BÖLÜM

8

Tiroid Sitolojisi: Güncel Durum

- Dr. Öğr.Üyesi Ayşegül AKSOY ALTINBOĞA
- Doç. Dr. Aylin KILIÇ YAZGAN
- Doç. Dr. Şefika Burçak POLAT

Özet

İnce iğne aspirasyon biyopsisi (İİAB) oldukça sık rastlanan tiroid nodüllerinin değerlendirilmesinde hızlı ve etkin bir tanısal yöntemdir. Tiroid İİAB ile hedeflenen neoplastik/malign nodüllerin diğer benign nodüllerden ayırımını yapması ve cerrahiye gidecek hastalara karar vermede yardımcı olmasıdır. Tiroid İİAB raporlarının klinisyene açık, net ve klinik olarak kullanışlı bir terminoloji ile iletilebilmesi çok önemlidir. Bethesda klasifikasyonu nondiagnostik/yetersiz, benign, önemi belirsiz atipi/önemi belirsiz folliküler lezyon, folliküler neoplazi/folliküler neoplazi şüphesi, malignite şüphesi, malign olmak üzere toplam 6 ayrı tanı kategorinin belirlendiği ve tiroid İİAB raporlamasında tüm dünyada yaygın olarak kullanılan bir yöntemdir. Her bir kategorinin belirli bir kanser riskine işaret ettiği bu sistem ayrıca her bir kategoriyi kanıta dayalı klinik yaklaşımlar ile ilişkilendirmiştir. Tiroid sitolojisini değerlendirirken özellikle kuşkulu gruplar için ayırıcı tanıda ek yardımcı yöntemlerden yardım almanın gerekliliği görülmektedir. Tiroid tümörlerinin patogenezinde yer alan mutasyonların ortaya konmasından sonra bu moleküler değişikliklerin preoperatif tanıda, tanıya yardımcı bir yöntem olarak kullanılması gündeme gelmeye başlamıştır. Sitolojik olarak kuşkulu ketegoride yer alan tiroid nodüllerini değerlendirmede kullanılan moleküler testler Gen ekspresyon temelli testler, gen mutasyon temelli testler ve mikroRNA temelli testlerdir.

Kaynaklar

1. Schlumberger M, Pacini F, Wiersinga WM, et al. Follw-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. Eur J of Endocrinol. 2004;151(5):539-548.
2. Hegedüs L. Clinical practice. The thyroid nodüle. N Engl J of Med. 2004;351(17):1764-1771
3. Pitman MB, Abele J, Ali S, et al. Technicques for thyroid FNA: Asynopsis of the National Cancer Institude Thyroid Fine Needle Aspiration State of the Science Conference. Diagn Cytopathol. 2008;36:407-424
4. Ali S, Cibas E 2018. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. Second edition. Springer, New York, NY.
5. Raab SS, Grzybicki DM, Audilovsky D, et al. Effectiveness of Toyota process redesign in reducing thyroid gland fine needle aspiration error. Am J Clin Pathol. 2006:126:585-592.
6. Demay RM 2012. Thyroid. In: The Art and Science of Cytopathology. Second edition. American Society for Clinical Pathology Press, Hong Kong; 2012 p.841-943.
7. Bode-Lesniewska B, Cochand-Priollet B, Straccia P, et al. Management of thyroid cytological materail, preanalytical procedures and bio-banking. Cytopathol. 2019;30(1):7-16.
8. Chong Y, Ji SJ, Kang CS, et al. Can liquid-based preperation substitute for conventional smear in thyroid fine-needle aspiration? A systematic review based on meta-analysis. Endocr connect.2017;6(8):817-829.
9. Sharma S, Agarwal S, Jain M, et al. Cytomorphological differences betweern liquid-based cytology and conventional smears in fine-needle aspirates of thyroid lesions. J Cytol. 2018;35(4)208-211.
10. Sharma Afify AM, Liu J, Al-Khafaji BM. Cytologic artifacts and pitfalls of thyroid fine-needle aspiration using ThinPrep: A comparative retrospective review. Cancer. 2001;93:179–86.
11. Cochand-Priollet B, Prat JJ, Polivka M, Thienpont L, Dahan H, Wassef M, et al. Thyroid fine needle aspiration: The morphological features on ThinPrep slide preparations. Eighty cases with histological control. Cytopathology. 2003;14:343–9.
12. Cibas E, Ali SZ. The 2017 Bethesda System for Reporting thyroid Cytopathology. Thyroid. 2017;27(11): 1341-6.
13. Baloch ZW, Cibas ES, Clark DP, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 2008;5:6.
14. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of Science Conference. Diagn Cytopathol 2008;36(6):425-37.
15. Ali S, cibas E. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. Second edition. Springer, New York, NY. 2010. P. 1-5.
16. Sudilovsky D. Interpretation of the paucicellular thyroid fine needle aspiration biopsy specimen. Pathol Case Rev. 2005;10(2):68-73.
17. Haider AS, Rakka EA, Dunkley C, ZAitoun BM. The impact of using defined criteria for adequacy of fine needle aspiration cytology of the thyroid in routine practice. Diagn Cytopathol. 2011;39(2):81-86
18. Gunes P, et al. A different perspective on evaluating the malignancy rate of the non-diagnostic category of the Bethesda system for reporting thyroid cytopathology: a single institute experience and review of the literatüre. PLos One. 2016;11(9):e0162745
19. Alexander EK, Heering JP, Benson CB, et al. Assessment of nondiagnostic ultrasound-guided fine needle aspriation of thyroid nodules. J Clin Endocrinol Metab. 2002;87:4924-7.
20. Sheffield BS, Masoudi H, Walker B, Wiseman SM. Preoperative diagnosis of thyroid nodules using the Bethesda system for reporting thyroid cytopathology: a comprehensive review and mata-analysis. Exp Rev Endo Metab. 2014;9:97-110.
21. Haugen BR, Alexander EK, Bible KC, et al. For the American Assocation Guidelines Task Force. 2015 American Thyroid Association management guidelines for adult patient with thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133.
22. Naim C, Karam R, Edde D. Ultrasound-guided fine-needle aspiration biopsy of the thyroid: methods to decrease the rate of unsatisfactory biopsies in the absence of an on-site pathologist. Can Assoc Radiol J. 2013;64(3):220-5.
23. Olson MT, Clark DP, Erozan YS, Ali SZ. Spectrum of risk of malignancy in subcategories of 'atypia of undetermined significance'. Acta Cytol. 2011;55(6):518-25.
24. Straccia P, Rossi ED, Bizzarro T, et al. A meta-analytic review of the Bethesda system for reporting thyroid cytopathology: has the rate of malignacy in indeterminate lesions been underestimated? Cancer Cytopathol. 2015;123(12):713-22.
25. Renshaw AA. Does a repeated benign aspirate change the risk of malignancy after an initial aatypical thyroid fine-needle aspiration? Am J Clin Pathol. 2010;134(5):788-92.
26. VanderLaan PA, Marquesee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle apirations: should repeated FNA be the prefered initial approach? Am J Clin Pathol. 2011;135(5):770-5.
27. Baloch Z, LiVolsi VA, Jain R, et al. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. Diagn Cytopathol. 2003;29:203-6.
28. Nikiforov YE, Carty SE, Chiosea SI, et al. Impact of multi-gene ThyroSeq next-generation sequencing assay on cancer diagnosis in thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance cytology. Thyroid. 2015;25(11):1217-23.
29. Krane JF, Cibas ES, Alexander EK, et al. Molecular analysis of residual ThinPrep material from thyroid FNAs increases diagnostic sensitivity. Cancer Cytopathol. 2015;123:356-61.

30. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules withindeterminate cytology. N Eng J Med. 2012;367(8):705-15
31. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. Cancer. 2007;111(5):306-15.
32. Deveci MS, Deveci G, LiVolsi Va, Baloch ZW. Fine needle aspiration of follicular lesions of the thyroid diagnosis and follow-up. Cytojournal. 2006;3:9.
33. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of 'follicular neoplasm': a gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol. 2002;26(1):41-4.
34. Schlinkert RT, van Heerden JA, Goellner JR, et al. Factors that predict malignant thyroid lesions when fine-needle aspiration is 'suspicious for follicular neoplasm'. Mayo Clin Proc. 1997;72(10):913-6.
35. Kelman AS, Rathan A, Leibowitz J, et al. Thyroid cytology and the risk of malignancy in thyroid nodules: importance of nuclear atypia in indeterminate specimens. Thyroid. 2001;11(3):271-7.
36. Elsheikh TM, Asa SL, Chan JK,, et al. Interobserver and intraobserver variation among experts in the diagosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. Am J Clin PAthol. 2008;130(5):736-44.
37. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. Cancer. 2007;111(5):306-15.
38. Yassa L, cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodüle diagnostic evaluation. Cancer. 2007;111(6):508-16.
39. Nikiforov YE, Carty SE, Chiosea SI, et al. Highly accurate diagnosis of cancer in thyroid nodules with molecular tests guide extent of thyroid surgery 767 follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014;120(23):3627-34.
40. Maximo V, Lima J, Prazeres H, et al. The biology and genetics of Hürthle cell tumorsof the thyroid. Endocr Relat Cancer. 2012;19(4):R131-47.
41. French CA, Alexander EK, Cibas ES, et al. Genetic and biological subgroups of low-stage follicular thyroid cancer. Am J Pathol. 2003;162(4):1053-60.
42. Nikiforova MN, Biddinger PW, Caudill CM, et al. PAX8-PPARgamma rearrangement in thyroid tumors:RT-PCR and immunohistochemical analyses. Am J Surg Pathol. 2002;26(8):425-37.
43. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol.2012;56(4):333-9.
44. Harvey AM, Mody DR, Amrikachi M. Thyroid fine-needle aspiration reporting rates and outcomes before and after Bethesda implementation within a combined academic and community hospital system. Arch Pathol Lab Med. 2013;137(11):1664-8.
45. Krauss EA, Mahon M, Fede JM, et al. Application of the Bethesda classification for thyroid fine-needle aspiration: institutional experience and meta-analysis. Arch Pathol Lab Med. 2016;140(10):1121-31.
46. Jo VY, Stelow EB, Dustin SM, et al. Malignancy risk for fine-needle aspiration of thyroid lesioms according to the Bethesda system for reporting cytopathology. Am J Clin Pathol. 2010;134(3):450-6.
47. Renshaw AA. Subclassification of atypical cells of undetermined significance in direct smears of fine-needle aspirations of the thyroid: distinct patterns and associated risk of malignancy. Cancer Cytopathol. 2011;119(5):322-7.
48. VanderLaan PA, Marqusee E, Krane JF. Features associcated with locoregional spread of papillary carcinoma correlate with diagnostic category in the Bethesda system for reporting thyroid cytopathology. Cancer Cytopathol. 2012;120(4):245-53.
49. Mastorakis E, Meristoudis C, Margari N, et al. Fine needle aspiration cytology og nodular thyroid lesions: a 2-year experience of the Bethesda system for reporting thyroid cytopathology in a large regional and a university hospital, with histological correlation. Cytopathology. 2014;25(2):120-8.
50. Deniwar A, Hambleton C, Thethi T, et al. Examining the Bethesda criteria risk stratification of thyroid nodules. Pathol Res Prac. 2015;211(5):345-8.
51. Sarkis LM, Norlen O, Aniss A, et al. The Australian experience with the Bethesda classification system for thyroid fine needle aspiration biopsies. Pathology. 2014;46(7):592-5.
52. Theoharis C, Adeniran AJ, Roman S, et al. The impact of implementing the Bethesda system for reporting of thyroid FNA at an academic center. Diagn Cytopathol. 2013;41(10):858-63.
53. Ferris RL, Baloch Z, Bernet V, et al. American Thyorid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. Thyroid. 2015:25(7):760-8
54. Strickland KC, Howitt, BE, Marqusee E, et al. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnositc categories. Thyroid. 2015;25(9):987-92.
55. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda system for reporting thyrıid cytopathology. Cancer Caytopathol. 2016;124(3):181-7.
56. Ellison E, Lapuerta P, Martin SE. Psammoma bodies in fine-needle aspirates of the thyroid: predictive value for papillary carcinoma. Cancer. 1998;84:169-175.
57. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelnes fort he management of medullary thyroid carcinoma. Thyroid 2015;25(567-610.
58. Papaparaskeva K, Nagel H, Droese M. Cytologic diagnosis of medullary carcinoma of the thyroid gland. Diagn Cytoathol. 2000;22:351-8.
59. Trimboli P, Treglia G, Guidobal-

di L, et al. Detection rate of FNa cytology in medullary thyroid carcinoma: a meta-analysis. Clin Endocrinol. 2015;82:280-5.
60. Trimboli P, Guidoboldi L, Bongiovanni M, et al. Use of fine-needle aspirate calsitonin to detect medullary thyroid carcinoma: a systematic review. Diagn Cytopathol. 2016;44:45-51.
61. Sobrinho Simoes M, Albores-Saavedra J, Tallini G, et al. Poorly diffrentiated carcionma. In: DeLellis R, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization classification of tumors: pathology and genetics of tumors of endocrine organs. Lyon: IARC Press:2004.
62. Volante M, Landolfi Chiusa L, et al. Poorl differentiated carcinomas of the thyroid with trabecular, insular, and solid patterns: a clinicopathologic study of 183 patients. Cancer. 2004;100(5):950-7.
63. Schmid KM, Hittmair A, Ofner C, et al. Metastatic tumors in fine needle aspiration biopsy of the thyroid. Acta Cytol. 1991;35:722-724.
64. Smit SA, Gharib H, Goellner JR. Fine-needle aspiration: usefulness for diagnosis and management of metastatic carcinoma to the thyroid. Arch Intern Med. 1987;147:311-12.
65. Papi G, Fadda G, Corsello SM, et al. Metastases to the thyroid gland: Prevalence, clinicopathological aspects and prognosis: a10-year experience. Clin Endocrinol. 2007:66(4):565-71.
66. Civantos F, Albores-Saavedra J, Nadji M, Morales AR. Clear cell variant of thyroid carcinoma. Am J surg Pathol. 1984;8:187-92.
67. Derringer GA, Thompson LDR, Frommelt RA, et al. Malignant lymphoma of the thyroid gland: A clinicopathologic study of 108 cases. Am J Surg Pathol. 2000;24:623-639.
68. Nikiforov Y,Baloch ZW. Clinical validation of the ThyroSeq v3 genomic classifier in thyroid nodules with indeterminate FNA cytology. Cancer Cytopathology 2019; 127(4): 225-30.
69. Nishimo M, Nikiforova M. Update on molecular testing for cytologically indeterminate thyroid nodules. Arch Pathol Lab Med 2018;142(4): 446-57.
70. Pusztaszeri M, Rossi E.D., Auger M, Baloch Z et al. The Bethesda system for reporting thyroid cytopathology : proposed modifications and updates for the second edition from an international panel. J Am Soc Cytopathology 2016;124(5): 307-16.
71. Rossi E.D., Larocca L.M,Pantanowitz L. Ancillary molecular testing of indeterminate thyroid nodules. Cancer Cytopathology 125(8):654-71.
72. Ali S, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. 2nd ed. CHAM, Switzerland: Springer; 2018.
73. Jug RC, Jiang XS. Molecular testing for indeterminate thyroid nodules :Performance of the Afirma gene expression classifier and ThyroSeq panel. Cancer Cytopathol 2018 ;126(7):417-80.
74. Rossi ED, Larocca LM, Pantanowitz L. Ancillary molecular testing of indeterminate thyroid nodules. Cancer Cytopathology 2018;126(8): 854-71
75. Nikiforov YE, Carty SE, Chiosea SI, Coyne C et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next- generation sequencing assay. Cancer 2014 ; 120(23) : 3627-34.
76. Bose S, Sacks W,Walts AE. Update on molecular testing for cytologically indeterminate thyroid nodules. Adv Anat Pathol 2019; 26: 114-23.
77. Gupta N, Dasyam AK, Carty SE, et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-patern cancers. J Clin Endocrinol Metab 2013;98: E914-E922.
78. Melo M, daRocha AG, Vinagre J, Batista R et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab 2014; 99(5):NE754-65.
79. Rivas MA, Nassar A, Zhang J, Casler JD et al. ThyroseqV2.0 molecular testing : a cost-effective approach for the evaluation of indeterminate thyroid nodules. Endocrine Practice 2018; 24(9) : 780-88.
80. Teshima G, Tokita K, Ryo E, Matsumoto F et al. Clinical impact of a cytological screening system using cyclin D! For the diagnosis of thyroid nodules. *BMC Cancer* 2019; 19(1) : 245.DOİ: 10.1186/S12885-019-5452-4.
81. Chain C, Legesse T, Heath JE, Staats PN. Digital image –assisted quantitative nuclear analysis improves diagnostic accuracy of thyroid fine needle aspiration cytology. Cancer Cytoptahology 2019 May 31.doi: 10.1002/cncy/22120.
82. Mu N, Juhlin CC, Tani E, Reihner E et al. High Ki-67 index in fine needle aspiration cytology of follicular thyroid tumors is associated with increased risk of carcinoma .Endocrine 2018; 61(2) : 293-02.
83. P. Song SJ, LiVolsi VA, Montone K, Baloch Z. Pre-operative features of non-invasive follicular thyroid neoplasms with papillary-like nuclear features: an analysis of their cytological, gene expression classifier and sonographic findings. Cytopathology 2017;28(6):488-94.
84. R: Jiang XS, Harrison GP, Datto MB. Young investigator challenge: molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Cancer Cytopathology 2016; 124[12)893-900.
85. Papathomas TG, Nose V. New and emerging biomarkers in Endocrine pathology. Adv Anat Pathol 2019; 26:198-09.
86. Baloch ZW, Seethala RR, Faquin WC, Papotti MG et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a changing paradigm in thyroid surgical pathology and implications for thyroid cytopathology. Cancer Cytopathology 2016; 124(9): 616-20.
87. Khatami F, Tavangar SM. Liquid Biopsy in thyroid cancer: new insight. Int J Hematol Oncol Stem Cell Res. 2018;12(3):235-248
88. Rappa G, Puglisi C, Santos MF, et al. Extracellular vesicles from thyroid carcinoma: The new frontier of liquid biopsy. Int J Mol Sci. 2019;20(5):1114.
89. Cote G.J., Evers C., Hu M.I., Grubbs E.G., Williams M.D., Hai T., Duose D.Y., Houston M.R., Bui J.H., Mehrotra M., et al. Prognostic significance of

circulating *RET* M918T mutated tumor DNA in patients with advanced medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. 2017;102:3591–3599. doi: 10.1210/jc.2017-01039.

90. Mohammadi-asl J, Larijani B, Khorgami Z, et al. Qualitative and quantitative promoter hypermethylation patterns of the P16, TSHR, RASSF1A and RARβ2 genes in papillary thyroid carcinoma. Med Oncol. 2011;28(4):1123–8.
91. Zane M, Agostini M, Enzo MV, et al. Circulating cell-free DNA, SLC5A8 and SLC26A4 hypermethylation, BRAFV600E: A non-invasive tool panel for early detection of thyroid cancer. Biomed Pharmacother. 2013;67(8):723–30.
92. Chuang TC, Chuang AY, Poeta L, et al. Detectable BRAF mutation in serum DNA samples from patients with papillary thyroid carcinomas. Head Neck. 2010;32(2):229–34
93. Janku F, Huang HJ, Claes B, et al. BRAF mutation testing in cell-free DNA from he plasma of patients with advanced cancers using a rapid, automated molecular diagnostics system. Mol Cancer Ther. 2016;15(6):1397–404.
94. Dent BM, Ogle LF, O'Donnell RL, et al. High-resolution imaging for the detection and characterisation of circulating tumour cells from patients with oesophageal, hepatocellular, thyroid and ovarian cancers. Int J Cancer. 2016;138(1):206–16
95. Xu JY, Handy B, Michaelis CL, et al. Detection and prognostic significance of circulating tumor cells in patients with metastatic thyroid cancer. J Clin Endocrinol Metab. 2016;101(11):4461–4467