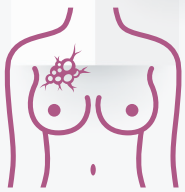

Bölüm 33
Erken Evre Meme Kanseri

Melis GÜLTEKİN [1]

Epidemiyoloji ve Risk Faktörleri

Meme kanserleri, tüm dünyada kadınlarda en sık görülen kanserlerdir ve kanser ölümlerinde birinci sırada yer alır (1). Günümüzde tarama programları ve adjuvan tedavideki gelişmeler ile mortalite oranları azalmasına karşın, halen kadınlarda en önemli morbidite ve mortalite nedenidir.

Tanıda meme kanserlerinin yaklaşık %70-80'ini erken evre (evre I-II) olgular oluşturur. Beş-yıllık sağkalım oranları evre I olgularda %98, evre II olgularda %92, evre III olgularda %75 ve evre IV olgularda ise %27'dir (2). Etiyolojisinde birçok risk faktörü tanımlanmıştır. Bu faktörler arasında en iyi bilinenler; kadın cinsiyet, ileri yaş, erken menarş, geç menopoz, nulliparite, geç gebelik yaşı, hormon replasman tedavisi, toraks radyoterapi (RT) öyküsü, dens meme yapısı, benign proliferatif meme hastalıkları, obezite, alkol, sigara, yüksek yağlı ve düşük lifli beslenme ve düşük fiziksel aktivitedir (3). Olguların yaklaşık %10'unda genetik yatkınlık ya da aile öyküsü mevcuttur. Meme kanserlerinde en sık görülen germline mutasyon BRCA1 ya da BRCA2 mutasyonudur. Bu olgularda ortalama yaşam boyu meme kanseri riski yaklaşık %70'tir (4).

Meme kanserlerinde histopatolojik alt tipe bakıldığında, olguların yaklaşık %70-80'ini invaziv duktal kanserler (İDK), %7'sini invaziv lobüler kanserler (İLK), %7'sini mikst duktal/lobüler kanserler ve %5'ini ise metaplastik, müsinöz, tübüler, medüller ve papiller gibi daha nadir görülen alt tipler oluşturur. Duktal karsinoma in situ (DKİS) ise heterojen bir spektruma sahip prekanseröz lezyonlardır.

Meme kanserleri gen ekspresyon özelliklerine göre 3 ana moleküler alt gruba ayrılır (5). Moleküler alt gruplar prognozun belirlenmesinde, tedavi yaklaşımının seçiminde ve sistemik tedavi ya da RT yanıtının öngörülmesinde rol oynar.

- **Luminal alt tip:** En sık görülen moleküler alt gruptur. Estrojen (ER) ve progesteron reseptörü (PR) pozitif meme kanserlerini içerir. ER ya da PR pozitifliği için immünohistokimyasal (İHK) olarak tümör hücrelerinin %1'den fazlasında boyanma gereklidir. Bu olgular endokrin tedavi için aday olgulardır. Ancak ER ekspresyonu %1 ile %10 arasında olan tü-

[1] Doç. Dr. Melis Gültekin, Hacettepe Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi AD., melisgultekin@hacettepe.edu.tr

daha da önemli hale getirmiştir. Günümüzde modern RT teknikleri ile toksisite oranları belirgin olarak azalmasına karşın nadiren uzun dönemde lenfödem, ciltte fibrozis, kardiyak toksisite, akciğer toksisitesi ve sekonder kanserler gelişebilir (109). Darby ve ark.'larının çalışmasında, ortalama kalp dozunda 1 Gy'lik artışın kardiyak hastalık riskinde %7,4 artışa neden olduğu gösterilmiştir (110). Bu nedenle tedavide mümkünse kalp koruyucu RT yaklaşımlarının uygulanması önerilir.

RT sonrası izlemde amaç lokal ya da bölgesel rekürrenslerin erken dönemde yakalanması ve gerekli tedavilerin metastaz gelişmeden önce uygulanmasıdır. Yine karşı meme kanserleri ya da ikinci primer kanserler açısından olgular yakın takip edilmelidir. Olgular ilk iki yıl 3-4 ayda bir, sonraki üç yıl 6 ayda bir ve beş yılı takiben ise yılda bir hikaye ve fizik muayene ile değerlendirilir. Rutin olarak yıllık mamografi çekilmesi önerilir. Rekürrens şüphesi olan olgularda ise gerekli ek tetkikler istenmelidir.

Kaynaklar

1 Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021.

2 DeSantis CE, Ma J, Gaudet MM et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019; 69 (6): 438-451.

3 Loibl S, Poortmans P, Morrow M et al. Breast cancer. Lancet 2021.

4 Kuchenbaecker KB, Hopper JL, Barnes DR et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017; 317 (23): 2402-2416.

5 Coates AS, Winer EP, Goldhirsch A et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015; 26 (8): 1533-1546.

6 Mandelson MT, Oestreicher N, Porter PL et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 2000; 92 (13): 1081-1087.

7 Hortobagyi GN, Connolly JL, D'Orsi CJ, et al (2017) Breast. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago, pp 588–628.

8 Schwartz GF, Giuliano AE, Veronesi U et al. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. Cancer 2002; 94 (10): 2542-2551.

9 Allred DC. Ductal carcinoma in situ: terminology, classification, and natural history. J Natl Cancer Inst Monogr 2010; 2010 (41): 134-138.

10 Goodwin A, Parker S, Ghersi D et al. Post-operative radiotherapy for ductal carcinoma in situ of the breast--a systematic review of the randomised trials. Breast 2009; 18 (3): 143-149.

11 Wapnir IL, Dignam JJ, Fisher B et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011; 103 (6): 478-488.

12 Cuzick J, Sestak I, Pinder SE et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011; 12 (1): 21-29.

13 Donker M, Litiere S, Werutsky G et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol 2013; 31 (32): 4054-4059.

14 Warnberg F, Garmo H, Emdin S et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. J Clin Oncol 2014; 32 (32): 3613-3618.

15 Early Breast Cancer Trialists' Collaborative G, Correa C, McGale P et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010; 2010 (41): 162-177.

16 Silverstein MJ, Lagios MD, Groshen S et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999; 340 (19): 1455-1461.

17 Rudloff U, Jacks LM, Goldberg JI et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ.

J Clin Oncol 2010; 28 (23): 3762-3769.

18 Solin LJ, Gray R, Hughes LL et al. Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study. J Clin Oncol 2015; 33 (33): 3938-3944.

19 B M. Randomized trial evaluating radiation following surgical excision for "good risk" DCIS: 12-Year report from NRG/RTOG 9804. . Int J Radiat Oncol Biol Phys 2018; 102(5): 1603.

20 Solin LJ, Gray R, Baehner FL et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013; 105 (10): 701-710.

21 Rakovitch E, Nofech-Mozes S, Hanna W et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat 2015; 152 (2): 389-398.

22 Bremer T, Whitworth PW, Patel R et al. A Biological Signature for Breast Ductal Carcinoma In Situ to Predict Radiotherapy Benefit and Assess Recurrence Risk. Clin Cancer Res 2018; 24 (23): 5895-5901.

23 Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. Cochrane Database Syst Rev 2012; 10: CD007847.

24 Margolese RG, Cecchini RS, Julian TB et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet 2016; 387 (10021): 849-856.

25 Chua BH, Link E, Kunkler I, et al. A randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast (BIG 3-07/TROG 07.01). Cancer Res 2021; 81: Abstract nr GS2-04.

26 Burstein HJ, Curigliano G, Loibl S et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol 2019; 30 (10): 1541-1557.

27 Montero A, Ciervide R, Garcia-Aranda M et al. Postmastectomy radiation therapy in early breast cancer: Utility or futility? Crit Rev Oncol Hematol 2020; 147: 102887.

28 Blichert-Toft M, Nielsen M, During M et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. Acta Oncol 2008; 47 (4): 672-681.

29 Litiere S, Werutsky G, Fentiman IS et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 2012; 13 (4): 412-419.

30 Fisher B, Jeong JH, Anderson S et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002; 347 (8): 567-575.

31 van Maaren MC, de Munck L, de Bock GH et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol 2016; 17 (8): 1158-1170.

32 Galimberti V, Cole BF, Viale G et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 2018; 19 (10): 1385-1393.

33 Giuliano AE, Ballman KV, McCall L et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318 (10): 918-926.

34 Jagsi R, Chadha M, Moni J et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. J Clin Oncol 2014; 32 (32): 3600-3606.

35 Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15 (12): 1303-1310.

36 American Society of Clinical Oncology (ASCO). The ASCO Post. SABCS 2018: AMAROS Trial: 10-Year Follow-up of Axillary Radiotherapy or Surgery in Early-Stage Breast Cancer. Available at: http://www.ascopost.com/News/59548 (Accessed on January 14, 2019). .

37 Savolt A, Peley G, Polgar C et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol 2017; 43 (4): 672-679.

38 Lyman GH, Temin S, Edge SB et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2014; 32 (13): 1365-1383.

39 Veronesi U, Marubini E, Mariani L et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 2001; 12 (7): 997-1003.

40 Ford HT, Coombes RC, Gazet JC et al. Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. Ann Oncol 2006; 17 (3): 401-408.

41 Clark RM, Whelan T, Levine M et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst 1996; 88 (22): 1659-1664.

42 Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011; 378 (9804): 1707-1716.

43 Whelan TJ, Pignol JP, Levine MN et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362 (6): 513-520.

44 Haviland JS, Owen JR, Dewar JA et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013; 14 (11): 1086-1094.

45 Shaitelman SF, Schlembach PJ, Arzu I et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. JAMA Oncol 2015; 1 (7): 931-941.

46 Owen JR, Ashton A, Bliss JM et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006; 7 (6): 467-471.

47 Brunt AM, Haviland JS, Sydenham M et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol 2020; 38 (28): 3261-3272.

48 Brunt AM, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020; 395: 1613-1626.

49 Offersen BV, Alsner J, Nielsen HM et al. Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial. J Clin Oncol 2020; 38 (31): 3615-3625.

50 Hickey BE, James ML, Lehman M et al. Fraction size in radiation therapy for breast conservation in early breast cancer. Cochrane Database Syst Rev 2016; 7: CD003860.

51 Bane AL, Whelan TJ, Pond GR et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. Ann Oncol 2014; 25 (5): 992-998.

52 Budach W, Bolke E, Matuschek C. Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials. Breast Care (Basel) 2015; 10 (4): 240-245.

53 Smith BD, Bellon JR, Blitzblau R et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018; 8 (3): 145-152.

54 Krug D, Baumann R, Combs SE et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. Strahlenther Onkol 2021; 197 (4): 269-280.

55 Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015; 16 (1): 47-56.

56 Romestaing P, Lehingue Y, Carrie C et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997; 15 (3): 963-968.

57 Kindts I, Laenen A, Depuydt T et al. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev 2017; 11: CD011987.

58 Vrieling C, van Werkhoven E, Maingon P et al. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial. JAMA

Oncol 2017; 3 (1): 42-48.

59 Valle LF, Agarwal S, Bickel KE et al. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. Breast Cancer Res Treat 2017; 162 (3): 409-417.

60 Polo A, Polgar C, Hannoun-Levi JM et al. Risk factors and state-of-the-art indications for boost irradiation in invasive breast carcinoma. Brachytherapy 2017; 16 (3): 552-564.

61 Coles CE, Griffin CL, Kirby AM, et al. Dose escalated simultaneous integrated boost radiotherapy for women treated by breast conservation surgery for early breast cancer: 3-year adverse effects in the IMPORT HIGH trial (CRUK/06/003) [abstract]. In: Proceedings of the 2018 San Antonio Breast Cancer Symposium; 2018 Dec 4-8; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2019;79(4 Suppl):Abstract nr GS4-05.

62 Horner-Rieber J, Forster T, Hommertgen A, et al. First 2-Year Results of the Multicenter, Randomized IMRTMC2 Trial (MINT): Intensity-Modulated Radiotherapy with Simultaneous Integrated Boost versus 3-D-Conformal Radiotherapy with Consecutive Boost for Breast Cancer Patients. Int J Radiat Oncol Biol Phys 2020; 108 (3): S10.

63 Van Parijs H, Vinh-Hung V, Fontaine C, et al. Quality of life in survivors of stage I-II breast cancer, 10 years outcome of a randomized clinical trial comparing post-operative hypofractionation with Tomotherapy versus conventional radiation treatment (TomoBreast) [abstract]. In: Proceedings of the 2019 San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2020;80(4 Suppl):Abstract nr P2-13-01.

64 Fisher B, Bryant J, Dignam JJ et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol 2002; 20 (20): 4141-4149.

65 Veronesi U, Orecchia R, Maisonneuve P et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013; 14 (13): 1269-1277.

66 Vaidya JS, Wenz F, Bulsara M et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014; 383 (9917): 603-613.

67 Correa C, Harris EE, Leonardi MC et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol 2017; 7 (2): 73-79.

68 Polgar C, Major T, Takacsi-Nagy Z et al. Breast-Conserving Surgery Followed by Partial or Whole Breast Irradiation: Twenty-Year Results of a Phase 3 Clinical Study. Int J Radiat Oncol Biol Phys 2021; 109 (4): 998-1006.

69 Ott OJ, Strnad V, Hildebrandt G et al. GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. Radiother Oncol 2016; 120 (1): 119-123.

70 Strnad V, Ott OJ, Hildebrandt G et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016; 387 (10015): 229-238.

71 Rodriguez N, Sanz X, Dengra J et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2013; 87 (5): 1051-1057.

72 Coles CE, Griffin CL, Kirby AM et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017; 390 (10099): 1048-1060.

73 Meattini I, Marrazzo L, Saieva C et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020; 38 (35): 4175-4183.

74 Whelan TJ, Julian JA, Berrang TS et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019; 394 (10215): 2165-2172.

75 Vicini FA, Cecchini RS, White JR et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage bre-

ast cancer: a randomised, phase 3, equivalence trial. Lancet 2019; 394 (10215): 2155-2164.

76 Wobb JL, Chen PY, Shah C et al. Nomogram for predicting the risk of locoregional recurrence in patients treated with accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys 2015; 91 (2): 312-318.

77 Recht A, Comen EA, Fine RE et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. J Clin Oncol 2016; 34 (36): 4431-4442.

78 Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol 2009; 91 (1): 23-32.

79 Poortmans PM, Collette S, Kirkove C et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med 2015; 373 (4): 317-327.

80 Whelan TJ, Olivotto IA, Parulekar WR et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med 2015; 373 (4): 307-316.

81 Poortmans PM, Weltens C, Fortpied C et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol 2020; 21 (12): 1602-1610.

82 Woodward WA, Barlow WE, Jagsi R et al. Association Between 21-Gene Assay Recurrence Score and Locoregional Recurrence Rates in Patients With Node-Positive Breast Cancer. JAMA Oncol 2020; 6 (4): 505-511.

83 Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384 (9938): 164-172.

84 Masuda N, Lee SJ, Ohtani S et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 2017; 376 (22): 2147-2159.

85 von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380 (7): 617-628.

86 Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013; 310 (14): 1455-1461.

87 Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg 2018; 105 (12): 1541-1552.

88 Montagna G, Mamtani A, Knezevic A et al. Selecting Node-Positive Patients for Axillary Downstaging with Neoadjuvant Chemotherapy. Ann Surg Oncol 2020; 27 (11): 4515-4522.

89 Burstein HJ, Curigliano G, Loibl S et al. Estimating the Benefits of Therapy for Early Stage Breast Cancer The St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019. Ann Oncol 2019.

90 Liljegren G, Holmberg L, Bergh J et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol 1999; 17 (8): 2326-2333.

91 Forrest AP, Stewart HJ, Everington D et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. Lancet 1996; 348 (9029): 708-713.

92 Killander F, Karlsson P, Anderson H et al. No breast cancer subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT. Eur J Cancer 2016; 67: 57-65.

93 Holli K, Saaristo R, Isola J et al. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. Br J Cancer 2001; 84 (2): 164-169.

94 Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013; 31 (19): 2382-2387.

95 Fyles AW, McCready DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004; 351 (10): 963-970.

96 Kunkler IH, Williams LJ, Jack WJ et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 2015; 16 (3): 266-273.

97 Blamey RW, Bates T, Chetty U et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. Eur J Cancer 2013;

49 (10): 2294-2302.

98 Fastner G, Sedlmayer F, Widder J et al. Endocrine therapy with or without whole breast irradiation in low-risk breast cancer patients after breast-conserving surgery: 10-year results of the Austrian Breast and Colorectal Cancer Study Group 8A trial. Eur J Cancer 2020; 127: 12-20.

99 Winzer KJ, Sauer R, Sauerbrei W et al. Radiation therapy after breast-conserving surgery; first results of a randomised clinical trial in patients with low risk of recurrence. Eur J Cancer 2004; 40 (7): 998-1005.

100 Kunkler IH, Williams LJ, Jack W, et al. Prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): Wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women =/> 65 years with early invasive breast cancer: 10 year results [abstract]. In: Proceedings of the 2020 San Antonio Breast Cancer Virtual Symposium; 2020 Dec 8-11; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2021;81(4 Suppl):Abstract nr GS2-03.

101 Wang F, Meszoely I, Pal T et al. Radiotherapy after breast-conserving surgery for elderly patients with early-stage breast cancer: A national registry-based study. Int J Cancer 2021; 148 (4): 857-867.

102 Liu FF, Shi W, Done SJ et al. Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy. J Clin Oncol 2015; 33 (18): 2035-2040.

103 Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012; 13 (4): e148-160.

104 Buszek SM, Lin HY, Bedrosian I et al. Lumpectomy Plus Hormone or Radiation Therapy Alone for Women Aged 70 Years or Older With Hormone Receptor-Positive Early Stage Breast Cancer in the Modern Era: An Analysis of the National Cancer Database. Int J Radiat Oncol Biol Phys 2019; 105 (4): 795-802.

105 Radiation Therapy Oncology Group (RTOG). Breast cancer atlas for radiation therapy planning: consensus definitions. Available from: http://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE%3d&tabid=236. .

106 Offersen BV, Boersma LJ, Kirkove C et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015; 114 (1): 3-10.

107 Smith BD, Bentzen SM, Correa CR et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys 2011; 81 (1): 59-68.

108 Wang SL, Fang H, Song YW et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019; 20 (3): 352-360.

109 Taylor C, Correa C, Duane FK et al. Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol 2017; 35 (15): 1641-1649.

110 Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368 (11): 987-998.