

Bölüm 38

OKÜLER MELANOMDA GÜNCEL YAKLAŞIM

Adil ÖZYILKAN¹
Hüseyin MERTSOYLU

GİRİŞ

Oküler melanom cilt melanomlarından sonra en sıklıkla görülen ikinci melanomlardır. Aynı zamanda göz kanserlerinde ise en sık görülen malign tümördür. Melanomlar gözde melanositlerin oldukları yerde olurlar ve en sık üvea da oluşur. Üvea dışta sklera içte retina arasında olan iris, corpus siliyare ve choroidi içeren yapıdır. Oküler melanomların %82.5 üvea da oluşmakta olup konjonktival melanomlar daha az sıklıkta görülür. Ocular melanomlar genellikle primer olup metastatik melanomlar ise orbita ve gözlerdeki tümörlerden %5 ni oluşturur.

EPİDEMİYOLOJİ

Oküler melanom milyonda 6 ,cilt melanomu ise 153.5 görülür(1). Amerika ve Avusturyada yapılan çalışmalarda Oküler melanom erkek/kadın oranı 1.29 olarak bulunmuştur.

Konjonktival melanom milyonda 0.4 görülürken üveal melanom 4.9 görülmüştür(1). Avrupada melanom incidansı kuzey güney arası farklılık gösterip güneyde milyonda 8 kuzeyde 2 nin altına kadar düşmektedir.(2a)

Oküler melanom oranları siyahlar ile karşılaştırıldığında beyazlar arasında 8-10 kat daha yüksektir. Diğer oküler melanomların aksine konjonktival melanom oranları siyahlara göre 2.6 kat daha fazladır.(3) Okular melanom insidansı yaşla birlikte artar yedinci sekizinci dekatta en yüksek seviyeye ulaşır. 60 yaş üstü beyaz erkeklerde konjonktiva melanom riski artmaktadır

¹ Lefkoşa Dar. Burhan Nalbantoğlu Devlet Hastanesi Göz Hastalıkları Kliniği, Lefkoşa, Kuzey Kıbrıs Türk Cumhuriyeti

KAYNAKLAR

1. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. *Cancer* 2005;103:1000-7
2. Virgili G, Gatta G, Ciccolallo L, Capocaccia R, Biggeri A, Crocetti E, Lutz JM, Paci E; EUROCA-RE working Group. Incidence of uveal melanoma in Europe. *Ophthalmology* 2007;114:2309-15
3. Shields CL, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR, Kelly CC, Rudich DS, Nagori AV, Wakade OA, Mehta S, Forte L, Long A, Dellacava EF, Kaplan B, Shields JA. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol* 2009;127:989-98.
4. Hu DN, Yu G, McCormick SA, Finger PT. Population-based incidence of conjunctival melanoma in various races and ethnic groups and comparison with other melanomas. *Am J Ophthalmol* 2008;145:418-423.
5. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC. Lifetime prevalence of uveal melanoma in white patients with ocular (dermal) melanocytosis. *Ophthalmology* 1998;105:195-8.
6. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. *Ophthalmology* 2005;112:1784-9.
7. Li HK, Shields CL, Mashayekhi A, Randolph JD, Bailey T, Burnbaum J, Shields JA. Giant choroidal nevus: clinical features and natural course in 322 cases. *Ophthalmology* 2010;117:324-33
8. Kanski *Clinical Ophthalmology* Second edition
9. Conway RM, Chua WC, Qureshi C, Billson FA. Primary iris melanoma: diagnostic features and outcome of conservative surgical treatment. *Br J Ophthalmol* 2007;85:848-54
10. Shields CL, Shields JA, Materin M, Gershenbaum E, Singh AD, Smith A. Iris melanoma: risk factors for metastasis in 169 consecutive patients. *Ophthalmology* 2001;108:172-8.
11. Shields CL, Naseripour M, Shields JA, Freire J, Cater J. Custom-designed, plaque radiotherapy for nonresectable iris melanoma in 38 patients; tumor control and ocular complications. *Am J Ophthalmol* 2003;135:648-56.
12. Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM, Schachat AP, Straatsma BR; Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings, COMS Report No. 18. *Arch Ophthalmol* 2001;119:969-82.
13. Collaborative Ocular Melanoma Study Group. The COMS Randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors; COMS report No. 28. *Arch Ophthalmol* 2006;124:1684-93
14. Hawkins BS; Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of preenucleation radiation of large choroidal melanoma; IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol* 2004;138:936-51.
15. Augsburger JJ. Is observation really appropriate for small choroidal melanomas. *Trans Am Ophthalmol Soc* 1993;91:147-175.
16. Robertson DM. Changing concepts in the management of choroidal melanoma. *Am J Ophthalmol* 2003;136:161-70.
17. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma; COMS Report No. 5. *Arch Ophthalmol* 1997;115:1537-44.
18. Kroll S, Char DH, Qulvey J, Castro J. A comparison of cause-specific melanoma mortality and all-cause mortality in survival analyses after radiation treatment for uveal melanoma. *Ophthalmology* 1998;105:2035-45.
19. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003;44:4651-9.
20. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study

- (COMS) ; COMS report no. 15. Arch Ophthalmol 2001; 119; 670-6.
21. Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes; report of two cases. Retina 2000;20;76-9.
 22. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, Hawkins BS, Hayman JA, Jalyesimi, I, Jampol LM, Kirkwood JM, Koh WJ, Robertson DM, Shaw JM, Stratsma BR, Thoma J; Collaborative Ocular Melanoma study Group, Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma ; Collaborative Ocular Melanoma Study Group Report No. 26 Arch Ophthalmol 2005 ; 123; 1639-43.
 23. Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jöckel KH, Becher R, Prognostic implications of monosomy 3 in uveal melanoma. Lancet 1996;347;1222-5.
 24. Sisley K, Rennie IG, Parsons MA, Jacques R, Hammond DW, Bell SM, Potter AM, Rees RC. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis Genes Chromosomes Cancer 1997; 19; 22-8.
 25. Aalto Y, Eriksson L, Seregard S, Larsson O, Knuutila S. Concomitant loss of chromosome 3 and whole arm losses and gains of chromosome 1,6, or 8 in metastasizing primary uveal melanoma Invest Ophthalmol Vis Sci 2001;42;313-7.
 26. White VA, Cahambers JD, Courtright PD, Chang Wy, Horsman DE . Correlation of cytogenetic abnormalities with the outcome of patients with uveal melanoma . Cancer 1998;83;354-359
 27. Kilic E, Naus NC, van Gils W, Klaver CC, van Til ME, Verbiest MM, Stijnen T, Mooy CM, Paridaens D, Beverloo HB, Luyten GP, de Klein A. Concurrent loss of chromosome arm 1p and chromosome 3 predicts a decreased disease-free survival in uveal melanoma patients . Invest Ophthalmol Vis Sci 2005;46;2253-7.
 28. Höglund M, Gisselsson D, Hansen GB, White VA, Sall T, Mitelman F, Horsman D. Dissecting Karyotypic patterns in malignant melanomas ; temporal clustering of losses and gains in melanoma karyotypic evolution . Int J Cancer 2004;108;57-65.
 29. Onken MD, Worly LA, Harbour JW. A Metastasis modifier locus on human chromosome 8p in uveal melanoma identified by integrative genomic analysis Clin Cancer Res 2008;14;3737-45.
 30. Parrella P, Sidransky D, Merbs SL, Allelotype of posterior uveal melanoma implications for a bifurcated tumor progression pathway . Cancer Res 1999;59;3032-7.
 31. Isager P, Enghoim G, Overgaard J, Storm H, Uveal and conjunctival malignant melanoma in Denmark 1943-97: observed and relative survival of patients followed through 2002. Ophthalmic Epidemiol 2006;13:85-96.
 32. Shields CL, Shields JA, Gündüz K, Cater J, Mercado GV, Groos N, Lally B, Conjunctival melanoma, risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients Arch Ophthalmol 2000;118:1497-507.
 33. Tuomaala S, Eskelin S, Tarkkanen A, Kivela T, Population -based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. Invest Ophthalmol Vis Sci 2002; 43:3399-408
 34. Missotten GS, Keijsers S, De Keizer RJ, De Wolff-Rouendaal D. Conjunctival melanoma in the Netherlands; a nationwide study. Invest Ophthalmol Vis Sci 2005;46;75-82
 35. Paridaens AD, McCartney AC, Minassian DC, Hungerford JL Orbital exenteration in 95 cases of primary conjunctival malignant melanoma. Br J Ophthalmol 1994;78:520-8.
 36. Lim M, Tatla T, Hersh D, Hungerford J. Patterns of regional head and neck lymph node metastasis in primary conjunctival malignant melanoma. Br J Ophthalmol 2006;90:1468-71.
 37. Davies H, Bignelli GR, Cox C, Stephens P, Edkins S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes, J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow T, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA, Mutations of the BRAF gene in human cancer. Nature 2002;417:949-54.
 38. Poynter, JN, Elder JT, Fullen DR, Nair RP, Soengas MS, Johnson TM, Redman B, Thomas NE,

- Gruber SB, BRAF and NRAS mutations in melanoma and melanocytic nevi. *Melanoma Res* 2006;16:267-73.
39. Fecher LA, Amaravadi RK, Flaherty KT, The MAPK pathway in melanoma. *Curr Opin Oncol* 2008;20:183-9.
 40. Zuidervaart W, van Nieuwpoort F, Stark M, Dijkman R, Packer L, Borgstein AM, Pavey S, vander Velden P, Out C, Jager MJ, Hayward NK, Gruis NA, Activation of the MAPK pathway is a common event in uveal melanomas although it rarely occurs through mutation of BRAF or RAS, *Br J Cancer* 2005;92:2032-8
 41. Veber A, Hengge UR, Urbanik D, Markwart A, Mirmohammadsaegh A, Reichel, MB, Wittekind C, Wiedemann p, Tannapfel A, Absence of mutations of the BRAF gene and constitutive activation of extracellular-regulated kinase in malignant melanomas of the uvea. *Lab Invest* 2003;83: 177-6.
 42. Cohen Y, Goldenberg-Cohen N, Parrella P, Chowers I, Merbs SL, Pe'er J, Sidransky D. Lack of BRAF mutation in primary uveal melanoma, *Invest Ophthalmol Vis Sci* 2003; 44 : 2876-8.
 43. Van Raamsdonk CD, Bezrookove V, Green G, Bauer J, Gaugler L, O'Brien JM, Simpson EM, Barsh GS, Bastian BC. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 2009;457:599-602.
 44. Van Raamsdonk CD, Griewank KG, Crosby MB, Garrido MC, Vemula, S, Wiesner T, Obenauf AC, Wackernagel W, Green G, Bouvier N, Sozen mm, Baimukanova G, Roy R Heguy A, Dolgalev I, Khanin R, BusamK, Speicher MR, O'Brien J, Bastian BC, Mutations in GNA11 in uveal melanoma, *N Engl J Med* 2010;363; 2191-9.
 45. Onken MD, Worley LA, Long MD, Duan S, Council ML, Bowcock AM, Harbour JW. Oncogenic mutations in GNAQ occur early in uveal melanoma. *Invest Ophthalmol Vis Sci* 2008;49:5230-4
 46. Dratviman-Storobinsky O, Cohen Y, Frenkel S, Pe'er J, Goldenberg –Cohen N. Lack of oncogenic GNAQ mutations in melanocytic lesions of the conjunctiva as compared to uveal melanoma. *Invest Ophthalmol Vis Sci* 2010;51:6180-2.
 47. Henriquez F, Janssen C, Kemp EG, Roberts F. The T1799A BRAF mutation is present in iris melanoma, *Invest Ophthalmol Vis Sci* 2007;48:4897-900.
 48. Gear H Williams H, Kemp EG, Roberts F. BRAF mutations in conjunctival melanoma. *Invest Ophthalmol Vis Sci* 2004;45:2484-8.
 49. Beadling C, Jacobson—Dunlop E, Hodi FS, Le C, Warrick A, Patterson, J, Town A, Hsrlow A, Cruz F 3rd, Azar S, Rubin BP, Muller S, West R, Heinrich MC, Corless CL. KIT gene mutations and copy number in melanoma subtypes. *Clin Cancer Res* 2008;14:6821-8.
 50. Harbour JW, Onken MD, Roberson ED, Duan S, Cao L, Worley LA, Council ML, Matatall Ka, Helms C, Bowcock AM. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* 2010;330:1410-3
 51. Abdel-Rahman MH, Pilarski R, Cebulla CM, Massengill JB Christopher BN, Boru G, Hovland P, Davidorf FH, Germline, BAP1 mutation predisposes to uveal melanoma , lung adeno carcinoma, meningioma, and other caners. *J med Genet* 2011;48:856-9
 52. Wiesner T, Obenauf AC, Mural R, Fried I, Grieb wank KG, Ulz P, Windpassinger C, Wackernagel W, Loy S, Wolf I, Viale, A, Lash AE, Pirun M, Socci ND, Rütten A, Palmedo G, Abramson D, Offit K, Ott A, Becker JC, Cerroni L, Kutzner H, Bastian BC, Speicher MR. Germline mutations in BAP1 predispose to melanocytic tumors . *Nat Genet* 2011;43:1018-21.
 53. Abdel-Rahman MH, Yang Y, Zhou XP, Craig EL, Davidorf FH, Eng C, High frequency of submicroscopic hemizygous deletion is a major mechanism of expression of PTEN in uveal melanoma. *J Clin Oncol* 2006;24:288-95
 54. Saraiva VS, Caissie AL, Segal L, Edelstein C, Burnier MN, Jr. Immunohistochemical expression of phospho-Akt in uveal melanoma. *Melanoma Res* 2005;15:245-50
 55. Triozzi PL, Eng C, Singh AD, Targeted therapy for uveal melanoma, *Cancer Treat Rev* 2008;84:247-58.
 56. Patel M, Smyth E, Chapman PB, Wolchok JD, Schwartz GK, Abramson DH, Carvajal RD, Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res* 2011;17:2087-100.

57. Shields JA , Shields CL, Mashayekhi A, Marr BP, Benavides R, Thangappan A ,Phan L, Eagle RC Jr. Primary acquired melanosis of the conjunctiva: experience with 311 eyes Trans Am Ophthalmol Soc 2007;105:61-71; discussion 71-2
58. Singh AD, Turell ME, Topham AK, Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology 2011;118:1881-5.
59. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma : a summary of 84,836 cases from the past decade . The American Cancer Society . Cancer 1998;83:1664-78
60. Leiter U, Meier F, Schittek B, Garbe C. The natural course of cutaneous melanoma . J Surg Oncol 2004;86:172-8.
61. van den Bosch T, Kiliç E, Paridaens D, de Klein A. Genetics of uveal melanoma and cutaneous melanoma : two of a kind ? Dermatol Res Pract 2010;2010:360136.