BÖLÜM 4

TİMİK TÜMÖRLER

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GİRİŞ

Timüs bezi ön mediastende yerleşik iki lobdan oluşan, T lenfositlerin gelişiminde rol alan lenfoepitelyal bir organdır (1). Timoma ve timik karsinom timüs bezinin epitelyal tümörleri (TET) olarak adlandırılır. TET'ler mediastinal kitlelerin yaklaşık %20-50'sini oluşturur (2, 3). Erişkinlerde anterior mediastenin en sık görülen tümörleridir (4). Timik karsinomlar timomaya göre daha nadir görülen agresif tümörlerdir. Toraks dışında, kardiyak ve mediastende azda olsa görülebilirler (5). Tüm TET'lerin metastaz yapma potansiyeli vardır (6). Plevra ve akciğer sıklıkla metastaz yaptıkları bölgeler olup kemik ve karaciğer metastaz bölgeleri arasında yer alır (7). Etiyoloji belli olmayıp belirgin risk faktörleri tanımlanamamıştır (8). Timomalar otoimmün paraneoplastik hastalıklarlada ilişkilidir (9). Timik karsinomalar timomaya göre daha yüksek atipi gösterirler. Timik karsinomun en yaygın görülen alt tipi skuamöz hücreli karsinomdur (10). Tip A, AB ve B1 timik tümörler sıklıkla erken evrede görülürken, Tip B2, B3 ve Tip C tümörler tanı konduğunda daha ileri evrede görülürler (11). Timik karsinoma Dünya Sağlık Örgütünün sınıflamasında Tip C sınıfındadır (12). Timik karsinomların çoğu tanı aşamasında, ileri evrede olup multimodalite tedaviler tercih edilir. Cerrahi, özellikle erken evre hastalık için ana tedavidir. Kemoterapi ve radyasyon tedavisi de dahil olmak üzere multimodalite tedavisi, lokal ileri hastalığı tedavi etmek için kullanılır (13). Progresyon gelişen olgularda ikinci sırada kemoterapi seçenekleri, tirozin kinaz inhibitörleri, hedefe yönelik ilaçlar ve immünoterapi gibi tedavilerle çeşitli oranlarda olumlu sonuçlar elde edilmektedir (14).

İNSİDANS VE MORTALİTE

Malignitelerin yaklaşık %0.2-%1.5'ini oluşturan TET'ler nadir tümörlerdir. Yıllık 100000'de 0.15 oranında görülürler (15). Kadın ve erkekte eşit sıklıkta görülür (16). En sık 40-60 yaş arasında görülmektedir (17). Timomaların 5 yıllık sağka-

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ması yapmak gerekmektedir (87). Everolimusun (mTOR inhibitörü) kullanıldığı çalışmada yüksek stabil yanıt oranları sağlanmıştır ancak artmış pnömonitis riski nedeni ile dikkatli kullanılması önerilmiştir (88).

SONUÇ

Timik tümörlerin erken evrelerinde tedavi mutlak cerrahi olup tümörün tam rezeksiyonu en önemli prognostik faktördür. Timik karsinomda postoperatif radyoterapi erken evre dışında rutin olup timomada cerrahi sonrası risk faktörleri varlığında uygulanabilir. Evre III ve IV timomalarda multimodalite tedavisi uygun bir yaklaşım gibi görünmektedir. İndüksiyon kemoterapisi rezeksiyon için uygun olmayan hastalarda kullanılabilir. İleri evre hastalarda ilk seride hasta tolere edebiliyorsa kombinasyon kemoterapi rejimleri kullanılmalıdır. İkinci sıra tedavide, mTOR inhibitörleri, tirozin kinaz inhibitörleri, immünoterapi ajanları, tek ajan kemoterapi veya kombinasyon kemoterapi rejimleri hasta performansı ve kullanılacak tedavilerin yan etki profilleri değerlendirilerek kullanılabilir.

KAYNAKLAR

1. M D, editor. Timik tümörler.2020.
2. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chinese medical journal. 2013;126(11):2186-91.
3. Karki S, Chalise S. Analysis of mediastinal lesions: A study of 27 cases. Journal of pathology of Nepal. 2011;1(2):114-7.
4. Wright M, Cameron D, Mathisen M, Douglas J. Mediastinal tumors: diagnosis and treatment. World journal of surgery. 2001;25(2):204-9.
5. Dib HR, Friedman B, Khouli HI, Gerber DR, Weiss RL. Malignant thymoma: a complicated triad of SVC syndrome, cardiac tamponade, and DIC. Chest. 1994;105(3):941-2.
6. Vladislav T, Jain RK, Alvarez R, Mehta RJ, Gökmen-Polar Y, Kesler KA, et al. Extrathoracic metastases of thymic origin: a review of 35 cases. Modern Pathology. 2012;25(3):370-7.
7. Khandelwal A, Sholl L, Araki T, Ramaiya N, Hatabu H, Nishino M. Patterns of metastasis and recurrence in thymic epithelial tumours: longitudinal imaging review in correlation with histological subtypes. Clinical radiology. 2016;71(10):1010-7.
8. Engels EA. Epidemiology of thymoma and associated malignancies. Journal of Thoracic Oncology. 2010;5(10):S260-S5.
9. Tormoehlen LM, Pascuzzi RM. Thymoma, myasthenia gravis, and other paraneoplastic syndromes. Hematology/oncology clinics of North America. 2008;22(3):509-26.
10. Tseng Y-L. Thymic carcinoma: a rare cancer requiring special attention. Formosan Journal of Surgery. 2011;44(4):136-40.
11. Scorsetti M, Leo F, Trama A, D'Angelillo R, Serpico D, Macerelli M, et al. Thymoma and thymic carcinomas. Critical reviews in oncology/hematology. 2016;99:332-50.
12. Metin SK. Timik tümörler. Mediyasten Hastalıkları ve Cerrahisi Bölüm.32:281-99.
13. Ogawa K, Toita T, Uno T, Fuwa N, Kakinohana Y, Kamata M, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. Cancer. 2002;94(12):3115-9.
14. Kelly RJ, Petrini I, Rajan A, Wang Y, Giaccone G. Thymic malignancies: from clinical management to targeted therapies. Journal of clinical oncology. 2011;29(36):4820.
15. Bushan K, Sharma S, Verma H. A review of thymic tumors. Indian journal of surgical oncology. 2013;4(2):112-6.

16. Safieddine N, Liu G, Cuningham K, Ming T, Hwang D, Brade A, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. Journal of Thoracic Oncology. 2014;9(7):1018-22.
17. Feng X-L, Lei X-B, Dong W-T, Yan L-F, Xin Y-K, Li G-F, et al. Incidence and clinical variable inter-relationships of thymic epithelial tumors in northwest China. Journal of thoracic disease. 2018;10(12):6794.
18. Ettinger DS, Riely GJ, Akerley W, Borghaei H, Chang AC, Cheney RT, et al. Thymomas and thymic carcinomas. Journal of the National Comprehensive Cancer Network. 2013;11(5):562-76.
19. Gripp S, Hilgers K, Wurm R, Schmitt G. Thymoma: prognostic factors and treatment outcomes. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1998;83(8):1495-503.
20. Masaoka A. Staging system of thymoma. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010;5(10 Suppl 4):S304-12.
21. Bhora FY, Chen DJ, Detterbeck FC, Asamura H, Falkson C, Filosso PL, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2014;9(9 Suppl 2):S88-96.
22. Ahmad U, Yao X, Detterbeck F, Huang J, Antonicelli A, Filosso PL, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. The Journal of thoracic and cardiovascular surgery. 2015;149(1):95-101. e2.
23. Harris C, Croce B, Xie A. Thymoma. Annals of Cardiothoracic Surgery. 2015;4(6):576.
24. Evoli A, Lancaster E. Paraneoplastic disorders in thymoma patients. Journal of Thoracic Oncology. 2014;9(9):S143-S7.
25. Okumura M, Fujii Y, Shiono H, Inoue M, Minami M, Utsumi T, et al. Immunological function of thymoma and pathogenesis of paraneoplastic myasthenia gravis. General thoracic and cardiovascular surgery. 2008;56(4):143-50.
26. Thompson CA. Pure red cell aplasia and thymoma. Journal of Thoracic Oncology. 2007;2(4):263-4.
27. Carter BW, Marom EM, Detterbeck FC. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. Journal of Thoracic Oncology. 2014;9(9):S102-S9.
28. Marom EM. Advances in thymoma imaging. Journal of thoracic imaging. 2013;28(2):69-83.
29. Benveniste MF, Rosado-de-Christenson ML, Sabloff BS, Moran CA, Swisher SG, Marom EM. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics. 2011;31(7):1847-61.
30. Sung YM, Lee KS, Kim B-T, Choi JY, Shim YM, Chin AY. 18F-FDG PET/CT of thymic epithelial tumors: usefulness for distinguishing and staging tumor subgroups. Journal of Nuclear Medicine. 2006;47(10):1628-34.
31. Pınar. G. Timik tümörler. Nadir Tümörler. 1. Baskı. Ankara:. 2020. In: Türkiye Klinikleri [Internet]. [p.26-9].
32. Detterbeck FC, Moran C, Huang J, Suster S, Walsh G, Kaiser L, et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. Journal of Thoracic Oncology. 2011;6(7):S1730-S8.
33. Lee GD, Kim HR, Choi SH, Kim Y-H, Kim DK, Park S-I. Prognostic stratification of thymic epithelial tumors based on both Masaoka-Koga stage and WHO classification systems. Journal of thoracic disease. 2016;8(5):901.
34. Kondo K, Van Schil P, Detterbeck FC, Okumura M, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors. Journal of Thoracic Oncology. 2014;9(9):S81-S7.
35. Venuta F, Rendina EA, Anile M, de Giacomo T, Vitolo D, Coloni GF. Thymoma and thymic carcinoma. General thoracic and cardiovascular surgery. 2012;60(1):1-12.

36. Cheufou DH, Valdivia D, Puhlvers S, Fels B, Weinreich G, Taube C, et al. Lymph node involvement and the surgical treatment of thymic epithelial and neuroendocrine carcinoma. The Annals of Thoracic Surgery. 2019;107(6):1632-8.
37. Park IK, Kim YT, Jeon JH, Kim H-S, Hwang Y, Seong YW, et al. Importance of Lymph Node Dissection in Thymic Carcinoma. The Annals of Thoracic Surgery. 2013;96(3):1025-32.
38. Hwang Y, Park IK, Park S, Kim ER, Kang CH, Kim YT. Lymph Node Dissection in Thymic Malignancies: Implication of the ITMIG Lymph Node Map, TNM Stage Classification, and Recommendations. Journal of Thoracic Oncology. 2016;11(1):108-14.
39. Clermidy H, Maury J-M, Collaud S, Drevet G, Ginoux M, Chalabreysse L, et al. Lymph node dissection in thymoma: is it worth it? Lung Cancer. 2021;157:156-62.
40. Weksler B, Shende M, Nason KS, Gallagher A, Ferson PF, Pennathur A. The role of adjuvant radiation therapy for resected stage III thymoma: a population-based study. The Annals of thoracic surgery. 2012;93(6):1822-9.
41. Huang J, Rizk NP, Travis WD, Riely GJ, Park BJ, Bains MS, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. The Journal of thoracic and cardiovascular surgery. 2009;138(1):26-31.
42. Regnard J-F, Magdeleinat P, Dromer C, Dulmet E, De Montpreville V, Levi J-F, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. The Journal of thoracic and cardiovascular surgery. 1996;112(2):376-84.
43. Kim ES, Putnam JB, Komaki R, Walsh GL, Ro JY, Shin HJ, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas. Lung cancer. 2004;44(3):369-79.
44. Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, et al. The management of thymoma: a systematic review and practice guideline. Journal of Thoracic Oncology. 2009;4(7):911-9.
45. Blumberg D, Port JL, Weksler B, Delgado R, Rosai J, Bains MS, et al. Thymoma: a multivariate analysis of factors predicting survival. The Annals of thoracic surgery. 1995;60(4):908-14.
46. Marulli G, Margaritora S, Lucchi M, Cardillo G, Granone P, Mussi A, et al. Surgical treatment of recurrent thymoma: is it worthwhile? European Journal of Cardio-Thoracic Surgery. 2016;49(1):327-32.
47. Giannopoulou A, Gkiozos I, Harrington KJ, Syrigos KN. Thymoma and radiation therapy: a systematic review of medical treatment. Expert review of anticancer therapy. 2013;13(6):759-66.
48. Mangi AA, Wright CD, Allan JS, Wain JC, Donahue DM, Grillo HC, et al. Adjuvant radiation therapy for stage II thymoma. The Annals of thoracic surgery. 2002;74(4):1033-7.
49. Ruffini E, Mancuso M, Oliaro A, Casadio C, Cavallo A, Cianci R, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. J Thorac Cardiovasc Surg. 1997;113(1):55-63.
50. Board PATE. Thymoma and Thymic Carcinoma Treatment (Adult)(PDQ®). PDQ Cancer Information Summaries [Internet]: National Cancer Institute (US); 2020.
51. Macchiarini P, Chella A, Ducci F, Rossi B, Testi C, Bevilacqua G, et al. Neoadjuvant chemotherapy, surgery, and postoperative radiation therapy for invasive thymoma. Cancer. 1991;68(4):706-13.
52. Venuta F, Rendina EA, Pescarmona EO, Tiziano De Giacomo M, Vegna ML, Fazi P, et al. Multimodality treatment of thymoma: a prospective study. The Annals of thoracic surgery. 1997;64(6):1585-92.
53. Markowiak T, Ansari MKA, Neu R, Schalke B, Marx A, Hofmann H-S, et al. Evaluation of Surgical Therapy in Advanced Thymic Tumors. Cancers. 2021;13(18):4516.
54. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. The Annals of thoracic surgery. 2003;76(3):878-84.
55. Park S, Ahn M-j, Ahn JS, Sun J-M, Shim YM, Kim J, et al. A prospective phase II trial of induc-

tion chemotherapy with docetaxel/cisplatin for Masaoka stage III/IV thymic epithelial tumors. Journal of Thoracic Oncology. 2013;8(7):959-66.
56. Girard N, Mornex F, Van Houtte P, Cordier J-F, Van Schil P. Thymoma: a focus on current therapeutic management. Journal of Thoracic Oncology. 2009;4(1):119-26.
57. Giaccone G. Treatment of malignant thymoma. Current opinion in oncology. 2005;17(2):140-6.
58. Hu E, Levine J. Chemotherapy of malignant thymoma. Case report and review of the literature. Cancer. 1986;57(6):1101-4.
59. Kunitoh H, Tamura T, Shibata T, Takeda K, Katakami N, Nakagawa K, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). British journal of cancer. 2010;103(1):6-11.
60. Lemma GL, Lee J-W, Aisner SC, Langer CJ, Tester WJ, Johnson DH, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. Journal of clinical oncology. 2011;29(15):2060.
61. Loehrer Sr PJ, Chen M, Kim K, Aisner SC, Einhorn LH, Livingston R, et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: an intergroup trial. Journal of clinical oncology. 1997;15(9):3093-9.
62. Ogawa K, Toita T, Uno T, Fuwa N, Kakinohana Y, Kamata M, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. Cancer. 2002;94(12):3115-9.
63. Litvak AM, Woo K, Hayes S, Huang J, Rimner A, Sima CS, et al. Clinical characteristics and outcomes for patients with thymic carcinoma: evaluation of Masaoka staging. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2014;9(12):1810-5.
64. Yano T, Hara N, Ichinose Y, Asoh H, Yokoyama H, Ohta M. Treatment and prognosis of primary thymic carcinoma. Journal of surgical oncology. 1993;52(4):255-8.
65. Korst RJ, Kansler AL, Christos PJ, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg. 2009;87(5):1641-7.
66. Kondo K. Optimal therapy for thymoma. The journal of medical investigation : JMI. 2008;55(1-2):17-28.
67. Jackson MW, Palma DA, Camidge DR, Jones BL, Robin TP, Sher DJ, et al. The impact of postoperative radiotherapy for thymoma and thymic carcinoma. Journal of Thoracic Oncology. 2017;12(4):734-44.
68. Koizumi T, Takabayashi Y, Yamagishi S, Tsushima K, Takamizawa A, Tsukadaira A, et al. Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC chemotherapy). American journal of clinical oncology. 2002;25(3):266-8.
69. Loehrer Sr PJ, Jiroutek M, Aisner S, Aisner J, Green M, Thomas Jr CR, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2001;91(11):2010-5.
70. Straka C, Ying J, Kong F-M, Willey CD, Kaminski J, Kim D. Review of evolving etiologies, implications and treatment strategies for the superior vena cava syndrome. Springerplus. 2016;5(1):1-13.
71. Carretta A, Ciriaco P, Muriana P, Bandiera A, Negri G. Surgical treatment of single and multiple thymoma recurrences. General Thoracic and Cardiovascular Surgery. 2020;68(4):350-6.
72. Liu H-C, Chen Y-J, Tzen C-Y, Huang C-J, Chang C-C, Huang W-C. Debulking surgery for advanced thymoma. European Journal of Surgical Oncology (EJSO). 2006;32(9):1000-5.
73. Attaran S, Acharya M, Anderson JR, Punjabi PP. Does surgical debulking for advanced stages of thymoma improve survival? Interactive cardiovascular and thoracic surgery. 2012;15(3):494-7.
74. Park S, Park IK, Kim YT, Lee GD, Kim DK, Cho JH, et al. Comparison of neoadjuvant chemotherapy followed by surgery to upfront surgery for thymic malignancy. The Annals of thoracic

surgery. 2019;107(2):355-62.
75. Gbolahan OB, Porter RF, Salter JT, Yiannoutsos C, Burns M, Chiorean EG, et al. A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(12):1940-8.
76. Yoh K, Goto K, Ishii Gi, Niho S, Ohmatsu H, Kubota K, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003;98(5):926-31.
77. Schmitt J, Loehrer Sr PJ. The role of chemotherapy in advanced thymoma. Journal of Thoracic Oncology. 2010;5(10):S357-S60.
78. Thomas A, Rajan A, Szabo E, Tomita Y, Carter CA, Scepura B, et al. A Phase I/II Trial of Belinostat in Combination with Cisplatin, Doxorubicin, and Cyclophosphamide in Thymic Epithelial Tumors: A Clinical and Translational StudyBelinostat plus Chemotherapy for Thymic Epithelial Tumors. Clinical Cancer Research. 2014;20(21):5392-402.
79. Giaccone G, Kim C, Thompson J, McGuire C, Kallakury B, Chahine JJ, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. The Lancet Oncology. 2018;19(3):347-55.
80. Katsuya Y, Fujita Y, Horinouchi H, Ohe Y, Watanabe S-i, Tsuta K. Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma. Lung Cancer. 2015;88(2):154-9.
81. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. The Lancet Oncology. 2017;18(5):587-98.
82. Rajan A, Heery CR, Thomas A, Mammen AL, Perry S, O'Sullivan Coyne G, et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (Avelumab) treatment in advanced thymoma. Journal for immunotherapy of cancer. 2019;7(1):1-12.
83. Thomas A, Rajan A, Berman A, Tomita Y, Brzezniak C, Lee M-J, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. The Lancet Oncology. 2015;16(2):177-86.
84. Remon J, Girard N, Mazieres J, Dansin E, Pichon E, Grellier L, et al. Sunitinib in patients with advanced thymic malignancies: Cohort from the French RYTHMIC network. Lung Cancer. 2016;97:99-104.
85. Ströbel P, Hohenberger P, Marx A. Thymoma and thymic carcinoma: molecular pathology and targeted therapy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010;5(10 Suppl 4):S286-90.
86. Mansfield A, Herbst R, Castro Jr G, Hui R, Peled N, Kim D-W, et al. Outcomes with pembrolizumab (pembro) monotherapy in patients (pts) with PD-L1–positive NSCLC with brain metastases: pooled analysis of KEYNOTE-001,-010,-024, and-042. Annals of Oncology. 2019;30:v604-v6.
87. Sato J, Satouchi M, Itoh S, Okuma Y, Niho S, Mizugaki H, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. The Lancet Oncology. 2020;21(6):843-50.
88. Zucali PA, De Pas T, Palmieri G, Favaretto A, Chella A, Tiseo M, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. Journal of Clinical Oncology. 2018;36(4):342-9.