

Kanser Tanısında ve Tedavi Sürecinde Likit Biyopsi Kullanımının Önemi

İkbal Cansu BARIŞ¹

GİRİŞ

Kanser, farklı şekilde evrimleşmekte olan genetik klonların progresyondan sorumlu olduğu dinamik bir hastalıktır (1). Son yıllarda kanser alanında artan bilgi birikimi ve teknolojik gelişmeler kişiye özgü hassas tıbbi onkolojiyi doğurmuştur. Hassas tıbbi onkolojinin temel amacı, kanserin tanı ve tedavisini geliştirmektir. Bu amaçla tedavi seçimine rehberlik etmek üzere biyobelirteçlerin belirlenmesine yardımcı olmak, hastalığın prognozunu tahmin edebilen bir moleküler alt tip sınıflandırması oluşturmak ve tümör progresyonunda rol oynayan somatik değişiklikleri karakterize etmek için tümör materyaline çeşitli genomik ve moleküler analizler uygulanmaktadır. Bu genomik ve moleküler analizleri gerçekleştirmek için tümörden parça almak genellikle mümkün olmayan ve hastalık sürecinde tümör heterojenitesinin takibine izin vermeyen invazif prosedürlere bağlıdır (2).

Kanserin klinik yönetiminde hassas tıbbi onkoloji, likit biyopsi (LB) tanı platformu aracılığıyla sağlanabilir. LB hastalık sürecinde tümör heterojenitesinin takibine izin veren ve invazif olmayan etkili bir yöntem olarak kabul edilmektedir (3).

Kanserde likit biyopsi (LB) kan, idrar, tükürük, plevral efüzyon sıvısı veya beyin omurilik sıvısı gibi vücut sıvılarında DNA, RNA, kanser hücreleri, ekstraselü-

¹ Arş. Gör. Dr, Pamukkale Üniversitesi, ibaris@pau.edu.tr

tedaviye yanıt tahmini ve hastalığın gerçek-zamanlı takibi için oldukça önemlidir (83). LB sayesinde kanser türüne özgü biyobelirteçlerin invazif olmayan yollarla tespitinin sağlanabilmesi yakın gelecekte moleküler biyoloji anlayışı ve tümör heterojenitesine yaklaşımda önemli bir değişimi temsil edecektir

KAYNAKÇA

1. Venesio T, Siravegna G, Bardelli A, Sapino A. Liquid biopsies for monitoring temporal genomic heterogeneity in breast and colon cancers. *Pathobiology* 2018;85:146–154.
2. Jameson JL, Longo DL. Precision medicine—Personalized, problematic, and promising. *N Engl J Med*. 2015;372:2229–2234.
3. Imamura T, Komatsu S, Ichikawa D, Kawaguchi T, Miyamae M, Okajima W, Ohashi T, Arita T, Konishi H, Shiozaki A et al. Liquid biopsy in patients with pancreatic cancer: Circulating tumor cells and cell-free nucleic acids. *World J Gastroenterol*. 2016;22:5627.
4. Pantel K, Alix-Panabières C. Circulating tumour cells in cancer patients: Challenges and perspectives. *Trends Mol Med* 2010;16:398–406.
5. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol* 2017;14:531–548.
6. Bardelli A, Pantel K. Liquid biopsies, what we do not know (yet). *Cancer Cell* 2017;31:172–179.
7. Tan GH, Nason G, Ajib K, Woon DTS, Herrera-Caceres J, Alhunaidi O, Perlis N. marter screening for prostate cancer. *World J Urol* 2019;37:991–999.
8. Porto-Mascarenhas EC, Assad DX, Chardin H, Gozal D, Canto GDL, Acevedo AC, Guerra ENS. Salivary biomarkers in the diagnosis of breast cancer: A review. *Crit Rev Oncol Hematol*. 2017;110:62–73.
9. Lawrence, H.P. Salivary markers of systemic disease: Noninvasive diagnosis of disease and monitoring of general health. *J Can Dent Assoc* 2002;68:170–174.
10. Zhang L, Farrell JJ, Zhou H, Elashoff D, Akin D, Park NH, Chia D, Wong DT Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010;138:949–957.
11. Humeau M, Vignolle-Vidoni A, Sicard F, Martins F, Bournet B, Buscail L, Torrisani J, Cordelier P. Salivary microRNA in pancreatic cancer patients. *PLoS ONE* 2015;10:e0130996.
12. Li X, Yang T, Lin J. Spectral analysis of human saliva for detection of lung cancer using surface-enhanced Raman spectroscopy. *J Biomed Opt* 2012;17: 037003.
13. Zhang L, Xiao H, Zhou H, Santiago S, Lee JM, Garon EB, Yang J, Brinkmann O, Yan X, Akin D, et al. Development of transcriptomic biomarker signature in human saliva to detect lung cancer. *Cell Mol Life Sci* 2012;69:3341–3350.
14. Wu ZZ, Wang JG, Zhang XL. Diagnostic model of saliva protein finger print analysis of patients with gastric cancer. *World J Gastroenterol* 2009;15:865–870.
15. Wang X, Kaczor-Urbanowicz KE, Wong DT. Salivary biomarkers in cancer detection. *Med Oncol*. 2017;34:7.

16. Heitzer E, Haque IS, Roberts CE, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet* 2018;20:71–88.
17. Wang J, Chang S, Li, G, Sun Y. Application of liquid biopsy in precision medicine: Opportunities and challenges. *Front Med.* 2017;11:522–527.
18. Barriere G, Fici P, Gallerani G, Fabbri F, Zoli W, Rigaud M. Circulating tumor cells and epithelial, mesenchymal and stemness markers: Characterization of cell subpopulations. *Ann Transl Med* 2014;2:109.
19. Maltoni R, Gallerani G, Fici P, Rocca A, Fabbri F. CTCs in early breast cancer: A path worth taking. *Cancer Lett.* 2016;376:205–210.
20. Nagrath S, Sequist LV, Maheswaran S, Bell DW, Irimia D, Ulkus L, Smith MR, Kwak EL, Digumarthy S, Muzikansky A et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature* 2007;450:1235–1239.
21. Lim M, Kim CJ, Sunkara V, Kim MH, Cho YK. Liquid biopsy in lung cancer: Clinical applications of circulating biomarkers (CTCs and ctDNA). *Micromachines (Basel)* 2018;9:E100.
22. Ashworth TR. A case of cancer in which cells similar to those in the tumors were seen in the blood after death. *Aust Med J* 1869;14:146–149.
23. Das V, Bhattacharya S, Chikkaputtaiah C, Hazra S, Pal M. The basics of epithelial-mesenchymal transition (EMT): A study from a structure, dynamics, and functional perspective. *J Cell Physiol.* 2019;234:14535–14555.
24. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J. Clin Investig* 2010;120:1420–1428.
25. Adams DL, Alpaugh RK, Tsai S, Tang CM, Stefansson S. Multi-Phenotypic subtyping of circulating tumor cells using sequential fluorescent quenching and restaining. *Sci Rep* 2016;6:33488.
26. Alix-Panabières, C, Pantel K. Circulating tumor cells: Liquid biopsy of cancer. *Clin Chem.* 2013;59:110–118.
27. Olivier CG, Carballido JR. Circulating tumor cells: Isolation, quantification, and relevance of their translation into clinical practice. *Actas Urol Esp* 2010;34:3–5.
28. Pantel K, Speicher M. The biology of circulating tumor cells *Oncogene* 2016;35:1216–1224.
29. Wang L, Balasubramanian P, Chen AP, Kummar S, Evrard YA, Kinders RJ. Promise and limits of the CellSearch platform for evaluating pharmacodynamics in circulating tumor cells. *Semin Oncol.* 2016;43:464–475.
30. Lv QB, Fu X, Jin HM, Xu HC, Huang ZY, Xu HZ, Chi YZ, Wu AM. The relationship between weight change and risk of hip fracture: Meta-analysis of prospective studies. *Sci Rep* 2015;5:16030.
31. Gahan P, Stroun M. The biology of circulating nucleic acids in plasma and serum (CNAPS). *Extracell Nucleic Acids* 2010;1:167–189.
32. Maltoni R, Casadio V, Ravaoli S, Foca F, Tumedei MM, Salvi S, Martignano F, Calistri D, Rocca A, Schirone A et al. Cell-free DNA detected by “liquid biopsy” as a potential prognostic biomarker in early breast cancer. *Oncotarget* 2017;8:16642–16649.
33. Rossi G, Mu Z, Rademaker AW, Austin LK, Strickland KS, Costa RLB, Nagy RJ, Zagonel V, Taxter TJ, Behdad A et al. Cell-free DNA and circulating tumor cells: Comprehensive liquid biopsy analysis in advanced breast cancer. *Clin Cancer Res.* 2018;24:560–568.

34. Sorber L, Zwaenepoel K, Deschoolmeester V, Van Schil P, Van Meerbeeck J, Lardon F, Rolfo C, Pauwels P. Circulating cell-free nucleic acids and platelets as a liquid biopsy in the provision of personalized therapy for lung cancer patients. *Lung Cancer* 2017;107:100–107.
35. Elazezy M, Joosse SA. Techniques of using circulating tumor DNA as a liquid biopsy component in cancer management. *Comput Struct Biotechnol J*. 2018;16:370–378.
36. Cheng F, Su L, Qian C. Circulating tumor DNA: A promising biomarker in the liquid biopsy of cancer. *Oncotarget* 2016;7:48832–48841.
37. García-Olmo DC, Domínguez C, García-Arranz M, Anker P, Stroun M, García-Verdugo JM, García-Olmo D. Cell-free nucleic acids circulating in the plasma of colorectal cancer patients induce the oncogenic transformation of susceptible cultured cells. *Cancer Res*. 2010;70:560–567.
38. Openshaw MR, Page K, Fernandez-Garcia D, Guttery, D.; Shaw, J.A. The role of ctDNA detection and the potential of the liquid biopsy for breast cancer monitoring. *Expert Rev. Mol. Diagn.* 2016;16:751–755.
39. Forshew T, Murtaza M, Parkinson C, Gale D, Tsui DW, Kaper F, Dawson SJ, Piskorz AM, Jimenez-Linan M Bentley D et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. *Sci Transl Med* 2012;4:136ra68.
40. Czeiger D, Shaked G, Eini H, Vered I, Belochitski O, Avriel A, Ariad S, Douvdevani A. Measurement of circulating cell-free DNA levels by a new simple fluorescent test in patients with primary colorectal cancer. *Am. J. Clin. Pathol.* 2011;135:264–270.
41. Beaver JA, Jelovac D, Balukrishna S, Cochran RL, Croessmann S, Zabransky DJ, Wong HY, Toro PV, Cidado J, Blair BG et al. Detection of cancer DNA in plasma of patients with early-stage breast cancer. *Clin Cancer Res*. 2014;20:2643–2650.
42. Otsuji K, Sasaki T, Tanaka A, Kunita A, Ikemura M, Matsusaka, K, Tada K, Fukayama M, Seto Y. Use of droplet digital PCR for quantitative and automatic analysis of the HER2 status in breast cancer patients. *Breast Cancer Res Treat.* 2017;162:11–18.
43. Funaki NO, Tanaka J, Kasamatsu T, Ohshio G, Hosotani R, Okino T, et al. Identification of carcinoembryonic antigen mRNA in circulating peripheral blood of pancreatic carcinoma and gastric carcinoma patients. *Life Sci*. 1996;59(25-26): 2187–99.
44. Souza MF, Kuasne H, Barros-Filho MC, Cilliao HL, Marchi FA, Fuganti PE, et al. Circulating mRNAs and miRNAs as candidate markers for the diagnosis and prognosis of prostate cancer. *PLoS One*. 2017;12(9):e0184094.
45. García V, García JM, Pena C, Silva J, Domínguez G, Lorenzo Y, et al. Free circulating mRNA in plasma from breast cancer patients and clinical outcome. *Cancer Lett*. 2008;263(2): 312–20.
46. Escors D, Gato-Cañas M, Zuazo M, Arasanz H García-Granda MJ, Vera R, Kochan G. The intracellular signalosome of PD-L1 in cancer cells. *Signal Transduct. Target Ther.* 2018;3:26.
47. Ishiba T, Hoffmann AC, Usher J, Elshimali Y, Sturdevant T, Dang M, Jaimes YCC, Tyagi R, Gonzalez R, Grino M et al. Frequencies and expression levels of programmed death ligand 1 (PD-L1) in circulating tumor RNA (ctRNA) in various cancer types. *Biochem Biophys Res Commun*. 2018;500:621–625.
48. Junqueira-Neto S, Batista IA, Costa JL, Melo SA. Liquid Biopsy beyond Circulating Tumor Cells and Cell-Free DNA. *Acta Cytol*. 2019;63:479–488.

49. Leong SP, Ballesteros-Merino C, Jensen, S.M.; Marwitz, S.; Bifulco, C.; Fox, B.A.; Skoberne, M. Novel frontiers in detecting cancer metastasis. *Clin. Exp. Metastasis* 2018;35:403–412.
50. Gao S, Chen LY, Wang P, Liu LM, Chen Z. MicroRNA expression in salivary supernatant of patients with pancreatic cancer and its relationship with ZHENG. *Biomed Res Int.* 2014;756347.
51. Tkach M, Théry C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. *Cell.* 2016;164:1226-1232.
52. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu Rev Cell Dev Biol.* 2014;30:255-89.
53. Kalluri R, LeBleu V S. Discovery of Double-Stranded Genomic DNA in Circulating Exosomes. *Cold Spring Harb Symp Quant Biol.* 2016;81:275-280.
54. Bortoluzzi S, Lovisa F, Gaffo E, Mussolin L. Small RNAs in Circulating Exosomes of Cancer Patients: A Minireview. *High Throughput* 2017;6.
55. Thakur BK, Zhang H, Becker A, Matei I, Huang Y, Costa-Silva B, Zheng Y, Hoshino A, Brazier H, Xiang J et al. Double-stranded DNA in exosomes: A novel biomarker in cancer detection. *Cell Res.* 2014;24:766–769.
56. Whiteside TL Tumor-Derived Exosomes and Their Role in Cancer Progression. *Adv Clin Chem.* 2016;74: 103-41.
57. Silva J, Garcia V, Rodriguez M, Compte M, Cisneros E, Veguillas P, et al. Analysis of exosome release and its prognostic value in human colorectal cancer. *Genes Chromosomes Cancer.* 2012;51:409–18.
58. Zhongrun Qian, Qi Shen, Xi Yang, Yongming Qiu, and Wenbin Zhang The Role of Extracellular Vesicles: An Epigenetic View of the Cancer Microenvironment. *Biomed Res Int.* 2015;2015:649161.
59. Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecol Oncol* 2008;110.
60. Yang S, Che SP, Kurywchak P, Tavormina JL, Gansmo LB, Correa de Sampaio P, et al. Detection of mutant KRAS and TP53 DNA in circulating exosomes from healthy individuals and patients with pancreatic cancer. *Cancer Biol Ther.* 2017;18:158–65.
61. Skog J, Würdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol.* 2008;10: 1470–6.
62. Pelloski CE, Ballman KV, Furth AF, Zhang L, Lin E, Sulman EP, et al. Epidermal growth factor receptor variant III status defines clinically distinct subtypes of glioblastoma. *J Clin Oncol.* 2007;25:2288–94.
63. An Z, Aksoy O, Zheng T, Fan QW, Weiss WA. Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies. *Oncogene.* 2018;37:1561–75.
64. Jia Y, Chen Y, Wang Q, Jayasinghe U, Luo X, Wei Q, Wang J, Xiong H, Chen, C, Xu B et al. Exosome: Emerging biomarker in breast cancer. *Oncotarget* 2017;8:41717–41733.
65. Yoshioka Y, Kosaka N, Konishi Y, Ohta H, Okamoto H, Sonoda H, Nonaka R, Yamamoto H, Ishii H, Mori, M et al. Ultra-sensitive liquid biopsy of circulating extracellular vesicles using ExoScreen. *Nat Commun.* 2014;5:3591.

66. Logozzi M, De Milito A, Lugini L, Borghi M, Calabro L, Spada M, et al. High levels of exosomes expressing CD63 and caveolin-1 in plasma of melanoma patients. *PLoS One*. 2009;4.
67. Rekker K, Saare M, Roost AM, Kubo AL, Zarovni N, Chiesi A, et al. Comparison of serum exosome isolation methods for microRNA profiling. *Clin Biochem*. 2014;47:135–8.
68. Goto T, Fujiya M, Konishi H, Sasajima J, Fujibayashi S, Hayashi A, et al. An elevated expression of serum exosomal microRNA-191,- 21, -451a of pancreatic neoplasm is considered to be efficient diagnostic marker. *BMC Cancer*. 2018;18:116.
69. George JN. Platelets. *Lancet*. 2000;355:1531–9.
70. Kuznetsov HS, Marsh T, Markens BA, Castano Z, Greene-Colozzi A, Hay SA, et al. Identification of luminal breast cancers that establish a tumor-supportive macroenvironment defined by proangiogenic platelets and bone marrow-derived cells. *Cancer Discov*. 2012;2:1150–65.
71. Cho MS, Bottsford-Miller J, Vasquez HG, Stone R, Zand B, Kroll MH, et al. Platelets increase the proliferation of ovarian cancer cells. *Blood*. 2012;120: 4869–72.
72. Bottsford-Miller J, Choi HJ, Dalton HJ, Stone RL, Cho MS, Haemmerle M, et al. Differential platelet levels affect response to taxane-based therapy in ovarian cancer. *Clin Cancer Res*. 2015;21:602-10.
73. Mantur M, Kemoni H, Pietruczuk M, Wasiluk A. Does renal carcinoma affect the expression of P-selectin on platelets? *Neoplasma*. 2002;49:243–5.
74. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High Platelet-to-Lymphocyte Ratio Predicts Poor Prognosis and Clinicopathological Characteristics in Patients with Breast Cancer: A Meta-Analysis. *BioMed Res Int*. 2017;2017:9503025.
75. Tjon-Kon-Fat LA, Lundholm M, Schröder M, Wurdinger T, Thellenberg-Karlsson C, Widmark A, et al. Platelets harbor prostate cancer biomarkers and the ability to predict therapeutic response to abiraterone in castration resistant patients. *Prostate*. 2018;78:48–53.
76. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet*. 2012;379:1591–601.
77. Best MG, Sol N, Kooi I, Tannous J, Westerman BA, Rustenburg F, et al. RNA-Seq of Tumor-Educated Platelets Enables Blood Based Pan-Cancer, Multiclass, and Molecular Pathway. *Cancer Diagnostics*. *Cancer Cell*. 2015;28:666–76.
78. Nilsson RJ, Karachaliou N, Berenguer J, Gimenez-Capitan A, Schellen P, Teixido C, et al. Rearranged EML4-ALK fusion transcripts sequester in circulating blood platelets and enable blood-based crizotinib response monitoring in non-small-cell lung cancer. *Oncotarget*. 2016 J;7:1066–75.
79. Nilsson RJ, Balaj L, Hulleman E, van Rijn S, Pegtel DM, Walraven M, et al. Blood platelets contain tumor-derived RNA biomarkers. *Blood*. 2011;118: 3680–3
80. Joosse SA, Pantel K. Tumor-Educated Platelets as Liquid Biopsy in Cancer Patients. *Cancer Cell*. 2015;28:552–4.
81. Denis MM, Tolley ND, Bunting M, Schwartz H, Jiang H, Lindemann S, et al. Escaping the nuclear confines: signal-dependent premRNA splicing in anucleate platelets. *Cell*. 2005;122:379–91.

82. Calverley DC, Phang TL, Choudhury QG, Gao B, Oton AB, Weyant MJ, et al. Significant downregulation of platelet gene expression in metastatic lung cancer. *Clin Transl Sci.* 2010;3:227–32.
83. Mangesh A Thorat. Liquid biopsy for cancer diagnosis and screening – The promise and challenges *Ann Clin Biochem.* 2019;56:420-423.