Journal of Breast Cancer Research

Yoneyama et al., J Breast Cancer Res. 2021;1(2):34-39.

Research Article

Analysis of treatment and outcomes in patients with locally advanced breast cancer

Kimiyasu Yoneyama*, Motohito Nakagawa, Asuka Hara

Department of Breast Surgery, Hiratsuka City Hospital, Hiratsuka, Japan

*Author for correspondence: Email: key13213@yahoo.co.jp

Received date: September 19, 2021
Accepted date: December 10, 2021

Citation: Yoneyama K, Nakagawa M, Hara A. Analysis of treatment and outcomes in patients with locally advanced breast cancer. J Breast Cancer Res. 2021;1(2):34-39.

Abstract

Background: Locally advanced (stage III) breast cancer has high local recurrence and distant metastasis rates and its prognosis is poor. Multimodal local treatment consisting of surgery/radiotherapy after chemotherapy is generally recommended. However, there are few reports on the treatment and prognosis of locally advanced breast cancer. In this study, we examined the treatment and prognosis of locally advanced breast cancer at our institution.

Patients and methods: We retrospectively examined the clinicopathological factors and prognosis of 76 patients with locally advanced breast cancer treated at our hospital from January 2007 to September 2020.

Results: The median patient age was 62.5 years (range, 31–101). Fifteen women were premenopausal and 61 were postmenopausal. The median tumor diameter was 5.3 cm (range, 1.5–11.0). Fifty-five cases were hormone receptor-positive, 21 were hormone receptor-negative, 11 were HER2-positive, and 64 were HER2-negative. Mastectomy was performed in 62 cases, partial resection in 14, sentinel lymph node biopsy in 15, and axillary dissection in 60. Thirty-one patients received postoperative radiotherapy. Chemotherapy was administered preoperatively in 47 cases and postoperatively in 34, and 48 received postoperative endocrine therapy. The chemotherapy consisted of anthracycline alone in 7 cases, a taxane alone in 4 cases, and a combination of anthracycline and a taxane in 44 cases. The median observation period was 43 months (range, 1–175), during which there were 25 recurrences and 18 deaths. Median recurrence-free survival was 38 months; the 5-year recurrence-free survival rate was 65.6% and the 5-year overall survival rate was 77.9%. Patients with recurrence were significantly more likely to be premenopausal and to have 4 or more lymph node metastases than those who remained recurrence-free. Multivariate analysis identified the number of lymph node metastases as a significant factor affecting recurrence-free survival.

Conclusion: Premenopausal status and presence of 4 or more lymph node metastases were prognostic factors affecting recurrence-free survival. Multimodal treatment should be particularly aggressive in patients with 4 or more lymph node metastases.

Keywords: Locally advanced breast cancer, Multimodality therapy

Background

Breast cancer is the most common cancer in women worldwide, including in the Japanese population. In Japan, 90,000 (1 in 9) persons are affected annually, and about 14,000 die from breast cancer each year. How to treat these cancers and improve the results of treatment is a very important issue. For early-stage breast cancer that is operable, it is common to perform surgery first and then combine chemotherapy and radiotherapy as needed based on the results of histopathological examination. With more widespread breast cancer screening in Japan, the number of breast cancers detected at an early stage is increasing. The above-mentioned methods are often used to treat breast cancer detected by screening. However, for a variety of reasons, it is also true that treatment is delayed in quite a few locally advanced (stage III) breast cancers. Locally advanced breast cancer has high rates of distant metastasis and local recurrence, and its prognosis is poor. So-called multimodal treatment is generally recommended, whereby combined local treatment (surgery, radiotherapy) is administered after pre-operative systemic chemotherapy. Locally advanced breast cancer is often difficult to treat and there are very few reports on its treatment and prognosis. In this study, we investigated the treatment and prognosis of locally advanced breast cancer at our institution.

Patients and Methods

Patients

Seventy-six women with locally advanced (stage III) breast cancer and no distant metastasis who underwent definitive surgery at Hiratsuka Municipal Hospital between January 2007 and September 2020 were enrolled. Women who had not undergone resection surgery, those who had bilateral breast cancer, and those with cancers in multiple organs were excluded. Information on clinical and pathological factors, treatment details, and the prognosis was retrospectively collected from the medical records. The study was approved by the institutional review board of Hiratsuka City Hospital. All patients provided written informed consent.

Statistical analysis

Groups were compared using Fisher's exact test and the t-test. Multivariate analysis was performed using logistic regression. Disease-free survival was measured from the time of the first surgery until the date of death or final follow-up. Survival curves were constructed using the Kaplan–Meier method. The statistical significance of between-group differences was assessed using the log-rank test. All statistical analyses were performed using JMP Pro version 10 for Mac OS (SAS Institute Japan Ltd., Tokyo, Japan). P-values <0.05 were considered statistically significant.

Results

The patient demographics and clinical characteristics are shown in **Table 1**. The median patient age was 62.5 years (range, 31-101). Fifteen women (20%) were premenopausal and 61 (80%) were postmenopausal. One patient (1%) had T1 disease, 9 (12%) had T2, 18 (24%) had T3, and 48 (63%) had T4. The N stage was N0 in 9 patients (12%), N1 in 47 (62%), N2 in 11 (14%), and N3 in 9 (12%). The clinical stage was IIIA in 25 cases (33%), IIIB in 41 (54%), and IIIC in 10 (13%). The median tumor diameter was 5.3 cm (range, 1.5-11.0).

Table 1: Patient demographics and clinicopathological characteristics.

	n=76	n (%)
Age, y		
Median	62.5	
Range	31-101	
Sex	Female	76 (100%)
	Male	0 (0%)
Menopausal status	Premenopausal	15 (20%)
	Postmenopausal	61 (80%)
T stage	1	1 (1%)
	2	9 (12%)
	3	18 (24%)
	4	48 (63%)
N stage	N0	9 (12%)
	N1	47 (62%)
	N2	11 (14%)
	N3	9 (12%)
Clinical stage	IIIA	25 (33%)
	IIIB	41 (54%)
	IIIC	10 (13%)
Tumor infiltration diameter, mm		
Median	53	
Range	15-110	
Lymph node metastases, n		
Median	3	
Range	0-30	
Estrogen receptor status	Negative	22 (29%)
	Positive	54 (71%)
Progesterone receptor status	Negative	37 (49%)
	Positive	39 (51%)
Hormone receptor status	Negative	21 (28%)
	Positive	55 (72%)
HER2 status	Negative	64 (84%)
	Positive	11 (16%)
Lymphovascular invasion	Negative	19 (25%)
	Positive	38 (50%)
	unknown	19 (25%)
Nuclear grade	1	11 (14%)
	2	19 (25%)
	3	34 (45%)
	Unknown	12 (16%)
Ki-67	High (>20%)	28 (37%)
	Low (≤20%)	28 (37%)
	Unknown	20 (26%)
Tumor subtype	Luminal	49 (64%)
	Luminal HER2	5 (7%)
	HER2	6 (8%)
	Triple-negative	16 (21%)

The median number of lymph node metastases was 3 (range, 0–30). Fifty-five patients (72%) were hormone receptor-positive, 21 (28%) were hormone receptor-negative, 11 (16%) were HER2-positive, and 64 (84%) were HER2-negative. The subtype was luminal in 49 cases (64%), luminal HER2 in 5 (7%), HER2 in 6 (8%), and triple-negative in 16 (21%).

The treatment details are shown in **Tables 2** and **3**. The surgical treatment was mastectomy in 62 cases (82%) and partial mastectomy in 14 (18%). Sentinel lymph node biopsy was performed in 15 cases (20%) and axillary lymph node dissection in 60 (79%). Chemotherapy was administered preoperatively in 47 patients (61%) and postoperatively in 34 (45%). Forty-eight (87%) of 55 hormone receptor-positive patients received postoperative endocrine therapy and 9 (82%) of 11 HER2-positive patients received anti-HER2 agents. Eighteen patients (24%) did not receive chemotherapy and 3 (4%) did not receive any medication. Chemotherapy consisted of anthracycline and a taxane in 44 patients (76%), anthracycline

alone in 7 patients (12%), and a taxane alone in 4 patients (7%). Postoperative radiotherapy was performed in 9 (64%) of 14 patients after partial mastectomy and in 22 (35%) of 62 patients after mastectomy. Thirty-one patients (41%) received multimodal treatment with chemotherapy, surgery, and radiotherapy. The median observation period was 43 months (range, 1-175).

Table 2: Treatment content.

	n=76	n (%)
Breast surgery	BP	14 (18%)
	BT	62 (82%)
Axillary surgery	Axillary lymph node dissection	60 (79%)
	None	1 (1%)
	Sentinel node biopsy	15 (20%)
Preoperative chemotherapy	Yes	47 (61%)
	No	29 (39%)
Postoperative chemotherapy	Yes	34 (45%)
	No	42 (55%)
Postoperative endocrine therapy	Yes	48 (63%)
	No	28 (37%)
Anti-HER2 therapy		9
Postoperative radiotherapy	Yes	31 (41%)
	No	45 (59%)
Chemotherapy + surgery + radiotherapy		31 (41%)
Chemotherapy + surgery		42 (55%)
Surgery only		3 (4%)
BP: partial mastectomy; BT: total mastectomy		

Table 3: Treatment content continued.

Preoperative chemotherapy, n=47 (61%)	
Anthracycline only	15 (32%)
Taxane only	2 (4%)
Anthracycline + taxane	21 (45%)
Anthracycline + taxane + anti-HER2	7 (15%)
Taxane + anti-HER2	2(4%)
Postoperative chemotherapy n=34 (45%)	
Anthracycline only	5 (14%)
Taxane only	3 (9%)
Anthracycline + taxane	15 (44%)
Anti-HER2 drug	8 (24%)
Oral anti-cancer agent	3 (9%)
Postoperative endocrine therapy, n=48 (87%)	
Aromatase inhibitor	30 (63%)
Tamoxifen	13 (27%)
Tamoxifen + luteinizing hormone-releasing hormone agonist	5 (10%)
Anti-HER2 therapy: HER2-positive, n=11	9 (82%)
Postoperative radiotherapy, n=31 (41%)	
Postmastectomy radiation therapy (BT: 62 cases)	22 (35%)
Breast + lymph nodes (BP: 14 cases)	9 (64%)

There were 25 recurrences. The initial recurrence was local in 9 cases, distant metastasis in 18, and both local recurrence and distant metastasis in 3. There were 18 deaths, 16 of which occurred as a result of the primary illness and 2 from multiple causes. Patients with recurrence were significantly more likely to be premenopausal and to have 4 or more lymph node metastases (**Table 4**).

Table 4: Comparison of clinicopathological variables according to recurrence status.

Variable		Recurrence-free	Recurrence	P-value
		n=51 (%)	n=25 (%)	
Menopausal status	Postmenopausal	46	15	<0.001
	Premenopausal	5	10	
T stage	1-3	18	10	0.689
	4	33	15	
Lymph node metastases, n	0-3	37	4	<0.001
	≥4	12	21	
Hormone receptor status	Positive	36	19	0.823
	Negative	15	6	
Postoperative radiotherapy	Yes	24	7	0.180
	No	27	18	
Anthracycline + taxane	Yes	36	15	0.355
	No	15	10	

Table 5: Variables correlated with recurrence-free survival.

		Univariate			Multivariate		
		Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Menopausal status	Postmenopausal	2.971	1.262-6.676	0.0139	1.284	0.536-2.996	0.565
	Premenopausal						
T stage	1-3	0.781	0.352-1.808	0.553			
	4						
Lymph node metastases, n	0-3	0.122	0.035-0.327	<0.0001	0.134	0.037-0.383	<0.0001
	≥4						
Hormone receptor status	Positive	0.719	0.296-2.001	0.501			
	Negative						
Postoperative radiotherapy	Yes	1.004	0.408-2.699	0.992			
	No						
Anthracycline + taxane	Yes	1.820	0.775-4.146	0.163			
	No						

Median recurrence-free survival was 38 months and the 5-year recurrence-free survival rate was 65.6%. In univariate analysis, menopausal status and number of lymph node metastases significantly affected the likelihood of recurrence-free survival; however, in multivariate analysis, only number of lymph node metastases remained a significant factor (**Table 5**). The 5-year overall survival rate for all cases was 77.9%.

Discussion

Patients with locally advanced (stage III) breast cancer are at high risk of systemic disease but should be treated with curative intent. Locally advanced breast cancer includes large tumors, especially those with skin infiltration and/or extensive metastasis to regional lymph nodes. The initial treatment is the same in all cases. In general, multimodal treatment consists of adding local treatment after systemic drug therapy. Preoperative chemotherapy is considered standard regardless of tumor subtype [1]. Preoperative endocrine therapy is considered acceptable for hormone receptor-positive locally advanced breast cancer in elderly patients with organ damage, those in whom adverse events associated with chemotherapy need to be avoided, and those in poor general condition. Given that there is no difference in the prognosis according to whether chemotherapy is administered preoperatively or postoperatively, upfront surgery is acceptable in patients with operable locally advanced breast cancer who are not concerned about breast preservation [2].

Preoperative chemotherapy

The standard preoperative chemotherapy regimen for HER2-negative disease and operable early-stage breast cancer is a sequential combination of an anthracycline-containing regimen and a taxane [3]. In HER2-positive cases, first an anthracycline-containing regimen and then a taxane plus a simultaneous combination regimen containing an anti-HER2 agent are used. It is desirable to administer both unless there is a specific reason, such as advanced age or a significant comorbidity. Dose-dense chemotherapy may also be considered. In the broad sense, dose-dense chemotherapy entails smaller drug doses and a shorter dosing interval without concomitant use of a granulocyte colony-stimulating factor (G-CSF) preparation. In the narrow sense, it is a method in which the type and dose of drug are the same and the dosing interval is shortened by using a G-CSF preparation in combination. Dose-dense chemotherapy with a G-CSF preparation is recommended in patients with adequate bone marrow function [4-6]. In addition to these standard regimens, attempts have been made to develop more potent treatment regimens for locally advanced breast cancer with a poor prognosis.

Locoregional therapy

The local treatment options are surgery alone, radiotherapy alone, and surgery plus postoperative radiotherapy after preoperative chemotherapy; however, surgery plus postoperative radiotherapy is recommended. Studies of locally advanced breast cancer have found no significant difference in the local recurrence rate or survival time between patients who undergo surgery alone or radiotherapy alone after chemotherapy [7,8]. However, when endocrine therapy or chemotherapy was administered after surgery, the local recurrence rate was significantly reduced by addition of radiotherapy [8]. A retrospective analysis of clinical trials that examined the outcomes of preoperative chemotherapy for locally advanced breast cancer found that the local recurrence rate and survival time were improved in patients who received postoperative radiotherapy [9]. In other retrospective studies, patients who underwent surgery and radiotherapy after preoperative systemic chemotherapy had a better prognosis than those who received only one treatment modality alone.

Mastectomy is a common surgical option, although partial mastectomy may be possible in some cases. In the present study, the partial mastectomy rate was 18%, which is low compared with the rate of 70% for all breast cancer cases at our hospital. Mastectomy was often selected because of large tumors and skin infiltration.

Axillary lymph node dissection is generally performed. In the case of N0 disease, a sentinel lymph node biopsy may be acceptable.

All cases of locally advanced N0 breast cancer are T4b, so skin infiltration is relatively mild, and preoperative chemotherapy has been successful in some cases. The extent of dissection should be determined by imaging after chemotherapy. Basically, dissection up to level 2 is recommended. If lymph node metastasis is extensive, dissection to the subclavian lymph node should be performed as needed.

The rate of metastasis to the internal thoracic lymph nodes may be as high as 28%–52% in patients with positive axillary lymph node metastasis and up to 20% in those with negative axillary lymph node metastasis but with a medial breast mass. However, it has been found that extended mastectomy with internal thoracic lymph node dissection does not improve the recurrence rate or the survival rate when compared with pectoralis major-preserving mastectomy. Internal thoracic lymph node dissection is not currently performed because of the complexity of the procedure and the widespread use of breast-conserving surgery [10]. In contrast, the Danish Breast Cancer Cooperative Group 82b and c study [11] and a meta-analysis of randomized controlled trials by the Early Breast Cancer Trialists' Collaborative Group [12] confirmed that irradiation of the chest wall, including the internal thoracic lymph node region, improves not only local control but also overall survival. Therefore, radiotherapy rather than internal thoracic lymph node dissection is considered to be the main treatment for this area. The same applies to the supraclavicular lymph nodes, which are normally treated by postoperative radiotherapy rather than excision.

Although radiotherapy is administered as part of multimodal treatment, there have been no relevant prospective randomized controlled studies on radiotherapy after preoperative chemotherapy. However, some retrospective studies have been reported, including one in patients in the National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 trials who underwent total mastectomy without radiotherapy after preoperative chemotherapy.

The clinical stage and the efficacy of chemotherapy have been shown to be significant predictors of lymph node recurrence [13]. A retrospective analysis of data from six prospective clinical trials conducted at the MD Anderson Cancer Center compared the outcomes between a group of 542 patients who received postoperative radiotherapy and a group of 134 patients who did not [14]. The 10-year local/regional lymph node recurrence rate was significantly higher in the non-irradiated group (22% vs 11%; p=0.0001). However, there was no significant difference in the 10-year overall survival rate between the two study groups. In the same study, a retrospective analysis of 106 patients who underwent total mastectomy after preoperative chemotherapy and achieved a pathological complete response found that those with clinical stage I–II disease in both groups had no local or regional lymph node recurrence for up to 10 years whether or not they received postoperative radiotherapy. However, the local and regional lymph node recurrence rate was significantly higher in patients with stage III disease who did not receive radiotherapy (p=0.040) [14]. By contrast, in another study that included 52 cases of clinical stage II–III ypN0 breast cancer for which preoperative chemotherapy was effective for lymph node metastasis, multivariate analysis did not show a significant correlation of presence or absence of radiotherapy with the recurrence-free survival rate, local/regional lymph node non-recurrence rate, or overall survival rate [15]. Unfortunately, all these reports are subject to bias in terms of background factors and treatment selection, so the strength of the evidence is considered to be very weak. At present, the recommendation is to determine the indication for postoperative radiotherapy according to the stage before preoperative chemotherapy, even if it is successful.

If partial breast resection is performed, the remaining breast is irradiated. The lymph node area should be irradiated if lymph node metastasis remains. However, even if there is no lymph node metastasis, it is better to perform irradiation according to the stage before chemotherapy.

The post-mastectomy irradiation rate at our facility was low during the study period, being performed in 64% of cases after partial mastectomy and in only 35% after mastectomy. However, although there was no effect on recurrence-free survival, the possibility that post-mastectomy radiotherapy helped to suppress local lymph node recurrence cannot be ruled out. Our finding of a local recurrence rate of 12% at our institution suggests that our treatment should be more aggressive and that multimodal treatment should be promoted. Radiotherapy is basically administered after surgery. However, if the tumor is still present after preoperative chemotherapy, preoperative irradiation may be considered to facilitate resection surgery.

Preoperative irradiation has been studied in the past [16]. Although our present study focused on patients in whom radical surgery was possible, preoperative irradiation may still be effective in unresectable cases. According to one report, the effect of radiation after resection is small [17]. However, preoperative irradiation is not often performed at present in Japan.

This study has some limitations in that it was performed at a single center, had a retrospective design, and included a small number of cases with a short observation period. The results obtained from our analysis are very likely to be different if a larger number of cases are collected. It should be remembered that this is a retrospective study with a small number of cases in a single institution. Further studies that include a large number of cases drawn from a database and a longer observation period may provide a clearer picture with regard to the most effective treatment for locally advanced breast cancer.

Conclusion

Locally advanced breast cancer has high local recurrence and distant metastasis rates and a poor prognosis. Multimodal treatment, namely, a combination of local treatment after preoperative systemic chemotherapy, is recommended. At our facility, the proportion of patients who receive radiotherapy has been very low. Although radiotherapy had no statistically significant effect on the prognosis, there is a good chance that irradiation will improve the outcome. In this study, being premenopausal and the presence of 4 or more lymph node metastases were significant factors affecting recurrence-free survival. Patients with locally advanced breast cancer require multimodal treatment that includes radiotherapy, especially those with 4 or more lymph node metastases.

References

1. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. Journal of Clinical Oncology. 2006 Apr 20;24(12):1940-9.

2. Perloff M, Lesnick GJ, Korzun A, Chu F, Holland JF, Thirlwell MP, et al. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. J Clin Oncol. 1988 Feb 1;6(2):261-9.

3. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews. Centre for Reviews and Dissemination (UK). 2008.

4. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. Journal of Clinical Oncology. 2003 Apr 15;21(8):1431-9.

5. Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. Journal of the National Cancer Institute. 2005 Dec 7;97(23):1724-33.

6. Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2× 2 factorial, randomised phase 3 trial. Lancet. 2015 May 9;385(9980):1863-72.

7. De Lena M, Varini M, Zucali R, Rovini D, Viganotti G, Valagussa P, et al. Multimodal treatment for locally advanced breast cancer. Result of chemotherapy-radiotherapy versus chemotherapy-surgery. Cancer Clinical Trials. 1981 Jan 1;4(3):229-36.

8. Olson JE, Neuberg D, Pandya KJ, Richter MP, Solin LJ, Gilchrist KW, et al. The role of radiotherapy in the management of operable locally advanced breast carcinoma: results of a randomized trial by the Eastern Cooperative Oncology Group. Cancer. 1997 Mar 15;79(6):1138-49.

9. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. Journal of Clinical Oncology. 2004 Dec 1;22(23):4691-9.

10. Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management—a systematic review. Journal of Clinical Oncology. 2008 Oct 20;26(30):4981-9.

11. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol. 2006 May 20;24(15):2268-75.

12. McGale P, Correa C, Cutter D, Duane F, Ewertz M, Gray R, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. The Lancet. 2014 Jun 21;383(9935):2127-35.

13. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer Jr CE, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. Journal of Clinical Oncology. 2012 Nov 10;30(32):3960.

14. McGuire SE, Gonzalez-Angulo AM, Huang EH, Tucker SL, Kau SW, Yu TK, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. International Journal of Radiation Oncology, Biology, Physics. 2007 Jul 15;68(4):1004-9.

15. 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). International Journal of Radiation Oncology, Biology, Physics. 2014 Jan 1;88(1):65-72.

16. Sousa C, Cruz M, Neto A, Pereira K, Peixoto M, Bastos J, et al. Neoadjuvant radiotherapy in the approach of locally advanced breast cancer. ESMO Open. 2020 Jan 1;5(2):e000640.

17. Koenig JL, Kozak MM, Sabolch A, Horst K, Tsai J, Wapnir IL, et al. Use of Preoperative Radiation Therapy in Early-stage and Locally Advanced Breast Cancer. Cureus. 2019 Sep;11(9).