Archives of Surgical Research | Invited Review

Recent Advances In Treatment And Radiation Therapy Of Breast Cancer

Ahmad Farooq[1], Misbah Masood[1], AbuBaker Shahid[1]

IMPORTANCE This review of literature will cover the recent advances in treatment of breast cancer. It will cover the molecular subtypes of breast cancer and treatment advancements in each subtype of breast cancer precisely. The role of neoadjuvant chemotherapy and advances in surgical techniques will also be discussed. One major aspect of breast cancer treatment is management of axilla, recent studies about axillary management will also be discussed. At the end there will be brief description about modern radiotherapy treatment schedules and techniques.

KEY WORDS Breast cancer, Estrogen Receptor, Progesterone receptor, Chemotherapy, human epidermal growth factor receptor 2, Radiotherapy.

HOW TO CITE Farooq A, Masood M, Shahid AB. Recent Advances In Treatment And Radiation Therapy Of Breast Cancer. *Archives of Surgical Research*. 2021, 2 (2):15-19. https://doi.org/10.48111/2021.02.04.

Invited review

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ahmad Farooq, M.Sc.
Oncology Department; INMOL Hospital; Wahdat Road; Lahore
aahmadfarooq@gmail.com
092-342-5073085
https://doi.org/10.48111/2021.02.04

Worldwide, breast cancer is the most frequently diagnosed cancer and second leading cause of cancer deaths in women[1]. One of the major challenge in breast cancer treatment is its heterogeneous nature of disease each having different treatment options[2]. In last few decades treatment of breast cancer has evolved a lot mainly due to advances in surgical techniques and development of new systemic treatment options[3]. In addition to this there are also many improvements in the field of radiation oncology [4].
Previously breast cancer was considered as surgical disease but now due to recent advances in treatment options it is no longer solely a surgical disease. A better knowledge of tumor biology has led to the development of new therapeutic options resulting in better treatment outcomes. Less morbid surgery in carefully selected patients with modern conformal radiotherapy have resulted in the decreased treatment toxicity and better quality of life among breast cancer survivors.

MOLECULAR SUBTYPES OF BREAST CANCER

Breast cancer is now no longer considered as a single disease and can be classified into various molecular subtypesby evaluating few biomarkers. These biomarkers include the presence of hormone receptors mainly Estrogen receptors [ER] and Progesterone receptors [PR] and over expression of human epidermal growth factor rector 2 neu (Her2neu) receptors. This sub categorization helps to direct adjuvant therapy and also choose the patients who may get benefit maximum from neoadjuvant treatment.

Subtype	Type of treatment	Notes
Luminal A-like ER-PR +ve Her2 -ve Low proliferation rate [Ki-67]	Endocrine treatment alone in most of cases if tumor size is less than 5cm and less than 4 nodes positive.	Chemotherapy can be considered in selected cases (high 21-gene RS, high risk on 70-gene assay or high grade disease)
Luminal B-like (HER2 negative) ER-PR +ve Higher Ki-67than Luminal A	Endocrine treatment in all cases, Chemotherapy for most.	
Luminal B-like (HER2 positive) ER-PR +ve Higher Ki-67than Luminal A	Chemotherapy + anti-HER2 therapy +endocrine therapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
HER-2 positive (non-luminal) ER-PR -ve	Chemotherapy + anti-HER2 therapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
Triple negative (ductal) ER-PR-HER2 -ve	Chemotherapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
Special Histological Types		
Endocrine-responsive	Endocrine therapy	Cribriform, tubular and mucinous
Endocrine-non-responsive	Chemotherapy	Apocrine,medullary ,metaplastic, adenoid cystic

Adapted and modified from Goldhirsch et al. (2013b)

ENDOCRINE TREATMENT FOR HORMONE RECEPTOR–POSITIVE BREAST CANCER

Tomoxifen is the historical standard treatment for breast cancer .The EBCTCG Mata analysis showed data of 15 years from multiple trails including more than 80,000 patients[5]. 5 years of tomoxifen administration resulted 41% reduction in disease recurrence (Hazard Ratio (HR) 0.59) and 34% reduction in disease recurrence (HR0.66).ATLAS trail compared 10 year versus 5 year of adjuvant tomoxifen and showed better overall survival (OS) and disease free survival (DFS) with longer treatment. Based on the result of this trail 10 year tomoxifen can be considered as standard in premenopausal patients[6].

In post-menopausal patients aromatase inhibitors (AI) improved the results as compared to tomoxifen.AI treatment has been investigated as first line therapy instead of tomoxifen[7] or subsequent treatment after 2-3 years completion of tomoxifen therapy[8] and as extended treatment after 5 years completion of tomoxifen[9]. In every scenario, the use of an AI has resulted in moderate improvements in DFS by reducing incidence of distal and local failure rates.

Some of the hormone-positive breast cancer patients have progressive disease during the hormonal treatment. Combining endocrine therapy with targeted treatments inhibiting other important cell regulatory pathways has proven a useful strategy for enhancing the efficacy of endocrine treatments. Cyclin dependent kinase 4/6 (CDK4/6) inhibitors have been studied in combination either with AIs as upfront treatment for hormonal positive metastatic breast cancer or with fulvestrant as second-line treatments. In both settings, addition of CDK4/6 inhibition dramatically improved the progression-free survival compared to outcomes for endocrine therapy alone [10, 11].

GENOMIC TESTING OF BREAST CANCER TO AVOID CHEMOTHERAPY

Recently, multi-gene signatures have been used to distinguish between patients with high, intermediate or low-risk of disease recurrence. The 21-gene assay (Oncotype DX®) has been shown to estimate the likelihood of recurrence in women with early-stage hormone positive breast cancer (tumor size less than 5 cm and maximum 3 nodes positive) were treated with hormones alone without chemotherapy [12]. The 70-gene assay (MammaPrint®) is used to estimate the risk of recurrence of early breast cancer (tumor size less than 5 cm and maximum 3 nodes positive). Results from different studies using these assays have shown that subsequent subset of patients will not receive chemotherapy that otherwise may have been planned for chemotherapy on the basis of pathological findings [13].

TARGETED TREATMENT FOR HER2-NEU EXPRESSING BREAST CANCER

HER2 expression was historically considered as poor prognostic factor associated with poor outcome of this subgroup. In 2005, results from various randomized trials that examined addition of trastuzumab (Herceptin) to the chemotherapy as adjuvant treatment for HER2-expressing breast cancer it showed marked improvements in DFS (overall reduction of 50%) and OS[14]. The standard duration of trastuzumab treatment is 1 year. Although short course (9 weeks) treatment of trastuzumab given with adjuvant chemotherapy is better than omitting trastuzumab in non affording patients[15].

Women with higher risk, typically stage II or III, HER2-positive breast cancers may get benefit with additional anti-HER2 therapy. The benefit seen with dual HER2-directed therapy resulted in evaluation of pertuzumab in the neoadjuvant setting. In NeoSphere trial 417 patients were randomly assigned to receive four cycles of docetaxel combined with either trastuzumab, pertuzumab, or both agents versus combination pertuzumab and trastuzumab without docetaxel (a non chemotherapy arm). The combination pertuzumab and trastuzumab with docetaxel achieved the highest pathological complete response (pCR)rate of 39.3%, compared with the other groups[16]. This trial, as well as the TRYPHAENA study[17] combined with the survival advantage seen with pertuzumab in the metastatic setting, led the FDA to give accelerated approval of this combination for neoadjuvant treatment of HER2-expressive breast cancer[18].

TRIPLE NEGATIVE BREAST CANCER, CURRENT TREATMENT OPTIONS

Triple negative breast cancer (TNBC) is more aggressive and have less treatment options as compared to Hormonal receptor positive (HR+) and HER2+ breast cancer. For TNBC main stay of treatment is chemotherapy. TNBC has higher response rate to chemotherapy as compared to hormonal positive disease. However, their recurrence and distal failure rates are more than other subtypes[19]. The overall median survival for patients with metastatic TNBC is about 12 months with standard available chemotherapy agents. The unavailability of targeted therapies like in other subtypes is associated with this poor outcome. The widely used systemic treatment option is only chemotherapy[20] with or without bevacizumab. The immunotherapy may be the future treatment option for triple negative breast cancer. Recently Tecentriq (atezolizumab) in combination with the chemotherapy medicine Abraxane (albumin-bound paclitaxel) has been approved for the treat of unresectable locally advanced or metastatic triple-negative and PD-L1-positive breast cancer[21].

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy is day by day becoming more popular in the patients with locally advanced breast cancer[22]. Such treatment approach has resulted in more breast-conserving therapy as compared to post-operative chemotherapy[23] and may reduce the need for more aggressive axillary nodal surgeries[24]. Benefit of neoadjuvant chemotherapy includes in vivo response assessment. Neoadjuvant chemotherapy is now preferably used in HER2-positive, or triple-negative cancers due to their higher response rates and pathological complete responses. Despite of these benefits, however neoadjuvant chemotherapy has not shown survival benefit over adjuvant chemotherapy in trials[25].

LESS-EXTENSIVE SURGERY FOR SELECTED PATIENTS

With the wide-spread use of breast screening and awareness programs led to detection of early breast cancer in these cases complete mastectomy or complete axillary dissection can be avoided, hence long-term treatment morbidity is minimized[26].The follow-up results of various clinical trials have shown that breast-conserving surgery combined with radiotherapy has an outcome similar to total mastectomy in terms of survival. In modern era, nearly 40% of all breast cancer patients can receive breast-conserving treatment, which resulted in better psychological outcome in this group of patients as compared to patient undergoing complete mastectomy. The advent of sentinel node biopsy has also led its use in clinically node negative tumors and carefully selected node positive cases after neoajuvant treatment, thereby reducing incidence of lymphedema which is one of the major treatment complications in breast cancer survivors[27].

Women who have strong wish for breast conserving therapy (BCT) but are not ideal candidates for the BCT due to tumor to breast size ratio, or who have locally advanced breast cancer (LABC), can be considered for neoadjuvant therapy. The class of patients most likely converted is having unicentric, higher grade, HER2-positive, or triple-negative cancers because these cancers are excellent responders to neoadjuvant treatment. Ultrasound guided percutaneous clipping should be done before starting of treatment to localize tumor bed accurately in cases where there is adequate of clinical response.

For patients with early breast cancer who are candidates of total mastectomy due to multifocal nature of disease, total skin-sparing mastectomy with conservation of the nipple areolar complex has shown similar results in local control. This approach will result in immediate breast reconstruction and will maximize the cosmetic results. Now days this approach is gaining popularity in patients who fulfill the selection criteria for this approach[28].

MANAGEMENT OF AXILLA

Surgical management of axilla is part of the local treatment of breast cancer. Extent of axillary surgery has decreased over time due to understanding that removal of axillary nodes has more of a prognostic than a therapeutic value. Following are some basic principles guiding axillary nodal management in patients not undergoing neoadjuvant therapy.

1. Most women with clinically negative axilla are candidates of Sentinel lymph nodal biopsy (SLNB). If sentinel node is negative no more dissection is required.
2. A substantial proportion with limited axillary involvement no longer requires complete Axillary lymph nodal dissection (ALND, level l and level ll).The American College of Surgeons Oncology Group (ACOSOG) Z0011 trail showed patients with clinical T1 or T2 lesions and clinically node negative axilla, and one or two positive sentinel nodes treated with lumpectomy followed Whole breast radiation with tangents fields and adjuvant systemic treatment, SLNB was non inferior to ALND [29]. ALND should be done in patients whose tumors do not fit Z11 criteria, who will not receive radiation or sentinel lymph identification is not possible.
3. In AMAROS (After Mapping of Axilla Radiotherapy or Surgery) patients with T1-T2 tumors and clinically negative nodes but sentinel positives nodes were randomly assigned to axillary surgery or radiation. Most patients have one positive sentinel node .Both patients treated with lumpectomy and mastectomies were enrolled. In this study local control was excellent in both arm but lymphedema incidence was lower in radiation arm[30]. Therefore omission of axillary dissection can be considered if axillary radiation is in plan.
4. Patients who are candidates for neoadjuvant chemotherapy patients with clinically negative axilla can undergo sentinel nodal surgery after completion of chemotherapy[31]. If sentinel nodes are negative no more axillary surgery is required.
5. Patients will palpable nodes will require axillary nodal dissection unless they receive neoadjuvant systemic treatment[32]. About 40 % of clinically palpable nodes initially will downstage with neoadjuvant chemotherapy. The likelihood of down staging of axilla with neoadjuvant chemotherapy is higher in patients with TNBC or Her2neu positive breast cancer for which this approach is particularly favored. But this approach should be individualized after discussing in multimodality meetings.

HYPO FRACTIONATED POST-MASTECTOMY RADIOTHERAPY

Multiple randomized studies compared the normal fractionated radiotherapy protocols (25Gy in 2.0 Gy single doses) with hypo fractionated radiotherapy protocols (single doses more than 2.0Gy in 5–16 fractions). Overall, hypo fractionated radiotherapy protocols did not differ with normal fractionated radiotherapy in term of local control, toxicity profile and cosmetic results[33, 34].

ACCELERATED PARTIAL BREAST IRRADIATION

The average time of adjuvant radiation is between 4-6 weeks and for some patients from distant areas this approach is not feasible. So for this purpose, a variety of accelerated options of treatment have been developed and have been shown safe and effective in various trails [35].These approaches include interstitial implants placed around the tumor bed, a single balloon catheter that can be afterloaded with a central radiation source (MammoSite) that is placed into the excision cavity, external beam conformal partial breast irradiation, and intraoperative single-dose irradiation.

BOOST THERAPY AFTER WHOLE BREAST RADIATION

Several randomized trials have proved that an application of a localized dose escalation (boost) Of 10-16 Gy to the tumor bed after whole breast radiation improves local control but with poor cosmetic outcomes [36].Generally boost is given after breast conservation surgery and T4 or margin positive disease after Mastectomy. Boost can be omitted after breast conservation surgery for very small tumor sizes like <2cm excised with good margins >1cm particularly in old age hormonal positive cases.

HEART SPARING BREAST RADIOTHERAPY

With the advent of modern radiotherapy techniques, the knowledge for cardiac toxicity of breast cancer radiotherapy has increased significantly especially in left sided tumors .A recent guideline by the German radiation oncology society[37] recommends a dose constraint of less than 2.5Gy for the mean heart dose for chest wall radiotherapy .Modern radiotherapy techniques like intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques can be used to reduce mean heart radiotherapy dose in order to minimize cardiac side effects.

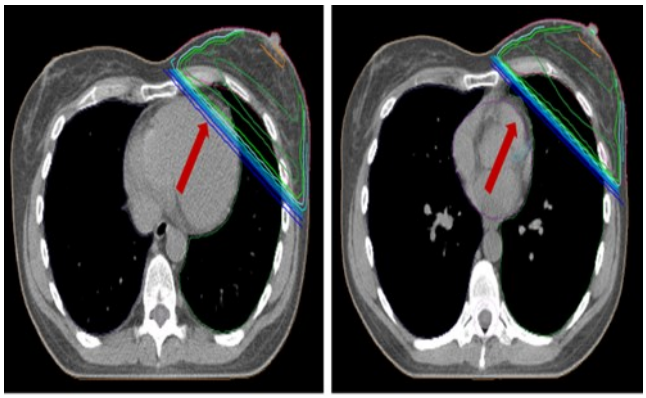

Figure: Sparing of heart volume in deep inspiration breath holding Technique (right) as compared to normal breathing (left) [38].

CONCLUSION

Over all like other cancers treatment of breast cancer needs a multidisciplinary approach. Participation of breast surgeons, medical and radiation oncologists in breast specific tumor boards can lead to much improvement in patient management. Fast growing research and with the better understanding of disease biology has given multiple treatment options even for stage 4 disease and improved overall survival in all stages of breast cancer.

ARTICLE INFORMATION Accepted for Publication: May 8,, 2021 Published Online: June 25, 2021.
https://doi.org/10.48111/2021.02.04

Author Affiliations. 1. Oncology Department; INMOL Hospital; Wahdat Road; Lahore

Financial Support and Sponsorship: Nil.
Conflicts of Interest: There are no conflicts of interest

REFERENCES

1. Polyak K. Heterogeneity in breast cancer. *J Clin Invest*. 2011;121(10):3786-3788. doi:10.3322/caac.21387.
2. Siegal R, Miller KD, Jemal A. Cancer statistics, 2012. *Ca Cancer J Clin*. 2014;64(1):9-29. doi:10.1172/JCI60534.
3. Wang SE, Sun YD, Zhao SJ, Wei F, Yang G. Breast conserving surgery (BCS) with adjuvant radiation therapy showed improved prognosis compared with mastectomy for early staged triple negative breast cancer patients Running title: BCS had better prognosis than mastectomy for early TNBC patients. *Math Biosci Eng MBE*. 2019;17(1):92-104. doi: 10.3934/mbe.2020005.
4. De Rose F, Fogliata A, Franceschini D, et al. Postmastectomy radiation therapy using VMAT technique for breast cancer patients with expander reconstruction. *Med Oncol*. 2019;36(6):1-8. doi: 10.1007/s12032-019-1275-z.
5. Group EBCTC. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-1717. doi: 10.1016/S0140-6736(05)66544-0.
6. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805-816 doi: 10.1016/S0140-6736(12)61963-1.
7. Sanz A, Del Valle ML. Extending Adjuvant Aromatase-Inhibitor Therapy to 10 Years. *N Engl J Med*. 2016;375(16):1590. doi:

10.1016/S0140-6736(04)17666-6.
8. Howell A. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365:60-62. doi: 10.1056/NEJMoa1604700.
9. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA. 17. *J Natl Cancer Inst*. 2005;97(17):1262-1271. doi: 10.1093/jnci/dji250.
10. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375(18):1738-1748. doi: 10.1056/NEJMoa1609709.
11. Sledge Jr GW, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. doi: 10.1200/JCO.2017.73.7585.
12. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017;165(3):573-583. doi: 10.1007/s10549-017-4358-6.
13. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(10):1134. doi: 10.1200/JCO.2015.65.2289.
14. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809-820. doi: 10.1056/NEJMoa0910383.
15. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283. doi: 10.1056/NEJMoa053028.
16. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9.
17. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284. doi: 10.1093/annonc/mdt182.
18. Swain SM, Baselga J, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734. doi: 10.1056/NEJMoa1413513.
19. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol*. 2008;26(8):1275-1281. doi:10.1200/JCO.2007.14.4147.
20. Berrada N, Delaloge S, Andre F. Treatment of triple-negative metastatic breast cancer: toward individualized targeted treatments or chemosensitization? *Ann Oncol*. 2010;21:vii30-vii35. doi:10.1093/annonc/mdq279.
21. Emens LA, Adams S, Barrios CH, et al. LBA16 IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab+ nab-paclitaxel vs placebo+ nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. *Ann Oncol*. 2020;31:S1148. doi: 10.1016/j.annonc.2020.08.2244.
22. 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(15):2544-2552. doi: 10.1002/cncr.29348.
23. Killelea BK, Yang VQ, Mougalian S, et al. Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. *J Am Coll Surg*. 2015;220(6):1063-1069. doi: 10.1016/j.jamcollsurg.2015.02.011.
24. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. *JAMA Oncol*. 2017;3(4):549-555. doi: 10.1001/jamaoncol.2016.4163.
25. 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*. 2018;19(1):27-39. doi: 10.1016/S1470-2045(17)30777-5.
26. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-1232. doi: 10.1056/NEJMoa020989.
27. 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):927-933. doi: 10.1016/S1470-2045(10)70207-2.
28. Giuliano AE, Ballman K V, 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. doi: 10.1097/SAP.0b013e31827e5333.
29. Piper M, Peled AW, Foster RD, Moore DH, Esserman LJ. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. *Ann Plast Surg*. 2013;70(4):435-437. doi: 10.1001/jama.2017.11470.
30. Mast ME, van Kempen-Harteveld L, Heijenbrok MW, et al. Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? *Radiother Oncol*. 2013;108(2):248-253. doi: 10.1016/S1470-2045(14)70460-7.
31. 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. doi: 10.1001/jama.2013.278932.
32. Morrow M, Dang CT. Sentinel node biopsy after neoadjuvant chemotherapy: a new standard for patients with axillary metastases? *JAMA*. 2013;310(14):1449-1450 doi: 10.1001/jama.2013.7844.
33. James ML, Lehman M, Hider PN, Jeffery M, Hickey BE, Francis DP. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database Syst Rev*. 2010;(11). doi: 10.1002/14651858.
34. Chitapanarux I, Klunklin P, Pinitpatcharalert A, et al. Conventional versus hypofractionated postmastectomy radiotherapy: a report on long-term outcomes and late toxicity. *Radiat Oncol*. 2019;14(1):1-10. doi: 10.1186/s13014-019-1378-x.
35. 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. doi: 10.1016/j.prro.2016.09.007.
36. 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. doi: 10.1016/S1470-2045(14)71156-8.
37. Piroth MD, Baumann R, Budach W, et al. Heart toxicity from breast cancer radiotherapy. *Strahlentherapie und Onkol*. 2019;195(1):1-12. doi: 10.1007/s00066-018-1378-z.
1. 38. Jan Haussmann, Stefanie Corradini, Carolin Nestle-Kraemling,et al. Recent advances in radiotherapy of breast cancer.*Radiation Oncology* 2020.15:71. doi10.1186/s13014-020-01501-x.