

Bölüm 35

JİNEKOLOJİK ONKOLOJİDE TÜMÖR MARKERLERİ

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GİRİŞ

Tümör markerleri, tümör veya doku tarafından üretilen, biyokimyasal veya immünokimyasal yöntemlerle hastanın doku, kan idrar, asit sıvısı veya diğer vücut sıvılarında ölçümleri yapılabilen maddelerdir. Genellikle glikoprotein yapıda antijenik oluşumlardır. Enzim, hormon, reseptör, büyüme faktörleri, biyolojik cevap modülatörleri de tümör markeri olarak kullanılabilir. (1) İdeal tümör markeri, o tümör tarafından salınmalı, patolojik ve fizyolojik olgular arasında değer farklılığı olmalı, vücut kompartmanlarında tespit edilebilir düzeylerde yükselmeli, sensitivitesi ve spesifitesi yüksek olmalı, düşük maliyetli olmalı, düzeyi tümör volümünü ve rezidüel tümörü yansıtmalıdır. (2) Güncel çalışmaların katkısıyla günümüzde indirekt tarama yoluyla saptanan DNA, RNA ve protein seviyeleri de yeni tümör markerlerinin keşfine imkan sağlamaktadır.

Bu bölümde jinekolojik onkolojinin sık görülen kanserleri olan over, endometrium ve serviks kanserlerinde yaygın kullanılan tümör markerlerine değineceğiz.

1. OVER KANSERLERİ VE TÜMÖR MARKERLARI

Over kanseri jinekolojik malignite bağlı ölümlerin en sık sebebi olup, malignitelelerin %95 i epitelyal kökenlidir. Kalan kısmı germ hücreli tümör ve seks kord stro-mal tümörlerdir. Türkiye’de yıllık yeni epitelyal over-tuba-periton kanseri vaka sayısı 2500-3500 arasında kabul edilmektedir. En sık 50-70 yaş arasında izlenmekte olup, ortalama görülme yaşı 63 tür. Hastaların %70’i tanı anında evre 3c ve üzeridir. US National Cancer Database Surveillance, Epidemiology, and End Results (SEER)’ e göre de hayat boyu over kanseri görülme riski 1.4% olarak bildirilmiştir. (3) Over kanseri tanı tarama ve takipte yaygın kullandığımız ve günümüzde çalış-

KAYNAKLAR

1. McShane LM, Altman DG, Sauerbrei W et al. Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol* 2005 23 (36):9067-9072.
2. Van Nagell JR Jr, Donaldson ES, Gay EC et al. Carcinoembryonic antigen in carcinoma of the uterine cervix: 1. The prognostic value of serial determination. *Cancer* 1978; 42:2428. <http://seer.cancer.gov/statfacts/html/ovary.html> (Accessed on April 24, 2012)
3. Kabawat SE, Bast Jr RC, Bhan AK, Welch WR, Knapp RC, Colvin RB. Tissue distribution of acoelomic epithelium-related antigen recognized by the monoclonal antibody OC125. *Int J Gynecol Pathol.* 1983;2:275-285.
5. Bon GG, Kenemans P, Verstraeten R, et al. Serum tumor marker immunoassays in gynecologic oncology: establishment of reference values. *Am J Obstet Gynecol* 1996;174(1 Pt 1):107-114.
6. Visintin I, Feng Z, Longton G et al. Diagnostic markers for early detection of ovarian cancer. *Clin Cancer Res* 2008 14 (4):1065-1072.
7. Jacobs IJ, Skates SJ, MacDonald N ve ark. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999;353:1207-10
8. Screening for Ovarian Cancer: An Updated Evidence Review for the U.S. Preventive Services Task Force, Editors Henderson JT¹, Webber EM¹, Sawaya GF¹. Source Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Feb. Report No.: 17-05231-EF-1. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.
9. ACOG Committee on Gynecologic Practice. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. *Int J Gynaecol Obstet* 2003;80:235-8
10. Jacobs I, Oram D, Fairbanks J et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990 97 (10):922-929
11. Karlsen MA, Sandhu N, Hogdall C et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. *Gynecol Oncol* 2012 127 (2):379-383.
12. Bast RC, Jr., Skates S, Lokshin A, Moore RG. Differential diagnosis of a pelvic mass: improved algorithms and novel biomarkers. *Int J Gynecol Cancer* 2012 22 Suppl 1:S5-8.
13. Nagele F, Petru E, Medl M ve ark. Preoperative CA-125: an independent prognostic factor in patients with stage I epithelial ovarian cancer. *Obstet Gynecol* 1995;86:259-64
14. Chi DS, Venkatraman ES, Masson V ve ark. The ability of preoperative serum CA-125 to predict optimal primary tumor cytoreduction in stage III epithelial ovarian carcinoma. *Gynecol Oncol* 2000;77:227-31
15. Fioretti P, Gadducci A, Ferdeghini M ve ark. The concomitant determination of different serum tumor markers in epithelial ovarian cancer: relevance for monitoring the response to chemotherapy and follow-up of patients. *Gynecol Oncol* 1992;44:155-60
16. Gadducci A, Sartori E, Zola P, et al. Serum CA125 assay in the early diagnosis of recurrent epithelial ovarian cancer: a CTF study. *Oncol Rep.* 1996;3:301-303.
17. Gallion HH, Hunter JE, van Nagell JR, et al. The prognostic implications of low serum CA 125 levels prior to the second-look operation for stage III and IV epithelial ovarian cancer. *Gynecol Oncol* 1992;46(1):29-32.
18. Roman LD, Muderspach LI, Burnett AF, et al. Carcinoembryonic antigen in women with isolated pelvic masses. Clinical utility? *J Reprod Med* 1998;43(5):403-407
19. Gocze PM, Szabo DG, Than GN, et al. Occurrence of CA 125 and CA 19-9 tumor-associated antigens in sera of patients with gynecologic, trophoblastic, and colorectal tumors. *Gynecol Obstet Invest* 1988;25(4):268-272.
20. Kerbrat P, Lhomme C, Fervers B, Guastalla JP, Thomas L, Tournemaine N, et al. Ovarian Cancer. *Br J Cancer* 2001,84(Suppl.2), 18-23.
21. Guadagni F, Roselli M, Cosimelli M, et al. CA 72-4 serum marker—a new tool in the management of carcinoma patients. *Cancer Invest* 1995;13(2): 227-238

22. Clauss A, Ng V, Liu J et al. Overexpression of elafin in ovarian carcinoma is driven by genomic gains and activation of the nuclear factor kappaB pathway and is associated with poor overall survival. *Neoplasia* 2010 12 (2):161-172
23. Granato T, Porpora MG, Longo F et al. HE4 in the differential diagnosis of ovarian masses. *Clin Chim Acta* 2015 446:147-155
24. Ahmed M, Behera R, Chakraborty G et al. Osteopontin: a potentially important therapeutic target in cancer. *Expert Opin Ther Targets* 2011 15 (9):1113-1126.
25. Nakae M, Iwamoto I, Fujino T et al. Preoperative plasma osteopontin level as a biomarker complementary to carbohydrate antigen 125 in predicting ovarian cancer. *J Obstet Gynaecol Res* 2006 32 (3):309-314.
26. Morello A, Sadelain M, Adusumilli PS. Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors. *Cancer Discov* 2016 6 (2):133-146.
27. Cheng WF, Huang CY, Chang MC et al. High mesothelin correlates with chemoresistance and poor survival in epithelial ovarian carcinoma. *Br J Cancer* 2009 100 (7):1144-1153.
28. Dong Y, Loessner D, Irving-Rodgers H et al. Metastasis of ovarian cancer is mediated by kallikrein related peptidases. *Clin Exp Metastasis* 2014 31 (1):135-147.
29. Kinose Y, Sawada K, Nakamura K, Kimura T. The role of microRNAs in ovarian cancer. *Biomed Res Int* 2014 2014:249393.
30. Yang D, Sun Y, Hu L et al. Integrated analyses identify a master microRNA regulatory network for the mesenchymal subtype in serous ovarian cancer. *Cancer Cell* 2013 23 (2):186-199
31. Vecchione A, Belletti B, Lovat F et al. A microRNA signature defines chemoresistance in ovarian cancer through modulation of angiogenesis. *Proc Natl Acad Sci U S A* 2013 110 (24):9845-9850
32. Schneider DT, Calaminus G, Gobel U. Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. *Pediatr Hematol Oncol* 2001;18:11-26
33. Kerbrat P, Lhomme C, Fervers B, Guastalla JP, Thomas L, Tournemaine N, et al. Ovarian Cancer. *Br J Cancer* 2001;84(Suppl.2), 18-23
34. Gerl A, Lamerz R, Clemm C ve ark. Does serum tumor marker half-life complement pretreatment risk stratification in metastatic nonseminomatous germ cell tumors? *Clin Cancer Res* 1996;2:1565-70
35. Moss DW, Henderson R et al: Enzymes, in: Tietz NW (ed) *Textbook of Clinical Chemistry*, WB Saunders Comp Canada, 1986: 619 - 774.
36. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol* 2003;21:1180-9
37. Boggess JE, Soules MR, Goff BA ve ark. Serum inhibin and disease status in women with ovarian granulosa cell tumors. *Gynecol Oncol* 1997;64:64-9
38. Lambert-Messerlian GM, Steinhoff M, Zheng W, et al. Multiple immunoreactive inhibin proteins in serum from postmenopausal women with epithelial ovarian cancer. *Gynecol Oncol* 1997;65(3):512-516.
39. Gultekin, M., et al., Trends of Gynecological Cancers in Turkey: Toward Europe or Asia? *Int J Gynecol Cancer*, 2017. 27(8S Suppl 1): p. S1-S9.
40. American College of O. and Gynecologists, ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. *Obstet Gynecol*, 2005. 106(2): p. 413-25.
41. Gadducci A, Ferdeghini M, Prontera C, et al. A comparison of pretreatment serum levels of four tumor markers in patients with endometrial and cervical carcinoma. *Eur J Gynaecol Oncol* 1990;11(4):283-288.
42. Patsner B, Orr JW Jr, Mann WJ Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. *Am J Obstet Gynecol* 1990;162(2):427-429.
43. Tsukamoto O, Miura K, Mishima H, et al. Identification of endometrioid endometrial carcinoma-associated microRNAs in tissue and plasma. *Gynecol Oncol*. 2014; 132(3): 715-721,
44. Li Z, Zhao X, Bai S, et al. Proteomics identification of cyclophilin a as a potential prognostic factor and therapeutic target in endometrial carcinoma. *Mol Cell Proteomics*. 2008; 7(10): 1810-1823,

45. Bie Y, Zhang Z. Diagnostic value of serum HE4 in endometrial cancer: a meta-analysis. *World J Surg Oncol*. 2014; 12: 169
46. Nakamura K, Hongo A, Kodama J, et al. Expression of matriptase and clinical outcome of human endometrial cancer. *Anticancer Research*. 2009; 29(5): 1685–1690
47. Denny L (2012) Cervical cancer: prevention and treatment. *Discov Med* 14:125–131
48. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. *Cancer* 1977;40:1621–8
49. Chou CY, Wang ST, Kuo HC, Tzeng CC, Yao BL. Serum level of squamous cell carcinoma antigen and tumor size is useful to identify preoperatively patients at high risk of cervical cancer. *Cancer* 1994;74:2497–501.
50. Bolli JA, Doering DL, Bosscher JR, et al. Squamous cell carcinoma antigen: clinical utility in squamous cell carcinoma of the uterine cervix. *Gynecol Oncol* 1994;55: 169–73.
51. Duk JM, Groenier KH, de Bruijn HW, et al. Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. *J Clin Oncol* 1996;14(1):111–118.
52. Pujol JL, Grenier J, Daures JP, Daver A, Pujol H, Michel FB. Serum fragments of cytokeratin subunit 19 measured by CYFRA 21–1 immunoradiometric assay as a marker of lung cancer. *Cancer Res* 1993;53:61–6.
53. Suzuki Y, Nakano T, Ohno T, Abe A, Morita S, Tsujii H. Serum CYFRA 21–1 in cervical cancer patients treated with radiation therapy. *J Cancer Res Clin Oncol* 2000;126: 332–6.
54. Molina R, Filella X, Augé JM, et al. CYFRA 21.1 in patients with cervical cancer: comparison with SCC and CEA. *Anticancer Res* 2005;25:1765–71.
55. Uhl-Steidl M, Muller-Holzner E, Zeimet AG, et al. Prognostic value of CD44 splices variant expression in ovarian cancer. *Oncology* 1995;52:400–6.
56. Subramanyam D, Rajendra W, Lokanatha V. Evaluation of soluble CD44 protein marker to distinguish the benign and squamous cell carcinoma cases in cervical cancer Patients. *Med Oncol* 2014;31:1–7.
57. Li Y, Wu T, Zhang B, Yao Y, Yin G. Matrix metalloproteinase-9 is a prognostic marker for patients with cervical cancer. *Med Oncol* 2012;29(5):3394–9.