

BÖLÜM

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Tiroidin Borderline Patolojilerinde Yaklaşım

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Özet

Tiroidin borderline tümörleri malignite potansiyeli kesin olmayan folliküler tümör (FT-UMP), malignite potansiyeli kesin olmayan iyi diferansiyeli tümör (WDT-UMP) ve papiller benzeri nükleer özellikler gösteren non-invaziv folliküler tiroid neoplazisi (NIFTP) olarak sınıflandırılır. WDT-UMP ve FT-UMP bütünüyle malignite kriterlerini karşılamayan, şüpheli yapısal yada sitolojik özellikler içeren borderline, kapsüllü, folliküler paternde tiroid tümörleridir. Tümör kapsüllü veya iyi sınırlı, vasküler veya kapsüler invazyonu kesin olmayan, papiller tiroid karsinomu (PTK) benzeri nükleer özellikleri göstermeyen bir tümör ise FT-UMP, kapsüllü veya iyi sınırlı, vasküler veya kapsüler invazyonu kesin olmayan ancak PTK benzeri nükleer özellikleri parsiyel ya da yaygın olarak izlenen bir tümörler ise WDT-UMP olarak adlandırılır. NIFTP ise kapsüllü folliküler varyant papiller tiroid karsinomunun (FVPTK) bir alt tipidir. FVPTK vakalarının bir kısmı kapsüllü veya iyi sınırlı olup, invaziv özellik göstermez ve klasik PTK'dan farklı moleküler profil sergiler. Bunlar nükleer özellikleri PTK benzeri olan ancak histopatolojik olarak folliküler adenoma benzeyen tümörlerdir. Bu bölümde, borderline tiroid tümörlerinin klinik, sitolojik, histopatolojik ve moleküler bulguları ile tedavisi konularından bahsedilecektir.

Anahtar kelimeler: Malignite potansiyeli kesin olmayan folliküler tümör, malignite potansiyeli kesin olmayan iyi diferansiyeli tümör, papiller benzeri nükleer özellikler gösteren non-invaziv folliküler tiroid neoplazisi

Sonuç

NIFTP tanısı şu anda morfolojik, moleküler ve biyolojik bilgilerin ışığında sentezlenen yeni bir yorumdur. Bu konseptin hala doğrulanmaya ve

gerekirse modifikasyona ihtiyacı vardır. Açıklığa kavuşması gereken konular onkositik folliküler paternli lezyonlar, multifokal lezyonlar ve 1 cm'den küçük lezyonlardır. Bu gruplar için ek çalışmalarına ihtiyaç vardır.

Kaynaklar

- Seethala RR, Baloch ZW, Barletta JA, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a review for pathologist. *Mod Pathol* 2018;31(1):39–55.
- Lloyd RV, Osamura RY, G. Klöppel, Rosai J. WHO Classification of Tumors of Endocrine Organs. 4th edn. (International Agency for Research on Cancer, Lyon, 2017). p. 66–80.
- Williams ED. Guest Editorial: Two proposals regarding the terminology of thyroid tumors. *Int J Surg Pathol* 2000; 8:181–3.
- De Lellis RA, Lloyd RV, Heitz PU. Pathology and genetics: tumours and endocrine organs, 3rd edn. WHO, Geneva, 2004.
- Hofman V, Lasalle S, Bonnetaud C, et al. Thyroid tumors of uncertain malignant potential: frequency and diagnostic reproducibility. *Virchows Arch* 2009;455(1):21–33.
- Liu Z, Zhou G, Nakamura M, et al. Encapsulated follicular thyroid tumor with equivocal nuclear changes, so-called well-differentiated tumor of uncertain malignant potential: a morphological, immunohistochemical and molecular appraisal. *Cancer Science* 2011;102(1): 288–94.
- Piana S, Frasoldati A, Di Felice E, et al. Encapsulated well-differentiated follicular –patterned thyroid carcinomas do not play a significant role in the fatality rayes from thyroid carcinoma . *Am J Surg Pathol* 2010;34(6): 868–72.
- Baser H, Topaloglu O, Tam AA, et al. Comparing Clinicopathologic and Radiographic Findings Between TT-UMP, Classical, and Non-Encapsulated Follicular Variants of Papillary Thyroid Carcinomas. *Endocr Pathol* 2016;27(3): 233-42.
- Nechifor-Boila A, Borda A, Sas- solas G, et al. Thyroid tumors of uncertain malignant potential: morphologic and immunohistochemical analysis of 29 cases. *Pathol Res Pract* 2015; 211: 320–5.
- Barroeta JE, Baloch ZW, Lal P, et al. Diagnostic value of differential expression of CK19, Galectin-3, HBME-1, ERK, RET, and p16 in benign and malignant follicular-derived lesions of the thyroid: an immunohistochemical tissue microarray analysis. *Endocr Pathol* 2006;17: 225–34.
- Barut F, Onak Kandemir N, Bektaş S, et al. Universal markers of thyroid malignancies: galectin-3, HBME-1, and cytokeratin-19. *Endocr Pathol* 2010; 21: 80–9.
- Scognamiglio T, Hyrek E, Kao J, Chen YT. Diagnostic usefulness of HBME1, galectin-3, CK19, and CITED1 and evaluation of their expression in encapsulated lesions with questionable features of papillary thyroid carcinoma. *Am J Clin Pathol* 2006;126:700–8
- Papotti M, Rodriguez J, De Pompa R, et al. Galectin-3 and HBME-1 expression in well-differentiated thyroid tumors with follicular architecture of uncertain malignant potential. *Mod Pathol* 2005;18:541–6.
- Sobrinho-Simões M, Eloy C, Magalhães J, et al. Follicular thyroidcarcinoma. *Mod Pathol* 2011; 24:10–8.
- Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol* 2016;2(8):1023–9.
- Tallini G, Tuttle RM, Ghossein RA. The history of the follicular variant of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2017;102(1):15–22.
- Liu J, Sing B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma A clinicopathologic study of a problematic entity. *Cancer* 2006;107(6):1255–4.
- Rivera M, Ricarte-Filho J, Knaud J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes [encapsulated vs infiltrative] reveals distinct BRAF and RAS mutation patterns. *Mod Pathol* 2010; 23(9): 1191–200.
- Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell* 2014;159(3): 676–90.
- Lau, RP, Paulsen JD, Brandler et al. Impact of the reclassification of “noninvasive encapsulated follicular variant of papillary thyroid carcinoma” to “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” on the Bethesda System for Reporting Thyroid Cytopathology: a large academic institution’s experience. *Am J Clin Pathol* 2017; 149(1):50–4.
- Hahn, SY, Shin JH, Lim HK, et al. Preoperative differentiation between noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and non-NIFTP. *Clin Endocrinol (Oxf)* 2017;86(3):444–50.
- Ruanpeng D, Cheungpasitporn W, Thongprayoon C, et al. Systematic Review and Meta-analysis of the Impact of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) on Cytological Diagnosis and Thyroid Cancer Prevalence. *Endocr Pathol* 2019;30(3):189–200.
- Jung R, Jiang X. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: An Evidence-Based Nomenclature Change. *Pathology Res Int* 2017; 2017:1057252.
- Kwon MR, Shin JH, Hahn SY, et

- al. Histogram analysis of greyscale sonograms to differentiate between the subtypes of follicular variant of papillary thyroid cancer. *Clin Radiol* 2018;73(6), 591. e1–591 e7.
25. Yang GCH, Fried K, Scognamiglio T. Sonographic and cytologic differences of NIFTP from infiltrative or invasive encapsulated follicular variant of papillary thyroid carcinoma: a Review of 179 Cases. *Diagn Cytopathol* 2017;45(6):533–41.
26. Yang GCH, Fried KO. Pathologic basis of the sonographic differences between thyroid cancer and noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Ultrasound* 2018;37(2):157–63.
27. Mahajan S, Agarwal S, Kocheri N, et al. Cytopathology of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a comparative study with similar patterned papillary thyroid carcinoma variants. *Cytopathology* 2018; 29(3):233–40.
28. Chandler JB, Colunga M, Prasad ML, et al. Identification of distinct cytomorphologic features in the diagnosis of NIFTP at the time of preoperative FNA: implications for patient management. *Cancer Cytopathol* 2017;125(11):865–75.
29. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid* 2017;27(11):1341–6.
30. Zhou H, Baloch ZW, Nayar R, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Implications for the risk of malignancy (ROM) in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). *Cancer Cytopathol* 2018; 126(1): 20–6.
31. 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 Thyroid Cytopathology. *Cancer Cytopathol* 2016;124(3):181–7.
32. Bongiovanni M, Giovannella L, Romanelli F, Trimboli P. Cytological Diagnoses Associated with Noninvasive Follicular Thyroid Neoplasms with Papillary-Like Nuclear Features According to the Bethesda System for Reporting Thyroid Cytopathology: A Systematic Review and Meta-Analysis. *Thyroid* 2019;29(2):222–228.
33. Strickland KC, Vivero M, Jo VY, et al. Preoperative cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a prospective analysis. *Thyroid* 2016;26(10):1466–71.
34. Vuong HG, Tran TTK, Bychkov A, et al. Clinical impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the risk of malignancy in the Bethesda system for reporting thyroid cytopathology: a meta-analysis of 14,153 resected thyroid nodules. *Endocr Pract* 2019;25(5):491–502.
35. Bychkov A, Keelawat S, Agarwal S, et al. Impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the Bethesda system for reporting thyroid cytopathology: a multi-institutional study in five Asian countries. *Pathology* 2018;50(4):411–7.
36. Li W, Sciallis A, Lew M, et al. Implementing noninvasive follicular thyroid neoplasm with papillary-like nuclear features may potentially impact the risk of malignancy for thyroid nodules categorized as AUS/FLUS and FN/SFN. *Diagn Cytopathol* 2018;46(2): 148–53.
37. Hang JF, Westra WH, Zhou AG, et al. The impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on the rate of malignancy for atypia of undetermined significance subcategories. *Cancer Cytopathol*. 2018;126(5):309–16.
38. Point du Jour K, Schmitt AC, Shen AY, Griffith CC. Application of Strict Criteria for Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features and Encapsulated Follicular Variant Papillary Thyroid Carcinoma: a Retrospective Study of 50 Tumors Previously Diagnosed as Follicular Variant PTC. *Endocr Pathol* 2018;29(1):35–42.
39. Kakudo K, El-Naggar AK, Hodak SP, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in thyroid tumor classification. *Pathol Int* 2018;68(6):327–33.
40. Thompson LDR, Poller DN, Kakudo K, et al. An International Interobserver Variability Reporting of the Nuclear Scoring Criteria to Diagnose Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: a Validation Study. *Endocr Pathol* 2018;29(3): 242–9.
41. Rossi ED, Faquin WC, Baloch Z, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) : update and diagnostic considerations-a review. *Endocr Pathol* 2019; 30(2): 155–62.
42. Mete O, Asa SL. Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. *Mod Pathol* 2011;24(12): 1545–52.
43. Strickland KC, Howitt BE, Barletta JA, et al. Suggesting the cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a retrospective analysis of atypical and suspicious nodules. *Cancer Cytopathol* 2018;126(2); 86–93.
44. Cho U, Mete O, Kim MH, et al. Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasms with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features. *Mod Pathol* 2017; 30(6): 810–25.
45. Nikiforov YE, Baloch ZW, Hodak SP, et al. Change in diagnostic criteria for noninvasive follicular thyroid neoplasm with papillarylike nuclear features. *Jama Oncol* 2018; 4(8):1125–6.
46. Xu B, Tallini G, Scognamiglio T, et al. Outcome of large noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid* 2017;27(4):512–7.
47. Rosario PW. Long-Term Outcomes of Patients with Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) \geq 4 cm Treated Without Radioactive Iodine. *Endocr Pathol* 2017;28(4):367–8.

48. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol*. 2016; 29: 698–707.
49. Hung YP, Barletta JA. A user's guide to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *Histopathology* 2018;72(1): 53–69.
50. Paulson VA, Shvidasani P, Angell TE et al. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features Accounts for More Than Half of "Carcinomas" Harboring RAS Mutations. *Thyroid* 2017;27(4):506–11.
51. Howitt BE, Jia Y, Sholl LM, Barletta JA. Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. *Thyroid* 2013;23(10): 1256–62.
52. Song YS, Won JK, Yoo SK, et al. Comprehensive transcriptomic and genomic profiling of subtypes of follicular variant of papillary thyroid carcinoma. *Thyroid* 2018; 28(11): 1468–78.
53. Afshami M, Karunamurthy A, Chiosea S, Nikiforova MN. Histopathologic and clinical characterization of thyroid tumors carrying the BRAF(K601E) mutation. *Thyroid* 2016; 26(2): 242–7.
54. Pool C, Walter V, Bann D, et al. Molecular characterization of tumors meeting diagnostic criteria for the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *Virchow's Arch* 2019;474(3):341–51.
55. Basolo F, Macerola E, Ugolini C, et al. The Molecular Landscape of Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): a literature review. *Adv Anat Pathol* 2017; 24(5): 252–8.
56. Borrelli N, Denaro M, Ugolini C, et al. miRNA expression profiling of "noninvasive follicular thyroid neoplasms with papillary-like nuclear features" compared with adenomas and infiltrative follicular variants of papillary thyroid carcinomas. *Mod Pathol* 2017;30(1): 39–51.
57. Fu G, Polyakova O, MacMillan C, et al. Programmed Death-Ligand 1 Expression Distinguishes Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma from Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features. *EBioMed* 2017;18:50–5.
58. Johnson DN, Sadow PM. Exploration of BRAFV600E as diagnostic adjuvant in the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *Hum Pathol* 2018;82:32–8.
59. 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.
60. Ghuzlan AA, Ramos HE, Schlumberger M. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Curr Opin Endocrinol Diabetes Obes* 2017;24(5):377–80.
61. Alves VAF, Kakudo K, LiVolsi V, et al. Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP): Achieving Better Agreement By Refining Diagnostic Criteria. *Clin (Sao Paulo)* 2018;73:e576.
62. Rivera M, Ricarte-Filho J, Patel S et al. Encapsulated thyroid tumors of follicular cell origin with high grade features (high mitotic rate/tumor necrosis): a clinicopathologic and molecular study. *Hum Pathol*. 2010; 41(2); 172–80.
63. Jiang XS, Harrison GP, Datto MB. Young investigator challenge:molecular testing in noninvasive follicular thyroid neoplasmwith papillary-like nuclear features. *Cancer* 2016; 124(12):893–900.
64. Xu B, Scogna M, Cohen PR et al. Metastatic thyroid carcinoma without identifiable primary tumor within the thyroid gland: a retrospective study of a rare phenomenon. *Hum. Pathol.* 2017; 65:133–9.