Turkish Journal of Clinics and Laboratory

To cite this article: Culcu S, Haberal E, Tamam S, Yuksel C, Aksel B, Dogan L. Is the platelet-lymphocyte ratio a useful tool for predicting sentinel lymph node metastasis in breast cancer patients receiving neoadjuvant therapy?. Turk J Clin Lab 2022; 3: 352-359.

Original Article

Is the platelet-lymphocyte ratio a useful tool for predicting sentinel lymph node metastasis in breast cancer patients receiving neoadjuvant therapy?

Neoadjuvan tedavi alan meme kanserli hastalarda trombosit-lenfosit oranının sentinel lenf nodu metastazı tahmininde yeri var mıdır?

Serdar Culcu*[1], Elifcan Haberal[2], Selim Tamam[1], Cemil Yuksel[3], Bulent Aksel[4], Lutfi Dogan[4]

[1]Ankara Universitesi Tıp Fakultesi, Cerrahi Onkoloji Bilim Dalı, Ankara, Türkiye

[2] Sağlık Bilimleri Üniversitesi, Ankara Şehir Sağlık Uygulama ve Araştırma Merkezi, Cerrahi Tıp Bilimleri Bölümü, Ankara, Türkiye

[3]Mersin Şehir Hastanesi, Mersin, Türkiye

[4]Sağlık Bilimleri Üniversitesi, Ankara Dr. Abdurrahman Yurtaslan Onkoloji Sağlık Uygulama ve Araştırma Merkezi, Ankara, Türkiye

ABSTRACT

Aim: Breast cancer is one of the cancers with the highest morbidity and mortality in women. Surgical excision of axillary lymph nodes facilitates staging and provides regional control in those with axillary metastases. Although SLNB is routinely performed in the management of patients with cN0 disease who underwent primary surgery, it is controversial when to perform SLNB in patients receiving neoadjuvant chemotherapy. In our study, we evaluated the success of the platelet/lymphocyte ratio before and after neoadjuvant therapy in predicting sentinel lymph node metastases in breast cancer patients receiving neoadjuvant therapy.

Materials and Methods: Patients who received neoadjuvant chemotherapy for locally advanced breast cancer in our clinic were evaluated. Among these patients, patients with histopathologically proven axilla metastases but no pathological lymph nodes in clinical examination and imaging methods after neoadjuvant therapy were evaluated.

Results: An average of 3.81 lymph node excisions were performed for sentinel lymph node sampling. We studied the PLR cut-off value with Roc-curve analysis. We found the cut-off value of 138.88 with a standard error of 0.061 (p=0.001). Patients with high PLR are more likely to have sentinel lymph node metastases than patients with low PLR (OR= 1.013, 95%CI: 1.005-1.021, p=0.002). We also found a significant positive correlation between PLR and the number of metastatic sentinel lymph nodes (p=0.005). Each unit increase in PLR can cause an increase of 0.004 units in the number of metastatic sentinel lymph nodes.

Conclusion: In patients receiving neoadjuvant chemotherapy, PLR plays an important role in predicting sentinel lymph node metastasis as a practical, simple, and inexpensive hematological indicator and may facilitate the selection of an appropriate treatment plan before surgery.

Keywords: Sentinel lymph node, Breast cancer, inflammatory parameters

Corresponding Author*: Serdar Culcu, Ankara University Faculty of Medicine, Department of Surgical Oncology, Ankara, Turkey
E-mail: serdarculcu@gmail.com
Orcid: 0000-0002-1136-1771
Doi: 10.18663/tjcl.1147959
Recevied: 24.07.2022 accepted: 10.09.2022

ÖZ

Amaç: Meme kanseri kadınlarda yüksek morbidite ve mortaliteye sahip kanserlerden biridir. Aksiller lenf nodlarının cerrahi olarak çıkarılması, aksiller metastazı olanlar hastalarda evrelemeyi kolaylaştırır ve lokal kontrol sağlar. Primer cerrahi uygulanan cN0 hastalığı olan hastaların yönetiminde SLNB rutin olarak uygulansa da neoadjuvan kemoterapi alan hastalarda SLNB'nin ne zaman uygulanacağı tartışmalıdır. Çalışmamızda neoadjuvan tedavi alan meme kanserli hastalarda neoadjuvan tedavi öncesi ve sonrası trombosit/lenfosit oranının sentinel lenf nodu metastazlarını öngörmedeki başarısını değerlendirdik.

Gereç ve Yöntemler: Kliniğimizde lokal ileri evre meme kanseri nedeniyle neoadjuvan kemoterapi alan hastalar değerlendirildi. Bu hastalardan neoadjuvan tedavi sonrası klinik muayene ve görüntüleme yöntemlerinde patolojik lenf nodu saptanmayan ancak öncesinde histopatolojik olarak aksilla metastazı saptanan hastalar değerlendirildi.

Bulgular: Sentinel lenf nodu örneklemesi için ortalama 3.81 lenf nodu eksizyonu yapıldı. Roc-eğrisi analizi ile PLR eşik değerini inceledik. 0.061 (p=0.001) standart hata ile cut-off değerini 138.88 bulduk. Yüksek PLR'si olan hastalarda, düşük PLR'si olan hastalara göre sentinel lenf nodu metastazı olması daha olasıdır (OR= 1.013, %95 CI: 1.005-1.021, p=0.002). Ayrıca PLR ile metastatik sentinel lenf nodu sayısı arasında da anlamlı bir pozitif korelasyon bulduk (p=0,005). PLR'deki her birim artış, metastatik sentinel lenf düğümlerinin sayısında 0,004 birimlik bir artışa neden olabilir.

Sonuç: Neoadjuvan kemoterapi alan hastalarda PLR pratik, basit ve ucuz bir hematolojik gösterge olarak sentinel lenf nodu metastazını öngörmede önemli bir rol oynar ve cerrahi öncesi uygun tedavi planının seçimini kolaylaştırabilir.

Anahtar Kelimeler: Sentinel lenf nodu, Meme kanseri, inflamatuar parametreler

Introduction

Breast cancer is one of the cancers with the highest morbidity and mortality in women [1]. Most patients have locally advanced disease and a poor prognosis at the time of diagnosis. The condition of the axillary lymph nodes is one of the most important prognostic factors. Surgical removal of axillary lymph nodes facilitates staging and provides regional control in those with axillary metastases. However, in clinically node-negative (cN0) patients, axillary dissection was replaced by sentinel lymph node biopsy (SLNB), and the rate of sentinel lymph node detection increased to 91-100% with clinical experience [2,3]. In randomized studies, it has been shown that false negative rates in women with cN0 disease are below 10% [4]. Although SLNB is routinely performed in the management of patients with cN0 disease who underwent primary surgery, it is controversial when to perform SLNB in patients receiving neoadjuvant chemotherapy (NACT). In our clinic, we apply SLNB in patients whose axillary lymph node involvement disappeared after neoadjuvant therapy.

Chronic inflammation has an important role in the carcinogenesis process. Chronic inflammation is known to promote the proliferation of malignant cells, angiogenesis, and thus metastasis [5]. Platelets stimulate tumor growth by releasing growth factors such as platelet-derived growth factors and transforming growth factor-β [6-10]. Lymphocytes, on the other hand, suppress the progression of cancer as a part of the host immune response [11]. Based on this idea, many studies have been conducted recently investigating the relationship between inflammatory and hematological blood parameters and cancer prognosis.

In our study, we evaluated the success of the platelet/lymphocyte ratio after neoadjuvant therapy in predicting sentinel lymph node metastases in breast cancer patients receiving neoadjuvant therapy.

Materials and Methods

Study Population and Design

Patients who were operated on with the diagnosis of breast cancer in our clinic between 2018 and 2021 were investigated retrospectively. Regardless of tumor size, patients with T4a on preoperative imaging and T4b on physical examination were evaluated. Patients who received neoadjuvant chemotherapy for locally advanced breast cancer in our clinic were evaluated. Among these patients, 76 patients with histopathologically proven axilla metastases but no pathological lymph nodes in clinical examination and imaging after neoadjuvant therapy were selected for the study protocol. Nine patients with hematological and rheumatological diseases, who also received a blood transfusion before the operation, were excluded from the study because they could give erroneous results in the parameters of inflammation. A total of 67 patients were included in the study. Demographic and clinical data were obtained by examining patient files retrospectively. In the evaluation of hematological parameters, routine blood tests performed while preparing the patients for the operation were taken into account. Platelet and lymphocyte values were found from the hemogram panel and platelet/lymphocyte ratios (PLR) were calculated. The success of this ratio in predicting metastatic sentinel lymph nodes and its relationship with the number of metastatic lymph nodes were investigated. All lymph nodes with radioactive uptake by gamma probe and stained with methylene blue were included

in the sentinel lymph node detection. Secondly, it was aimed to find a cut-off value for the PLR. The relationship of this value with metastatic sentinel lymph node, number of lymph node metastases, pathological tissue diagnosis, tumor localization, tumor size, and histopathological parameters were examined. It was investigated whether the PLR cut-off value could be a test with high sensitivity and specificity in the detection of metastatic sentinel lymph nodes after neoadjuvant therapy. Approval for the study was obtained from the ethics committee of our hospital.

Statistical analysis

SPSS v22.0 was used in our study. Pearson chi-square and Fischer exact were used in the analysis of categorical data since it was a two-group study. Student T was used for scaled parametric data and Mann Whitney U was used for scaled non-parametric data. Pearson test was used in correlation analysis and the linear regression test was used in regression analysis. The cut-off value was found by ROC curve analysis. The statistical significance level was taken as 0.05.

Results

We retrospectively evaluated 67 patients in total. All of the patients in our study were female. 33 of the patients are in the premenopausal period and the mean age is 48.84 (range 34-71). When the primary tissue diagnoses were examined, 60 patients were non-special type (NST), 6 patients were invasive ductal carcinoma (IDC), and 1 patient was tubular carcinoma. While the tumor was located in the upper outer quadrant in 25 patients, the tumor was located in the central quadrant in 21 patients, in the lower outer quadrant in 12 patients, the upper inner quadrant in 4 patients, and the lower inner quadrant in 5 patients. For sentinel lymph node sampling, an average of 3.81 (range 1-10) lymph node excisions were performed. In 33 of the patients, sentinel lymph node metastases were positive and the mean metastatic sentinel lymph node count was 0.79 (range 0-5). The mean platelet count was 313.35×109/L, lymphocyte 2.08×109/L, and the mean platelet/lymphocyte 169.69×109/L. The demographic and clinical data of the patients included in the study are shown in Table 1 in detail. Since our study investigated the success of the platelet/lymphocyte ratio calculated after neoadjuvant treatment in locally advanced breast cancer patients in predicting metastatic sentinel lymph nodes, we first tested the platelet/lymphocyte ratios (PLR) for distribution and homogeneity. We evaluated the metastatic sentinel lymph node relationship of PLR, which was not successful in distribution and homogeneity tests, with a non-parametric test. According to the Mann-Whitney U test, the median PLR value of patients with metastatic sentinel lymph nodes was 181.02, and the median PLR value of patients without metastasis in the sentinel lymph node was 119.52 (p=0.001). After this difference was statistically significant, we studied the PLR cut-off value for the metastatic sentinel lymph node with Roc-curve analysis. We found the cut-off value of 138.88 with a standard error of 0.061 (p=0.001) (Figure 1). First, we divided the patients into two groups according to the cut-off result we found. The first group consists of patients with PLR below 138.88, and the second group consists of patients with PLR above 138.88. The distribution of the patients according to the groups is homogeneous. The first group consists of 34 patients, the second group consists of 33 patients. The mean age of the patients in the first group was 49.79, and the second group was 47.85. There is a statistically significant difference in the distribution of the groups according to the platelet and lymphocyte counts. The mean lymphocyte in the first group was 2.55±0.67×109/L and in the second group, it was 1.60±0.38 (p<0.001). The median PLR of the first group was 105.53, and the median the PLR of the second group was 236.66 (p<0.001). There was no statistically significant difference in the distribution of both groups according to cancer diagnoses, tumor localization, lymphovascular invasion (LVI) perineural invasion (PNI) status, tumor size, and the number of lymph nodes removed for sentinel lymph node sampling (Table 2). We found no significant difference in the distribution of PLR cut-off groups according to metastatic sentinel lymph node status and metastatic sentinel lymph node number (p=0.179 and p=0.372, respectively). However, we found a significant relationship between PLR and the probability of metastasis in the sentinel lymph node. Accordingly, patients with high PLR have a higher probability of metastasis in the sentinel lymph node than patients with low PLR (OR= 1.013, 95%CI: 1.005-1.021, p=0.002) (Table 3). We also found a significant positive correlation between PLR and the number of metastatic sentinel lymph nodes (p=0.005). We also confirmed this relationship with the regression test. According to our analysis, each unit increase in PLR can cause an increase of 0.004 units in the number of metastatic sentinel lymph nodes (Table 4).

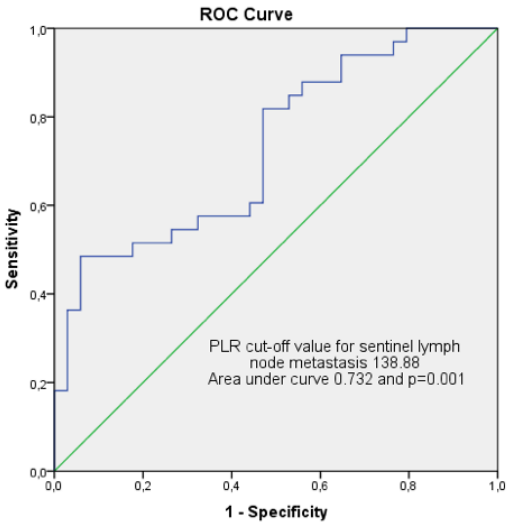

Figure 1. ROC curve analysis of Platelet-lymphocyte ratio(PLR) for Metastatic Sentinel Lymph Node status in neoadjuvant breast cancer patients

Table 1. Demographic and Clinicopathological Distribution of All Patients	
Age, year, mean±SD, range (min-max)	48.84±8.94 (34-71)
Platelet/lymphocyte ratio, mean±SD, range (min-max)	169.69±76.04 (68.83-357.14)
lymphocyte, ×109/L, mean±SD, range (min-max)	2.08±0.72 (0.85-4.23)
Platelet, ×109/L, mean±SD, range (min-max)	313.35±86.97 (180-536)
Primary Cancer Diagnosis, n(%)	
IDC	6 (9%)
NST	60 (89.6%)
Tubular carcinoma	1 (1.5%)
Mammography	
Brads 4	8 (11.9%)
Brads 5	38 (56.7%)
Brads 6	21 (31.3%)
Tumor Localization	
Central quadrant	21 (31.3%)
Upper inner quadrant	4 (6%)
Upper outer quadrant	25 (37.3%)
Lower inner quadrant	5 (7.5%)
Lower outer quadrant	12 (17.9%)
Grade	
Grade I	3 (4.5%)
Grade II	31 (46.2%)
Grade III	33 (49.3%)
LVI status	
Absent	49 (73.1%)
Present	18 (26.9%)
PNI status	
Absent	56 (83.6%)
Present	11 (18.4%)
Tumor size, mm, mean±SD, range (min-max)	29.42±14.69 (4-91)
SLNB dissection, number, mean±SD, range (min-max)	3.81±2.14 (1-10)
Metastatic Sentinel lymph node status	
Absent	34 (50.7%)
Present	33 (49.3%)
Metastatic node, number, mean±SD, range	0.79±1.06 (0-5)
ALND status	
Absent	34 (50.7%)
Present	33 (49.3%)
SD, standard deviation; Min, minimum; Max, maximum; Alnd, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; IDC, invasive ductal carcinoma; NST, no special type; LVI, lymphovascular invasion; PNI, perineural invasion	

Table 2. Association between platelet-lymphocyte ratio and clinicopathological factors			
Clinicopathological Factors	No. Of Patients (%)		
	PLR ↓ Group (34 patients 50.7%)	PLR ↓ Group (33 patients 49.3%)	P value
Age, year, mean±SD, range (min-max)	49.79±9.96(34-71)	47.85±7.77(36-64)	p=0.377†
Platelet/lymphocyte ratio, mean±SD, median,range (min-max)	109.01±19.70 105.53 (68.83-138.76)	232.22±59.84 236.66 (139-357.14)	p<0.001§
lymphocyte, ×109/L, mean±SD, median, range (min-max)	2.55±0.67 2.43 (1.33-4.23)	1.60±0.38 1.50 (0.85-2.44)	p<0.001§
Platelet, ×109/L, mean±SD, range (min-max)	272.85±68.76(180-473)	355.08±84.78(235-536)	p<0.001†
Primary Cancer Diagnosis, n(%)			p=0.438‡
IDC	4 (11.8%)	2 (6.1%)	
N	30 (88.2%)	30 (90.9)%	
Tubular carcinoma	0 (0%)	1 (3%)	
Tumor Localization			p= 0.570‡
Central quadrant	ST11 (32.4%)	10 (30.3%)	
Upper inner quadrant	1 (2.9%)	3 (9.1%)	
Upper outer quadrant	11 (32.4%)	14 (42.4%)	
Lower inner quadrant	3 (8.8%)	2 (6.1%)	
Lower outer quadrant	8 (23.5%)	4 (12.1%)	
LVI status			p=0.084‡
Absent	28 (82.4%)	21 (63.6%)	
Present	6 (17.6%)	12 (36.4%)	
PNI status			p=0.297‡
Absent	30 (88.2%)	26 (78.8%)	
Present	4 (11.8%)	7 (21.2%)	
Tumor size, mm, mean±SD, range (min-max)	28.76±14.81 (10-91)	30.09±14.75 (4-70)	p=0.715†
SLNB dissection, number, mean±SD, median, range (min-max)	3.47±1.67 3 (1-7)	4.15±2,51 4 (1-10)	p=0.385§
Metastatic Sentinel lymph node status			p=0.179‡
Absent	20 (58.8%)	14 (42.4%)	
Present	14 (41.2%)	19 (57.6%)	
Metastatic node, number, mean±SD, median, range (min-max)	0.74±1.08 0 (0-3)	0.85±1.06 1 (0-5)	p=0.372§

SD, standard deviation; Min, minimum; Max, maximum; † Student T test; ‡χ2 tests; §Mann Whitney U test

SLNB, sentinel lymph node biopsy; Idc, invasive ductal carcinoma; Nst, no special type; LVI, lymphovascular invasion; PNI, perineural invasion

Table 3. Univariate analyses of PLR for Sentinel lymph node metastasis		
Clinicopathological Factor	Univariate analysis	
	OR (95% CI)	p value
Platelet-lymphocyte ratio	1.013 (1.005-1.021)	0.002

Table 4. Correlation & regression analysis between platelet-lymphocyte ratio and metastatic sentinel lymph node number						
Correlation						
Clinicopathological Factors		N		rho		p value
1-Platelet-lymphocyte ratio 2-Metastatic sentinel lymph node number		67		0.340		0.005
Regression						
Dependent Variable	Independent Variable	B	95% CI for B	t	R	p value
Metastatic sentinel lymph node number	Platelet-lymphocyte ratio	0.004	0.001-0.007	2.392	0,28	0.020

Discussion

In many studies, it has been suggested that neutrophils, lymphocytes, leukocytes, and PLR are important biomarkers that can predict carcinogenesis and metastases [12-14]. Based on this idea, the prognostic significance of PLR has been investigated in many cancer types [15]. It has been stated that increased systemic inflammatory markers such as neutrophil/lymphocyte (NLR) and PLR are associated with poor prognosis in metastatic breast cancer [16]. Although there are many studies on the prognostic importance of PLR in breast cancer, there are limited studies on the relationship between sentinel lymph node metastasis and PLR [17]. To our knowledge, there is no study in the literature examining the relationship between PLR and sentinel lymph node metastasis in breast cancer patients who received neoadjuvant therapy. In our study, we examined the relationship between PLR and sentinel lymph node metastasis in patients with locally advanced breast cancer. We retrospectively calculated the PLR of 67 breast cancer patients after NACT. We observed that high PLR was associated with sentinel lymph node metastasis after neoadjuvant chemotherapy in advanced breast cancer patients. NACT is an effective treatment for locally advanced breast cancer and is increasingly being used [18]. The advantages of NACT include reducing the pathological stage and enabling potential breast-conserving treatment. The high morbidity of axillary dissection has raised SLNB in patients returning to CN0 after NACT. There are debates about the ideal approach for these patients, and data on the oncological safety of SLNB alone are insufficient [19]. Results from single-center studies show that SLNB is safe and local recurrences are rare for this subset of patients [20]. Current recommendations in leading breast cancer guidelines for this patient group are based on weak scientific evidence. However, some surgeons do not support SLNB by citing a lack of data [25]. The ACOSOG-Z1071, SENTINA, and SN-FNAC trials are large-scale studies investigating the safety of SLNB in patients who are cN+ and return to cN0 after NACT [21,22,24]. In these studies, false negative rates of SLNB are generally over 10%. These rates can be improved by marking the biopsied lymph nodes and using methods such as the double mapping technique [26]. To increase the reliability of SLNB in our clinic, we mark the lymph nodes on a biopsy and use a double-mapping method. Removal of a minimum of two or three lymph nodes in sentinel lymph node dissection can reduce false negative rates below 10% [21,22,24,26]. With this in mind, we are making an effort to produce more SLNs (mean number 3.81). The feasibility of sentinel lymph node surgery after NACHT in patients with cN+ can be determined by clinical examination and ultrasound [22,26]. Based on the results of our study, we think that if PLR is high in these patients, more attention should be paid and combined imaging studies should be performed to evaluate the axilla if necessary. The ACOSOG Z0011 study suggested that ALND may not be performed in patients with breast cancer who meet the criteria of the Z0011 study with 1 or 2 sentinel lymph nodes positive [27]. The IBCSG 23-01 study suggested that ALND may not be performed in patients with one or more SLN micrometastases [28]. Since axillary metastases may be limited to SLN in all patients with positive SLN, studies have focused on investigating the non-SLN metastasis prediction model of SLN-positive patients [29]. We think that more care should be taken during SLN or ALND in patients with high PLR, and more lymph nodes should be removed if necessary.

The main limitations of our study are that it is retrospective, single-centered, and has a low number of patients. In addition, the neoadjuvant chemotherapeutic regimens used in the patients included in the study are not homogeneous. However, the validity of the PLR cut-off value we found should be supported by prospective studies with a large sample size. We think that this study is valuable because it is the first study in the literature to question the relationship between PLR and sentinel lymph node metastasis in breast cancer patients who have undergone neoadjuvant treatment.

Conclusion

In summary, PLR plays an important role in predicting sentinel lymph node metastasis as a practical, simple, and inexpensive hematological indicator in patients receiving neoadjuvant chemotherapy for locally advanced breast cancer and may facilitate the selection of an appropriate treatment plan before surgery.

Ethics approval

This retrospective study has been approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (2000).

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Chagpar AB, Martin RC, Scoggins CR, et al. Factors predicting failure to identify a sentinel lymph node in breast cancer. Surgery. 2005;138(1):56-63. doi:10.1016/j.surg.2005.03.003
3. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. Ann Surg Oncol. 2010;17(7):1854-1861. doi:10.1245/s10434-010-0945-z
4. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007;8(10):881-888. doi:10.1016/S1470-2045(07)70278-4
5. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow?. Lancet. 2001;357(9255):539-545. doi:10.1016/S0140-6736(00)04046-0
6. Betsholtz C, Johnsson A, Heldin CH, Westermark B, Lind P, Urdea MS, Eddy R, Shows TB, Philpott K, Mellor AL et al: Cdna sequence and chromosomal localization of human plateletderived growth factor a-chain and its expression in tumour cell lines. Nature 320(6064): 695-699, 1986. PMID: 3754619. DOI: 10.1038/320695a0
7. Ross R, Masuda J, Raines EW, Gown AM, Katsuda S, Sasahara M, Malden LT, Masuko H and Sato H: Localization of pdgf-b protein in macrophages in all phases of atherogenesis. Science 248(4958): 1009-1012, 1990. PMID: 2343305. DOI: 10.1126/science.2343305
8. Heldin CH and Westermark B: Growth factors: Mechanism of action and relation to oncogenes. Cell 37(1): 9-20, 1984. PMID: 6373015. DOI: 10.1016/0092-8674(84)90296-4
9. Miyazono K, Yuki K, Takaku F, Wernstedt C, Kanzaki T, Olofsson A, Hellman U and Heldin CH: Latent forms of tgf-beta: Structure and biology. Ann NY Acad Sci 593: 51-58, 1990. PMID: 2375598. DOI: 10.1111/j.1749-6632.1990.tb16099.x
10. Sporn MB, Roberts AB. Transforming growth factor-beta. Multiple actions and potential clinical applications. JAMA. 1989;262(7):938-941. doi:10.1001/jama.262.7.938
11. Lin EY, Pollard JW. Role of infiltrated leucocytes in tumour growth and spread. Br J Cancer. 2004;90(11):2053-2058. doi:10.1038/sj.bjc.6601705
12. Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol. 2021;14(1):173. Published 2021 Oct 21. doi:10.1186/s13045-021-01187-y
13. Liu Z, Wang Y, Luo X, Wang Y, Zhang L, Wang T. Prevalence of programmed death-1 ligand-1 (PD-L1) and infiltrating lymphocytes in human gastric carcinogenesis. Int J Clin Exp Pathol. 2017;10(12):11754-11759. Published 2017 Dec 1.
14. Zhu H, Cao X. NLR members in inflammation-associated carcinogenesis. Cell Mol Immunol. 2017;14(5):403-405. doi:10.1038/cmi.2017.14
15. Zhang Y, Jiang C, Li J, Sun J, Qu X. Prognostic significance of preoperative neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with gallbladder carcinoma. Clin Transl Oncol. 2015;17(10):810-818. doi:10.1007/s12094-015-1310-2
16. Koh CH, Bhoo-Pathy N, Ng KL, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer. 2015;113(1):150-158. doi:10.1038/bjc.2015.183
17. Morkavuk ŞB, Kocaöz S, Korukluoğlu B. Diagnostic value of Platelet/lymphocyte Ratio (PLR) for predicting sentinel axillary lymph node positivity in early-stage breast cancer compared with ultrasonography. Int J Clin Pract. 2021;75(12):e14939. doi:10.1111/ijcp.14939
18. Rusthoven CG, Rabinovitch RA, Jones BL, et al. The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis. Ann Oncol. 2016;27(5):818-827. doi:10.1093/annonc/mdw046
19. Morrow M, Khan AJ. Locoregional Management After Neoadjuvant Chemotherapy. J Clin Oncol. 2020;38(20):2281-2289. doi:10.1200/JCO.19.02576
20. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol. 2016;42(3):361-368. doi:10.1016/j.ejso.2015.11.019
21. 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. doi:10.1200/JCO.2014.55.7827
22. 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

23. Classe JM, Loaec C, Gimbergues P, 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. 2019;173(2):343-352. doi:10.1007/s10549-018-5004-7

24. Kuehn T, Bauerfeind I, Fehm T, 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. doi:10.1016/S1470-2045(13)70166-9

25. Caudle AS, Bedrosian I, Milton DR, et al. Use of Sentinel Lymph Node Dissection After Neoadjuvant Chemotherapy in Patients with Node-Positive Breast Cancer at Diagnosis: Practice Patterns of American Society of Breast Surgeons Members. Ann Surg Oncol. 2017;24(10):2925-2934. doi:10.1245/s10434-017-5958-4

26. Cavalcante FP, Millen EC, Zerwes FP, Novita GG. Role of Axillary Surgery After Neoadjuvant Chemotherapy. JCO Glob Oncol. 2020;6:238-241. doi:10.1200/JGO.19.00351

27. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918-926. doi:10.1001/jama.2017.11470

28. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomized, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-1393. doi:10.1016/S1470-2045(18)30380-2

29. Yang X, Ma X, Yang W, Shui R. Clinical significance of extranodal extension in sentinel lymph node-positive breast cancer. Sci Rep. 2020;10(1):14684. Published 2020 Sep 7. doi:10.1038/s41598-020-71594-7