



KEMOTERAPİYE BAĞLI GELİŞEN KARDİYAK YAN ETKİLERDEN KORUNMA VEYA HAFİFLETİLMESİNE YÖNELİK KLİNİK YAKLAŞIMLAR VE KARDİYOTOKSİSİTE TEDAVİSİ

Mesut KARATAŞ¹

ANTI-KANSER TEDAVİLERE BAĞLI GELİŞEN KARDİYAK YAN ETKİLERİN YÖNETİLMESİNE YÖNELİK TEDAVİ SEÇENEKLERİ

Kardiyak Yan Etki Potansiyeli Yüksek Kemoterapi Öncesi

Potansiyel kardiyotoksik kemoterapi öncesi kardiyak koruma stratejisinin belirlenmesi ve zamanlaması çok farklı klinik değişkenlere bağlıdır. Hastanın daha önceden kardiyovasküler hastalığa sahip olması, planlanan anti-kanser ilacın tipi, daha önce yüksek riskli kemoteropatik ilaç kullanımı öyküsünün olması ve kontrol edilmemiş ya da edilemeyen kardiyovasküler risk faktörlerine sahip olması gibi değişkenlere sahip hastalarda daha sıkı risk faktörü kontrolü sağlanmalı ve bu hasta grubunda kemoterapi tedavisi öncesi profilaktik kalp koruyucu tedavi planlanması daha büyük önem taşır. (1-3)

Örneğin hasta kanada risk skorlamasına göre düşük risklide olsa, yüksek doz yada kümülatif doz antrasiklin (yaklaşık 250-300 mg/m² ve ya üstünde) verilecek olan kanser hastalarına tedavi mutlaka önerilmektedir. Yapılan OVERCOME çalışmasında hematopoetik sistem malignitesi nedeniyle yüksek doz antrasiklin (>250-300 mg/m²) verilen hastalar tedaviden öncesinde 2(iki) gruba ayrılmış, (Standart dozlarda kalp yetmezliği tedavisi verilen ve verilmeyen şeklinde) ve gruplardan birine standart kalp yetmezliği dozunda enalapril ve karvedilol başlanırken diğer gruba sadece kemoteropatik ilaç uygulanmış. Sadece kemoteropatik ilaç alan hastaların 6 aylık takiplerinde sol ventrikül ejeksiyon fraksiyonunda azalma gözlenirken, Enalapril ve karvedilol alan kolda sol ventrikül ejeksiyonun fraksiyonu korunmuştur. (1) Her ne kadar overco-

¹ Uzm. Dr., SBÜ Dr. Siyami Ersek Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği mesut.cardio@gmail.com

için hastaların karotis doppler yöntemi ile asemptomatik karotis arter hastalığı açısından araştırılmasında fayda vardır.

Valvülopatiler

Radyoterapiye bağlı kalp kapak hastalığı özellikle radyoterapiye bağlı geç bir komplikasyon olarak karşımıza çıkmakta ve ortalama tanı süresi yaklaşık >20 yıldır. (132) Radyoterapi almış hastaların uzun dönem takiplerinde çok az hasta da normofonksiyonel aort kapağına rastlanılmıştır. Benzer şekilde her ne kadar ilişkisi tam açıklanamamış olsa da çocukluk çağında kanser tedavisi görmüş ve hayatta kalmış hastaların uzun dönem takiplerinde normalde daha fazla oranda triküspit yetersizliğine rastlanılmıştır. (133) Kanser tedavisen bağlı kalp kapak hastalığı tanısı alan hastaların çoğunluğu kanser takipleri bitmiş olan hastalardır ve çok ilginç bir şekilde bu hastaların mevcut medikal kayıtlarında radyasyon öyküsü sıklıkla yoktur. (134) Avrupa ve Amerikan görüntüleme dernekleri (EACVI/ASE) semptomları olan hastalarda ekokardiyografi ile değerlendirme önermektedir. (135) Semptomsuz hastalar içinse radyoterapi-den sonraki onuncu yılda ve sonraki her 5 yılda bir ekokardiyografi ile kapak fonksiyonlarının değerlendirilmesini önermektedir. (135)

Özellikle thoraks bölgesine alınan radyoterapinin uzun dönem komplikasyonu olarak gelişen mediastinal ciddi kalsifikasyon veya fibrozis gibi trans-toraksik görüntülemeyi önemli derecede kısıtlayan durumların varlığında TÖE (Transözefegiyal ekokardiyografi) yol gösterici olabilir. Bunun yanında mitral kapak morfolojisinin değerlendirilmesinde üç boyutlu EKO (Ekokardiyografi) faydalı olabilir. Ekokardiyografik görüntülemenin sınırlarını aşan veya hesaplamaların bizi yanıltabileceği durumlar da kardiyak MR (Manyetik rezonans) yararlı olabilir. (136)

KAYNAKLAR

1. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzo M, Esteve J. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol 2013;61:2355–2362.
2. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland A, Storås TH, Hagve TA, Rosjo H, Steine K, Geisler J, Omland T. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebocontrolled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37:1671–1680.
3. Pituskin E, Haykowsky M, Mackey JR, Thompson RB, Ezekowitz J, Koshman S, Oudit G, Chow K, Pagano JJ, Paterson I. Rationale and design of the Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial (MANTICORE 101—Breast): a

- randomized, placebo-controlled trial to determine if conventional heart failure pharmacotherapy can prevent trastuzumabmediated left ventricular remodeling among patients with HER2+ early breast cancer using cardiac MRI. *BMC Cancer* 2011;11:318.
4. Barac A, Murtagh G, Carver JR, Chen MH, Freeman AM, Herrmann J, Iliescu C, Ky B, Mayer EL, Okwuosa TM, Plana JC, Ryan TD, Rzeszut AK, Douglas PS. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *J Am Coll Cardiol* 2015;65:2739–2746.
 5. Clarke E, Lenihan D. Cardio-oncology: a new discipline in medicine to lead us into truly integrative care. *Future Cardiol* 2015;11:359–361.
 6. Okwuosa TM, Barac A. Burgeoning cardio-oncology programs: challenges and opportunities for early career cardiologists/faculty directors. *J Am Coll Cardiol* 2015;66:1193–1197.
 7. Albin A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* 2010;102:14–25.
 8. Speyer JL, Green MD, Zeleniuch-Jacquotte A, Wernz JC, Rey M, Sanger J, Kramer E, Ferrans V, Hochster H, Meyers M. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. *J Clin Oncol* 1992;10:117–127.
 9. Venturini M, Michelotti A, Del Mastro L, Gallo L, Carnino F, Garrone O, Tibaldi C, Molea N, Bellina RC, Pronzato P, Cyrus P, Vinke J, Testore F, Guelfi M, Lionetto R, Bruzzi P, Conte PF, Rosso R. Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. *J Clin Oncol* 1996;14:3112–3120.
 10. Swain SM, Whaley FS, Gerber MC, Ewer MS, Bianchini JR, Gams RA. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. *J Clin Oncol* 1997;15:1333–1340.
 11. Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, Colan SD, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, Samson Y, Schorin MA, Gelber RD, Sallan SE. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004;351:145–153.
 12. Marty M, Espie M, Llombart A, Monnier A, Rapoport BL, Stahalova V, Dexrazoxane Study Group. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Ann Oncol* 2006;17:614–622.
 13. Huh WW, Jaffe N, Durand JB, Munsell MF, Herzog CE. Comparison of doxorubicin cardiotoxicity in pediatric sarcoma patients when given with dexrazoxane versus as continuous infusion. *Pediatr Hematol Oncol* 2010;27:546–557.
 14. Asselin BL, Devidas M, Chen L, Franco VI, Pullen J, Borowitz MJ, Hutchison RE, Ravindranath Y, Armenian SH, Camitta BM, Lipshultz SE. Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: a report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. *J Clin Oncol* 2016;34:854–862.
 15. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev* 2011;6:CD003917.
 16. Tebbi CK, London WB, Friedman D, Villaluna D, De Alarcon PA, Constine LS, Mendenhall NP, Spoto R, Chauvenet A, Schwartz CL. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007;25:493–500.
 17. Barry EV, Vrooman LM, Dahlberg SE, Neuberger DS, Asselin BL, Athale UH, Clavell LA, Larsen EC, Moghrabi A, Samson Y, Schorin MA, Cohen HJ, Lipshultz SE, Sallan SE, Silverman LB. Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol* 2008;26:1106–1111.

18. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A 3rd, von Hoff D, Schuchter LM. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009;27:127–145.
19. European Medicines Agency. Questions and answers on the review of dexrazoxane-containing medicines, powder for solution for infusion, 500 mg. Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Dexrazoxane_31/WC500108011.pdf. Date last accessed 12 April 2016.
20. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, Inanc T, Oguzhan A, Eryol NK, Topsakal R, Ergin A. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258–2262.
21. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, Kalay N, Dikilitas M, Yarlioglu M, Karaca H, Berk V, Ardic I, Ergin A, Lam YY. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. *Int J Cardiol* 2013;167:2306–2310.
22. Akpek M, Ozdogru I, Sahin O, Inanc M, Dogan A, Yazici C, Berk V, Karaca H, Kalay N, Oguzhan A, Ergin A. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. *Eur J Heart Fail* 2015;17:81–89.
23. Nakamae H, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K, Yamane T, Hino M. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. *Cancer* 2005;104:2492–2498.
24. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
25. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging* 2014;15:324–331.
26. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, Welles L, Winer E, TLC D-99 Study Group. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. *Cancer* 2002;94:25–36.
27. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivatives for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev* 2010;5:CD005006.
28. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, Catane R, Kieback DG, Tomczak P, Ackland SP, Orlandi F, Mellars L, Alland L, Tendler C, CAELYX Breast Cancer Study Group. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/ Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004;15:440–449.
29. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, Jones SE, Wadler S, Desai A, Vogel C, Speyer J, Mittelman A, Reddy S, Pendergrass K, Velez-Garcia E, Ewer MS, Bianchini JR, Gams RA. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. *J Clin Oncol* 1997;15:1318–1332.
30. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport* 2009;12:428–434. 2

31. Jones LW, Liu Q, Armstrong GT, Ness KK, Yasui Y, Devine K, Tonorezos E, Soares-Miranda L, Sklar CA, Douglas PS, Robison LL, Oeffinger KC. Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2014;32:3643–3650.
32. Low CA, Beckjord E, Bovbjerg DH, Dew MA, Posluszny DM, Schmidt JE, Lowery AE, Nutt SA, Arvey SR, Rechis R. Correlates of positive health behaviors in cancer survivors: results from the 2010 LIVESTRONG survey. *J Psychosoc Oncol* 2014;32:678–695.
33. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465. 259. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JJ, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Somerfield MR, Falanga A, American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33:654–656.
34. Türk Kardiyo Derna Arş 2017 32 ESC Klinik Kılavuzları Komitesi durum bildirgesi
35. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M, PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebocontrolled, double-blind study. *Lancet Oncol* 2009;10:943–949.
36. Frere C, Debourdeau P, Hij A, Cajfinger F, Nonan MN, Panicot-Dubois L, Dubois C, Farge D. Therapy for cancer-related thromboembolism. *Semin Oncol* 2014;41:319–338.
37. Carrier M, Khorana AA, Moretto P, Le Gal G, Karp R, Zwicker JJ. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. *Am J Med* 2014;127:82–86 e81.
38. Akl EA, Ramly EP, Kahale LA, Yosuico VE, Barba M, Sperati F, Cook D, Schunemann H. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database Syst Rev* 2014;10:CD006468.
39. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, Rasmussen SL, Blumenschein GR, Freireich EJ. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982;96:133–139.
40. Torti FM, Bristow MR, Howes AE, Aston D, Stockdale FE, Carter SK, Kohler M, Brown-BW Jr., Billingham ME. Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. Assessment by endomyocardial biopsy. *Ann Intern Med* 1983;99:745–749.
41. Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, Spreafico C, Laffranchi A, Caraceni A, Martini C. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995;13:2688–2699.
42. Boyle EM, Morschhauser F. Pixantrone: a novel anthracycline-like drug for the treatment of non-Hodgkin lymphoma. *Expert Opin Drug Saf* 2015;14:601–607.
43. Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². *Ann Oncol* 2000;11:1029–1033.
44. Lotrionte M, Palazzoni G, Natali R, Comerchi G, Abbate A, Di Persio S, Biondi-Zoccai GG. Appraising cardiotoxicity associated with liposomal doxorubicin by means of tissue Doppler echocardiography end-points: rationale and design of the LITE (Liposomal doxorubicin-Investigational chemotherapy Tissue Doppler imaging Evaluation) randomized pilot study. *Int J Cardiol* 2009;135:72–77.
45. Sparano JA, Makhson AN, Semiglazov VF, Tjulandin SA, Balashova OI, Bondarenko IN, Bogdanova NV, Manikhas GM, Oliynychenko GP, Chatikhine VA, Zhuang SH, Xiu L, Yuan

- Z, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol* 2009;27:4522–4529.
46. Rafiyath SM, Rasul M, Lee B, Wei G, Lamba G, Liu D. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a metaanalysis. *Exp Hematol Oncol* 2012;1:10.
 47. Lotrionte M, Palazzoni G, Abbate A, De Marco E, Mezzaroma E, Di Persio S, Frati G, Loperfido F, Biondi-Zoccai G. Cardiotoxicity of a non-pegylated liposomal doxorubicin-based regimen versus an epirubicin-based regimen for breast cancer: the LITE (Liposomal doxorubicin-Investigational chemotherapy-Tissue Doppler imaging Evaluation) randomized pilot study. *Int J Cardiol* 2013;167:1055–1057.
 48. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, McIntyre KJ, Pippen JE, Bordelon JH, Kirby R, Sandbach J, Hyman WJ, Khandelwal P, Negron AG, Richards DA, Anthony SP, Mennel RG, Boehm KA, Meyer WG, Asmar L. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006;24:5381–5387.
 49. Holmes FA, Rowinsky EK. Pharmacokinetic profiles of doxorubicin in combination with taxanes. *Semin Oncol* 2001;28:8–14.
 50. Salvatorelli E, Menna P, Cascegna S, Liberi G, Calafiore AM, Gianni L, Minotti G. Paclitaxel and docetaxel stimulation of doxorubicinol formation in the human heart: implications for cardiotoxicity of doxorubicin-taxane chemotherapies. *J Pharmacol Exp Ther* 2006;318:424–433.
 51. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. *J Clin Oncol* 2005;23:7685–7696.
 52. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, Swain SM, Brown A, Fehrenbacher L, Vogel VG, Seay TE, Rastogi P, Mamounas EP, Wolmark N, Bryant J. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005;23:7811–7819.
 53. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J, Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273–1283.
 54. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sanchez Rovira P, Piccart-Gebhart MJ, HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369:29–36.
 55. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Gatrex V, Ward C, Strahle C, McFadden E, Dolci MS, Gelber RD, Herceptin Adjuvant Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–1672.
 56. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673–1684.

57. Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of beta-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. *Circ Heart Fail* 2013;6:420–426.
58. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, Plummer CJ, Wardley AM, Verrill MW. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 2009;100:684–692.
59. Scott JM, Khakoo A, Mackey JR, Haykowsky MJ, Douglas PS, Jones LW. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. *Circulation* 2011;124:642–650.
60. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res* 2009;15:4963–4967.
61. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirim A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949–3003.
62. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009;8:191–202.
63. Oleksowicz L, Bruckner HW. Prophylaxis of 5-fluorouracil-induced coronary vasospasm with calcium channel blockers. *Am J Med* 1988;85:750–751.
64. Eskilsson J, Albertsson M. Failure of preventing 5-fluorouracil cardiotoxicity by prophylactic treatment with verapamil. *Acta Oncol* 1990;29:1001–1003.
65. Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev* 2013;39:974–984.
66. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993;270:1949–1955.
67. Prosnitz RG, Chen YH, Marks LB. Cardiac toxicity following thoracic radiation. *Semin Oncol* 2005;32(2 Suppl 3):S71–S80.
68. Louwe RJ, Wendling M, van Herk MB, Mijneer BJ. Three-dimensional heart dose reconstruction to estimate normal tissue complication probability after breast irradiation using portal dosimetry. *Med Phys* 2007;34:1354–1363. ESC Klinik Kılavuzları Komitesi durum bildirgesi 33 Türk KardiyoDern Arş 2017
69. Bruzzaniti V, Abate A, Pinnaro P, D'Andrea M, Infusino E, Landoni V, Soriani A, Giordano C, Ferraro A, Strigari L. Dosimetric and clinical advantages of deep inspiration breath-hold (DIBH) during radiotherapy of breast cancer. *J Exp Clin Cancer Res* 2013;32:88.
70. Xu Q, Chen Y, Grimm J, Fan J, An L, Xue J, Pahlajani N, Lacouture T. Dosimetric investigation of accelerated partial breast irradiation (APBI) using CyberKnife. *Med Phys* 2012;39:6621–6628.

71. Bartlett FR, Colgan RM, Donovan EM, McNair HA, Carr K, Evans PM, Griffin C, Locke I, Haviland JS, Yarnold JR, Kirby AM. 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.
72. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Birmingham M, Patle A, Badabhagani MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K. Natriuretic peptidebased screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;310:66–74.
73. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
74. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, Rubino M, Veglia F, Fiorentini C, Cipolla CM. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213–220.
75. Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, Border WL, Feijen EA, Green DM, Meacham LR, Meeske KA, Mulrooney DA, Ness KK, Oeffinger KC, Sklar CA, Stovall M, van der Pal HJ, Weathers RE, Robison LL, Yasui Y. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol* 2015;33:394–402.
76. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging* 2014;15:324–331.
77. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, Welles L, Winer E, TLC D-99 Study Group. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. *Cancer* 2002;94:25–36.
78. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivatives for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev* 2010;5:CD005006.
79. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, Catane R, Kieback DG, Tomczak P, Ackland SP, Orlandi F, Mellars L, Alland L, Tendler C, CAELYX Breast Cancer Study Group. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/ Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004;15:440–449.
80. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, Jones SE, Wadler S, Desai A, Vogel C, Speyer J, Mittelman A, Reddy S, Pendergrass K, Velez-Garcia E, Ewer MS, Bianchini JR, Gams RA. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. *J Clin Oncol* 1997;15:1318–1332.
81. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport* 2009;12:428–434.
82. Jones LW, Liu Q, Armstrong GT, Ness KK, Yasui Y, Devine K, Tonorezos E, Soares-Miranda L, Sklar CA, Douglas PS, Robison LL, Oeffinger KC. Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2014;32:3643–3650.
83. Low CA, Beckjord E, Bovbjerg DH, Dew MA, Posluszny DM, Schmidt JE, Lowery AE, Nutt SA, Arvey SR, Rechis R. Correlates of positive health behaviors in cancer survivors: results from the 2010 LIVESTRONG survey. *J Psychosoc Oncol* 2014;32:678–695.
84. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465.

85. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Somerfield MR, Falanga A, American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33:654–656.
86. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M, PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebocontrolled, double-blind study. *Lancet Oncol* 2009;10:943–949.
87. Frere C, Debourdeau P, Hij A, Cajfinger F, Nonan MN, Panicot-Dubois L, Dubois C, Farge D. Therapy for cancer-related thromboembolism. *Semin Oncol* 2014;41:319–338.
88. Carrier M, Khorana AA, Moretto P, Le Gal G, Karp R, Zwicker JI. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. *Am J Med* 2014;127:82–86 e81.
89. Akl EA, Ramly EP, Kahale LA, Yosucio VE, Barba M, Sperati F, Cook D, Schunemann H. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database Syst Rev* 2014;10:CD006468.
90. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, Rasmussen SL, Blumenschein GR, Freireich EJ. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982;96:133–139.
91. Torti FM, Bristow MR, Howes AE, Aston D, Stockdale FE, Carter SK, Kohler M, Brown-BW Jr., Billingham ME. Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. Assessment by endomyocardial biopsy. *Ann Intern Med* 1983;99:745–749.
92. Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, Spreafico C, Laffranchi A, Caraceni A, Martini C. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995;13:2688–2699.
93. Boyle EM, Morschhauser F. Pixantrone: a novel anthracycline-like drug for the treatment of non-Hodgkin lymphoma. *Expert Opin Drug Saf* 2015;14:601–607.
94. Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². *Ann Oncol* 2000;11:1029–1033.
95. Lotrionte M, Palazzoni G, Natali R, Comerchi G, Abbate A, Di Persio S, Biondi-Zoccai GG. Appraising cardiotoxicity associated with liposomal doxorubicin by means of tissue Doppler echocardiography end-points: rationale and design of the LITE (Liposomal doxorubicin-Investigational chemotherapy-Tissue Doppler imaging Evaluation) randomized pilot study. *Int J Cardiol* 2009;135:72–77.
96. Sparano JA, Makhson AN, Semiglazov VF, Tjulandin SA, Balashova OI, Bondarenko IN, Bogdanova NV, Manikhas GM, Oliynychenko GP, Chatikhine VA, Zhuang SH, Xiu L, Yuan Z, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol* 2009;27:4522–4529.
97. Rafiyath SM, Rasul M, Lee B, Wei G, Lamba G, Liu D. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a metaanalysis. *Exp Hematol Oncol* 2012;1:10.
98. Lotrionte M, Palazzoni G, Abbate A, De Marco E, Mezzaroma E, Di Persio S, Frati G, Loperfido F, Biondi-Zoccai G. Cardiotoxicity of a non-pegylated liposomal doxorubicin-based regimen versus an epirubicin-based regimen for breast cancer: the LITE (Liposomal doxorubicin-Investigational chemotherapy-Tissue Doppler imaging Evaluation) randomized pilot study. *Int J Cardiol* 2013;167:1055–1057.

99. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, McIntyre KJ, Pippen JE, Bordelon JH, Kirby R, Sandbach J, Hyman WJ, Khandelwal P, Negron AG, Richards DA, Anthony SP, Mennel RG, Boehm KA, Meyer WG, Asmar L. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006;24:5381–5387.
100. Holmes FA, Rowinsky EK. Pharmacokinetic profiles of doxorubicin in combination with taxanes. *Semin Oncol* 2001;28:8–14.
101. Salvatorelli E, Menna P, Cascegna S, Liberi G, Calafiore AM, Gianni L, Minotti G. Paclitaxel and docetaxel stimulation of doxorubicinol formation in the human heart: implications for cardiotoxicity of doxorubicin-taxane chemotherapies. *J Pharmacol Exp Ther* 2006;318:424–433.
102. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. *J Clin Oncol* 2005;23:7685–7696.
103. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, Swain SM, Brown A, Fehrenbacher L, Vogel VG, Seay TE, Rastogi P, Mamounas EP, Wolmark N, Bryant J. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005;23:7811–7819.
104. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buysse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J, Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273–1283.
105. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sanchez Rovira P, Piccart-Gebhart MJ, HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369:29–36.
106. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Gatreux V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD, Herceptin Adjuvant Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–1672.
107. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673–1684.
108. Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of beta-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. *Circ Heart Fail* 2013;6:420–426.
109. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, Plummer CJ, Wardley AM, Verrill MW. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 2009;100:684–692.
110. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, Criscitello C, Goldhirsch A, Cipolla C, Roila F, ESMO Guidelines Working Group. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012;23(Suppl 7):vii155–vii166

111. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res* 2009;15:4963–4967.
112. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Knuuti J, Valgimigli M, Bueno H, Claes MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, HAMILIOS M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons-Sel A, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949–3003.
113. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009;8:191–202.
114. Oleksowicz L, Bruckner HW. Prophylaxis of 5-fluorouracil-induced coronary vasospasm with calcium channel blockers. *Am J Med* 1988;85:750–751.
115. Eskilsson J, Albertsson M. Failure of preventing 5-fluorouracil cardiotoxicity by prophylactic treatment with verapamil. *Acta Oncol* 1990;29:1001–1003.
116. Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev* 2013;39:974–984.
117. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993;270:1949–1955.
118. Prosnitz RG, Chen YH, Marks LB. Cardiac toxicity following thoracic radiation. *Semin Oncol* 2005;32(2 Suppl 3):S71–S80.
119. Louwe RJ, Wendling M, van Herk MB, Mijnheer BJ. Three-dimensional heart dose reconstruction to estimate normal tissue complication probability after breast irradiation using portal dosimetry. *Med Phys* 2007;34:1354–1363.
120. Bruzzaniti V, Abate A, Pinnaro P, D'Andrea M, Infusino E, Landoni V, Soriani A, Giordano C, Ferraro A, Strigari L. Dosimetric and clinical advantages of deep inspiration breath-hold (DIBH) during radiotherapy of breast cancer. *J Exp Clin Cancer Res* 2013;32:88.
121. Xu Q, Chen Y, Grimm J, Fan J, An L, Xue J, Pahlajani N, Lacouture T. Dosimetric investigation of accelerated partial breast irradiation (APBI) using CyberKnife. *Med Phys* 2012;39:6621–6628.
122. Bartlett FR, Colgan RM, Donovan EM, McNair HA, Carr K, Evans PM, Griffin C, Locke I, Haviland JS, Yarnold JR, Kirby AM. 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.
123. McCabe MS, Bhatia S, Oeffinger KC, Reaman GH, Tyne C, Wollins DS, Hudson MM. American Society of Clinical Oncology statement: achieving high-quality cancer survivorship care. *J Clin Oncol* 2013;31:631–640.
124. Lenihan DJ, Oliva S, Chow EJ, Cardinale D. Cardiac toxicity in cancer survivors. *Cancer* 2013;119(Suppl 11):2131–2142.
125. Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, Dumontet C, Thieblemont C, Arnaud P, Antal D, Bouafia F, Coiffier B. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol* 2004;22:1864–1871.

126. de Azambuja E, Ameye L, Diaz M, Vandenbossche S, Aftimos P, Bejarano Hernandez S, Shih-Li C, Delhay F, Focan C, Cornez N, Vindevoghel A, Beauduin M, Lemort M, Paesmans M, Suter T, Piccart-Gebhart M. Cardiac assessment of early breast cancer patients 18 years after treatment with cyclophosphamide-, methotrexate-, fluorouracil- or epirubicin-based chemotherapy. *Eur J Cancer* 2015;51:2517–2524.
127. Mitani I, Jain D, Joska TM, Burtneess B, Zaret BL. Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiology in the current era. *J Nucl Cardiol* 2003;10:132–139.
128. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? *J Clin Oncol* 2008;26:1201–1203.
129. Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. *J Clin Oncol* 2012;30:3657–3664.
130. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743–749.
131. Koppelmans V, Vernooij MW, Boogerd W, Seynaeve C, Ikram MA, Breteler MM, Schagen SB. Prevalence of cerebral small-vessel disease in long-term breast cancer survivors exposed to both adjuvant radiotherapy and chemotherapy. *J Clin Oncol* 2015;33:588–593.
132. Glanzmann C, Huguenin P, Lutolf UM, Maire R, Jenni R, Gumpfenberg V. Cardiac lesions after mediastinal irradiation for Hodgkin's disease. *Radiation Oncol* 1994;30:43–54.
133. Armstrong GT, Joshi VM, Zhu L, Srivastava D, Zhang N, Ness KK, Stokes DC, Krasin MT, Fowler JA, Robison LL, Hudson MM, Green DM. Increased tricuspid regurgitant jet velocity by Doppler echocardiography in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. *J Clin Oncol* 2013;31:774–781.
134. Copeland KA, Hosmane VR, Jurkowitz C, Kolm P, Bowen J, DiSabatino A, Banbury MK, Strasser JF, Weintraub WS, Doorey AJ. Frequency of severe valvular disease caused by mediastinal radiation among patients undergoing valve surgery in a community-based, regional academic medical center. *Clin Cardiol* 2013;36:217–221.
135. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, Cosyns B, Coucke P, Dulgheru R, Edvardsen T, Gaemperli O, Galderisi M, Griffin B, Heidenreich PA, Nieman K, Plana JC, Port SC, Scherrer-Crosbie M, Schwartz RG, Sebag IA, Voigt JU, Wann S, Yang PC, European Society of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, Society of Cardiovascular Computed Tomography. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;14:721–740.
136. Machann W, Beer M, Breunig M, Stork S, Angermann C, Seufert I, Schwab F, Kolbl O, Flentje M, Vordermark D. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 2011;79:1117–1123.