Timing of Initiation of Adjuvant Chemotherapy in Breast Cancer at Bataan General Hospital Among Early-Stage Breast Cancer patients from May 2015 to January 2020

Mariae Mistica Edquid MD,[1] and Jose Enrique Y. Montoya MD[1]

Abstract

Background: Studies reported survival benefits from early initiation of adjuvant chemotherapy from the time of mastectomy among breast cancer patients.

Objectives: The researchers aimed to determine if early initiation of adjuvant chemotherapy among early-stage breast cancer patients undergoing modified radical mastectomy at Bataan General Hospital and Medical Center has increased the patient's survival. We also want to asses if the Bataan General Hospital and Medical Center department of Oncology is rendering adjuvant chemotherapy as compared to the international standards. We also want to know the factors affecting the timing of initiation of adjuvant chemotherapy among the subjects.

Methods: A retrospective cohort study involving chart review covering the year May 2015 to January 2020 for stage 1 to 3 breast cancer patients, with a histopathologic confirmation, underwent definitive/curative breast surgery, and had started on adjuvant cytotoxic chemotherapy are included in the study.

Results and Conclusion: In this retrospective study, we observed that time to initiation of adjuvant chemotherapy among breast cancer patients at Bataan General Hospital and Medical Center does not significantly improve overall survival of patients. The BGHMC Department of Oncology service is trailing the cut off 12 weeks or 84 days of initiation of adjuvant chemotherapy from the date of mastectomy. We also used the factors that affects the timing of initiation of adjuvant chemotherapy and found out that these variables cannot predict whether it will increase the patient's survival since our sample size is too small.

Keywords: Early breast cancer, adjuvant chemotherapy, modified radical mastectomy, survival benefits

Introduction

Cancer is a disease wherein human body cells grow uncontrollably that it spreads to other parts of the body. It can start almost anywhere in the human body, which is made up of trillions of cells. Cancer is a genetic disease– that is, it is caused by changes to genes that control the way our cell's function, especially how they grow and divide.

Breast cancer is one of the most common cancers among women. In the study conducted by the WHO in 2012, it states that breast cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related death. It is the most common invasive cancer in women and the second leading cause of cancer death in women after lung cancer. More so, the number of cancer cases will rise from 14 million in 2012 to 22 million within the next two decades.[1]

Tumor markers play a crucial role in predicting breast cancer behavior. Hormone receptor-positive tumor cells tend to respond better to hormone therapy, leading to higher chances of survival and better prognosis.

Adjuvant therapy is a critical initial medical intervention alongside surgery to reduce the risk of cancer recurrence. Even after successful surgery, microscopic cancer remnants may persist undetected. Neoadjuvant therapy, administered prior to primary treatment, also reduces the risk of recurrence and can enhance the effectiveness of subsequent treatments like surgery or radiation. Accordingly, there are several types of

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[1] Department of Oncology, Bataan General Hospital and Medical Center, Balanga City Bataan
Corresponding Author: Mariae Mistica Edquid MD eMail: edkidmic@gmail.com

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adjuvant therapy that are used; these includes: chemotherapy, hormone therapy, radiation therapy, immunotherapy, and targeted therapy.

One of these treatments may better suit a patient's condition, hence it is important to consider the factors which may contribute to the procedure.[2] Accordingly, Efstathiou, et.al, emphasized that adjuvant chemotherapy allows for pathologic staging and avoids delay in potentially curative local therapy. However, no randomized trials have compared neoadjuvant to adjuvant chemotherapy in patients undergoing definitive local therapy. Nonetheless, a significant progression-free survival (PFS) benefit at 3 years and 5 years was observed when patients were randomized to adjuvant chemotherapy compared with observation.[3]

Consequently, mastectomy rates have significantly increased over the last decades, likely due to the rising trend of risk-reducing mastectomies (RRM) in the treatment and prevention of breast cancer. Growing evidence suggests that aggressive risk-reducing surgical strategies are only justified in high-risk breast cancer situations. Thus, both private and public medical institutions in the country are working together to meet the demand and satisfaction of the patients. Moreover, Wang, et.al., concluded that breast cancer surgery and radiotherapy (RT) have demonstrated better prognosis than modified radical mastectomy (MRM) only and MRM+RT treatments for early-staged triple-negative breast cancer (TNBC) patients.[4]

This was opposed by Pomponio, et.al wherein their results showed that time to adjuvant chemotherapy (TTC) was not significantly associated with disease free survival (DFS) nor overall survival (OS) in patient receiving chemotherapy for operable TNBC. The results were reassuring for patients electing mastectomy with immediate reconstruction, who may experience a longer TTC. Thus, the results were seen as higher risk for delayed TTC.[5]

Bataan General Hospital Medical Center (BGHMC) in particular, with its 73 years of service, has geared the institution in catering to patients' medical needs as imposed on its goals and with the provision of Universal Health Care specifically with cancer patients, not only from the province of Bataan, but even nationwide.

The present study deals with the timing and initiation of adjuvant chemotherapy among early-stage breast cancer patients undergoing MRM in BGHMC. It seeks to define the impact of said treatment on patients' medical improvements and challenges.

Statement of the Problem. The general problem of the study is to determine the effect of timing of initiation of adjuvant chemotherapy among early-stage breast cancer patients undergoing MRM at BGHMC.

Specifically, this study seeks to answer the following questions:

1. How does the timing of adjuvant chemotherapy affect the breast cancer patients' overall survival rate?
2. What is the number of days interval between breast surgery and adjuvant chemotherapy in BGHMC Department of Oncology?
3. Identify the factors affecting the timing of initiation of adjuvant chemotherapy
4. Compare the standards set by the BGHMC in rendering adjuvant chemotherapy service among early-stage breast cancer patients undergoing MRM as compared to the international standards.

Operational Definition of Terms

Alive. Patient who are still alive beyond August 2021.

Adjuvant chemotherapy. The use of cytotoxic chemotherapy after breast cancer surgery.

Early-Stage Breast Cancer. Breast cancer that has not spread beyond the breast of axillary lymph nodes. Example of which are breast cancer stage l, llA, llB, or lllA.

ER (Estrogen Receptor). The breast cancer cells that receive their growth signals from the hormone estrogen.

HER2 (Human Epidermal Receptor 2). A protein found on breast cancer patients that belongs to the epidermal growth factor family and is one of the poor prognostic indicators for breast cancer.

Location. A particular place where a person or organization is situated.

Not alive. Patient who are deceased beyond August 2021.

PR (Progesterone Receptor). The breast cancer cells that receive their growth signals from the hormone progesterone.

Primary caregiver. A person assisting the patient from the time of breast cancer diagnosis up to the start of adjuvant chemotherapy.

Methodology

This is a retrospective cohort study involving chart review covering the years May 2015 to January 2020 for Stage 1 to Stage 3 breast cancer patients, with histopathologic confirmation, who underwent definitive/curative breast surgery, and had started on adjuvant cytotoxic chemotherapy were included.

Inclusion criteria. Stage 1 to Stage 3 breast cancer patients, with histopathologic confirmation and underwent definitive/curative breast surgery, and had started on adjuvant cytotoxic chemotherapy.

Exclusion criteria. Stage 4 breast cancer patients, and patients who had neoadjuvant chemotherapy were excluded.

Sampling. The study employed convenience sampling to determine which charts will be reviewed in the study.

Suitable cases from BGHMC medical records section were selected based on the inclusion and exclusion criteria, covering the years May 2015 to January 2020. Data was then cross referenced with the Section of Medical Oncology Cancer Registry to ensure accuracy. Clinical profile such as address, primary care giver, educational attainment, nodal status, tumor grade, estrogen, progesterone, and HER2/neu receptor status, if available, were obtained. Timing of initiation of adjuvant chemotherapy was defined as start of first dose of chemotherapy from the date of mastectomy. A cut-off of 12 weeks or 84 days will be considered as delay. Possible reasons of delay will be recorded as well.

Potential sources of selection bias such as disease severity or comorbidity that can influence both treatment source and outcomes were addressed by excluding those who received neoadjuvant therapy and patients with advanced stages of breast cancer. Random sampling of charts will be most ideal to address this bias, however, convenience sampling was the most efficient method since sample size was small and included cases are relatively rare.

Data Analysis. Categorical variables were expressed using descriptive statistics (percentages, range) and continuous variables were expressed as mean $\pm$ standard deviation (SD). All statistical analyses were carried out using *SPSS version 20©* at 95% confidence level and $p \leq 0.05$ level of significance.

Significance of the Study

The study is deemed significant to the following entities.

Breast Cancer Patients. This may offer a clearer perspective and guidelines to patients on understanding the importance of proper timing and/or intervention of adjuvant chemotherapy.

BGHMC Department of Oncology. The findings of the study may serve as basis for further implementation on the process of adjuvant chemotherapy which will cater to both the institution and the patients' needs. This may also be a model to other hospitals in the province to render the same existing service to breast cancer patients.

Medical Practitioners: Doctors and Nurses. The findings of the study may give better basis on how to further deal with patients who have breast cancer and its treatment. Moreover, it may encourage medical practitioners to seek more effective medication to respond to the needs of the patients.

Bataan General Hospital Medical Center Stakeholders. As a public hospital in the province of Bataan, the findings of the study may provide a more specific scheme in terms of the medical practices concerning adjuvant chemotherapy. Specifically, the results of the present study may be basis on further development and/or execution of some other procedures or program to maintain best practices for the betterment of the patient.

Ethical Considerations. Since this study deals with chart review of the BGHMC patients, informed consent will not be necessary. Research subjects will not be subjected to any harm in any ways. Instead of informed consent, a letter of permission to access data will be addressed to the Medical Center Chief of BGHMC. Once permission was granted, data were extracted from the BGHMC record section and Section of Medical Oncology Cancer Registry. All the obtained data were treated with utmost confidentiality and care. The protection of the privacy of research participants were ensured. The data were stored in a locked cabinet and will be kept until the end of the training of the primary investigator. Access to the data will be limited only to the investigators of this study.

Results

A total of 65 patients were included. *Table I* shows the total number of patients who underwent mastectomy followed by adjuvant chemotherapy at BGHMC. Fifty-two patients out of 65 were alive (80%), while 13 patients (20%) were died. The table also shows a total of 54 (83%) patients who received adjuvant chemotherapy within 12 weeks of diagnosis with 11 (17%) patients receiving it 12 weeks after mastectomy. Median time to adjuvant chemotherapy was 54 days.

Table II shows the ER, PR, and HER2 status of breast cancer patients. A total of 51 patients obtained the ER and PR test. Among these, a total of 37 (73%) patients were ER positive and a total of 32 (49%) patients were PR positive. Among 37 patients who are ER positive, only 31 (83.78%) of them were alive. A total of 32 (62.75%) patients were PR positive, and 26 (81.25%) of these patients were alive. On the other hand, a total of 49

Table I. Characteristics of Breast Cancer Patients Included in the Study

	No. (%)
Underwent mastectomy and adjuvant therapy	
Alive	52 (80)
Dead	13 (20)
Timing of adjuvant therapy	
<12 weeks	54 (83)
>12 weeks	11 (17)

Table II. ER, PR, and HER2 status of breast cancer patients

	No. (%) Alive	No. (%) Dead	Total
ER status			
Negative	10 (24)	4 (40)	14 (27)
Positive	31 (76)	6 (60)	37 (73)
Total	41 (80)	10 (20)	51
PR status			
Negative	15 (34)	4 (40)	19 (37)
Positive	26 (63)	6 (60)	32 (63)
Total	41 (80)	10 (20)	51
HER2 status			
Equivocal	4 (10)	1 (10)	5 (10)
Negative	27 (69)	5 (50)	32 (65)
Positive	8 (21)	4 (40)	12 (25)
Total	39 (80)	10 (20)	49

patients obtained a HER2 test. Among these, a total of 12 (18.46%) out of 65 patients were HER2 positive and 8 (66.67%) patients were alive, while 4 (33.3%) were dead.

Table III shows the staging of cancer among breast cancer patients. A total of 25 (38%) of patients have Stage 2 breast cancer, 19 (76%) of them were alive. A total of 2 (3.08%) of patients have stage 2A breast cancer and 1 (50%) of them was deceased. 38 (58.46%) of patients have stage 3 breast cancer, 31 (81.58%) of these patients were alive. A total of 40 (61.54%) patient has positive nodes, 30 (75%) out of 40 patients were still alive.

Table IV shows the location of patient from Bataan General Hospital and Medical Center. A total of 20 (31%) patients are from Balanga Bataan from which BGHMC is located. A total of 9 (13.85%) from Orani, 6 (9.23%) from Hermosa, 6 (9.23%) Mariveles, 6 (9.23%) Orion, 5 (7.69%) from Dinalupihan, 4 (6.15%) from Abucay, 3 (4.62%) from Pilar, 2 (3.08%) from Limay, 2 (3.08%) from Samal, 1(1.54%) from Manila and 1 (1.54 %) from Zambales.

Table V shows the primary caregiver of patients. A total of 24 (32.31%) patients had their husbands as their primary care giver, 21 (87.5%) of them were alive. A total of 18 (27.69%) patients whose primary care giver are their sister, with 14 (77.78%) of them alive. Eleven (16.92%) of patient's primary caregiver are their daughter, with eight (72.73 %) of them still alive. Three (4.62%) of the patients had their sons as primary care giver, with one (33.3%) patient deceased. Three (4.62 %) patients had their mother as primary caregiver, with two (66.67%) of them alive. Two (3.08%) patients have their cousin as primary caregiver and both were alive. One (1.54%) patient had a primary caregiver of sister-in-law who is still alive. Another one (1.54%) patient had an aunt as primary caregiver but died. In our study, the husband participated more in the extensive process of caring for their wives who have breast cancer.

Table VI shows the educational attainment of the patients. A total of 18 (27.69%) patients are college graduates, 16 (88.89%) of whom patients were alive. A total of seven (10.77%) patients were college undergraduate, five (71.43%) of these patients were alive. Fifteen (23.08%) patients had primary education and one (6.67%) of them died. A total of 23 (35.38%) patients had secondary education, of whom 17 (73.91%) patients were alive. Two (3.08%) patients had vocational education and both died.

Table VII shows the logistic regression of the factors studied. This analysis is used to predict or give the probability if the patient will be alive or not based on one or multiple patients' data or variables. Since the p value of patient's age, sex, days interval from mastectomy to adjuvant chemotherapy, residence, primary caregiver, educational attainment, tumor grade, nodes positive, ER, PR, HER2 positive and stage of breast cancer are > 0.05, all the patients' data or variables cannot be used to predict survival rate of patients of BGHMC based on the data we have.

Table III. Distribution of Patients According to Stage of Breast Cancer

	No. (%) Alive	No. (%) Deceased	Total
Stage			
2	19	5	25 (38)
3	31	7	38 (58)
2A	1	1	2 (3)
Total	51	13	65

Table IV. Distribution of Patients According to Place of Residence.

Residence	No. Alive	No. Dead	Total
Abucay	4	0	4
Balanga	13	7	20
Dinalupihan	4	1	5
Hermosa	3	3	6
Limay	2	0	2
Manila	1	0	1
Mariveles	5	1	6
Orani	9	0	9
Orion	6	0	6
Pilar	2	1	3
Samal	2	0	2
Zambales	1	0	1
Total	52	13	65

Table V. Distribution of Patients According to their Primary Care Giver

Primary Care Giver	No. Alive	No. Dead	Total
Auntie	0	1	1
Cousin	2	0	2
Daughter	8	3	11
Daughter in Law	1	0	1
Husband	21	3	24
Mother	2	1	3
Niece	1	0	1
Sister	14	4	18
Sister-in-Law	1	0	1
Son	2	1	3
Total	52	13	65

Table VI. Distribution of Patients According to Educational Attainment

Educational Attainment	No. Alive	No. Dead	Total
College	16	2	18
College Undergrad	5	2	7
Primary	14	1	15
Secondary	17	6	23
Vocational	0	2	2
Total	52	13	65

Table VII. Logistic regression of Factors

	Estimate	Std. Error	Z value	Pr(<|z|)
(Intercept)	-8.233e+00	4.602e+00	-1.789	0.0736
Interval	1.012e-04	3.724e-04	0.272	0.7857
Residence	3.258e-01	2.410e-01	1.352	0.1763
Primary Caregiver	-1.366e-01	2.595e-01	-0.526	0.5986
Educational Attainment	3.109e-01	3.017e-01	1.031	0.3027
Positive Nodes	-1.299e-01	1.012e-01	-1.284	0.1992
Tumor Grade	-1.418e+00	8.170e-01	-1.284	0.1992
ER Positive	2.522e-02	1.717e+00	0.015	0.9883
PR Positive	-1.190e+00	1.875e+00	-0.635	0.5256
HER2 Positive	1.176e+00	7.102e-01	1.655	0.0978
STAGE	1.642e+00	1.053e+00	1.560	0.1188
Total	52	13	65	

Discussion

Early initiation and survival rates. We did a retrospective cohort study involving chart review covering the years May 2015 to January 2020 to determine the effect on overall survival of early initiation of adjuvant chemotherapy among early-stage breast cancer patients who underwent MRM at BGHMC. In the study, a total of 54 (83%) patients received adjuvant chemotherapy within 12 weeks of diagnosis, and 11 (17%) patients had it >12 weeks after mastectomy.

According to the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines in 2019, adjuvant systemic therapy should be started without undue delays. Administration of adjuvant chemotherapy >12 weeks after surgery decreases its efficacy.[6] Chavez-MacGregor stated that adjuvant chemotherapy improves outcomes of patients with breast cancer. However, the optimal timing of chemotherapy initiation is unknown. Delayed administration can decrease the benefit of cytotoxic systemic therapies. For patients with breast cancer, adverse outcomes are associated with delaying initiation of adjuvant chemotherapy 91 or more days.[7] Desch et al. recommend starting chemotherapy within 120 days of diagnosis, while Hershman et al. noted increased mortality with delays over three months, especially in elderly patients.[8] Chavez-McGregor et al. found worse survival with delays beyond 90 days post-mastectomy, particularly in TNBC.[7] Similarly, Heeg, et.al. mentioned that initiation of adjuvant chemotherapy beyond 30 days is associated with decreased 10 years overall survival in TNBC patients who underwent BCS.

Therefore, timelier initiation of chemotherapy in TNBC patients undergoing BCS seems warranted. Adjuvant chemotherapy in invasive breast cancer is associated with reduced mortality, but its effectiveness depends on patient and tumor characteristics. Local guidelines on the timing of adjuvant chemotherapy post-surgery are still lacking.[9]

It is sufficient to say that the Section of Medical Oncology of the Department of Internal Medicine somehow follows the recommendation of ESMO Clinical Practice Guidelines. However, early initiation of adjuvant chemotherapy among patients of BGHMC did not improve its overall survival rate based on our data. This is opposite to existing literature wherein data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG, 2011) states that the early use of an anthracycline-containing regimen compared with no treatment resulted in decreased breast cancer mortality from 36% to 29% (RR 0.79, 95% CI 0.72-0.85), and decreased overall mortality from 40% to 35% (RR 0.84, 95% CI 0.78-0.91).[10]

Hormone receptor positivity outcomes. Breast cancer can generally be classified into three biological subgroups, each of which has a significant impact on the type of treatment that should be used: 1) those that express the estrogen receptor (ER), 2) those that express the human epidermal growth factor receptor 2 (HER2), with or without ER expression, and 3) those that do not express either of these receptors, as well as the progesterone receptor (PR; triple-negative). Even though there is little chance of curing metastatic breast cancer, there have been appreciable advancements in survival due to more efficient systemic medicines, such as endocrine therapy (ET) for the management of hormone-sensitive illness. In the study, only 51 (78%) patients out of 65 obtained the ER and PR test. According to the National Breast Cancer Foundation, hormone receptor testing is recommended for all breast cancer patients. This is used to determine treatment options and prognosis.[11]

Among 51 patients, a total of 37 (73%) patients were ER positive and a total of 32 (49%) patients were PR positive. Among 37 patients who are ER positive, 31 (83.78%) of them were alive. Subsequently, among of 32 (62.75%) patients who were PR positive, 26 (81.25%) of them were alive.

This shows that patients who are hormone receptor positive have better prognosis and survival rate. This generalization is supported by Lois where he said that Luminal A tumors, which probably make up about 40 percent of all breast cancers, usually have high expression of ER-related genes, low expression of the HER2 cluster of genes, and low expression of proliferation-related genes, are the most common subtype and, in general, carry the best prognosis of all breast cancer subtypes.[12] Additionally, ER expression predicts patients who will benefit from endocrine

therapy. Although patients with PR positive tumors also have better outcomes when treated with endocrine therapy, PR status is heavily dependent on ER. Therefore, it does not appear that PR+ has an independently predictive value, especially when the ER status is known.[13]

In terms of HER2 positivity, a total of 49 patients obtained a HER2 test. Among these, a total of 12 (18.46%) out of 65 patients were HER2 positive and 8 (66.67%) patients were alive, while four (33.3%) were deceased. Results showed that more than half of the patients with HER2 positivity were alive.

According to the American Society of Clinical Oncology, HER2 overexpression is associated with high rates of disease recurrence and death only in the absence of adjuvant systemic therapy. However, the value of this prognostic information in clinical practice is questionable, particularly with the earlier use of HER2-directed agents in the neoadjuvant and adjuvant setting.[14] Patients included in the study were treated with adjuvant therapy, therefore, we cannot conclude whether results of the study was consistent or not with existing literature.

Other factors affecting survival rate. In terms of residence, a total of 20 (31%) patients from Balanga Bataan, from which BGHMC is located, showed the highest survival rate among others. We might conclude that the location of hospital impacts patients who are willing to receive treatment. However, residence does not predict the survival rate of these patients. This can be explained by the sampling bias present in the study wherein gathered data included members of the intended population that has a higher sampling probability than others. In other words, patient records are obtained from the same location, therefore, there is also a higher probability that they will compose most of the sampled population.

Additionally, no existing literature proves that hospital location improves breast cancer treatment outcomes. This is also true for other factors such as primary caregiver and educational attainment of the patient. Subsequently, results of the study showed that all the patients' data or variables cannot be used to predict survival rate of patients of BGHMC.

Avino et al. emphasized the importance of involving patients, plastic surgeons, and oncologists in deciding the timing of breast reconstruction after mastectomy, which can significantly impact quality of life.[15]

Conclusion

In this retrospective study, we observed that time to initiation of adjuvant chemotherapy among breast cancer patients at Bataan General Hospital and Medical Center does not significantly improve overall survival of patients. We use logistic regression for the small sample size. Ideally, we can use the Kaplan Meir Analysis to estimate the patient's survival curve, however large sample size is needed to estimate the survival.

We concluded in the study that the BGHMC Department of Oncology service is trailing the cut-off of 12 weeks or 84 days of initiation of adjuvant chemotherapy from the date of mastectomy. The factors that affect the intervention of adjuvant chemotherapy are the patient's location from the hospital, as it impacts the patient's willingness to receive treatment. Another factor that affects the intervention of chemotherapy are the presence of primary caregiver and educational attainment. Majority of patients have their husbands as their primary caregiver since they are the frequent companions in the house. Most of our patients attained secondary education.

For the Department of Medical Oncology at BGHMC, this can be a model to continue implementation of the standard of care when it comes to timing of initiation of chemotherapy from the time of mastectomy. For the doctors and nurses involved, they should be aware of the present situation within our institution. As the care of patients with breast cancer increases in complexity, we must remember that the management of our patients should be guided by team of oncologists, residents and nurses who should be united in a multidisciplinary group to formulate and implement treatment recommendations in an organized and efficient manner.

For the future researchers, we recommend you to continue the study once we have enough population to estimate the patient's survival when it comes to the timing of the initiation of chemotherapy from the time of breast surgery.

References

1. World Health Organization. Latest world cancer statistics Global cancer burden rises to 14.1 million new cases in 2012: Marked increase in breast cancers must be addressed. International Agency for Research on Cancer 2013 December 12.
2. Cancer Treatment. Mayo Foundation for Medical Education and Research. 2021
3. Efstathiou, J et al. Adjuvant Chemotherapy after Definitive Local Therapy. Clinical Radiation Oncology (Fourth Edition) Chapter 54 p1096 2016
4. Wang, S et al. Breast conserving surgery with adjuvant radiation therapy showed improved prognosis compared with mastectomy for early staged triple negative breast cancer patients. Mathematical Biosciences and Engineering 2019 PMID: 31731341 DOI: 10.3934/mbe.2020005
5. Pomponio, K. et al. Does time to adjuvant chemotherapy (TTC) affect outcomes in patients with triple-negative breast cancer? Breast Cancer Research and treatment PMID: 31119565, 2019 Aug;177(1):137-143. doi: 10.1007/s10549-019-05282-0. Epub 2019
6. Cardoso. F. et al ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. European Society of Medical Oncology. 2019
7. Chavez-MacGregor M. et al. Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer. JAMA

Oncol. Mar;2(3):322-9. doi: 10.1001/jamaoncol.2015.3856 2016

8. Desh C. et al. American Society of Clinical Oncology/National Comprehensive Cancer Network quality measures. J Clin Oncol. ; 26 (21): 3631-3637 2018

9. Heeg, M. et al.Association between initiation of adjuvant chemotherapy beyond 30 days after surgery and overall survival among patients with triple-negative breast cancer. 2020 Jul 1;147(1):152-159. doi: 10.1002/ijc.32788. PMID: 31721193 PMCID: PMC7317578. 2019

10. Early Breast Cancer Trialists' Collaborative Group. 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 randomized trials. Lancet.
    PMID: 22019144 PMCID: PMC3254252 DOI: 10.1016/S0140-6736(11)61629-2 2011

11. NBCF team. About Breast Cancer. National Breast Cancer Foundation, INC. Available from:https://www.nationalbreastcancer.org/about-breast-cancer/

12. Loi, S. et al. Definition of clinically distinct molecular subtypes in estrogen receptor-positive breast carcinomas through genomic grade. Journal of Clinical Oncology 2007 PMID: 17401012

13. Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. Lancet. 2011 PMID: 21802721 PMCID: PMC3163848

14. American Society of Clinical Oncology. Breast Cancer: Types of treatment 2020. Retrieved from https://www.cancer.net

15. Avino, A. et al. Timing between Breast Reconstruction and Oncologic Mastectomy-One Center Experience. Medicina (Kaunas) 2020 Feb 20;56(2):86. doi: 10.3390/medicina56020086. PMID: 32093278 PMCID: PMC7073902 2020