

Bölüm 20

PRİMER SİSTEMİK TEDAVİ SONRASI CERRAHİ TEDAVİ

Nurhan Haluk BELEN¹

GİRİŞ

NCCN kılavuzunda evresi 1-2a-2b-3a (T₃N₁M₀) olan invaziv meme kanserleri, erken evre (operabl) meme kanseri olarak tanımlanmıştır.⁽¹⁾ Günümüzde erken evre meme kanserinin ana tedavisi halen cerrahi tedavi olmakla birlikte, cerrahi öncesinde uygulanan terapiler ile elde edilen bazı avantajlar sayesinde, daha iyi kozmetik-onkolojik sonuçlara ulaşmak amaçlanmaktadır.⁽²⁾

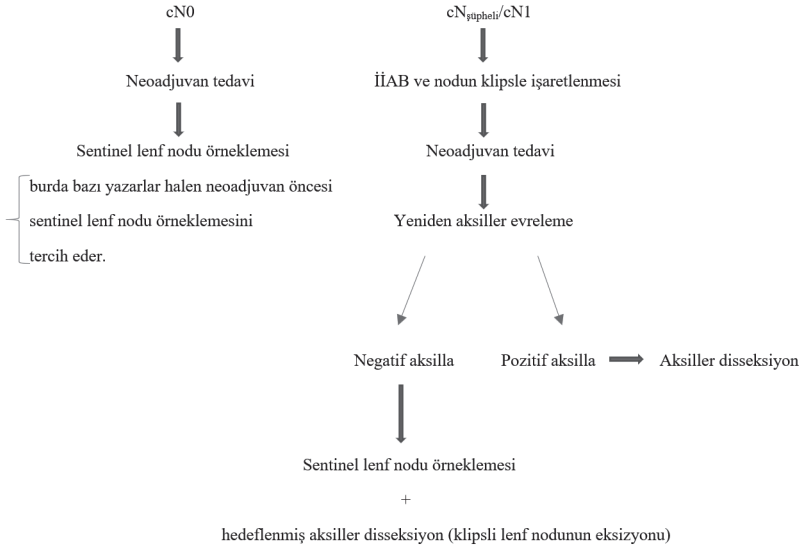
Bana ayrılan bu bölümde ana hatlarıyla erken evre meme kanserinin, neoadjuvan terapi sonrası, cerrahi tedavisiyle ilgili yaklaşımları aşağıdaki ana başlıklar altında, güncel gelişmeler ışığında aktarmaya çalışacağım.

- 1- Neoadjuvan tedavi neden tercih edilir?
- 2- Neoadjuvan tedavinin etkisi nasıl değerlendirilir?
- 3- Neoadjuvan tedavi sonrasında primer tümöre yaklaşım nasıl olmalıdır?
- 4- Neoadjuvan tedavi sonrasında aksillaya yaklaşım nasıl olmalıdır?

Erken Evre Meme Kanserinde Neoadjuvan Tedavinin Yeri

Halsted'in 1894 yılında radikal mastektomi ameliyatını tanımlamasından günümüze kadar geçen sürede meme cerrahisi, meme koruyucu teknikler, onkoplastik cerrahi teknikler, cilt-nipple-areola koruyucu mastektomi operasyonlarının tanımlanması ile giderek minimal invaziv cerrahi şekline evrilmektedir. Bu değişimi sağlayan ana etmenler, görüntüleme tekniklerindeki gelişmeler ile erken tanı konulabilmesi, girişimsel radyolojik tekniklerin kullanımının yaygınlaşması, tümör biyolojisinin daha iyi anlaşılacak hedefe yönelik terapilerin geliştirilmesi ve primer tümör ile aksilla'ya yaklaşımda neoadjuvan terapilerin etkin bir biçimde kullanımınıdır.

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Şekil 2. Neoadjuvan tdv. sonrası aksillaya yaklaşım.(İİAB:ince iğne aspirasyon biopsisi)

KAYNAKÇA

1. Breast Cancer. NCCN clinical practice guidelines in oncology versiyon 3.2019 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 6 Eylül 2019
2. Pernaut C, Lopez F, Ciruelos E. Standard Neoadjuvant Treatment in Early/Locally Advanced Breast Cancer. Breast Care 2018; 13(4):244-249.
3. Schwartz GF, Hortobagyi GN. Proceedings of the consensus conference on neoadjuvant chemotherapy in carcinoma of the breast. Cancer 2004;100:2512-32
4. Fisher B, Bryant J, Wolmark N, et al: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16: 2672– 2685.
5. Gianni L, Baselga J, Eiermann W, et al: Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009; 27: 2474–2481.
6. Scholl SM, Asselain B, Palangie T, et al. Neoadjuvant chemotherapy in operable breast cancer. Eur J Cancer 1991; 27: 1668–1671.
7. Mauriac L, MacGrogan G, Avril A, et al. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124month median follow-up. Ann Oncol 1999; 10: 47–52.
8. Mougalian SS, Soulos PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer 2015; 121: 2544–52.
9. Clough KB, Acosta-Marín V, Nos C, et al. Rates of neoadjuvant chemotherapy and oncoplastic surgery for breast cancer surgery: a French national survey. Ann Surg Oncol 2015; 11: 3504–11.
10. Vugts G, Maaskant-Braat AJ, Nieuwenhuijzen GA, Roumen RM, Luiten EJ, Voogd AC. Patterns of care in the administration of neoadjuvant chemotherapy for breast cancer. A population-based study. Breast J 2016; 22: 316–21.
11. Mieog JS, van de Velde CJ. Neoadjuvant chemotherapy for early breast cancer. Expert Opin Pharmacother. 2009;10(9):1423–34.
12. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical

- adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol* 2008; 26: 778–785
13. Fisher B, Gunduz N, Coyle J, et al. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res* 1989; 49: 1996–2001.
 14. Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res* 1979;39:3861-5
 15. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979;63:1727-33
 16. Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2017; 19(1): 27-39
 17. 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: 164–72.
 18. Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 2013; 31: 3623–30.
 19. Mieog JS, van der Hage JA, van de Velde CJ: Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007;CD005002.
 20. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr.* 2001;30(30):96–102.
 21. Fowler AM, Mankoff DA, Joe BN. Imaging Neoadjuvant Therapy Response in Breast Cancer. *Radiology.* 2017;285(2):358–375.
 22. Keune JD, Jeffe DB, Schootman M, et al. Accuracy of ultrasonography and mammography in predicting pathologic response after neoadjuvant chemotherapy for breast cancer. *Am J Surg.* 2010;199(4):477–484.
 23. Lobbes MBI, Prevos R, Smidt M, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review. *Insights Imaging.* 2013;4(2):163–175.
 24. Yuan Y, Chen XS, Liu SY, Shen KW. Accuracy of MRI in prediction of pathologic complete remission in breast cancer after preoperative therapy: a meta-analysis. *AJR Am J Roentgenol.* 2010;195(1):260–268.
 25. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst.* 2013;105(5):321–333.
 26. Yi G, Pan SM, Ren J, Yang ZX, Jiang GQ. Role of Magnetic Resonance Imaging in Detection of Pathologic Complete Remission in Breast Cancer Patients Treated With Neoadjuvant Chemotherapy: A Meta-analysis. *Clin Breast Cancer.* 2017;17(4):245–255.
 27. Marinovich ML, Sardanelli F, Ciatto S, et al. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: Systematic review of the accuracy of MRI. *Breast.* 2012;21(5):669–677.
 28. Prevos R, Smidt ML, Tjan-Heijnen VCG, et al. Pre-treatment differences and early response monitoring of neoadjuvant chemotherapy in breast cancer patients using magnetic resonance imaging: a systematic review. *Eur Radiol.* 2012;22(12):2607–2616.
 29. Woolf DK, Padhani AR, Taylor NJ, et al. Assessing response in breast cancer with dynamic contrast-enhanced magnetic resonance imaging: Are signal intensity–time curves adequate? *Breast Cancer Res Treat.* 2014;147(2):335–343.
 30. Li SP, Makris A, Beresford MJ, et al. Use of dynamic contrast-enhanced MR imaging to predict survival in patients with primary breast cancer undergoing neoadjuvant chemotherapy. *Radiology.* 2011;260(1):68–78.
 31. Partridge SC, McDonald ES. Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. *Magn Reson Imaging Clin N Am.* 2013;21(3):601–624.
 32. Wu LM, Hu JN, Gu HY, Hua J, Chen J, Xu JR. Can diffusion-weighted MR imaging and cont-

- rast-enhanced MR imaging precisely evaluate and predict pathological response to neoadjuvant chemotherapy in patients with breast cancer? *Breast Cancer Res Treat.* 2012;135(1):17–28.
33. Schelling M, Avril N, Nahrig J, et al. Positron emission tomography using [18F] Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol.* 2000;18(8):1689–1695.
 34. Lee HW, Lee HM, Choi SE, et al. The Prognostic Impact of Early Change in 18F-FDG PET SUV After Neoadjuvant Chemotherapy in Patients with Locally Advanced Breast Cancer. *J Nucl Med.* 2016;57(8):1183–1188
 35. Tan W, Yang M, Yang H, et al. Predicting the response to neoadjuvant therapy for early-stage breast cancer: tumor-, blood-, and imaging-related biomarkers. *Cancer Manag Res.* 2018; 10:4333-47
 36. Schmitz A. M. Th., Teixeira S. C., Pengel K. E. et al. Monitoring tumor response to neoadjuvant chemotherapy using MRI and 18F-FDG PET/CT in breast cancer subtypes. *PLoS One.* 2017; 12(5):e0176782
 37. Ellis MJ. Lessons in precision oncology from neoadjuvant endocrine therapy trials in ER+ breast cancer. *Breast.* 2017; 34(Suppl 1):S104–7.
 38. Sinn HP, Schmid H, Junkermann H, et al. Histologic regression of breast cancer after primary (neoadjuvant) chemotherapy [in German]. *Geburtshilfe Frauenheilkd.* 1994; 54:552-558.
 39. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol.* 2005; 23:5983-5992.
 40. Baselga J, Bradbury I, Eidtmann H, et al. First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer. *Cancer* 2010; Res 70 (suppl; abstr S3-3).
 41. Steger GG, Greil R, Jakesz R, et al. A randomized phase III study comparing epirubicin, docetaxel and capecitabine (EDC) to epirubicin and docetaxel (ED) as neoadjuvant treatment for early breast cancer: First results of ABCSG-24. *Eur J Cancer.* 2009; 7 (suppl; abstr 3)
 42. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2003; 21:4165-4174.
 43. Sataloff DM, Mason BA, Prestipino AJ, et al. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. *J Am Coll Surg.* 1995; 180:297-306.
 44. Symmans WF, Peintinger F, Hatzis C, et al: Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25:4414-4422.
 45. Ogston KN, Miller ID, Payne S, et al: A new histological grading system to assess response of breast cancers to primary chemotherapy: Prognostic significance and survival. *Breast.* 2003; 12:320-327.
 46. American Joint Committee on Cancer.(2010) *AJCC Cancer Staging Manual.* New York, Springer.
 47. Redden MH, Fuhrman GM. Neoadjuvant chemotherapy in the treatment of breast cancer. *Surg Clin North Am.* 2013;93(2):493–9.
 48. Ellis MJ, et al. Outcome prediction for estrogen receptor-positive breast cancer based on post-neoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst* 2008;100:1380e8.
 49. Ellis MJ, et al. Ki67 proliferation Index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the american College of Surgeons Oncology group Z1031 trial (alliance). *J Clin Oncol* 2017. JCO2016694406.
 50. Dowsett M, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst* 2007;99:167e70.
 51. Olson Jr JA, et al. Improved surgical outcomes for breast cancer patients receiving neoadju-

- vant aromatase inhibitor therapy: results from a multicenter phase II trial. *J Am Coll Surg* 2009;208:906-914.
52. Espinosa-Bravo M, Sao Avilés A, Esgueva A, et al: Breast conservative surgery after neoadjuvant chemotherapy in breast cancer patients: comparison of two tumor localization methods. *Eur J Surg Oncol* 2011; 37: 1038-1043.
 53. Feliciano Y, Mamtani A, Morrow M, et al: Do calcifications seen on mammography after neoadjuvant chemotherapy for breast cancer always need to be excised? *Ann Surg Oncol* 2017; 24: 1492-1498.
 54. Kim Y-S, Chang JM, Moon H-G, et al: Residual mammographic microcalcifications and enhancing lesions on MRI after neoadjuvant systemic chemotherapy for locally advanced breast cancer: correlation with histopathologic residual tumor size. *Ann Surg Oncol* 2016; 23: 1135-1142.
 55. Ramos M, Díez JC, Ramos T, et al: Intraoperative ultrasound in conservative surgery for non-palpable breast cancer after neoadjuvant chemotherapy. *Int J Surg* 2014; 12: 572-577.
 56. Rubio IT, Esgueva-Colmenarejo A, Espinosa-Bravo M, et al: Intraoperative ultrasound-guided lumpectomy versus mammographic wire localization for breast cancer patients after neoadjuvant treatment. *Ann Surg Oncol* 2016; 23: 38-43.
 57. Chan BKY, Wiseberg-Firtell JA, Jois RHS, et al: Localization techniques for guided surgical excision of nonpalpable breast lesions. *Cochrane Database Syst Rev* 2015; 20:CD009206.
 58. Loibl S, von Minckwitz G, Raab G, Blohmer JU, Dan Costa S, Gerber B, et al. Surgical procedures after neoadjuvant chemotherapy in operable breast cancer: results of the GEPARUO trial. *Ann Surg Oncol*. 2006;13(11):1434-42.
 59. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012;13(6):e270D6.
 60. Shim SJ, Park W, Huh SJ, Choi DH, Shin KH, Lee NK, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys*. 2014;88(1):65-72.
 61. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. *Plast Reconstr Surg*. 2009;124(2):395-408.
 62. Berbers J, van Baardwijk A, Houben R, et al. Reconstruction: before or after postmastectomy radiotherapy? A systematic review of the literature. *Eur J Cancer*. 2014;50(16):2752-62.
 63. Agresti R, Sandri M, Gennaro M, et al: Evaluation of local oncologic safety in nipple-areola complex-sparing mastectomy after primary chemotherapy: a propensity score-matched study. *Clin Breast Cancer* 2017; 17: 219-231.
 64. Santoro S, Loreti A, Cavaliere F, et al: Neoadjuvant chemotherapy is not a contraindication for nipple sparing mastectomy. *Breast* 2015; 24: 661-666.
 65. Chagpar AB, Killelea BK, Tsangaris TN, et al: A randomized, controlled trial of cavity shave margins in breast cancer. *N Engl J Med* 2015; 373: 503-510.
 66. Rea D, Tomlins A, Francis A: Time to stop operating on breast cancer patients with pathological complete response? *Eur J Surg Oncol* 2013; 39: 924-930.
 67. Jochelson MS, Lampen-Sachar K, Gibbons G, et al: Do MRI and mammography reliably identify candidates for breast conservation after neoadjuvant chemotherapy? *Ann Surg Oncol* 2015; 22: 1490-1495.
 68. Di Cosimo S, Campbell C, Azim HA, et al: The use of breast imaging for predicting response to neoadjuvant lapatinib, trastuzumab and their combination in HER2-positive breast cancer: results from NeoALTTO. *Eur J Cancer* 2018; 89: 42-48.
 69. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-33.

70. Posther KE, McCall LM, Blumencranz PW, et al. Sentinel node skills verification and surgeon performance: data from a multicenter clinical trial for early-stage breast cancer. *Ann Surg.* 2005;242(4):593–599.
71. Tan VKM, Goh BKP, Fook-Chong S, et al: The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer – a systematic review and meta-analysis. *J Surg Oncol* 2011; 104: 97–103.
72. Hino M, Sano M, Sato N, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy in a patient with operable breast cancer. *Surg Today* 2008;38(7):585–591.
73. Cohen LF, Breslin TM, Kuerer HM, Ross MI, Hunt KK, Sahin AA. Identification and evaluation of axillary sentinel lymph nodes in patients with breast carcinoma treated with neoadjuvant chemotherapy. *Am J Surg Pathol* 2000;24(9):1266–1272.
74. Vigario A, Sapienza MT, Sampaio AP, Piato JR, Barros N, Barros A, et al. Primary chemotherapy effect in sentinel node detection in breast cancer. *Clin Nucl Med* 2003;28(7):553–557
75. Veronesi P, Rodriguez-Fernandez J, Intra M. Controversies in the use of sentinel nodes: micro-invasion, post surgery and after preoperative systemic treatment. *Breast* 2007;16 suppl 2:S67–70.
76. Iwase H, Yamamoto Y, Kawasoe T, Ibusuki M. Advantage of sentinel lymph node biopsy before neoadjuvant chemotherapy in breast cancer treatment. *Surg Today.* 2009;39(5):374–80.
77. Mamounas EP, Brown A, Stewart Anderson S, et al. Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Breast Cancer: Results From National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2005; 12:2694-2702.
78. Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. *J Clin Oncol.* 2009;27(5):726–732.
79. Pecha V, Kolarik D, Kozevnikova R, et al. Sentinel lymph node biopsy in breast cancer patients treated with neoadjuvant chemotherapy. *Cancer.* 2011;117(20):4606–4616.
80. Classe JM, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. *Breast Cancer Res Treat.* 2018;173(2):343–352.
81. Xing Y, Foy M, Cox D.D et al. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *British J. of Surg.* 2006; 93: 539–546
82. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, 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.
83. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013;14(7): 609–618.
84. Murphy BL, L Hoskin T, Heins CDN, et al. Preoperative prediction of node-negative disease after neoadjuvant chemotherapy in patients presenting with node-negative or node-positive breast cancer. *Ann Surg Oncol.* 2017;24(9): 2518–2525.
85. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015;33(3):258–264.
86. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol.* 2016;34(10):1072–1078.