

Diferansiye Tiroid Kanseri Preoperatif Klinik ve Moleküler Risk Sınıflaması

- Prof. Dr. Oya TOPALOĞLU
- Dr. Öğr. Üyesi Berna ÖĞMEN
- Uz. Dr. Fatma Dilek DELLAL KAHRAMANCA

Özet

Diferansiye tiroid kanserlerinde son dönemde kılavuzlarda da öne çıkan en önemli nokta hastalığı tedavi ederken tedaviye bağlı morbiditeyi ve aşırı tedaviyi en aza indirmektedir. Çok-düşük riskli (invazyon, metastaz, agresif sitoloji veya moleküler belirteç bulgusu olmayan intratiroidal, papiller mikrokarsinom) hastalarda artık aktif takip de bir tedavi seçeneği iken, düşük-orta riskli hastalarda total tiroidektomi yerine sınırlı cerrahi yapılması kararı da değerlendirilmelidir. Bu nedenle preoperatif risk sınıflaması gündeme gelmiştir. Preoperatif risk sınıflamasında klinik risk değerlendirilmesi öncelikli olarak yapılmalıdır. Klinik risk sınıflamasında özellikle yaş, anamnez, fizik muayene ile fokal ve uzak metastaz değerlendirmesi, aile öyküsü, ultrasonografi ile tümör özellikleri ve boyun lenf nodlarının değerlendirilmesi yapılmalıdır. Ancak tek başına klinik riski değerlendirerek tedavide doğru kararlar vermek mümkün olmayabilir. Çünkü zaman zaman klinik riski düşük ancak agresif seyirli vakalarla da karşılaşmak mümkündür. Buna göre düşük riskli hastaları aşırı tedavi etmek veya agresif seyirli olabilecek bir hastayı da yetersiz tedavi etmek olasıdır. Bu nedenle son dönemlerde moleküler-genetik risk sınıflaması da gündeme gelmiştir. Bunlar içerisinde en fazla prognostik önemi bilinen mutasyonlar BRAF V600E ve TERT promoter mutasyonlarıdır. Özellikle bu iki mutasyonun birlikteliğinin agresif seyir, mortalite ve uzak metastaz ile ilişkili olduğu gösterilmiştir.

yeterli gibi görünürken daha büyük intratiroidal tümörü olanlarda BRAF (+) olanlarda daha agresif tedavi gündeme gelebilir (total tiroidektomi, profilaktik lenf nodu diseksiyonu, RAİ ablasyonu gibi) (68). BRAF (-) olan mikropapiller kanserlerde aktif takip de düşünülebilir. Tüm bu bilgiler ışığında BRAF V600E+TERT promoter mutasyonu veya RAS+ TERT promoter mutasyonu olan hastaların hastalığın agresif seyri ve yüksek mortalitesi ile agresif tedavi edilmesi de mantıklı gibi görünmektedir. Mikropapiller PTK dahi olsa bu mutasyonları birlikte taşıyanlarda total tiroidektomi önerilmesi makul bir tedavi yaklaşımıdır. İlerleyen yıllarda elde edilen veriler arttıkça bu hastalarda törepatik veya profilaktik LN diseksiyonu ve RAİ ablasyonu da gündeme gelecektir (68).

Tek başına RAS mutasyonu olan sitolojisi benign nodüller izlenebilirken, RAS (+) indeterminate nodüllere ve klinik olarak düşük riskli RAS (+) DTK'larda sınırlı cerrahi yapılabilir (68).

Sonuç olarak, kılavuzlarda vurgulandığı şekli ile DTK vakalarında preoperatif risk sınıflaması hangi hastalara aktif takip ya da sınırlı cerrahi yapılacağını hangi hastaların da daha geniş cerrahilerle agresif şekilde tedavi edileceğini belirlemede önemlidir. Özellikle bu yaklaşımla DTK'larda cerrahiye bağlı morbiditeyi azaltmak ayrıca yeterli veya aşırı tedaviyi en aza indirmek mümkün olacaktır. Bu nedenle tüm DTK hastalarına mutlaka preoperatif klinik risk sınıflaması yapmak ve mümkünse bunu moleküler belirteçlerle desteklemek uygun bir yaklaşım olacaktır.

Kaynaklar

- Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26(1):1-133.
- Lubitz CC, Sosa JA. The changing landscape of papillary thyroid cancer: Epidemiology, management, and the implications for patients. *Cancer* 2016;122:3754-9.
- Ito Y, Miyauchi A. Nonoperative management of low-risk differentiated thyroid carcinoma. *Curr Opin Oncol* 2015;27(1):15-20.
- Miyauchi A, Kudo T, Miya A, et al. Prognostic impact of serum thyroglobulin doubling-time under thyrotropin suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy. *Thyroid* 2011;21(7):707-16.
- Miyauchi A, Kudo T, Kihara M, et al. Relationship of biochemically persistent disease and thyroglobulin-doubling time to age at surgery in patients with papillary thyroid carcinoma. *Endocr J* 2013;60(4):415-21.
- Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* 2014;24(1):27-34.
- Navas-Carrillo D, Ríos A, Rodríguez JM, et al. Familial nonmedullary thyroid cancer: screening, clinical, molecular and genetic findings. *Biochim Biophys Acta* 2014;1846(2):468-76.
- Ji Wang L, Zhendong L, Shuchun L, et al. Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma. *Acta Otorhinolaryngol Ital* 2015;35(4):234-42.
- Hillenbrand A, Varhaug JE, Brauckhoff M, et al. Familial nonmedullary thyroid carcinoma-clinical relevance and prognosis. A European multicenter study. *ESES Vienna presentation. Langenbecks Arch Surg* 2010;395(7):851-8.
- Sippel RS, Caron NR, Clark OH. An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. *World J Surg* 2007;31(5):924-33.
- Hayashi Y, Lagarde F, Tsuda N, et al. Papillary microcarcinoma of the thyroid among atomic bomb survivors: tumor characteristics and radiation risk. *Cancer* 2010;116(7):1646-55.
- Hoang JK, Branstetter BF 4th, Gaf-ton AR, et al. Imaging of thyroid carcinoma with CT and MRI: approaches to common scenarios. *Cancer Imaging* 2013;13(1):128-39.
- Wein RO. Management of the locally aggressive thyroid carcinoma. *Am J Otolaryngol* 2005;26(3):186-92.
- Machado NO, Chopra PJ, Al Hamdani A. Papillary Carcinoma of the Thyroid Presenting Primarily as Cervical Lymphadenopathy: An approach to management. *Sultan Qaboos Univ Med J* 2009;9(3):328-32.
- Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. *Surgery* 2006;39(3):357-62.
- de Giorgi V, Alfaioli B, Massi D, et al. Solitary cutaneous metastasis as the first sign of relapse of thyroid carcinoma: a clinical, dermoscopic-pathologic case study. *Dermatol Surg* 2009;35(3):523-6.
- Lee J, Soh EY. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors. *Ann Surg* 2010;251(1):114-9.
- Tam AA, Ozdemir D, Aydın C, et al. Association between preoperative thyrotrophin and clinicopat-

- hological and aggressive features of papillary thyroid cancer. *Endocrine* 2018;59(3):565-72.
19. Zheng J, Li C, Lu W, et al. Quantitative assessment of preoperative serum thyrotropin level and thyroid cancer. *Oncotarget* 2016;7:34918-29.
 20. McLeod DS, Watters KF, Carpenter AD, et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose response meta-analysis. *J Clin Endocrinol Metab* 2012;97:2682-92.
 21. Kim HK, Yoon JH, Kim SJ, et al. Higher TSH level is a risk factor for differentiated thyroid cancer. *Clin Endocrinol* 2013;78:472-7.
 22. He LZ, Zeng TS, Pu L, et al. Thyroid hormones, autoantibodies, ultrasonography, and clinical parameters for predicting thyroid cancer. *Int J Endocrinol* 2016;2016:8215834.
 23. Petric R, Besic H, Besic N. Preoperative serum thyroglobulin concentration as a predictive factor of malignancy in small follicular and Hürthle cell neoplasms of the thyroid gland. *World J Surg Oncol* 2014;12:282.
 24. Petric R, Perhavec A, Gazic B, Besic N. Preoperative serum thyroglobulin concentration is an independent predictive factor of malignancy in follicular neoplasms of the thyroid gland. *J Surg Oncol* 2012;105(4):351-6.
 25. Kim H, Kim YN, Kim HI, et al. Preoperative serum thyroglobulin predicts initial distant metastasis in patients with differentiated thyroid cancer. *Sci Rep* 2017;7(1):16955.
 26. Jo K, Kim MH, Ha J, et al. Prognostic value of preoperative anti-thyroglobulin antibody in differentiated thyroid cancer. *Clin Endocrinol* 2017;87(3):292-9.
 27. Yeh MW, Bauer AJ, Bernet VA, et al; American Thyroid Association Surgical Affairs Committee Writing Task Force. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. *Thyroid* 2015;25(1):3-14.
 28. Calcaterra NA, Lutfi W, Suman P, et al. Concordance of pre-operative clinical stage with pathologic stage in patients ≥ 45 years old with well-differentiated thyroid cancer. *Endocr Pract* 2018;24(1):27-32.
 29. Zhang J, Fei M, Dong Y, et al. Preoperative ultrasonographic staging of papillary thyroid carcinoma with the Eighth American Joint Committee on Cancer Tumor-Node-Metastasis Staging System. *Ultrasound Q* 2019 Jul 17. doi: 10.1097/RUQ.0000000000000469. [Epub ahead of print]
 30. Tuttle M, Morris LF, Haugen B, Shah J, Sosa JA, Rohren E, Subramaniam RM, Hunt JL, Perrier ND. Thyroid-Differentiated and Anaplastic Carcinoma (Chapter 73). In: Amin MB, Edge SB, Greene F, Byrd D, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley J, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, eds. *AJCC Cancer Staging Manual*. 8th ed. New York City: Springer International Publishing; 2017.
 31. Salvatore B, Klain M, Nicolai E, et al. Prognostic role of FDG PET/CT in patients with differentiated thyroid cancer treated with 131-iodine empiric therapy. *Medicine (Baltimore)* 2017;96(42):e8344.
 32. Are C, Hsu JF, Ghossein RA, et al. Histological aggressiveness of fluorodeoxyglucose positron-emission tomogram (FDG-PET)-detected incidental thyroid carcinomas. *Ann Surg Oncol* 2007;14(11):3210-5.
 33. Kwon SY, Choi EK, Kong EJ, et al. Prognostic value of preoperative 18F-FDG PET/CT in papillary thyroid cancer patients with a high metastatic lymph node ratio: a multicenter retrospective cohort study. *Nucl Med Commun* 2017;38(5):402-6.
 34. Pryma DA, Schöder H, Gönen M, et al. Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients. *J Nucl Med* 2006;47(8):1260-6.
 35. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. *Lancet* 2013; 381: 1058-69.
 36. Miccoli P, Materazzi G, Macerola E, Bakkar S. Tailored surgery according to molecular analysis in differentiated thyroid carcinomas. *Gland Surg* 2018; 7(Suppl 1):S30-3.
 37. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. *World J Surg* 2016; 40: 516-22.
 38. Danilovic DLS, Lima EU, Domingues RB, et al. Pre-operative role of BRAF in the guidance of the surgical approach and prognosis of differentiated thyroid carcinoma. *Eur J Endocrinol* 2014; 619-25.
 39. Zatelli MC, Trasforini G, Leoni S, et al. BRAF V600E mutation analysis increases diagnostic accuracy for papillary thyroid carcinoma in fine-needle aspiration biopsies. *Eur J Endocrinol* 2009; 161: 660-6.
 40. Yip L, Sosa JA. Molecular-Directed Treatment of Differentiated Thyroid Cancer. *Advances in Diagnosis and Treatment. JAMA Surg* 2016; 151(7): 663-70.
 41. Tufano RP, Teixeira GV, Bishop J, et al. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. *Medicine (Baltimore)* 2012; 91(5): 274-86.
 42. Kim TH, Park YJ, Lim JA, et al. The association of the BRAF (V600E) mutation with prognostic factors and poor clinical outcome in papillary thyroid cancer: a meta-analysis. *Cancer* 2012; 118(7): 1764-73.
 43. Xing M. BRAF mutation in thyroid cancer. *Endocr Relat Cancer* 2005; 12(2): 245-62.
 44. Elisei R, Viola D, Torregrossa L, et al. The BRAF^{V600E} mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroidal papillary thyroid carcinoma: Single institution results from a large cohort study. *J Clin Endocrinol Metab* 2012; 97: 4390-8.
 45. Ma B, Wang Y, Yang S, Ji Q. Predictive factors for central lymph node metastasis in patients with cN0 papillary thyroid carcinoma: a systematic review and meta-analysis. *Int J Surg* 2016; 289: 153-61.
 46. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab* 2005; 90: 6373-9.
 47. Xing M, Clark D, Guan H, et al. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J Clin Oncol*. 2009; 27: 2977-82.

48. Lin KL, Wang OC, Zhang XH, et al. The BRAF mutation is predictive of aggressive clinicopathological characteristics in papillary thyroid microcarcinoma. *Ann Surg Oncol* 2010; 17: 3294-300.
49. Liu C, Chen T, Liu Z. Associations between BRAF(V600E) and prognostic factors and poor outcomes in papillary thyroid carcinoma: a meta-analysis. *World J Surg Oncol* 2016;14: 241.
50. Yip L, Wharry LI, Armstrong MJ, et al. A clinical algorithm for fine-needle aspiration molecular testing effectively guides the appropriate extent of initial thyroidectomy. *Ann Surg* 2014; 260: 163-8.
51. Xing M. Prognostic utility of BRAF mutation in papillary thyroid cancer. *Mol Cell Endocrinol* 2010; 321: 86-93.
52. Howell GM, Nikiforova MN, Carty SE, et al. BRAF V600E mutation independently predicts santral compartment lymph node metastasis in patients with papillary thyroid cancer. *Ann Surg Oncol* 2013; 20: 47-52.
53. Gandolfi G, Sancisi V, Torricelli F, et al. Allele percentage of the BRAF V600E mutation in papillary thyroid carcinomas and corresponding lymph node metastases: no evidence for a role in tumor progression. *J Clin Endocrinol Metab* 2013; 98: 934-42.
54. Xing M. Clinical utility of RAS mutations in thyroid cancer: a blurred Picture now emerging clearer. *BMC Med* 2016; 14: 12.
55. Medici M, Kwong N, Angell TE, et al. The variable phenotype and low-risk nature of RAS-positive thyroid nodules. *BMC Med* 2015; 13: 184.
56. Alzahrani AS, Alsaadi R, Murugan AK, et al. TERT promoter mutations in thyroid cancer. *Horm Cancer* 2016; 7(3): 165-77.
57. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocr Relat Cancer* 2016; 23(3): 143-55.
58. Melo M, da Rocha AG, Vinagre J, et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. *J Clin Endocrinol Metab* 2014; 99(5): 754-65.
59. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary cancer with highest recurrence. *J Clin Oncol* 2014; 32: 2718-26.
60. Moon S, Song YS, Kim YA, et al. Effects of coexistent BRAFV600E and TERT promoter mutations on poor clinical outcomes in papillary thyroid cancer: a meta-analysis. *Thyroid* 2017; 27: 651-60.
61. Landa I, Ganly I, Chan TA, et al. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metab* 2013; 98(9): 1562-6.
62. Liu X, Bishop J, Shan Y, et al. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. *Endocr Relat Cancer* 2013; 20(4): 603-10.
63. Liu R, Bishop J, Zhu G, et al. Mortality risk stratification by combining BRAF V600E and TERT promoter mutations in papillary thyroid cancer: genetic duet of BRAF and TERT promoter mutations in thyroid cancer mortality. *JAMA Oncol* 2017; 3(2): 202-8.
64. Yang X, Li J, Li X, et al. TERT promoter mutation predicts radio-iodine refractory character in distant metastatic differentiated thyroid cancer. *J Nucl Med* 2017; 58(2): 258-65.
65. Sohn SY, Park WY, Shin HT, et al. Highly concordant key genetic alterations in primary tumors and matched distant metastases in differentiated thyroid cancer. *Thyroid* 2016; 26(5): 672-82.
66. Shen X, Liu R, Xing M. A six-genotype genetic prognostic model for papillary thyroid cancer. *Endocr Relat Cancer* 2017; 24(1): 41-52.
67. Song YS, Lim JA, Choi H, et al. Prognostic effects of TERT promoter mutations are enhanced by coexistence with BRAF or RAS mutations and strengthen the risk prediction by the ATA or TNM staging system in differentiated thyroid cancer patients. *Cancer* 2016; 122(9): 1370-9.
68. Xing M. Genetic-guided risk assessment and management of thyroid cancer. *Endocrinol Metab Clin N Am* 2019; 48: 109-24.
69. Huang Y, Qu S, Zhu G, et al. BRAF V600E mutation-assisted risk stratification of solitary intratiroidal papillary thyroid cancer for precision treatment. *J Natl Cancer Inst* 2018; 110(4): 362-70.