme yöntemlerindeki gelişmelerin ivme kazanması ile kısmen geri planda kalmış olup, son yıllarda pozitron görüntülemenin yaygınlık kazanması ve yeni pozitron yayıcı ajanların kullanıma girmesi ile bu hastaların değerlendirilmesinde fonksiyonel görüntülemeler, özellikle SPECT/BT ve PET/BT gibi hibrid görüntülemeler, her aşamada rol üstlenmektedir. Cerrahi ve medikal tedavilerin yetersiz kaldığı olgularda da yine radyonüklid tedaviler, hastalığın kontrolünde düşük yan etki profili ile son yıllarda önemli bir tedavi seçeneği olarak algoritmalarda yerleşik hale gelmiştir.

Kaynaklar

1. Pitt SC, Moley JF. Medullary, Anaplastic, and Metastatic Cancers of the Thyroid. Seminars in Oncology 2010;37(6):567-79.
2. Machens A, Dralle H. Surgical treatment of medullary thyroid cancer. Recent results. Cancer Res. 2015;204:187–205
3. Pacini F, Castagna MG, Brilli L et al. ESMO Guidelines Working Group. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii110-9
4. Pacini F, Castagna MG, Cipri C, et al. Medullary thyroid carcinoma. Clin Oncol (R Coll Radiol) 2010;22(6):475-85
5. Kloos RT, Eng C, Douglas B. et al. Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association Thyroid. 2009;19(6):565-612
6. Machens A, Dralle H J. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. Clin Endocrinol Metab 2010;95(6):2655-63
7. Shambaugh GE, Quinn JL, Oyasu R, et al. Disparate Thyroid Imaging: Combined Studies With Sodium Pertechnetate Tc 99m and Radioactive Iodine. JAMA. 1974;228(7):866–9.
8. Bombardieri, E., Aktolun, C., Baum, R. P., et al. 111 In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2003:30(12): 140-7.
9. Ercan M.T., Gulaldi N.C., Unsal I.S., et al. Evaluation of Tc-99m(V) DMSA for imaging in ammatory lesions: an experimental study. Ann Nucl Med. 1996;10(4):419–23.
10. Papantoniou V., Tsiouris S., Mainta E., et al. Imaging in situ breast carcinoma (with or without an invasive component) with technetium-99m pentavalent dimercaptosuccinic acid and technetium-99m 2-methoxy isobutyl isonitrile scintimammography. Breast Cancer Res. 2005;7(1):33–45.
11. Clarke S, II PJ, Gambhir SS. In: MEdullary Thyroid cancer. 3 ed. Clarke S, Il PJ, Gambhir SS, editors. Churchill Livingstone; 2004 pp:165-174
12. Clarke S, Lazarus C, Maisey M. Experience in imaging medullary thyroid carcinoma using 99mTc (V) dimercaptosuccinic acid (DMSA). Henry Ford Hosp Med J. 1989;37(3-4):167-8.
13. Chopra A. [99mTc]-Pentavalent dimercaptosuccinic acid. 2010 Jun 11 [Updated 2010 Jul 29]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013
14. Verga U, Muratori F, Di Sacco G, et al. The role of radiopharmaceuticals MIBG and (V) DMSA in the diagnosis of medullary thyroid carcinoma. Henry Ford Hosp Med J. 1989;37(3-4):175-7
15. Papotti M, Kumar U, Volante M, et al. Immunohistochemical detection of somatostatin receptor types 1- 5 in medullary carcinoma of the thyroid. Clin Endocrinol. 2001;54: 641–9
16. de Vries LH, Lodewijk L, Willems SM et al.. SSTR2A expression in medullary thyroid carcinoma is correlated with longer survival Endocrine. 2018 Dec;62(3):639-47
17. Papotti M, Croce S, Bello M, et al. Expression of somatostatin receptor types 2, 3 and 5 in biopsies and surgical specimens of human lung tumours. Correlation with preoperative octreotide scintigraphy. Virchows Arch. 2001;439(6):787–97
18. Hick RJ. Use of molecular targeted agents for diagnosis, staging and therapy of neuroendocrine malignancy. Cancer Imaging. 2010;10:83-91
19. Frank-Raue K, Bihl H, Dörr U, et al. Somatostatin receptor imaging in persistent medullary thyroid car- cinoma. Clin Endocrinol. 1995;42:31–7.
20. Kwekkeboom DJ, Reubi JC, Lamberts SW, et al. In vivo somatostatin receptor imaging in medullary carcinoma. J Clin Endocrinol Metab. 1993;76:1413–7.

21. Baudin E, Lumbroso J, Schlumberger M, et al. Comparison of octreotide scintigraphy and conventional imaging in medullary thy- roid carcinoma. J Nucl Med. 1996;37:912–6.
22. Bernà L, Chico A, Matías-Guiu X, et al. Use of somatostatin ana- logue scintigraphy in the localizatio- on of recurrent medullary thyroid carcinoma Eur J Nucl Med. 1998 Nov;25(11):1482-8
23. Rufini V, Castaldi P, Treglia G, et al. Nuclear medicine procedures in the diagnosis and therapy of medullary thyroid carcinoma. Biomed Pharmacother. 2008;62:139–46.
24. Behr M, Becker W. Metabolic and receptor imaging of metastatic medullary thyroid cancer: does anti-CEA and somatostatin receptor scintigraphy allow for prognostic predictions? Eur J Nucl Nucl Med. 1999;26(1):70-1.
25. Gabriel M, Decristoforo C, Donnemiller E, et al. An intrapatient comparison of 99mTc-EDDA/HYNIC-TOC with 111In-DTPA-octreotide for diagnosis of somatostatin receptor-expressing tumors. J Nucl Med. 2003;44:708–16
26. Okarvi SM. Recent progress in fluorine-18 labelled peptide radiopharmaceuticals Eur J Nucl Med 2001;28:929–38
27. Aslani A, Snowdon GM, Bailey DL, et al. Gallium-68 DOTATATE Production with Automated PET Radiopharmaceutical Synthesis System: A Three Year Experience. Asia Oceania J Nucl Med Biol. 2014;2(2):75-86.
28. Giraudet AL, Vanel D, Leboulleux S, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Endocrinol Metab 2007;92(11):4185-90.
29. Beheshti M, Pocher S, Vali R, et al. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. Eur Radiol 2009; 19(6):1425-34.
30. Kauhanen S, Schalin-Jantti C, Seppanen M, et al. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer. J Nucl Med 2011;52(12):1855-63
31. Luster M, Karges W, Zeich K, et al. Clinical value of 18- fluorinefluorodihydroxyphenylalanine positron emission tomography/computed tomography in the follow-up of medullary thyroid carcinoma. Thyroid 2010;20(5):527-33.
32. Treglia G, Castaldi P, Villani MF, et al. Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 2012;39(4):569-80.
33. Verbeek HH, Plukker JT, Koopmans KP, et al. Clinical relevance of 18F-FDG PET and 18F-DOPA PET in recurrent medullary thyroid carcinoma. J Nucl Med 2012;53(12):1863-71.
34. Treglia G, Villani MF, Giordano A et al. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 fluorodeoxyglucose positron emission tomography: a meta-analysis. Endocrine 2012;42(3):535-45
35. Rodríguez-Bel L, Sabaté-Llobera A, Rossi-Seoane S, et al. Diagnostic Accuracy of 18F-FDG PET/CT in Patients With Biochemical Evidence of Recurrent, Residual, or Metastatic Medullary Thyroid Carcinoma. Clin Nucl Med. 2019 Mar;44(3):194-200
36. 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(4):501-7
37. Adams S, Baum RP, Hertel A, et al. Metabolic (PET) and receptor (SPET) imaging of well and less well-differentiated tumours: comaprison with the expression of the Ki-67 antigen. Nucl Med Commun 1998:19(7):641-7
38. Skoura E, Datseris IE, Rondogianni P, et al. Correlation between calcitonin levels and [^{18}F] FDG PET/CT in the detection of recurrence in patients with sporadic and hereditary medullary thyroid cancer. ISRN Endocrinol 2012; 2012:37523
39. DeLuca S, Fonti R, Camera L, et al. Multimodal imaging with ^{18}F-FDG-PET/CT and ^{111}In-Octreotide SPECT in patients with metastatic medullary thyroid carcinoma. Ann Nucl Med 2016;30(3):234-41
40. Salaun PY, Campion L, Ansquer C, et al. ^{18}F-FDG PET predicts survival after pretargeted radioimmunotherapy in patients with progressive metastatic medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2014 Aug;41(8):1501-10.
41. Werner RA, Bundschuh RA, Higuchi T, Javadi MS, et al. Volumetric and texture analysis of pretherapeutic 18F-FDG PET can predict overall survival in medullary thyroid cancer patients treated with Vandetanib. Endocrine. 2019 Feb;63(2):293-300.
42. Lussey-Lepoutre C, Hindié E, Montravers F et al. The current role of 18F-FDOPA PET for neuroendocrine tumor imaging. Médecine Nucl. 2016;40:20–30.
43. Rasul S, Hartenbach S, Rebhan K, [18F]DOPA PET/ceCT in diagnosis and staging of primary medullary thyroid carcinoma prior to surgery Eur J Nucl Med Mol Imaging. 2018;45(12):2159-69.
44. Treglia G, Cocciolillo F, Di Nardo F, et al. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 dihydroxyphenylalanine positron emission tomography: a meta-analysis. Acad Radiol. 2012 Oct;19(10):1290-9.
45. Romero-Lluch AR, Cuenca-Cuenca JI, Guerrero-Vázquez G et al. Diagnostic utility of PET/CT with 18F-DOPA and 18F- FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff. Eur. J. Nucl. Med. Mol. Imaging 2017;44:2004–13.
46. Archier A, Heimburger C, Guerin C, et al. (18)F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2016;43(6):1027-33.
47. Caobelli F, Chiaravalloti A, Evangelista L, et al. Predictive and prognostic value of 18F-DOPA PET/CT in patients affected by recurrent medullary carcinoma of the thyroid. Ann Nucl Med. 2018;32(1):7-15.
48. G. Treglia, P. Castaldi, M.F. Villani et al. Comparison of 18F- DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with

recurrent medullary thyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging 2012; 39:569–80
49. Treglia G, Rufini V, Salvatori M, et al. PET imaging in recurrent medullary thyroid carcinoma. Int. J. Mol. Imaging 2012, 324686.
50. Slavikova K, Montravers F, Treglia G et al. What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr. Radiopharm.2013;6:96–105.
51. Bozkurt MF, Virgolini I, Bargolona S et al, Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F–DOPA Eur J Nucl Med Mol Imaging 2017;44:1588–1601
52. Teunissen JJM, Kwekkeboom DJ, Valkema R, et al. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr. Relat. Cancer 2011:18(Suppl 1), 27–51
53. Rahmim A, Zahidi H. PET versus SPECT: strengths, limitations and challenges. Nucl Med Commun 2008;29:193–207
54. Yamaga LY, Cunha ML, Campos Neto GC, et al. 68Ga-DOTATATE PET/CT in recurrent medullary thyroid carcinoma: a lesion-by-lesion comparison with 111In-octreotide SPECT/CT and conventional imaging Eur J Nucl Med Mol Imaging 2017;44:1695–1701
55. Treglia, G., Tamburello, A., Giovanella, L. Detection rate of somatostatin receptor PET in patients with recurrent medullary thyroid carcinoma: a systematic review and a meta-analysis. Hormones 2017;16(4):362-72
56. Giraudet AL, Vanel D, Leboulleux S, et al: Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Oncol 2007;92:4185-90
57. Giraudet AL, Ghulzan A, Auperin A, et al. Progression of medullary thyroid carcinoma: Assessment with calcitonin and carcinoembryonic antigen doubling times. Eur J Endocrinol 2008;158:239-46
58. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25(6):567–610.
59. Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639–46
60. 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(2):134–41.
61. Baum RP, Kulkarni HR: THERANOSTICS: From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radio- nuclide therapy—The Bad Berka experience. Theranostics 2012;2:437-47
62. aum RP, Kulkarni HR, Carreras C. Peptides and receptors in image-guided therapy: Theranostics for neuroendocrine neoplasms. Semin Nucl Med 2012;42:190-207
63. eubi JC, Horisberger U, Laissue J. High density of somatostatin receptors in veins surrounding human cancer tissue: Role in tumor-host interaction? Int J Cancer 1994;56:681-688
64. Iten F, Muller 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(22 Pt 1):6696–702.
65. Vaisman F, de Castro PH, Lopes FP, et al. Is there a role for peptide receptor radionuclide therapy in medullary thyroid cancer? Clin Nucl Med. 2015;40(2):123–7.
66. Beukhof, C.M., Brabander, T., van Nederveen, F.H. et al. Peptide receptor radionuclide therapy in patients with medullary thyroid carcinoma: predictors and pitfalls BMC Cancer 2019;19: 325.