

# BÖLÜM

# 14

## Diferansiyel Tiroid Kanseri Postoperatif Risk Sınıflaması: Risk Sınıflamasına Göre Tedavi Yaklaşımı

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### Özet

Diferansiyel tiroid kanserli hastaların büyük çoğunluğunda prognoz mükemmel olmakla birlikte; % 10 hastada lokal nüks ve/veya uzak metastaz ve nadiren de mortalite görülebilmektedir. Bu nedenle vakaların çoğunluğunu oluşturan, hastalık spesifik mortalite ve morbidite açısından düşük riskli hastalarda aşırı tedaviden kaçınmak gereklidir. Ayrıca yüksek riskli hastalarda yetersiz tedavi durumundan kaçınmaya dikkat edilmelidir. Bunun için uygun ve aktif bir izlem önemli hedeflerden biridir. Günümüzde tiroid kanser tedavisi tek tip bir yaklaşımından ziyade, riske dayalı tedavi yaklaşımına doğru bir geçiş göstermiştir. Bu değişim, hastalık spesifik mortalite, yapısal hastalığın persistans/nüks riski, tedavi yeterliliği gibi durumları öngören ve erken takibi mümkün kılan risk değerlendirme araçlarının gelişmesi ile gerçekleşmiştir. Tiroid kanseri için birçok farklı sınıflama ve evreleme sistemi geliştirilmiştir. Dahası tanı, tedavi ve takibi için klinik pratikte birçok rehber yayınlanmıştır. Amerikan Tiroid Derneği'nin (American Thyroid Association) (ATA) 2009'da yayınladığı rehber tiroid kanser yönetiminde önemli bir etkisi olan yapısal hastalığın nüks ve persistans riskini dikkate alarak risk sınıflandırmasını kuvvetle önermiştir. 2015 yılında revize edilerek ve ek öneriler ile yeni ATA kılavuzu yayınlanmıştır. Amerikan Ortak Kanser Komitesi (American Joint Committee on Cancer (AJCC) ve Uluslararası Kanser Savaş Komitesi (International Union Against Cancer Committee (UICC)'nin önerdiği TNM sınıflaması ise mortalite riskini saptamak için kullanılır. Bu sınıflama literatürdeki kanıt düzeyine göre periyodik olarak güncellenen tek sınıflama sistemidir. AJCC/TNM Evreleme Sistemi, hastalık spesifik sağkalımı önlemek için, ATA risk sınıflandırma sistemi ise hastalık nüks riskini tahmin etmek için dizayn edilmiştir. Bu riske dayalı yaklaşımda tedavi ve takip önerileri her hasta için bireyselleştirilmiştir. Diferansiyel tiroid kanseri (DTK)'nın yönetimi, başlangıç risk derecesini dikkate alarak planlanmalıdır. Bu plan; riske göre tiroid uyarıcı hormon (TSH) baskı düzeyi, radyoaktif iyot kararı, izlem aralığı ve takip edilecek tetkikleri içermelidir. Diğer önemli ek yaklaşım tedaviye cevap ölçütlerini ve sonuçlarına göre dinamik risk değerlendirmesidir. Bu strateji, her bir hastanın hem klinik durumunun hem de her vizitdeki takip planının sürekli olarak yeniden değerlendirilmesini sağlayarak takibin bireyselleştirilmesini sağlar.

etki profiline ve hastalığı yöneten ekibin tedavi stratejisine ve hastanın tercih ve değerlerinin değerlendirilmesine dayanmalıdır (95)

RAI'nin tedavi hedefleri; remnan ablasyon, adjuvan tedavi veya bilinen rezidüel veya nüks hastalığın tedavisi olarak tanımlanmalıdır (96);

**Remnan ablasyon;** normal rezidüel fonksiyonel tiroid dokusunun belirtilen amaçlarla I-131 kullanılarak tıhrip edilmesidir; (1) takip eden serum Tg seviyelerinin yorumlanması kolaylaştmak, (2) takip eden takip RAI tüm vücut taramalarında lokorejyonel ve/veya metastatik hastalığın saptanmasının duyarlılığının artırılması, (3) takip eden herhangi bir I-131 tedavisinin terapötik etkisini maksimize etmek, (4) ablasyon öncesi taramada tanımlanmayan veya ablasyon öncesi tarama yapılmadığında şüphelenilen durumlarda ek hastalık bölgelerini tanımlayan postablatif taramayı kolaylaştmak (6,97).

**Adjuvan tedavi;** tiroid kanserinin potansiyel nüksünü ve mortalitesini azaltmak için bilinmeyecek mikroskopik tiroid kanser ve/veya şüphelenilen ancak kanıtlanamayan rezidüel tiroid kanserini tıhrip etmek için I-131'in kullanılmasıdır (6,97). Böylelikle hastalık nüksünü azaltır, hastalık-spesifik sağkalımı iyileştirir (6,95)

**Tedavi;** Tiroid kanserinin potansiyel nüksünü ve mortalitesini azaltmak ve/veya palyasyonu amacıyla bilinen lokorejyonel ve/veya uzak metastazların I-131 kullanılarak tıhrip edilmesidir (6,97). Böylelikle remisyona girmeyi kolaylaştırılabilir, DSS'ı ve progresyonsuz sağkalımı iyileştirilbilir (6,95)

Ablasyon ve adjuvan RAI uygulaması için 2015 ATA rehberinde (6) özeti ; 1- Düşük riskli

DTK'de rutin olarak RAI ablasyonu önerilmemektedir (nüks riskini değiştirecek bireysel faktörler, hastalığın takibinde kolaylık sağlamak ve hastanın tercihleri de dikkate alınmalıdır) 2-Kötü özellikler yokluğunda unifokal PTMK'de RAI rutin önerilmemektedir (kuvvetli öneri), 3-Kötü özellikler yokluğunda multifokal PTMK'de RAI rutin önerilmemektedir (zayıf öneri). 4-Orta riskli DTK'de RAI düşünülebilir. 5-Yüksek riskli hastalarda RAI rutin önerilmektedir.

## Sonuç

Son 10-20 yılda düşük riskli tiroid kanseri prevalansındaki çarpıcı artış DTK için geleneksel "tek tip yaklaşımının" yeniden değerlendirilmesine bağlanmıştır. Hasta yönetiminde daha bireyselleştirilmiş yaklaşıma doğru olan bu geçiş DTK'lı hastalarda tanı, başlangıç tedavisi, adjuvan tedavi ve takipde daha fazla risk temelli yaklaşıma yol açmıştır (6). Bu durum hastalık spesifik mortalite ve yapısal/biyokimyasal hastalık nüks riskini öngörmeye yönelik yaklaşımımızın kapsamlı bir değerlendirmesini gerektirmektedir.

Sonuç olarak, risk sınıflandırması temel ve etkin bir yaklaşımdır. AJCC sistemi ile hastalık-iliskili ölüm riskinin, ATA sistemi ile nüks/persistent riskinin tahmin edildiği çok basamaklı bir süreçdir. Başlangıç yönetim önerilerine şekil vermek için kullanılmaktadır. Tedaviye cevabı değerlendirmesi ile elde edilen veriler dinamik risk sınıflandırmasına olanak sağlamaktadır. Dinamik risk değerlendirmesine göre hasta yönetimi hem yetersiz tedavi hem de aşırı tedavi durumlarını engelleyecektir.

## Kaynaklar

1. Schmidbauer B, Menhart K, Hellwig D, et al. Differentiated Thyroid Cancer-Treatment: State of the Art. Int J Mol Sci 2017;18(6). doi: 10.3390/ijms18061292.
- 2- Mehmet Uludag, Adnan Isgor. What has Changed About the Eight Edition of the Differentiated Thyroid Carcinomas TNM Classification System? How will it Effect the Clinical Practice? S.E.E.A.H.
3. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet 2016;388(10061):2783-95.
4. Lim H, Devesa SS, Sosa JA, et al. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 2017;317(13):1338-48.
5. Castagna MG, Maino F, Cipri C, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur J Endocrinol 2011;165(3):441-6.
6. 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 Can-

- cer. *Thyroid* 2016;26 (1):1–133.
7. Tuttle RM. Risk-adapted management of thyroid cancer. *Endocr Pract* 2008;14(6):764–74.
  8. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid* 2010;20(12):1341–9.
  9. Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. *Thyroid* 2011;21(12):1317–22.
  10. Tarasova VD, Tuttle RM. A Risk-adapted Approach to Follow-up in Differentiated Thyroid Cancer. *Rambam Maimonides Med J* 2016;7(1). doi: 10.5041/RMMJ.10231.
  11. Vaisman F, Tuttle RM. Clinical Assessment and Risk Stratification in Differentiated Thyroid Cancer. *Endocrinol Metab Clin North Am* 2019;8(1):99–108.
  12. Leenhardt L, Erdogan MF, Hegedus L, et al. 2013 European thyroid association guidelines for cervical ultrasound scan and ultrasound-guided techniques in the postoperative management of patients with thyroid cancer. *Eur. Thyroid J* 2013;2(3):147–59.
  13. Silberstein EB, Alavi A, Balon HR, et al. The SNMMI practice guideline for therapy of thyroid disease with 131 I 3.0. *J. Nucl. Med.* 2012;53(10):1633–51.
  14. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur. J. Nucl. Med. Mol. Imaging* 2008;35(10):1941–59.
  15. Takami H, Ito Y, Okamoto T, et al. Revisiting the guidelines issued by the Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons: A gradual move towards consensus between Japanese and western practice in the management of thyroid carcinoma. *World J. Surg* 2014;38(8):2002–10.
  16. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19(11):1167–214.
  17. Rondeau G, Tuttle RM. Similarities and differences in follicular cell-derived thyroid cancer management guidelines used in Europe and the United States. *Semin Nucl Med* 2011;41(2):89–95.
  18. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. *Endocrinol Metab Clin North Am* 2014;43(2):401–21.
  19. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. *Eur J Cancer* 1979;15(8):1033–41.
  20. Hay ID, Grant CS, Taylor WF, et al. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 1987;102(6):1088–95.
  21. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988;104(6):947–53.
  22. DeGroot LJ, Kaplan EL, McCormick M, et al. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990;71(2):414–24.
  23. Hay ID, Bergstrahl EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 1993;114(6):1050–7; discussion 1057–8.
  24. Lang BH, Lo CY, Chan WF, et al. Staging systems for papillary thyroid carcinoma: a review and comparison. *Ann Surg* 2007;245(3):366–78.
  25. D'Avanzo A, Ituarte P, Treseler P, et al. Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. *Thyroid* 2004;14(6):453–58.
  26. Akslen LA. Prognostic importance of histologic grading in papillary thyroid carcinoma. *Cancer* 1993;72(9):2680–85.
  27. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97(5):418–28.
  28. Noguchi S, Murakami N, Kawamoto H. Classification of papillary cancer of the thyroid based on prognosis. *World J Surg* 1994;18(4):552–57.
  29. Shaha AR, Loree TR, Shah JP. Intermediate-risk group for differentiated carcinoma of thyroid. *Surgery* 1994;116(6):1036–40; discussion 1040–1.
  30. Lerch H, Schober O, Kuwert T, et al. Survival of differentiated thyroid carcinoma studied in 500 patients. *J Clin Oncol* 1997;15(5):2067–75.
  31. Sherman SI, Brierley JD, Sperling M, et al. Prospective multicenter study of thyroiscarcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. *Cancer* 1998; Sep 1;83(5):1012–21.
  32. Wong RM, Bresee C, Braunstein GD. Comparison with published systems of a new staging system for papillary and follicular thyroid carcinoma. *Thyroid* 2013;23(5):566–74.
  33. Beenken S, Roye D, Weiss H, et al. Extent of surgery for intermediate-risk well-differentiated thyroid cancer. *Am J Surg* 2000;179(1):51–6.
  34. Sebastian SO, Gonzalez JM, Paricio PP, et al. Papillary thyroid carcinoma: prognostic index for survival including the histological variety. *Arch Surg* 2000;135(3):272–7.
  35. Sugitani I, Kasai N, Fujimoto Y, et al. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery* 2004;135(2):139–48.
  36. Yildirim E. A model for predicting outcomes in patients with differentiated thyroid cancer and model performance in comparison with other classification systems.

- J Am Coll Surg 2005;200(3):378-92.
37. Vrachimis A, Gerss J, Stoyke M, et al. No significant difference in the prognostic value of the 5th and 7th editions of AJCC staging for differentiated thyroid cancer. *Clin Endocrinol (Oxf)* 2014;80(6):911-7.
- 38- Tae Yoon Lee, Sohee Lee , Ja Seong Bae. Staging of Differentiated Thyroid Cancer from a Single Institution: Comparison of the 7th and 8th Editions of AJCC/UICC Staging. *J Endocr Surg* 2017; 17(2):80-88.
39. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17(6):1471-4.
40. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What changed and why? *Thyroid* 2017;27(6):751-6.
41. Pontius LN, Oyekunle TO, Thomas SM, et al. Projecting Survival in Papillary Thyroid Cancer: A Comparison of the Seventh and Eighth Editions of the American Joint Commission on Cancer/Union for International Cancer Control Staging Systems in Two Contemporary National Patient Cohorts. *Thyroid* 2017;27(11):1408-16.
42. Shteinshnaider M, Muallem Kalovich L, Koren S, et al. Reassessment of Differentiated Thyroid Cancer Patients Using the Eighth TNM/AJCC Classification System: A Comparative Study. *Thyroid* 2018;28(2):201-9.
43. Van Velsen EFS, Stegenga MT, van Kemenade FJ, et al. Comparing the Prognostic Value of the Eighth Edition of the American Joint Committee on Cancer/Tumor Node Metastasis Staging System Between Papillary and Follicular Thyroid Cancer. *Thyroid* 2018;28(8):976-81.
44. Pacini F, Schlumberger M, Dralle H, et al.: European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;154(6):787-803.
45. Hannequin P, Liehn JC, Delisle MJ. Multifactorial analysis of survival in thyroid cancer. Pitfalls of applying the results of published studies to another population. *Cancer* 1986;58(8):1749- 55.
- 46- Black J and Kim L. Differentiated Thyroid Cancer: Prognostic and Risk Assessment Systems. In: A.T. Mancino, L.T. Kim (eds.). Management of Differentiated Thyroid Cancer. USA, Springer; 2017.p.189-204
47. Lee YM, Cho JW, Hong SJ, et al. Dynamic risk stratification in papillary thyroid carcinoma measuring 1 to 4 cm. *J Surg Oncol* 2018;118(4):636-43.
48. Ozkan E, Soydal C, Nak D, et al. Dynamic risk stratification for predicting the recurrence in differentiated thyroid cancer. *Nucl Med Commun* 2017;38(12):1055-59.
49. Pitoia F, Bueno F, Urciuoli C, et al. Outcome of patients with differentiated thyroid cancer risk stratified according to the American thyroid association and LatinAmerican thyroid society risk of recurrence classification systems. *Thyroid* 2013;23(11):1401-7.
50. Vaisman F, Momesso D, Bulzico D, et al. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. *Clin Endocrinol (Oxf)* 2012;77(1):132-8.
- 51- Tuttle RM, Alzahrani AS. Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-up. *J Clin Endocrinol Metab* 2019. doi: 10.1210/jc.2019-00177.[Epub ahead of print]
52. Ganly I, Nixon IJ, Wang LY, et al. Survival from differentiated thyroid cancer: What has age got to do with it? *Thyroid* 2015;25(10):1106-14.
53. Jonklaas J, Nogueras-Gonzalez G, Munsell M, et al; National Thyroid Cancer Treatment Cooperative Study Group. The impact of age and gender on papillary thyroid cancer survival. *J Clin Endocrinol Metab* 2012; 97(6):E878-87.
54. Nixon IJ, Kuk D, Wreesmann V, et al. Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer. *Ann Surg Oncol* 2016; 23(2):410-5.
55. Nixon IJ, Wang LY, Migliacci JC, et al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. *Thyroid* 2016;26(3):373-80.
56. Kim M, Kim YN, Kim WG, et al. Optimal cut-off age in the TNM Staging system of differentiated thyroid cancer: is 55 years better than 45 years? *Clin Endocrinol (Oxf)* 2017;86(3): 438-43.
57. Hay ID, Johnson TR, Thompson GB, et al. Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence. *Surgery* 2016;159(1):11-9.
58. Ito Y, Tomoda C, Uruno T, et al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World J Surg* 2006;30(5):780-6.
59. Nixon IJ, Ganly I, Patel S, et al. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery* 2011;150(6):1242-9.
60. Ito Y, Tomoda C, Uruno T, et al. Minimal extrathyroid extension does not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the age of 45 years. *Surg Today* 2006;36(1):12-8.
61. Randolph G, Duh QY, Heller KS, et al. The Prognostic Significance of Nodal Metastases from Papillary Thyroid Carcinoma can be Stratified Based on the Size and Number of Metastatic Lymph Nodes, as Well as the Presence of Extranodal Extension ATA Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery. *Thyroid* 2012;22(11):1144-52.
62. Kim TH, Kim YN, Kim HI, et al. Prognostic value of the eighth edition AJCC TNM classification for differentiated thyroid carcinoma. *Oral Oncol* 2017;71:81-6.
63. Suh S, Kim YH, Goh TS, et al.

- Outcome prediction with the revised American joint committee on cancer staging system and American thyroid association guidelines for thyroid cancer. *Endocrine* 2017;58(3):495-502.
64. Kim M, Kim WG, Oh HS, et al. Comparison of the Seventh and Eighth Editions of the American Joint Committee on Cancer/Union for International Cancer Control Tumor-Node-Metastasis Staging System for Differentiated Thyroid Cancer. *Thyroid* 2017;27(9):1149-55.
  65. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001;86(4):1447-63.
  66. Pitoia F, Erika A, Tala Jury HP, et al. Biochemical persistence in thyroid cancer: is there anything to worry about? *Endocrine* 2014;46(3):532-37.
  67. Sung TY, Cho JW, Lee YM, et al. Dynamic Risk Stratification in Stage I Papillary Thyroid Cancer Patients Younger Than 45 Years of Age. *Thyroid* 2017;27(11):1400-07.
  68. Brierley JD, Panzarella T, Tsang RW, et al. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer* 1997;79(12):2414-23.
  69. Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2018;68(1):55-63.
  70. Ghaznavi SA, Ganly I, Shaha AR, et al. Using the ATA risk stratification system to refine and individualize the AJCC 8th edition disease specific survival estimates in differentiated thyroid cancer. *Thyroid* 2018;28(10):1293-300.
  71. Shah S, Boucail L. Effect of age on response to therapy and mortality in patients with thyroid cancer at high risk of recurrence. *J Clin Endocrinol Metab* 2018;103(2):689-97.
  72. Miyauchi A, Kudo T, Miya A, et al. Prognostic impact of serum thyroglobulin doubling-time under TSH suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy. *Thyroid* 2011;21(7):707-16.
  73. Momesso DP, Vaisman F, Yang SP, et al. Dynamic risk stratification in patients with differentiated thyroid cancer treated without radioactive iodine. *J Clin Endocrinol Metab* 2016;101(7):2692-700.
  74. Leboulleux S, Schroeder PR, Schlumberger M, et al. The role of PET in follow-up of patients treated for differentiated epithelial thyroid cancers. *Thyroid* 2001;11(12):1169-75.
  75. Wang W, Larson SM, Tuttle RM, et al. Resistance of [18F]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine. *Thyroid* 2001;11(12):1169-75.
  76. Richard RJ, Wan Q, Grewal RK, et al. Larson real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]Fluoro-2-Deoxy-D-glucose positron emission tomography scanning. *J Clin Endocrinol Metab* 2006;91(2):498-505.
  77. Esteva D, Muros MA, Llamas-Elvira JM, et al. Clinical and pathological factors related to 18F-FDG-PET positivity in the diagnosis of recurrence and/or metastasis in patients with differentiated thyroid cancer. *Ann Surg Oncol* 2009;16(7):2006-13.
  78. Rivera M, Ghossein RA, Schoder H, et al. Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. *Cancer* 2008;113(1):48-56.
  79. Ricarte-Filho JC, Ryder M, Chitale DA, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct Clinical Assessment and Risk Stratification 107 pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res* 2009;69(11): 4885-93.
  80. Yang X, Li J, Li X, et al. TERT Promoter mutation predicts radioiodine-refractory character in distant metastatic differentiated thyroid cancer. *J Nucl Med* 2017;58(2):258-65.
  81. Penna GC, Pestana A, Cameselle JM, et al. TERTp mutation is associated with a shorter progression free survival in patients with aggressive histology subtypes of follicular-cell derived thyroid carcinoma. *Endocrine* 2018;61(3):489-98.
  82. 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.
  83. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol* 2014;32(25):2718-26.
  84. Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2018;68(1):55-63.
  85. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;67(2):93-9.
  86. Jin A, Xu J, Wang Y. The role of TERT promoter mutations in postoperative and preoperative diagnosis and prognosis in thyroid cancer. *Medicine (Baltimore)* 2018;97(29): e11548
  87. Kim TH, Ki CS, Kim HS, et al. Refining Dynamic Risk Stratification and Prognostic Groups for Differentiated Thyroid Cancer With TERT Promoter Mutations. *J Clin Endocrinol Metab* 2017;102(5):1757-64.
  88. Vuong HG, Altibi AMA, Duong UNP, et al. Prognostic implication of BRAF and TERT promoter mutation combination in papillary thyroid carcinoma-A meta-analysis. *Clin Endocrinol (Oxf)* 2017;87(5):411-17.
  89. Vuong HG, Duong UN, Altibi AM, et al. A meta-analysis of prognostic roles of molecular markers in papillary thyroid carcinoma. *Endocr Connect* 2017;6(3):R8-R17.
  90. Xing M. Prognostic utility of BRAF mutation in papillary thy-

- roid cancer. *Mol Cell Endocrinol* 2010;321(1):86-93.
91. Yin DT, Yu K, Lu RQ, et al. Clinico-pathological significance of TERT promoter mutation in papillary thyroid carcinomas: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2016;85(2):299-305.
92. Haymart MR, Esfandiari NH, Stang MT, et al. Controversies in the management of low-risk differentiated thyroid cancer. *Endocr Rev* 2017;38(4):351-78.
93. Tuttle RM, Sabra MM. Selective use of RAI for ablation and adjuvant therapy after total thyroidectomy for differentiated thyroid cancer: a practical approach to clinical decision making. *Oral Oncol* 2013;49(7):676-83.
94. Vaisman F, Momesso D, Bulzico DA, et al. Thyroid Lobectomy Is Associated with Excellent Clinical Outcomes in Properly Selected Differentiated Thyroid Cancer Patients with Primary Tumors Greater Than 1 cm. *Journal of thyroid research* 2013;2013:398194
- 95- Tuttle RM. Controversial Issues in Thyroid Cancer Management. *J Nucl Med* 2018;59(8):1187-94.
96. Van Nostrand D. Selected Controversies of Radioiodine Imaging and Therapy in Differentiated Thyroid Cancer. *Endocrinol Metab Clin North Am* 2017; 46(3):783-93.
97. Van Nostrand D. The benefits and risks of I-131 therapy in patients with welldifferentiated thyroid cancer. *Thyroid* 2009;19(12):1381-91.