



KANSER HASTALARINDA İMMUNOTERAPİ VE HEDEFE YÖNELİK TEDAVİLERE BAĞLI MİYOKARD FONKSİYONLARINDA BOZULMA VE KALP YETMEZLİĞİ

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İMMUNOTERAPİ VE HEDEFE YÖNELİK TEDAVİLER

Kanser tedavisinde radyoterapi ve cerrahinin yanı sıra en sık kullanılan terapötiklerden biri kemoterapidir (1). Alkilleyici ajanlar ve antimetabolitler gibi geleneksel kemoterapi ajanları, sadece tümör hücreleri gibi hızlı bölünen hücreleri değil, aynı zamanda sindirim endoteli, kıl folikülü, kemik iliği ve kalp gibi dokulardaki normal hücreleri de etkilemektedir. Spesifik olmayan bu ilaçlar, kardiyotoksisite dahil çok çeşitli yan etkiye neden olmaktadır (2). Genel olarak kanser tedavisinin kardiyovasküler komplikasyonları arasında kalp yetmezliği, koroner arter hastalığı, aritmiler, QT uzaması, valvüler hastalık, arteriyel hipertansiyon, tromboembolik hastalık ve periferik vasküler hastalık yer alır. Avrupa Kalp Cemiyeti'ne göre, kalp yetmezliğine yol açan kardiyotoksisite, sol ventrikül ejeksiyon fraksiyonunda (LVEF) %10'dan fazla düşerek normal değer altına inmesi (%50) veya global longitudinal strainde başlangıca göre %15'den fazla azalması olarak tanımlanır (3).

Geleneksel tedavinin normal dokulardaki toksisitesinden dolayı daha az yan etkiye sahip olan immunoterapiler ve hedefe yönelik tedaviler geliştirilmiştir. Kanser tedavisinde immunoterapi ve hedefe yönelik tedavi tıpta en hızlı büyüyen alanlardan biridir.

Hedefe yönelik tedavi

İnsan epidermal büyüme faktörü reseptörü 2 (HER2) sinyalinin antikorlarla veya trozin kinaz inhibitörleriyle inhibisyonu yapan ilaçların diğer geleneksel tedavilere ek olarak verilmesi HER2 pozitif meme kanseri hastalarında

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rilmiştir (103). Ayrıca maruz kalınan radyasyon dozunu azaltmak için derin inspirasyonda nefes tutma tekniği ya da solunumsal gating de kullanılabilir. Bu yöntem, alandaki kalp hacmi en aza indirildiğinde ışın verilmesini sağlar ve bir çalışmada solunumsal gating ile görüntüleme alanındaki kalp hacminin yaklaşık %80 azaltılabileceği gösterilmiştir (104). Sol taraflı meme kanseri olan hastaların bazılarında, supin pozisyonda iken derin inspirasyonda nefes tutma tekniği ile tüm kalbin ve sol inen koroner arterin radyasyon dozunun azaltılabildiği saptanmıştır (105). Başka bir çalışmada ise, meme dokusu büyük olan kadınlarda, pron pozisyonun alandaki kalp hacmini %85 azaltarak kalp dozu azalttığı gösterilmiştir (106).

Sonuç olarak, radyasyona bağlı kardiyotoksisitenin değerlendirilmesi, maruziyet ve kalp hastalığı arasında geçen sürenin uzun olması nedeni ile zordur. En iyi strateji, RT sırasında tedavinin bireyselleştirilerek doz maruziyetinin azaltılması ve kardiyovasküler risk faktörlerinin kontrol altına alınması ile kardiyotoksisiteyi önlemeye çalışmaktır. Kardiyologların tedavi ekibine dahil olarak tedavinin planlanmasında ve hastaların izlemlerinde yardımcı olması önerilir.

KAYNAKLAR

1. DeVita VT, Jr., Chu E. A history of cancer chemotherapy. *Cancer research* 2008;68:8643-53.
2. Chen ZI, Ai DI. Cardiotoxicity associated with targeted cancer therapies. *Molecular and clinical oncology* 2016;4:675-81.
3. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *European heart journal* 2016;37:2768-801.
4. Jelovac D, Emens LA. HER2-directed therapy for metastatic breast cancer. *Oncology (Williston Park, NY)* 2013;27:166-75.
5. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science (New York, NY)* 1987;235:177-82.
6. Chien KR. Myocyte survival pathways and cardiomyopathy: implications for trastuzumab cardiotoxicity. *Seminars in oncology* 2000;27:9-14; discussion 92-100.
7. Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nature medicine* 2002;8:459-65.
8. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nature reviews Cancer* 2007;7:332-44.
9. Maurea N, Coppola C, Piscopo G, et al. Pathophysiology of cardiotoxicity from target therapy and angiogenesis inhibitors. *Journal of cardiovascular medicine (Hagerstown, Md)* 2016;17 Suppl 1 Special issue on Cardiotoxicity from Antitubercular Drugs and Cardioprotection:e19-e26.
10. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010;28:3910-6.

11. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2002;20:1215-21.
12. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003;97:2869-79.
13. Zambelli A, Della Porta MG, Eleuteri E, et al. Predicting and preventing cardiotoxicity in the era of breast cancer targeted therapies. *Novel molecular tools for clinical issues. Breast (Edinburgh, Scotland)* 2011;20:176-83.
14. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;23:7820-6.
15. De Keulenaer GW, Doggen K, Lemmens K. The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anti-cancer therapy. *Circulation research* 2010;106:35-46.
16. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England journal of medicine* 2001;344:783-92.
17. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006;24:4107-15.
18. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009;27:2638-44.
19. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017;35:893-911.
20. Agunbiade TA, Zaghlol RY, Barac A. Heart Failure in Relation to Tumor-Targeted Therapies and Immunotherapies. *Methodist DeBakey cardiovascular journal* 2019;15:250-7.
21. Mohan N, Shen Y, Endo Y, et al. Trastuzumab, but Not Pertuzumab, Dysregulates HER2 Signaling to Mediate Inhibition of Autophagy and Increase in Reactive Oxygen Species Production in Human Cardiomyocytes. *Mol Cancer Ther* 2016;15:1321-31.
22. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *The New England journal of medicine* 2012;366:109-19.
23. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist* 2013;18:257-64.
24. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *The New England journal of medicine* 2012;367:1783-91.
25. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *The New England journal of medicine* 2006;355:2733-43.
26. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008;83:679-86.
27. Varricchi G, Galdiero MR, Marone G, et al. Cardiotoxicity of immune checkpoint inhibitors. *ESMO open* 2017;2:e000247.
28. Wan MT, Ming ME. Nivolumab versus ipilimumab in the treatment of advanced melanoma: a critical appraisal: ORIGINAL ARTICLE: Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; 377:1345-56. *Br J Dermatol* 2018;179:296-300.

29. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol* 2016;13:473-86.
30. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *The New England journal of medicine* 2016;375:1749-55.
31. Jain V, Mohebtash M, Rodrigo ME, et al. Autoimmune Myocarditis Caused by Immune Checkpoint Inhibitors Treated With Antithymocyte Globulin. *J Immunother* 2018;41:332-5.
32. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol* 2018;19:e447-e58.
33. Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. *Nat Rev Mol Cell Biol* 2016;17:611-25.
34. Bates DO. Vascular endothelial growth factors and vascular permeability. *Cardiovasc Res* 2010;87:262-71.
35. Hoeben A, Landuyt B, Highley MS, et al. Vascular endothelial growth factor and angiogenesis. *Pharmacol Rev* 2004;56:549-80.
36. Kerbel RS. Tumor angiogenesis. *The New England journal of medicine* 2008;358:2039-49.
37. Hood JD, Meininger CJ, Ziche M, et al. VEGF upregulates eNOS message, protein, and NO production in human endothelial cells. *Am J Physiol* 1998;274:H1054-8.
38. Rhea IB, Oliveira GH. Cardiotoxicity of Novel Targeted Chemotherapeutic Agents. *Current treatment options in cardiovascular medicine* 2018;20:53.
39. Launay-Vacher V, Deray G. Hypertension and proteinuria: a class-effect of antiangiogenic therapies. *Anticancer Drugs* 2009;20:81-2.
40. Kruzliak P, Novák J, Novák M. Vascular endothelial growth factor inhibitor-induced hypertension: from pathophysiology to prevention and treatment based on long-acting nitric oxide donors. *Am J Hypertens* 2014;27:3-13.
41. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;99:1232-9.
42. Choueiri TK, Schutz FA, Je Y, et al. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol* 2010;28:2280-5.
43. Sundararajan S, Kumar A, Poongkunran M, et al. Cardiovascular adverse effects of targeted antiangiogenic drugs: mechanisms and management. *Future Oncol* 2016;12:1067-80.
44. Taimeh Z, Loughran J, Birks EJ, et al. Vascular endothelial growth factor in heart failure. *Nat Rev Cardiol* 2013;10:519-30.
45. Hawkes EA, Okines AF, Plummer C, et al. Cardiotoxicity in patients treated with bevacizumab is potentially reversible. *J Clin Oncol* 2011;29:e560-2.
46. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet (London, England)* 2007;370:2011-9.
47. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer* 2008;112:2500-8.
48. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. *Ann Pharmacother* 2009;43:490-501.
49. Choueiri TK, Mayer EL, Je Y, et al. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. *J Clin Oncol* 2011;29:632-8.
50. Qi WX, Fu S, Zhang Q, et al. Bevacizumab increases the risk of severe congestive heart failure in cancer patients: an up-to-date meta-analysis with a focus on different subgroups. *Clin Drug Investig* 2014;34:681-90.
51. Ghatalia P, Morgan CJ, Je Y, et al. Congestive heart failure with vascular endothelial growth factor receptor tyrosine kinase inhibitors. *Crit Rev Oncol Hematol* 2015;94:228-37.
52. Verma N, Swain SM. Bevacizumab and heart failure risk in patients with breast cancer: a thorn in the side? *J Clin Oncol* 2011;29:603-6.

53. Ky B, Vejpongsa P, Yeh ET, Force T, et al. Emerging paradigms in cardiomyopathies associated with cancer therapies. *Circ Res* 2013;113:754-64.
54. Kluetz PG, Chingos DT, Basch EM, et al. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting 2016;35:67-73.
55. Small HY, Montezano AC, Rios FJ, Savoia C, et al. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. *The Canadian journal of cardiology* 2014;30:534-43.
56. Chintalgattu V, Ai D, Langley RR, et al. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. *J Clin Invest* 2010;120:472-84.
57. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *The New England journal of medicine* 2007;356:115-24.
58. Guo J, Jin J, Oya M, et al. Safety of pazopanib and sunitinib in treatment-naïve patients with metastatic renal cell carcinoma: Asian versus non-Asian subgroup analysis of the COMPARZ trial. *J Hematol Oncol* 2018;11:69.
59. Haas NB, Manola J, Ky B, et al. Effects of Adjuvant Sorafenib and Sunitinib on Cardiac Function in Renal Cell Carcinoma Patients without Overt Metastases: Results from ASSURE, ECOG 2805. *Clin Cancer Res* 2015;21:4048-54.
60. Narayan V, Keefe S, Haas N, et al. Prospective Evaluation of Sunitinib-Induced Cardiotoxicity in Patients with Metastatic Renal Cell Carcinoma. *Clin Cancer Res* 2017;23:3601-9.
61. Nowell PC. The minute chromosome (Phl) in chronic granulocytic leukemia. *Blut* 1962;8:65-6.
62. Erikson J, Griffin CA, ar-Rushdi A, et al. Heterogeneity of chromosome 22 breakpoint in Philadelphia-positive (Ph+) acute lymphocytic leukemia. *Proc Natl Acad Sci U S A* 1986;83:1807-11.
63. Singh AP, Umbarkar P, Tousif S, et al. Cardiotoxicity of the BCR-ABL1 tyrosine kinase inhibitors: Emphasis on ponatinib. *International journal of cardiology* 2020;316:214-21.
64. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. *The New England journal of medicine* 1999;341:164-72.
65. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *The New England journal of medicine* 2001;344:1031-7.
66. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *The New England journal of medicine* 2003;349:1423-32.
67. O'Dwyer ME, Druker BJ. STI571: an inhibitor of the BCR-ABL tyrosine kinase for the treatment of chronic myelogenous leukaemia. *Lancet Oncol* 2000;1:207-11.
68. Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006;12:908-16.
69. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 2009;23:1054-61.
70. Hatfield A, Owen S, Pilot PR. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. *Nat Med* 2007;13:13; author reply 5-6.
71. Remsing Rix LL, Rix U, Colinge J, et al. Global target profile of the kinase inhibitor bosutinib in primary chronic myeloid leukemia cells. *Leukemia* 2009;23:477-85.
72. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *The New England journal of medicine* 2012;367:2075-88.
73. Valent P, Hadzijušufovic E, Scherthaner GH, et al. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood* 2015;125:901-6.

74. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018;132:393-404.
75. Singh AP, Glennon MS, Umbarkar P, et al. Ponatinib-induced cardiotoxicity: delineating the signalling mechanisms and potential rescue strategies. *Cardiovasc Res* 2019;115:966-77.
76. Sharma A, Burrridge PW, McKeithan WL, et al. High-throughput screening of tyrosine kinase inhibitor cardiotoxicity with human induced pluripotent stem cells. *Sci Transl Med* 2017;9.
77. Mearini G, Schlossarek S, Willis MS, et al. The ubiquitin-proteasome system in cardiac dysfunction. *Biochim Biophys Acta* 2008;1782:749-63.
78. Yewdell JW. Not such a dismal science: the economics of protein synthesis, folding, degradation and antigen processing. *Trends Cell Biol* 2001;11:294-7.
79. Yerlikaya A, Kanbur E. The Ubiquitin-Proteasome Pathway and Resistance Mechanisms Developed Against the Proteasomal Inhibitors in Cancer Cells. *Curr Drug Targets* 2020;21:1313-25.
80. Hershko A, Ciechanover A. The ubiquitin system. *Annu Rev Biochem* 1998;67:425-79.
81. Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res* 2007;67:6383-91.
82. Danhof S, Schreder M, Rasche L, et al. 'Real-life' experience of preapproval carfilzomib-based therapy in myeloma - analysis of cardiac toxicity and predisposing factors. *Eur J Haematol* 2016;97:25-32.
83. Koulaouzidis G, Lyon AR. Proteasome Inhibitors as a Potential Cause of Heart Failure. *Heart Fail Clin* 2017;13:289-95.
84. Esparís-Ogando A, Alegre A, Aguado B, et al. Bortezomib is an efficient agent in plasma cell leukemias. *Int J Cancer* 2005;114:665-7.
85. Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res* 2010;70:1970-80.
86. Bockorny M, Chakravarty S, Schulman P, et al. Severe heart failure after bortezomib treatment in a patient with multiple myeloma: a case report and review of the literature. *Acta Haematol* 2012;128:244-7.
87. Gupta A, Pandey A, Sethi S. Bortezomib-induced congestive cardiac failure in a patient with multiple myeloma. *Cardiovasc Toxicol* 2012;12:184-7.
88. Honton B, Despas F, Dumontel N, et al. Bortezomib and heart failure: case-report and review of the French Pharmacovigilance database. *Fundam Clin Pharmacol* 2014;28:349-52.
89. Reneau JC, Asante D, van Houten H, et al. Cardiotoxicity risk with bortezomib versus lenalidomide for treatment of multiple myeloma: A propensity matched study of 1,790 patients. *Am J Hematol* 2017;92:E15-e7.
90. Xiao Y, Yin J, Wei J, Shang Z. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. *PLoS One* 2014;9:e87671.
91. Ruschak AM, Slassi M, Kay LE, Schimmer AD. Novel proteasome inhibitors to overcome bortezomib resistance. *J Natl Cancer Inst* 2011;103:1007-17.
92. Cole DC, Frishman WH. Cardiovascular Complications of Proteasome Inhibitors Used in Multiple Myeloma. *Cardiol Rev* 2018;26:122-9.
93. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica* 2013;98:1753-61.
94. Rygiel K. Cardiotoxic effects of radiotherapy and strategies to reduce them in patients with breast cancer: An overview. *J Cancer Res Ther* 2017;13:186-92.
95. Yeboa DN, Evans SB. Contemporary Breast Radiotherapy and Cardiac Toxicity. *Semin Radiat Oncol* 2016;26:71-8.
96. Lewis GD, Farach A. Cardiovascular Toxicities of Radiation Therapy. *Methodist DeBakey cardiovascular journal* 2019;15:274-81.

97. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys* 2010;76:656-65.
98. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* (London, England) 2000;355:1757-70.
99. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-65.
100. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993;270:1949-55.
101. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma. *J Clin Oncol* 2016;34:235-43.
102. Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2017;35:1395-402.
103. Canney PA, Sanderson R, Deehan C, et al. Variation in the probability of cardiac complications with radiation technique in early breast cancer. *Br J Radiol* 2001;74:262-5.
104. Lu HM, Cash E, Chen MH, et al. Reduction of cardiac volume in left-breast treatment fields by respiratory maneuvers: a CT study. *Int J Radiat Oncol Biol Phys* 2000;47:895-904.
105. Bartlett FR, Colgan RM, Donovan EM, et al. The UK HeartSpare Study (Stage IB): randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery. *Radiother Oncol* 2015;114:66-72.
106. Formenti SC, DeWyngaert JK, Jozsef G, et al. Prone vs supine positioning for breast cancer radiotherapy. *JAMA* 2012;308:861-3.