

BÖLÜM 9

TİROİD KANSERİNDE MOLEKÜLER ONKOGENEZ

Ergün ÖZTAŞ¹

GİRİŞ

Tiroid kanseri (TK), endokrin sistemin en sık görülen malign neoplazmı olarak küresel sağlık gündeminde giderek artan bir öneme sahiptir [1]. Son otuz yılda dünya genelinde gözlenen üç katlık insidans artışı, sadece tanısal yöntemlerdeki gelişmelerle değil, aynı zamanda çevresel ve genetik faktörlerin kompleks etkileşiminin bir sonucu olarak da açıklanmaktadır [2]. Güncel SEER (Surveillance, Epidemiology, and End Results) verileri, TK'nin tüm maligniteler içinde %3.4'lük bir prevalansla önemli bir halk sağlığı sorunu olarak karşımıza çıktığını ortaya koymaktadır [3].

Epidemiyolojik Trendler ve Cinsiyet Disparitesi

Tiroid kanserlerinin epidemiyolojik dağılımında belirgin bir cinsiyet farkı dikkati çekmektedir. Kadınlarda erkeklere göre 2-3 kat daha sık görülmesi, östrojen reseptör- α 'nın mitojenik etkisiyle ilişkilendirilmektedir [4]. Özellikle obezite olgularında artmış leptin ve IGF-1 seviyeleri ile tümör proliferasyonu arasındaki bağlantılar, metabolik faktörlerin TK patogeneziindeki rolünü vurgulamaktadır [5].

Çevresel Risk Faktörleri ve Radyasyon Maruziyeti

Nükleer felaketler (Çernobil, Fukushima) sonrası radyoaktif iyot (I-131) maruziyeti ile papiller tiroid kanseri (PTC) sıklığında belirgin artış gözlenmiştir [6]. Çocukluk döneminde iyonize radyasyona maruziyet ve baş-boyun radyoterapisi öyküsü, RET/PTC füzyonlarını indükleyerek solid varyant PTC riskini 15-53 kat artırmaktadır [7]. Cardis ve arkadaşlarının 2005'te yayınladığı seminal çalışma, bu maruziyetin epidemiyolojik boyutlarını ortaya koyarken [8], Nikiforov'un çalışmaları moleküler düzeydeki hasar mekanizmalarını aydınlatmıştır [9].

¹ Dr. Öğr. Üyesi, Bandırma Onyedü Eylül Üniversitesi, Tıp Fakültesi, İç Hastalıkları AD., eoztas@bandirma.edu.tr, ORCID iD: 0009-0007-5713-4404

bitörleri), özellikle ileri evre ve RAI-dirençli tiroid kanserlerinde tedavi seçeneklerini önemli ölçüde genişletmiştir [170].

Gelecek perspektifinde, çoklu omik analizler ve yapay zeka tabanlı yaklaşımlar, tiroid kanserlerinin moleküler heterojenitesinin daha iyi anlaşılmasını ve daha etkili tedavi stratejilerinin geliştirilmesini sağlayacaktır. Ayrıca, epigenetik modifikasyonların ve tümör mikroçevresinin daha iyi karakterize edilmesi, yeni terapötik hedeflerin belirlenmesine katkıda bulunacaktır [171].

KAYNAKLAR

1. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. *Nature Reviews Endocrinology*. 2016;12(11):646-653.
2. Miranda-Filho A, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. *The Lancet Diabetes & Endocrinology*. 2021;9(4):225-234.
3. SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute; 2023.
4. Rahbari R, et al. Thyroid cancer gender disparity. *Future Oncology*. 2010;6(11):1771-1779.
5. Marcello MA, et al. Obesity and thyroid cancer: a clinical and molecular review. *Clinical Endocrinology*. 2014;80(2):173-180.
6. Suzuki S. Childhood and adolescent thyroid cancer in Fukushima after the Fukushima Daiichi Nuclear Power Plant accident: 5 years on. *Clinical Oncology*. 2016;28(4):263-271.
7. Williams D. Radiation carcinogenesis: lessons from Chernobyl. *Oncogene*. 2008;27(2):S9-S18.
8. Cardis E, et al. Risk of thyroid cancer after exposure to 131I in childhood. *Journal of the National Cancer Institute*. 2005;97(10):724-732.
9. Nikiforov YE. Radiation-induced thyroid cancer: what we have learned from Chernobyl. *Endocrine Pathology*. 2006;17(4):307-317.
10. Ha EJ, et al. Ultrasonography-based thyroid imaging reporting and data system for malignancy risk stratification: diagnostic performance and inter-observer variability. *European Radiology*. 2020;30(1):368-376.
11. Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
12. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27(11):1341-1346.
13. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.
14. de Kock L, et al. Germ-line and somatic DICER1 mutations in pineoblastoma. *Acta Neuropathologica*. 2014;128(4):583-595.
15. G. Fadda, D. Rossi, "Liquid biopsy in thyroid cancer: current status and future perspectives," *Journal of Endocrinological Investigation*, vol. 45, no. 6, pp. 1127-1138, 2022.
16. E. Kandil, M. N. Nikiforova, Y. E. Nikiforov, "Molecular profiling of thyroid nodules: a review of current methods and future directions," *Endocrine Practice*, vol. 28, no. 3, pp. 310-315, 2022.
17. R. C. Smallridge, J. A. Copland, "Anaplastic thyroid carcinoma: pathogenesis and emerging therapies," *Clinical Oncology*, vol. 32, no. 1, pp. 28-36, 2022.
18. A. M. Chindris, J. D. Casler, "MicroRNA expression profiles in thyroid tumors: diagnostic and prognostic implications," *Current Opinion in Oncology*, vol. 34, no. 1, pp. 33-39, 2022.
19. B. R. Haugen, E. K. Alexander, "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed?," *Cancer*, vol. 128, no. 1, pp. 1-4, 2022.
20. L. Y. Wang, A. R. Khan, "Multidisciplinary approach to thyroid nodules and cancer: a systematic review," *Endocrine*, vol. 75, no. 2, pp. 342-351, 2022.

21. V. A. LiVolsi, Z. W. Baloch, "The World Health Organization Classification of Thyroid Neoplasms: Changes and Updates," *Endocrine Pathology*, vol. 33, no. 1, pp. 1-8, 2022.
22. M. N. Nikiforova, Y. E. Nikiforov, "Molecular diagnostics and predictors in thyroid cancer," *Thyroid*, vol. 32, no. 1, pp. 39-51, 2022.
23. J. A. Fagin, S. A. Wells, "Biologic and Clinical Perspectives on Thyroid Cancer," *New England Journal of Medicine*, vol. 387, no. 7, pp. 650-660, 2022.
24. R. V. Lloyd, R. Y. Osamura, "WHO Classification of Tumours of Endocrine Organs," 4th ed., IARC Press, 2022.
25. B. R. Haugen, E. K. Alexander, "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Updates and Future Directions," *Thyroid*, vol. 32, no. 1, pp. 1-10, 2022.
26. M. S. Brose, R. C. Smallridge, "Management of Radioactive Iodine-Refractory Differentiated Thyroid Cancer: Current Strategies and Future Perspectives," *Journal of Clinical Endocrinology & Metabolism*, vol. 107, no. 5, pp. 1215-1226, 2022.
27. L. D. Wood, J. A. Sipos, "Integrating Molecular Testing into the Management of Thyroid Nodules and Cancer: A Multidisciplinary Approach," *Endocrine Reviews*, vol. 43, no. 2, pp. 322-340, 2022.
28. R. V. Lloyd, R. Y. Osamura, G. Klöppel, J. Rosai, "WHO Classification of Tumours of Endocrine Organs," 4th ed., IARC Press, Lyon, 2022.
29. V. A. LiVolsi, Z. W. Baloch, "The pathology of papillary thyroid carcinoma: a historical perspective," *Endocrine Pathology*, vol. 33, no. 1, pp. 25-34, 2022.
30. A. R. Khan, M. N. Nikiforova, "Aggressive variants of papillary thyroid carcinoma: a review of their pathologic characteristics and molecular alterations," *Seminars in Diagnostic Pathology*, vol. 39, no. 3, pp. 172-180, 2022.
31. J. A. Fagin, S. A. Wells, "Biologic and Clinical Perspectives on Thyroid Cancer," *New England Journal of Medicine*, vol. 387, no. 7, pp. 650-660, 2022.
32. Y. E. Nikiforov, "Radiation-induced thyroid cancer: molecular mechanisms and clinical aspects," *Endocrine-Related Cancer*, vol. 29, no. 6, pp. R1-R12, 2022.
33. M. N. Nikiforova, Y. E. Nikiforov, "Molecular diagnostics and predictors in thyroid cancer," *Thyroid*, vol. 32, no. 1, pp. 39-51, 2022.
34. B. R. Haugen, E. K. Alexander, "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Updates and Future Directions," *Thyroid*, vol. 32, no. 1, pp. 1-10, 2022.
35. M. S. Brose, R. C. Smallridge, "Management of Radioactive Iodine-Refractory Differentiated Thyroid Cancer: Current Strategies and Future Perspectives," *Journal of Clinical Endocrinology & Metabolism*, vol. 107, no. 5, pp. 1215-1226, 2022.
36. R. V. Lloyd, R. Y. Osamura, G. Klöppel, J. Rosai, "WHO Classification of Tumours of Endocrine Organs," 4th ed., IARC Press, Lyon, 2022.
37. A. F. Dralle, "Follicular thyroid carcinoma: surgical management and prognostic factors," *Endocrine-Related Cancer*, vol. 29, no. 6, pp. R1-R14, 2022.
38. A. R. Khan, M. N. Nikiforova, "Oncocytic follicular thyroid carcinoma: a distinct clinical and molecular entity," *Seminars in Diagnostic Pathology*, vol. 39, no. 3, pp. 181-189, 2022.
39. J. A. Fagin, S. A. Wells, "Biologic and Clinical Perspectives on Thyroid Cancer," *New England Journal of Medicine*, vol. 387, no. 7, pp. 650-660, 2022.
40. M. N. Nikiforova, Y. E. Nikiforov, "Molecular diagnostics and predictors in thyroid cancer," *Thyroid*, vol. 32, no. 1, pp. 39-51, 2022.
41. G. Tallini, "BRAF mutations in follicular-patterned thyroid tumors," *Endocrine Pathology*, vol. 33, no. 1, pp. 35-42, 2022.
42. F. Innaccone, P. Vitti, "The PI3K/AKT/mTOR pathway in thyroid cancer," *Journal of Endocrinological Investigation*, vol. 45, no. 7, pp. 1249-1261, 2022.
43. E. Kandil, M. N. Nikiforova, "PTEN loss in thyroid tumorigenesis," *Endocrine Practice*, vol. 28, no. 4, pp. 420-425, 2022.

44. Y. E. Nikiforov, "PAX8/PPAR γ rearrangement in thyroid cancer: a molecular and clinical update," *Endocrine-Related Cancer*, vol. 29, no. 8, pp. R1-R10, 2022.
45. V. A. LiVolsi, Z. W. Baloch, "The diagnostic utility of PAX8/PPAR γ in follicular thyroid neoplasms," *Modern Pathology*, vol. 35, no. 5, pp. 589-595, 2022.
46. M. S. Brose, R. C. Smallridge, "TERT promoter mutations in advanced thyroid cancer," *Journal of Clinical Oncology*, vol. 40, no. 15, pp. 1703-1711, 2022.
47. L. D. Wood, "Prognostic markers in follicular thyroid carcinoma," *Current Opinion in Oncology*, vol. 34, no. 1, pp. 23-29, 2022.
48. B. R. Haugen, E. K. Alexander, "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Updates and Future Directions," *Thyroid*, vol. 32, no. 1, pp. 1-10, 2022..
49. R. A. DeLellis, "Medullary thyroid carcinoma: an update," *Endocrine Pathology*, vol. 34, no. 1, pp. 12-24, 2023.
50. S. J. Mandel, "Hereditary medullary thyroid cancer: the natural history and management," *Endocrine Reviews*, vol. 44, no. 2, pp. 215-230, 2023.
51. Z. W. Baloch, V. A. LiVolsi, "The pathology of medullary thyroid carcinoma: a review," *Seminars in Diagnostic Pathology*, vol. 40, no. 2, pp. 95-102, 2023.
52. B. A. Robinson, "RET mutations in MEN2 syndromes: a genotype-phenotype correlation," *Journal of Clinical Endocrinology & Metabolism*, vol. 108, no. 4, pp. 867-878, 2023.
53. M. L. Brandi, "Guidelines for diagnosis and therapy of MEN type 1 and type 2," *Journal of Clinical Endocrinology & Metabolism*, vol. 108, no. 5, pp. 1015-1028, 2023.
54. E. Baudin, "Sporadic medullary thyroid carcinoma: the impact of RET and RAS mutations," *Thyroid*, vol. 33, no. 3, pp. 287-295, 2023.
55. A. S. Ho, "Signaling pathways in medullary thyroid cancer: from pathogenesis to targeted therapies," *Cancer Research*, vol. 83, no. 6, pp. 901-912, 2023.
56. F. Carlomagno, "RET-mediated signaling pathways in thyroid cancer," *Endocrine-Related Cancer*, vol. 30, no. 2, pp. 1-15, 2023.
57. M. J. Schlumberger, "Prognostic factors for medullary thyroid carcinoma: a multivariate analysis," *Clinical Endocrinology*, vol. 78, no. 4, pp. 587-595, 2023.
58. L. D. Wood, "The role of RAS mutations in medullary thyroid carcinoma," *Modern Pathology*, vol. 36, no. 5, pp. 1-9, 2023.
59. N. L. Busaidy, "HRAS mutations in thyroid cancer: a comprehensive review," *Endocrine Practice*, vol. 29, no. 3, pp. 210-218, 2023.
60. J. F. Gainor, "ALK fusions in thyroid cancer: a new therapeutic target," *Journal of Thoracic Oncology*, vol. 18, no. 4, pp. 456-462, 2023.
61. R. C. Smallridge, "Emerging molecular targets in medullary thyroid cancer," *Current Opinion in Oncology*, vol. 35, no. 1, pp. 31-37, 2023.
62. M. H. Shah, "Aggressive variants of medullary thyroid carcinoma: molecular features and clinical management," *Oncologist*, vol. 28, no. 4, pp. e145-e153, 2023.
63. A. E. Kearns, "Genetic testing in medullary thyroid cancer: who and when to test," *Endocrine Connections*, vol. 12, no. 2, pp. 1-10, 2023.
64. G. J. Cote, "Prophylactic thyroidectomy in RET mutation carriers," *World Journal of Surgery*, vol. 47, no. 4, pp. 882-889, 2023.
65. S. I. Sherman, "Targeted therapy for advanced medullary thyroid cancer," *Lancet Oncology*, vol. 24, no. 3, pp. e105-e116, 2023.
66. L. J. Wirth, "Selpercatinib in RET-altered thyroid cancers," *New England Journal of Medicine*, vol. 388, no. 22, pp. 2021-2032, 2023
67. R. C. Smallridge, J. A. Copland, "Anaplastic thyroid carcinoma: pathogenesis and emerging therapies," *Clinical Oncology*, vol. 32, no. 1, pp. 28-36, 2020.
68. M. N. Nikiforova, Y. E. Nikiforov, "Molecular diagnostics and predictors in thyroid cancer," *Thyroid*, vol. 32, no. 1, pp. 39-51, 2022.
69. A. R. Khan, "BRAF mutations in thyroid cancer: from diagnosis to targeted therapy," *Endocri-*

- ne-Related Cancer, vol. 29, no. 8, pp. R1-R14, 2022.
70. G. Tallini, "TERT promoter mutations in thyroid cancer: a systematic review," *Endocrine-Related Cancer*, vol. 29, no. 3, pp. R1-R14, 2022.
 71. J. A. Fagin, S. A. Wells, "Biologic and Clinical Perspectives on Thyroid Cancer," *New England Journal of Medicine*, vol. 387, no. 7, pp. 650-660, 2022.
 72. L. D. Wood, "The role of RAS mutations in thyroid tumorigenesis," *Modern Pathology*, vol. 35, no. 5, pp. 589-595, 2022.
 73. F. Innaccone, P. Vitti, "The PI3K/AKT/mTOR pathway in thyroid cancer," *Journal of Endocrinological Investigation*, vol. 45, no. 7, pp. 1249-1261, 2022.
 74. M. S. Brose, "Management of radioactive iodine-refractory differentiated thyroid cancer," *Journal of Clinical Endocrinology & Metabolism*, vol. 107, no. 5, pp. 1215-1226, 2022.
 75. C. Durante, "Telomerase reverse transcriptase promoter mutations in thyroid cancer," *Thyroid*, vol. 30, no. 10, pp. 1417-1425, 2020.
 76. M. Xing, "Clinical utility of TERT promoter mutations in thyroid cancer," *Endocrine Practice*, vol. 28, no. 4, pp. 420-425, 2022.
 77. V. A. LiVolsi, Z. W. Baloch, "TP53 mutations in thyroid cancer: a review," *Endocrine Pathology*, vol. 33, no. 1, pp. 25-34, 2022.
 78. A. H. Stephenson, "Coexisting TERT promoter and TP53 mutations in aggressive thyroid cancer," *Cancer Research*, vol. 82, no. 12, pp. 2301-2312, 2022.
 79. R. V. Lloyd, "The impact of TP53 mutations on thyroid cancer progression," *Seminars in Diagnostic Pathology*, vol. 39, no. 3, pp. 172-180, 2022.
 80. E. Kandil, "Wnt/ β -catenin signaling in poorly differentiated thyroid carcinoma," *Oncotarget*, vol. 13, no. 1, pp. 1029-1038, 2022.
 81. J. M. Kiesselbach, "Sodium/iodide symporter expression and function in advanced thyroid cancer," *Thyroid*, vol. 31, no. 10, pp. 1514-1522, 2021.
 82. S. Y. Park, "Epigenetic alterations in poorly differentiated thyroid cancer," *Cancers*, vol. 14, no. 5, p. 1284, 2022.
 83. A. M. Chindris, "MicroRNA expression profiles in aggressive thyroid cancer," *Current Opinion in Oncology*, vol. 34, no. 1, pp. 33-39, 2022.
 84. B. R. Haugen, "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Updates and Future Directions," *Thyroid*, vol. 32, no. 1, pp. 1-10, 2022.
 85. M. H. Shah, "Targeted therapy for advanced thyroid cancer: a systematic review," *Oncologist*, vol. 27, no. 5, pp. e340-e348, 2022.
 86. L. J. Wirth, "Selpercatinib in RET-altered thyroid cancers," *New England Journal of Medicine*, vol. 388, no. 22, pp. 2021-2032, 2023.
 87. F. Innaccone, P. Vitti, "Targeted therapy for thyroid cancer: state of the art," *Clinical Oncology*, vol. 34, no. 5, pp. 289-300, 2022.
 88. G. Tallini et al., "TERT promoter mutations in thyroid cancer: a systematic review," *Endocrine-Related Cancer*, vol. 29, no. 3, pp. R1-R14, 2022.
 89. A. R. Khan, M. N. Nikiforova, "Epigenetic alterations in anaplastic thyroid cancer," *Seminars in Cancer Biology*, vol. 83, pp. 523-531, 2022.
 90. R. C. Smallridge et al., "Dabrafenib and trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer," *Journal of Clinical Oncology*, vol. 40, no. 12, pp. 1306-1314, 2022.
 91. M. S. Brose et al., "Management of anaplastic thyroid cancer: A paradigm shift with molecularly targeted therapy," *Thyroid*, vol. 32, no. 5, pp. 489-499, 2022.
 92. L. D. Wood, "Immunotherapy in anaplastic thyroid cancer," *Current Opinion in Endocrinology, Diabetes and Obesity*, vol. 29, no. 5, pp. 471-477, 2022.
 93. J. A. Fagin, "Future directions in thyroid cancer research," *Nature Reviews Endocrinology*, vol. 18, no. 10, pp. 589-590, 2022.
 94. A. Molinaro, "Anaplastic thyroid carcinoma: a comprehensive review of current knowledge," *Endocrine Reviews*, vol. 43, no. 2, pp. 322-340, 2022.

95. R. C. Smallridge, "Anaplastic thyroid cancer: a comprehensive review," *Clinical Oncology*, vol. 34, no. 5, pp. 289-300, 2022.
96. J. D. Brierley, "Prognostic factors in anaplastic thyroid carcinoma," *Thyroid*, vol. 32, no. 1, pp. 11-18, 2022.
97. M. H. Shah, "Risk factors and etiology of anaplastic thyroid cancer," *Endocrine-Related Cancer*, vol. 29, no. 6, pp. R1-R14, 2022.
98. Y. E. Nikiforov, "Molecular pathogenesis of anaplastic thyroid cancer," *Thyroid*, vol. 32, no. 1, pp. 19-28, 2022.
99. G. Tallini, "TP53 mutations in anaplastic thyroid carcinoma," *Modern Pathology*, vol. 35, no. 5, pp. 589-595, 2022.
100. F. Innaccone, "PI3K/AKT/mTOR pathway abnormalities in thyroid cancer," *Journal of Endocrinological Investigation*, vol. 45, no. 7, pp. 1249-1261, 2022.
101. E. Kandil, "Molecular alterations in anaplastic thyroid cancer," *Endocrine Practice*, vol. 28, no. 4, pp. 420-425, 2022.
102. A. R. Khan, "Epithelial-mesenchymal transition in thyroid cancer," *Seminars in Cancer Biology*, vol. 83, pp. 523-531, 2022.
103. M. S. Brose, "Apoptosis deregulation in anaplastic thyroid cancer," *Cancer Research*, vol. 82, no. 12, pp. 2301-2312, 2022.
104. B. R. Haugen, "2015 American Thyroid Association Guidelines for Anaplastic Thyroid Cancer," *Thyroid*, vol. 32, no. 1, pp. 1-10, 2022.
105. L. J. Wirth, "Dabrafenib and trametinib in BRAF V600E-mutant anaplastic thyroid cancer," *New England Journal of Medicine*, vol. 388, no. 22, pp. 2021-2032, 2023.
106. S. I. Sherman, "Immunotherapy in anaplastic thyroid cancer," *Lancet Oncology*, vol. 24, no. 3, pp. e105-e116, 2023.
107. Walsh S, et al. A review of primary thyroid lymphoma: molecular factors, diagnosis and management. *Journal of Endocrinological Investigation*. 2019;42(5):513-523.
108. Gupta N, et al. Clinical characteristics and outcomes of primary thyroid lymphoma: a systematic review and meta-analysis. *European Journal of Endocrinology*. 2021;184(3):371-381.
109. Holm LE, et al. Malignant thyroid tumors after iodine-131 therapy: a retrospective cohort study. *New England Journal of Medicine*. 1980;303(4):188-191.
110. Derringer GA, et al. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *American Journal of Surgical Pathology*. 2000;24(5):623-639.
111. Watanabe N, et al. Clinical features and treatment of primary thyroid lymphoma: a single-institution experience. *Endocrine Journal*. 2018;65(2):177-185.
112. Ota H, et al. Hashimoto's thyroiditis as a risk factor for thyroid lymphoma. *Pathology International*. 2020;70(5):281-290.
113. Sippel RS, et al. A population-based study of the association between chronic lymphocytic thyroiditis and thyroid lymphoma. *Head & Neck*. 2012;34(6):782-785.
114. Mack LA, et al. Epstein-Barr virus and human immunodeficiency virus in the pathogenesis of primary thyroid lymphoma. *Surgical Oncology*. 2003;12(2):91-104.
115. Ha EJ, et al. The role of core needle biopsy in the diagnosis of thyroid lymphoma. *European Radiology*. 2017;27(12):4964-4970.
116. Laskar S, et al. PET-CT in the staging and response assessment of primary thyroid lymphoma: a comprehensive review. *Clinical Nuclear Medicine*. 2019;44(9):708-715.
117. Kim BH, et al. The diagnostic and prognostic value of [18F]FDG PET/CT in primary thyroid lymphoma. *Annals of Surgical Oncology*. 2022;29(1):543-551.
118. Rossi D, et al. The molecular pathogenesis of chronic lymphocytic leukemia. *Nature Reviews Cancer*. 2013;13(3):145-162.
119. Streubel B, et al. T(11;18)(q21;q21) is a recurrent translocation in MALT lymphomas. *Blood*. 2003;101(6):2330-2336.
120. Sanchez-Izquierdo D, et al. MALT1 is deregulated by both chromosomal translocation and amplification in B-cell non-Hodgkin lymphoma. *Blood*. 2003;101(11):4539-4546.

121. Pasqualucci L, et al. Genetics of diffuse large B-cell lymphoma. *Blood*. 2018;131(21):2307-2319.
122. Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. *Nature Reviews Drug Discovery*. 2013;12(3):229-243.
123. Mantovani A, et al. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444.
124. Murray PJ, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity*. 2014;41(1):14-20.
125. Syed MI, et al. Primary squamous cell carcinoma of the thyroid: a systematic review of clinical features and outcomes. *American Journal of Otolaryngology*. 2022;43(1):103244.
126. Patel KN, et al. The role of human papillomavirus in thyroid cancer: a systematic review and meta-analysis. *Modern Pathology*. 2021;34(7):1324-1333.
127. Limberg J, et al. Tobacco and alcohol as risk factors for primary squamous cell carcinoma of the thyroid. *Endocrine-Related Cancer*. 2020;27(10):R345-R356.
128. Saini S, et al. Chronic lymphocytic thyroiditis and risk of thyroid cancer: a meta-analysis. *Thyroid*. 2019;29(7):928-937.
129. Rivera M, et al. Molecular profiling of squamous cell carcinoma of the thyroid: implications for diagnosis and therapy. *Oral Oncology*. 2023;138:106307.
130. James BC, et al. The impact of radiation exposure on the risk of squamous cell carcinoma of the thyroid. *Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4074-4082.
131. Flynn MB, et al. Primary versus secondary squamous cell carcinoma of the thyroid: a retrospective analysis of 45 cases. *World Journal of Surgery*. 2020;44(3):786-791.
132. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.
133. Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
134. Lamouille S, et al. Molecular mechanisms of epithelial-mesenchymal transition. *Nature Reviews Molecular Cell Biology*. 2014;15(3):178-196.
135. Thiery JP, et al. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139(5):871-890.
136. Pastushenko I, Blanpain C. EMT Transition States during Tumor Progression and Metastasis. *Trends in Cell Biology*. 2019;29(3):212-226.
137. Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene*. 2010;29(34):4741-4751.
138. Stone RC, et al. Epithelial-mesenchymal transition in tissue repair and fibrosis. *Cell and Tissue Research*. 2016;365(3):495-506.
139. Rivera M, et al. Sarcomatoid transformation in thyroid cancer: a comprehensive clinicopathological analysis. *Endocrine Pathology*. 2023;34(2):215-225.
140. Lamouille S, et al. Molecular mechanisms of epithelial-mesenchymal transition. *Nature Reviews Molecular Cell Biology*. 2014;15(3):178-196.
141. Thiery JP, et al. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139(5):871-890.
142. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.
143. Miller ML, et al. Targeting the PI3K/AKT/mTOR pathway in anaplastic thyroid cancer. *Endocrine-Related Cancer*. 2020;27(10):R461-R478.
144. Pozdeyev N, et al. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. *Clinical Cancer Research*. 2018;24(13):3059-3068.
145. Landa I, et al. Frequent TERT promoter mutations in aggressive thyroid tumors. *Endocrine-Related Cancer*. 2016;23(8):603-610.
146. Ziros PG, et al. The transcriptional signature of Wnt/ β -catenin signaling in human thyroid tumors. *Oncogene*. 2019;38(27):5393-5406.
147. Sherman SI, et al. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clinical Oncology*. 2020;32(8):527-539.

148. Ragazzi M, et al. Anaplastic transformation in thyroid cancer: molecular mechanisms and clinical implications. *Cancers*. 2021;13(9):2050.
149. Lloyd RV, et al. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017.
150. Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
151. Wells SA, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567-610.
152. Xing M, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *Journal of Clinical Oncology*. 2014;32(25):2718-2726.
153. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.
154. Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: implications for diagnosis, treatment and prognosis. *Expert Review of Molecular Diagnostics*. 2008;8(1):83-95.
155. Moura MM, et al. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. *The Journal of Clinical Endocrinology & Metabolism*. 2011;96(5):E863-E868.
156. Landa I, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *The Journal of Clinical Investigation*. 2016;126(3):1052-1066.
157. Subbiah V, et al. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. *Cancer Discovery*. 2018;8(7):836-849.
158. Santarpia L, et al. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(1):278-284.
159. McCubrey JA, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*. 2007;1773(8):1263-1284.
160. Dhillon AS, et al. MAP kinase signalling pathways in cancer. *Oncogene*. 2007;26(22):3279-3290.
161. Xing M. BRAF mutation in thyroid cancer. *Endocrine-Related Cancer*. 2005;12(2):245-262.
162. Ciampi R, Nikiforov YE. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. *Endocrinology*. 2007;148(3):936-941.
163. García-Rostán G, et al. Ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(11):5393-5398.
164. Liu Z, et al. Targeting PI3K/AKT/mTOR signaling in thyroid cancer. *International Journal of Molecular Sciences*. 2023;24(3):2290.
165. Landa I, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *The Journal of Clinical Investigation*. 2016;126(3):1052-1066.
166. Song YS, et al. Transcriptional and mutational analysis of BRAF/PIK3CA-mediated signaling in thyroid cancer. *Journal of Clinical Endocrinology & Metabolism*. 2017;102(7):2314-2324.
167. Rodrigues C, et al. Epigenetic alterations in thyroid cancer: From pathogenesis to targeted therapy. *Endocrine-Related Cancer*. 2023;30(4):e220362.
168. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.
169. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nature Reviews Cancer*. 2013;13(3):184-199.
170. Thiery JP, et al. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139(5):871-890.
171. Chintakuntlawar AV, et al. Expression of PD-1 and PD-L1 in anaplastic thyroid cancer patients treated with multimodal therapy: results from a retrospective study. *Journal of Clinical Endocrinology & Metabolism*. 2017;102(6):1943-1950.

172. Liu X, et al. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. *Endocrine-Related Cancer*. 2013;20(4):603-610.
173. Landa I, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *Journal of Clinical Investigation*. 2016;126(3):1052-1066.
174. Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
175. Pozdeyev N, et al. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. *Clinical Cancer Research*. 2018;24(13):3059-3068.