

Bölüm 9

MESANE KANSERİNİN TANI VE TAKİBİNDE KULLANILAN SERUM VE İDRAR BELİRTEÇLERİ

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GİRİŞ

Mesane kanseri genitoüriner kanserler içinde Amerika Birleşik Devletleri'nde en sık görülen ikinci kanserdir (1). Dünyada ise tüm kanserler içinde en sık görülen onbirinci kanser olma özelliği taşımaktadır (2). Dünya genelinde yaşa göre standardize edilmiş insidans erkeklerde 8.9 (100.000 kişi –yıl) ve kadınlarda 2.2 (2008 verileri) iken Avrupa'daki erkeklerde 27 ve kadınlarda 6 olarak görülmüştür (2).

Genellikle gelişmiş ülkelerde sıklığı giderek artış göstermektedir. Değişici epitel hücreli kanserler %90 oranında en sık görülen histolojik tip olmakla birlikte yassı hücreli kanserler ve adeno kanserler mesane de görülen diğer kanser tipleridir (3).

Mesane kanserinin tanısı sistoskopi, sitoloji ve çıkarılan materyalin patolojik değerlendirilmesi ile konur. Eğer yapılan tetkiklerde mesane kanseri saptanmış veya üriner sitoloji pozitif bulunmuş ise; tanısal sistoskopi atlanır ve anestezi altında şüpheli alan biyopsileri veya tümör rezeksiyonu uygulanır (4). Ancak başlangıç tedavisine rağmen olguların %30-85'inde endoskopik rezeksiyondan sonra tümör tekrarı görülür ve bunların %16-25'i daha yüksek dereceli tümörler ortaya çıkar (3). Kas invazyonu saptanmayan tümörlerin yaklaşık %10'unda izlem sırasında invaziv veya metastatik kanser gelişir.

Mesane kanseri tanısı konulduktan sonra hastalık için uygulanan izlem süreçleri hastalığın tanısını koymak kadar önemlidir. Rutin olarak uygulanması önerilen sistoskopi ve idrarın sitolojik değerlendirilmesidir. Ancak sistoskopinin invaziv bir işlem olması ve idrarın sitolojik değerlendirilmesinin düşük duyarlılığı yeni belirteçlerin tanımlanması gerekliliğini ortaya çıkarmıştır. Bu derlemede tanı ve/veya izlemede halen kullanılan veya geliştirilme aşamasında olan mesane tümör belirteçleri gözden geçirilmiştir.

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KAYNAKLAR

1. Dinçel Ç.(edit) Üroonkoloji kitabı. Genişletilmiş ikinci baskı. Mete Basımevi. İzmir 2013;251-523
2. Ferlay J, Bray F, Forman D, et al. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No.10 2010, International Agency for Research on Cancer: Lyon, France. Globocan 2008 v1.2
3. Walsh PC, Retik AB, Vaughan ED, et al Campbell Urology. 8. Baskı. 4.Cilt. Ankara: Güneş Kitabevi; 2005. s.2732-65
4. Babjuk M, Böhle A, Burger E, et al. Guidelines on non-muscle invasive bladder cancer 2014
5. Parker J, Spiess P. Current and Emerging Bladder Cancer Urinary Biomarkers. The Scientific World Journal 2011; 11; 1103-12.
6. Pruthi RS. The value of urine cytology in the diagnosis and management of urinary tract malignancies.Pathology case reviews. 2000;5(2):102-10.
7. Turbat-Herrera EA, Colom H. The dilemma of urinary cytology revisited. Pathology case reviews. 2000; 5(2):95-101.
8. Planz B, Jochims E, Deix T, et al. The role of urinary cytology for detection of bladder cancer. Eur J Surg Oncol 2005;31(3):304-8.
9. Badalament RA, Fair WR, Whitmore WF,et al. The relative value of cytometry and cytology in the management of bladder cancer. Semin Urol 1988;6:22-30.
10. Tribukait B, EI-Bedeiwy A, Shaaban AA. Prediction of lymph node metastases in bladder carcinoma with deoxyribonucleic acid flow cytometry. J Urol 1990; 144:884-87
11. Golijanin D, Shapiro A, Pode D. Immunostaining of cytokeratin 20 in cells from voided urine for detection of bladder cancer. J. Urol. 2000;164: 1922–25.
12. Rotem D, Cassel A, Lindenfeld N, et al. Urinary cytokeratin 20 as a marker for transitional cell carcinoma. Eur. Urol. 2000; 37: 601–4.
13. Fernandez-Gomez J, Rodriguez-Martinez JJ, Barmadah SE et al. Urinary CYFRA 21.1 is not a useful marker for the detection of recurrences in the follow-up of superficial bladder cancer. Eur. Urol. 2007; 51: 1267–74.
14. Bavaccini, S., Casadio, V., Amadori, D. The current role of telomerase in the diagnosis of bladder cancer. Indian J. Urol 2005, 25, 40–46.
15. Ito H, Kyo S, Kanaya T. Expression of human telomerase subunits and correlation with telomerase activity in urothelial cancer. Clin Cancer Res 1998;4:1603–8
16. Mitra AP, Cote RJ. Molecular screening for bladder cancer: progress and potential. Nature Reviews Urology 2010 (7): 11–20
17. Tilki D, Burger M, Dalbagni N et al. Urine markers for detection and surveillance of non-muscle-invasive bladder cancer, European Urology 2011(60): 3; 484–492
18. Babjuk M, Böhle A, Burger M. Et all. Guidelines on Non-muscle invasive bladder cancer (Ta,T1 and CIS). European Association of Urology guidelines 2015
19. Pardoll DM, Vogelstein B, Coffey DS. A fixed site of DNA replication in eukaryotic cells. Cell 1980;19.
20. Ramakumar, S., Buhuiyan, J., Besse, JA. et al. Comparison of screening tests in the detection of bladder cancer. J Urol, 1999;161:388
21. Sarosdy, MF, Hudson, MA., Ellis, WJ. et al. Improved detection of recurrent bladder cancer using Bard BTA Stat test. Urology 1997; 50: 349
22. Pode, D., Shapiro, A., Wald, M. et al. Noninvasive detection of bladder cancer with the BTA stat test. J Urol 2005;161: 443

23. Oge O, Kozacı D, Gemalmaz H. The BTA stat test is nonspecific for hematuria: an experimental hematuria model. *J Urol.* 2002 Mar;167(3):1318-9; discussion 1319-20.
24. Compton DA, Cleveland DW. Numa is required for the proper completion of mitosis. *J Cell Biol* 1993;120:947-157.
25. Carpinto, G.A., Stadler, W.M., Briggman V. Et al. Urinary nuclear matrix protein as a marker for transitional cell carcinoma of the urinary tract. *J. Urol.* 1996, 156, 1280–1285.
26. Ponsky LE, Sharma S, Pandrangi L, et al. Screening and monitoring for bladder cancer: Refining the use of NMP22. *J Urol* 2001; 166:75–8.
27. Grossman HB, Messing E, Soloway M, et al. Detection of bladder cancer using a point-of-care proteomic assay. *JAMA* 2005;293:810–6.
28. Attallah AM, Sakr HA, Ismail H, et al. An office-based immunodiagnostic assay for detecting urinary nuclear matrix protein 52 in patients with bladder cancer. *BJU Int* 2005;96:334–9.
29. Yokota K, Kanda K, Inoue Y, et al. Semi-quantitative analysis of telomerase activity in exfoliated human urothelial cells and bladder transitional cell carcinoma. *Br J Urol* 1998;82: 727–32.
30. Lee MY, Tsou MH, Cheng MH, et al. Clinical application of NMP22 and urinary cytology in patients with hematuria or a history of urothelial carcinoma. *World J Urol* 2000;18:401–5.
31. Weikert S, Krause H, Wolff I, et al. Quantitative evaluation of telomerase subunits in urine as biomarkers for noninvasive detection of bladder cancer. *Int J Cancer* 2005;117:274–80.
32. Sanchini MA, Gunelli R, Nanni O, et al. Relevance of urine telomerase in the diagnosis of bladder cancer. *JAMA* 2005;294:2052–6
33. Skacel M, Fahmy M, Brainard JA, et al. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. *J Urol* 2003;169:2101–5.
34. Myers-Irvin JM, Landsittel D, Getzenberg RH. Use of the novel marker BLCA-1 for the detection of bladder cancer. *J Urol* 2005; 174:64–8.
35. Myers-Irvin JM, Van Le TS, Getzenberg RH. Mechanistic analysis of the role of BLCA-4 in bladder cancer pathobiology. *Cancer Res* 2005; 65:7145–50.
36. Van Le TS, Myers J, Konety BR, et al. Functional characterization of the bladder cancer marker, BLCA-4. *Clin Cancer Res* 2004; 10:1384–91.
37. Konety BR, Nguyen TS, Brenes G, et al. Clinical usefulness of the novel marker BLCA-4 for the detection of bladder cancer. *J Urol* 2000;164:634–9.
38. Konety BR, Nguyen TS, Dhir R, et al. Detection of bladder cancer using a novel nuclear matrix protein, BLCA-4. *Clin Cancer Res* 2000; 6:2618–25.
39. Van Le TS, Miller R, Barder T, et al. Highly specific urine-based marker of bladder cancer. *Urology* 2005; 66:1256–60.
40. Sharp JD, Hausladen DA, Maher MG, et al. Bladder cancer detection with urinary survivin, an inhibitor of apoptosis. *Front Biosci* 2002;7:e36–41.
41. Lokeshwar VB, Habuchi T, Grossman, B et al. Bladder tumor markers beyond cytology: International Consensus on bladder tumor markers. *Urology* 2005;66(Suppl 1):35–63
42. Lokeshwar VB, Getzenberg RH. Voided urine markers. In: Lerner SP, Schoenberg M, Sternberg C, editors. *Text book of bladder cancer.* London (UK): T&F-Informa, 2006. p. 65–137
43. Ohsawa I, Nishimura T, Kondo Y, et al. Detection of urine survivin in 40 patients with bladder cancer. *J Nippon Med Sch* 2004; 71:379–83
44. Shariat SF, Casella R, Khoddami SM, et al. Urine detection of survivin is a sensitive marker for the noninvasive diagnosis of bladder cancer. *J Urol* 2004;171:626–30
45. Hijazi A, Devonec M, Bouvier R, et al. Flow cytometry study of cytokeratin 18 expression according to tumor grade and deoxyribonucleic acid content in human bladder tumors. *J. Urol.* 1989; 141: 522–6.

46. Babjuk M, Soukup V, Pesl M et al. Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pT1 bladder urothelial carcinoma. *Urology* 2008; 71: 718
47. Mungan NA, Vriesema JLJ, Thomas CMG, et al. Urinary bladder cancer test: A new urinary tumor marker in the follow-up of superficial bladder cancer. *UROLOGY* 2000;56 (5).
48. Fernandez-Gomez J, Rodriguez-Martinez JJ, Barmadah SE et al. Urinary CYFRA 21.1 is not a useful marker for the detection of recurrences in the follow-up of superficial bladder cancer. *Eur. Urol.* 2007; 51: 1267-74.
49. Ewing R, Tate GM, Hetherington JW. Urinary fibrin/ fibrinogen degradation products in transitional cell carcinoma of the bladder. *Br J Urol* 1987; 59: 53-58.
50. Jayachandran S, Unni Mooppan MM, Wax SH, et al. The value of urinary fibrin/ fibrinogen degradation products as tumor markers in urothelial carcinoma. *J Urol* 1984; 132:21-23.
51. Wajzman Z, Williams PD, Greco J, et al. Further study of fibrinogen degradation products in bladder cancer detection. *Urology* 1978; 12: 659-661.
52. Pirtskkalaishvili G, Getzenberg RH, Konety BR. Use of urine-based markers for detection and monitoring of bladder cancer. *Tech Urol* 1999; 5: 179-184.
53. Johnston B, Morales A, Emerson L. Rapid detection of bladder cancer: A Comparative study of point of care tests. *J Urol* 1997; 158: 2098-2101
54. Lokeshwar, VB. and Soloway, MS. Current bladder tumor tests: does their projected utility fulfill clinical necessity? *J. Urol* 2001, 165, 1067-1077.
55. Schroeder GL, Lorenzo-Gomez MF, Hautmann SH, et al. A side-by-side comparison of cytology and biomarkers, HA-HAase, hematuria detection, BTAStat, UBC-Rapid for bladder cancer detection. *J Urol* 2004;172:1123-6.
56. Lokeshwar VB, Obek C, Pham HT, et al. Urinary hyaluronic acid and hyaluronidase: Markers for bladder cancer detection and evaluation of grade. *J Urol* 2000;163:348 -56.
57. Lokeshwar VB, Schroeder GL, Selzer MG, et al. Bladder tumor markers for monitoring recurrence and screening comparison of hyaluronic acid hyaluronidase and BTA-Stat tests. *Cancer* 2002;95:61-72.
58. Lodde M, Mian C, Compj E et al. uCyt+ test: alternative to cystoscopy for less-invasive follow-up of patients with low risk of urothelial carcinoma. *Urology* 2006; 67: 950-4.
59. Pode, D., Golijanin, D., Sherman, et al. Immunostaining of Lewis X in cells from voided urine, cytopathology, and ultrasound for noninvasive detection of bladder tumors. *J. Urol* 1998, 159, 389-393.
60. Golijanin, D., Sherman, Y., Shapiro, A., et al. Detection of bladder tumors by immunostaining of the Lewis X antigen in cells from voided urine. *Urology* 1995, 46, 179-177.
61. Sawczuk IS, Pickens CL, Vasa UR, et al. DD23 Biomarker. A prospective clinical assessment in routine urinary cytology specimens from patients being monitored for TCC. *Urol Oncol* 2002;7:185-90.
62. Gilbert SM, Veltri RW, Sawczuk A, et al. Evaluation of DD23 as a marker for detection of recurrent transitional cell carcinoma of the bladder in patients with a history of bladder cancer. *Urology* 2003; 61:539-43.
63. Golijanin D, Shapiro A, Pode D. Immunostaining of cytokeratin 20 in cells from voided urine for detection of bladder cancer. *J. Urol.* 2000;164: 1922-5.
64. Rotem D, Cassel A, Lindenfeld N. et al. Urinary cytokeratin 20 as a marker for transitional cell carcinoma. *Eur. Urol.* 2000; 37: 601-4.
65. Bavaccini, S., Casadio, V., Amadori, A, et al. The current role of telomerase in the diagnosis of bladder cancer. *Indian J. Urol* 2005, 25, 40-46.
66. Ito H, Kyo S, Kanaya T, et al. Expression of human telomerase subunits and correlation with telomerase activity in urothelial cancer. *Clin Cancer Res* 1998;4:1603-8.
67. Kim NW, Piatyszek MA, Prowse KR, et al. Specific association of human telomerase activity with immortal cells and cancer. *Science* 1994;266:2011-5.

68. Chen CH, Chen RJ. Prevalence of telomerase activity in human cancer, *Journal of the Formosan Medical Association*, vol. 110, no. 5, pp. 275–289, 2011.
69. Eissa S, Swellam M, Ali-Labib R, et al. Detection of telomerase in urine by 3 methods: evaluation of diagnostic accuracy for bladder cancer. *J. Urol.* 2007; 178 (Pt 1): 1068–72.
70. Wu XX, Kakehi Y, Takahashi T, et al. Telomerase activity in urine after transurethral resection of superficial bladder cancer and early recurrence. *Int J Urol* 2000;7:210–7.
71. Yokota K, Kanda K, Inoue Y, et al. Semi-quantitative analysis of telomerase activity in exfoliated human urothelial cells and bladder transitional cell carcinoma. *Br J Urol* 1998;82: 727–32.
72. Lee MY, Tsou MH, Cheng MH, et al. Clinical application of NMP22 and urinary cytology in patients with hematuria or a history of urothelial carcinoma. *World J Urol* 2000;18:401–5.
73. Weikert S, Krause H, Wolff I, et al. Quantitative evaluation of telomerase subunits in urine as biomarkers for noninvasive detection of bladder cancer. *Int J Cancer* 2005;117:274–80.
74. Sanchini MA, Gunelli R, Nanni O, et al. Relevance of urine telomerase in the diagnosis of bladder cancer. *JAMA* 2005;294:2052–6
75. Hijazi A, Devonec M, Bouvier R, et al. Flow cytometry study of cytokeratin 18 expression according to tumor grade and deoxyribonucleic acid content in human bladder tumors. *J. Urol.* 1989; 141: 522–6.
76. Babjuk M, Soukup V, Pesl M et al. Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pT₁ bladder urothelial carcinoma. *Urology* 2008; 71: 718
77. Skacel M, Fahmy M, Brainard JA, et al. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. *J Urol* 2003;169:2101–5.
78. Gofrit ON, Zorn KC, Silvestre J, et al. The predictive value of multitargeted fluorescent in-situ hybridization in patients with history of bladder cancer. *Urol Oncol* 2008;26:246–9.
79. Sarosdy ME, Schellhammer P, Bokinsky G, et al. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer. *J Urol* 2002;168:1950–4.
80. Catto JW, Alcaraz A, Bjartell AS, et al. MicroRNA in prostate, bladder, and kidney cancer: a systematic review. *Eur Urol* 2011;59:671–81.
81. Valadi H, Ekstrom K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 2007;9:654–9.
82. Hanke M, Hoefig K, Merz H, et al. A robust methodology to study urine microRNA as tumor marker: microRNA-126 and microRNA-182 are related to urinary bladder cancer. *Urol Oncol* 2010; 28:655–61.
83. Catto JW, Miah S, Owen HC, et al. Distinct microRNA alterations characterize high- and low-grade bladder cancer. *Cancer Res* 2009;69:8472–81.
84. O’Sullivan P, Sharples K, Dalphin M, et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with haematuria. *J Urol* 2012;188:741–7.
85. Miah S, Dudzic E, Drayton RM, et al. An evaluation of urinary microRNA reveals a high sensitivity for bladder cancer. *Br J Cancer* 2012;107:123–8.
86. Steiner G, Schoenberg MP, Linn JF, et al. Detection of bladder cancer recurrence by microsatellite analysis of urine. *Nat Med* 1997;3:621–4.
87. Van der Aa MN, Zwarthoff EC, Steyerberg EW, et al. Microsatellite analysis of voided-urine samples for surveillance of low-grade non-muscle-invasive urothelial carcinoma: feasibility and clinical utility in a prospective multicenter study (Cost-Effectiveness of Follow-up of Urinary Bladder Cancer trial [CEFUB]). *Eur Urol* 2009;55:659–67.
88. Wosnitzer MS, Domingo-Domenech J, Castillo-Martin M, et al. Predictive value of microtubule associated proteins tau and stathmin in patients with nonmuscle invasive bladder cancer receiving adjuvant intravesical taxane therapy. *J Urol* 2012;186:2094–100.
89. Acikalın D, Oner U, Can C, et al. Predictive value of maspin and Ki-67 expression in transurethral resection specimens in patients with T1 bladder cancer. *Tumori* 2012;98:344–50.
90. Gkialas I, Papadopoulos G, Iordanidou L. et al. Evaluation of urine tumor-associated trypsin inhibitor, CYFRA 21-1, and urinary bladder cancer antigen for detection of high-grade bladder carcinoma. *Urology* 2008;