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New concept in selecting blue dye injection site effect on clinical outcome of early-stage breast cancer patients: a retrospective cohort

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Abstract

Background Clinico-anatomical review and pilot studies demonstrated that intraparenchymal injection at any site, even those not containing the index lesion, or periareolar injections should provide concordant outcomes to peritumoral injections.

Method This was a single-center retrospective cohort at King Chulalongkorn Memorial Hospital. The electronic medical records of patients were characterized into conventional and new injection concept groups. The inclusion criteria were patients who had either a mastectomy or BCS along with SLNB. We excluded patients who underwent ALND, received neoadjuvant therapy, or had non-invasive breast cancer. The primary outcome was the 5-year rate of breast cancer regional recurrence. Additionally, we reported on the re-operation rate, disease-free period, distant disease-free period, mortality rate, and recurrence rates both locoregional and systemic. Recurrences were identified through clinical assessments and imaging. Surgical technique: 3 ml of 1%isosulfan blue dye was injected, with the injection site varying according to the specific concept being applied. In cases of SSM and NSM following the new concept, the blue dye was injected at non-periareolar and non-peritumoral sites. After the injection, a 10-minute interval was observed without massaging the injection site. Following this interval, an incision was made to access the SLNs, which were subsequently identified, excised, and sent for either frozen section analysis or permanent section examination.

Result There were no significant differences in DFS, DDFS or BCSS between the two groups ($p=0.832$, 0.712, 0.157). Although the re-operation rate in the NI group was approximately half that of the CI group, this difference was not statistically significant ($p=0.355$).

Conclusion Our study suggests that tailoring isosulfan blue dye injection site based on operation type rather than tumor location is safe and effective approach for SLN localization in early-stage breast cancer. However, this study has limitations, including being a single-center study with low recurrence and death cases. Future studies should aim to increase the sample size and follow-up period.

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Keywords Customizing the injection site of blue dye according to the type of surgery is effective for SLN localization., Novel blue dye injection concept providing probable benefit in decreasing re-operation rate, New concept of injecting the intraparenchymal blue dye at a quadrant other than of the index lesion should provide concordant outcome as conventional periareolar site, Alternating site of blue dye injection as per surgical procedure is recommended, to ensure a better visualization of the surgical field

Introduction

Cabanas' work previously demonstrated that the sentinel lymph node (SLN) is the first lymph node to receive drainage directly from a tumor [1–3]. This is critical information, as tumor cells typically spread in a sequential manner from peritumoral lymphatics to the SLN, and then to more distant lymph nodes. Identification and biopsy of SLNs consequently became an ideal nodal staging method for many cancers, including breast [4–7]. More recently, the ACOSOG Z11 Study comparing axillary lymph node dissection (ALND) versus SLN dissection alone in women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 SLNs containing metastases showed no overall survival benefit for the ALND arm, even with long term follow-up [2, 8–10]. The status of the SLN is therefore important in deciding whether ALND is necessary, particularly in early stages, as noted by Bianchi et al. (1994) and Veronesi et al. (2003) [11, 12], usage of which decreased ALND-related lymphedema complications in nearly half of the patients to 1-2% [4, 13].

The concept of dual mapping was first described by Morton et al. in 1992 where cutaneous lymphoscintigraphy was used to identify SLNs for biopsy [5]. While the standard for identifying SLN for biopsy is a dual tracer technique, blue dye alone is also acceptable and can be readily employed in institutions with limited access to nuclear tracer [14]. In most developing countries, including Thailand, single blue dye tracer is predominantly used [15]. There are two main sites of dye injection: peritumoral and periareolar [16]. Each have their own disadvantages on specific surgical procedures [9, 17]. One of the most crucial drawbacks of peritumoral injection is discoloration of the surgical field from blue dye staining. This issue also affects nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) procedures when the blue dye is injected periareolarly. Additionally, this technique can result in prolonged periareolar tattooing, a notable concern in these surgical contexts [18, 19].

According to Sappey et al.(1874), Rouviere(1938) and Grant et al. (1953) breast lymphatics originate as a dense network that lies in the interlobular connective tissue then follow the mammary ducts centripetally to the subareolar lymphatic plexus [5]. Efferent vessels from any quadrant of the breast pass to axillary nodes (75%) and the remainder drain principally to the internal mammary chain (25%) [20, 21]. Review of anatomical and clinical considerations led to a new concept of injecting the intraparenchymal blue dye at a quadrant other than of the index lesion. In the pilot study by Bianchi et al., 30 consecutive patients with clinically node-negative breast cancer, who had positive findings on mammograms and cytology, underwent SLNB using radioguided surgery and vital blue dye mapping. Initially, each patient received either a subdermal (ID) or peritumoral (IP) injection of a radiotracer above the tumor site to localize the first draining lymph node visible on either dynamic or static planar imaging. Then, a second injection of the radiotracer was given, with the site of injection varying for each patient. In the study, group 4 received an above-lesion ID and an IP injection in the opposite quadrant, while group 5 had both above-lesion ID and peritumoral IP [11]. Both resulted in no false SLNs which support the argument that intraparenchymal injection at any site may lead to the same SLN identification rate. Conventional periareolar injections do not change based on tumor location, whether in the periareolar area or any other quadrant. By the same token, this rationale may also apply to our new conceptual proposal that blue dye injection at any quadrant, even those not containing the index lesion, or periareolar injections should provide concordant outcomes to peritumoral injections. Changing the way we do these dye injections should benefit procedures such as lumpectomies, where periareolar injections would be preferred to peritumoral injections, and in NSM and SSM where the injection site should be remote to the periareolar region and to tumor to ensure a better visualization of the surgical field.

We carried out a retrospective review of patients who underwent breast conserving surgery (BCS) or mastectomy with sentinel lymph node biopsy (SLNB) over a period of 5 years to compare the rates of regional recurrence between the traditional approach and the novel injection concept. The secondary outcome was the mean distant-disease free survival duration. The mean disease-free survival, breast cancer specific survival, mortality rate and other sites of recurrence, local and systemic, and mean re-operation rate after BCS are also reported.

Material & method

This study was a single-center retrospective cohort analysis conducted at King Chulalongkorn Memorial Hospital. We reviewed the electronic medical records of patients who underwent breast cancer surgery from May 2016 to

November 2023. The inclusion criteria were patients who had either a mastectomy or BCS along with SLNB. We excluded patients who underwent ALND, received neoadjuvant therapy, or had non-invasive breast cancer.

The study compared demographic data and clinicopathological factors between two groups, defined by the conventional and the new injection sites. The factors analyzed included age, type of surgery, final pathological diagnosis, tumor staging, presence of an extensive intraductal component, extracapsular extension, multifocality/centricity, and adjuvant therapy received. Adjuvant therapies considered were chemotherapy, hormonal therapy, targeted therapy, and radiotherapy.

The primary outcome was the 5-year rate of breast cancer regional recurrence. Additionally, we reported on the re-operation rate, disease-free period, distant disease-free period, mortality rate, and recurrence rates both locoregional and systemic. Recurrences were identified through clinical assessments and imaging.

Surgical technique

3 ml of 1%isosulfan blue dye was injected, with the injection site varying according to the specific concept being applied. In cases of SSM and NSM following the new concept, the blue dye was injected at non-periareolar and non-peritumoral sites. After the injection, a 10-minute interval was observed without massaging the injection site. Following this interval, an incision was made to access the SLNs, which were subsequently identified, excised, and sent for either frozen section analysis or permanent section examination.

Statistical analysis

Electronic medical records were reviewed and analyzed using microsoft excel version 2019. IBM SPSS Statistics ver 26.0(IBM Corp., Armonk, NY, USA) was used for statistical analyses. Continuous variables were reported as mean with standard deviation. Categorical variables were listed as numbers with percentages and compared using Pearson chi-square and fisher's exact tests. Independent T-test statistical significance was defined as P values <0.05 for all variables.

Result

Between May 2016 to November 2023, 979 consecutive patients underwent breast cancer surgery at King Chulalongkorn Memorial Hospital. 316 patients met the inclusion criteria, of which 226 patients had dye injection in the conventional manner (CI group), while 90 patients had dye injection according to our concept (NI group) of any quadrant not containing the index tumor and not periareolar in SSM and NSM (Fig 1). Invasive breast carcinoma is the most common pathology among patients. The clinicopathology of this group (Tumor T stage, Node status, Histopathology, and special features) is shown in Table 1 which shows no statistically significant differences between groups. The tumor sizes in the CI and NI groups were T1 in 127(56.2%) and 51(56.7%) patients, T2 in 93(41.2%) and36(40.0%) patients, T3 in 3(1.3%) and 3(3.3%) patients, and T4 in 3(1.3%) and 0(0.0%) patients respectively, which were not statistically significant ($p=0.879$). Nodal statuses in the CI and NI groups were N0 in 192(85.0%) and 80(88.9%) patients, N1 in 25(11.1%) and 9(10.0%) patients, N2 in 7(3.1%) and N1(1.1%) patients, and N3 in 2(0.9%) and 0(0.0%)

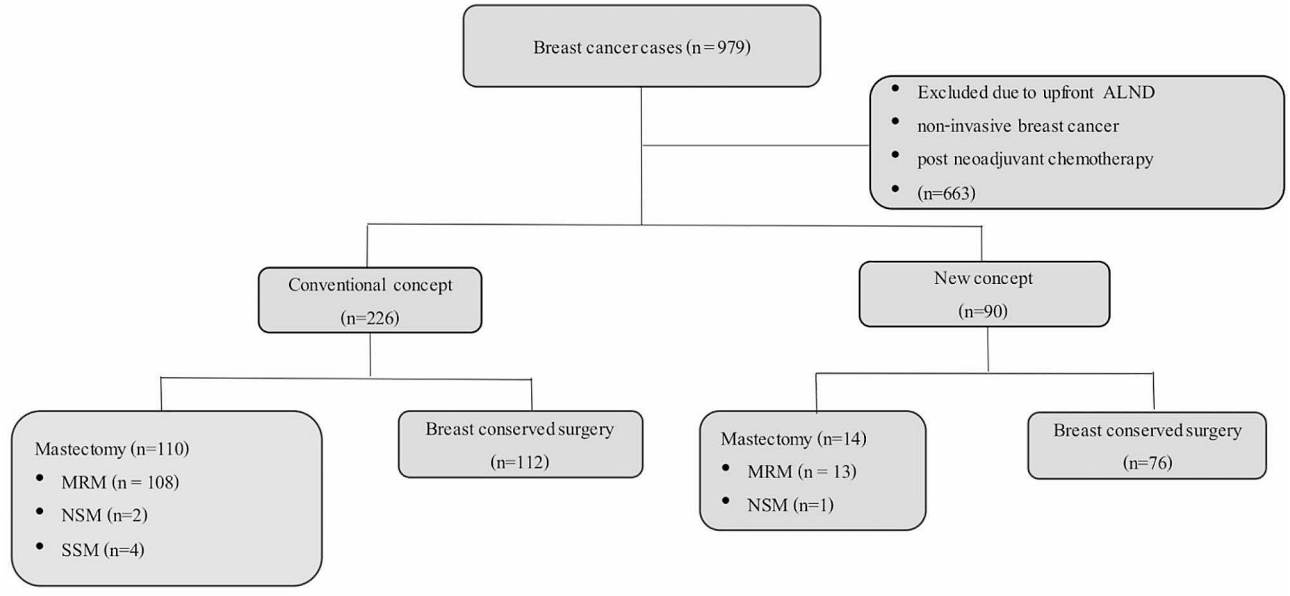

Fig. 1 The diagram illustrated number of patients in each varying injection concept

Table 1 Tumor characteristics and patient demographic information

Variable	Convention injection concept (*n* = 226)	New injection site concept (*n* = 90)	*P*-value
Tumor T stage			0.879
T1	127 (56.2%)	51 (56.7%)	
T2	93 (41.2%)	36 (40.0%)	
T3	3 (1.3%)	3 (3.3%)	
T4	3 (1.3%)	0 (0.0%)	
Node status			0.204
0	192 (85.0%)	80 (88.9%)	
1	25 (11.1%)	9 (10.0%)	
2	7 (3.1%)	1 (1.1%)	
3	2 (0.9%)	0 (0.0%)	
Histopathology			0.934
Ductal carcinoma in situ with microinvasive	6 (2.7%)	4 (4.4%)	
Invasive breast carcinoma	197 (87.2%)	76 (84.4%)	
Invasive lobular carcinoma	5 (2.2%)	3 (3.3%)	
invasive mammary carcinoma	3 (1.3%)	0 (0.00%)	
Invasive papillary carcinoma	1 (0.4%)	0 (0.00%)	
Mucinous	7 (3.1%)	4 (4.4%)	
Tubular	2 (0.9%)	0 (0.00%)	
mixed invasive ductal carcinoma of no special type	3 (1.3%)	2 (2.2%)	
medullary	0 (0.0%)	1 (1.1%)	
Metaplastic carcinoma	2 (0.9%)	0 (0.00%)	
Special feature			
Extensive intraductal component	12 (5.3%)	2 (2.2%)	0.230
Extracapsular extension	6 (2.7%)	2 (2.2%)	0.826
Multi focal lesion	9 (4.0%)	1 (1.1%)	0.189
Mean age (± SD); yrs.	57.62 (± 13.711)	53.37 (± 10.169)	0.003
Mean follow-up period (± SD); yrs.	5.31 (± 2.992)	5.60 (± 0.950)	0.368

Table 2 Treatment regimen of patients in each group

Variable	Conventional injection concept (*n* = 226)	New injection site concept (*n* = 90)	*p*-value
Surgical operation			< 0.001
MRM with SLNB	108 (47.8%)	13 (14.4%)	
NSM with SLNB	2 (0.9%)	1 (1.1%)	
SSM with SLNB	4 (1.8%)	0 (0.0%)	
Breast conserving surgery with SLNB	112 (49.6%)	76 (84.4%)	
Chemotherapy			0.400
C1	43 (19.0%)	11 (12.2%)	
C2	58 (25.7%)	27 (30.0%)	
C3	5 (2.2%)	1 (1.1%)	
No	120 (53.1%)	51 (56.7%)	
Hormonal therapy			0.713
H1	125 (55.3%)	44 (48.9%)	
H2	3 (1.3%)	0 (0.00%)	
No	49 (21.7%)	40 (44.4%)	
Other	49 (21.7%)	6 (6.7%)	
Targeted therapy			0.304
Yes	17 (7.5%)	10 (11.1%)	
No	209 (92.5%)	80 (88.9%)	
Radiotherapy			< 0.001
Yes	134 (59.3%)	78 (86.7%)	
No	92 (40.7%)	12 (13.3%)	

Table 3 Description of events

Events	Conventional injection site concept (*n* = 226)	New injection site concept (*n* = 90)
Local recurrence	2	1
Regional recurrence	1	1
Distant recurrence	2	2
Death	2	1

patients, respectively. There were no statistically significant differences between each group ($p=0.204$). There were no statistical differences between both groups in terms of histopathology ($p=0.934$), the most common of which was invasive carcinoma in both groups, consisting of 197(87.2%) and 76(84.4%) cases in CI and NI groups respectively. Special features including extensive intraductal components ($p=0.230$), extracapsular extension($p=0.826$) and multi-focal lesions ($p=0.189$) were not significantly different between both groups. Statistically significant differences were found only in the administration of radiation therapy and type of surgical procedure between the two groups ($p<0.001$), while adjuvant chemotherapy, adjuvant hormonal therapy and targeted therapy were equally distributed between both groups (Table 2). Most patients received BCS with SLNB followed closely by MRM with SLNB, in CI group, which was also true of the NI group, although the ratio of patients who underwent BCS was higher (49.6% vs. 84.4% respectively). Very few regional recurrences occurred in each group. The mean follow-up period, disease free survival and overall survival of patients who underwent conventional and new injection site dye administration are demonstrated in Table 4.

After a mean follow-up of 5.31 and 5.60 years in the CI and NI groups respectively, nine patients experienced recurrence. Five patients in the CI group experienced local ($n=2$), regional ($n=1$) or distant ($n=2$) recurrence. Four patients in the NI group experienced local ($n=1$), regional ($n=1$), or distant ($n=2$) recurrence (Table 3).

The mean re-operation rate after BCS was 4.42% in the CI group and 2.22% in the NI group ($p=0.355$). The mean 5-year disease free survival (DFS) was 2.735 years (95%CI, 2.243–3.226) and 1.678 years (95%CI, 0.457–2.898) in the CI and NI groups, respectively ($p=0.832$).

The mean distant disease-free survival was 2.714 years (95%CI, 2.166–3.262) in the CI group and 2.466 years (95%CI, 1.194–3.738) in the NI group ($p=0.712$). The mean of breast cancer-specific survival was 3.619 years (95%CI, 3.158–4.081) in the CI group and 2.921 years in the NI group ($p=0.157$) (Table 4).

Discussion

Anatomically, drainage of SLNs occur through a dense network that lies in the interlobular connective tissue then follows the mammary ducts centripetally to the subareolar lymphatic plexus. It follows that lymph from most parts of the breast enters the subareolar plexus before entering the axillary SLN [2, 3]. This assumption also aligns with a study by Bianchi et al., where there was no false negative rate in group 4 where patients were injected with an above-lesion ID and an IP injection in the opposite quadrant, and in group 5 where patients had both above-lesion ID and peritumoral IP [11]. This suggests that intraparenchymal injection at any site irrespective of index tumor location may lead to the same identification rate.

The gold standard for identifying SLNs for biopsy is a dual tracer technique but in most developing countries including Thailand blue dye play a key role as a single identifying tracer due to limited access to nuclear tracer [14]. However, this approach comes with the problem of surgical plane discoloration when the isosulfan blue dye is injected peritumorally [14].

Based on an anatomical and clinical review, we propose a new concept for the injection site of blue dye, aiming to minimize local adverse events such as staining from the dye. Prior studies have demonstrated that periareolar injections are effective in SNLs localization and that this injection site need not vary with the tumor's location [14]. This led us to develop a new paradigm in isosulfan blue injection where blue dye is injected in a quadrant different from the lesion's location. For instance, when BCS is planned, peritumoral injection is not done and instead, periareolar injection or injection in a quadrant different to that of the index tumor is completed to spare the surgical plane around the tumor. If SSM is instead planned, neither peritumoral nor periareolar injections are performed, as dye staining and surgical plane discoloration both peritumorally and periareolarly are problematic. Instead, parenchymal injection is performed in a quadrant different from that of the tumor. We propose that this should yield clinical outcomes comparable to injections in the same quadrant as the index lesion.

In our study, age was the only significant factor that varied between both groups. The adjuvant treatment regimen was also mostly similar, and only radiation therapy was found to be significantly different between the two groups. A significant difference in surgical operation selected was observed, mainly influenced by patient age, tumor characteristics, and surgeon preference [13, 15]. The mean follow-up time for CI and NI groups did not significantly differ ($p=0.368$).Due to a limited number of SSM and NSM cases, we focused mainly on the re-operation rate of patients who underwent BCS. Although the re-operation rate in the NI group was approximately half that of the CI group, this difference was not statistically significant ($p=0.355$) due to the small sample size. There were no significant differences in DFS, DDFS or BCSS between the two groups. Extending the follow-up time is critical to investigate the clinical difference between groups. [22]

There are several restrictions on this study. First off, the fact that this is a single-center study may limit how broadly the results can be applied. The study's power is additionally impacted by the small number of cases. Nonetheless, this work would be crucial in establishment of future studies of the concept that customizing the injection site of isosulfan blue dye according to the type of surgery, instead of the tumor's location, is a safe and effective approach for SLN localization in early-stage breast cancer. Further study with larger sample sizes and longer follow-up times was required to reach a definite conclusion.

Conclusion

Our study suggests that tailoring isosulfan blue dye injection site based on operation type rather than tumor location is safe and effective for SLN localization. Our five-year retrospective analysis at a single center revealed that this alternative injection method does not impact clinical outcomes while offering the advantage of reducing surgical site staining during the procedure. Ultimately further studies with greater patient numbers are required to standardize this technique.

Table 4 Comparison of survival outcomes between conventional and new concept

	Conventional injection site concept ($n=226$)	New injection site concept ($n=90$)	*P*-value
re-operation rate after BCS(%);case	10 (4.42%)	2 (2.22%)	0.355
Mean disease free survival (DFS) (95%CI); yrs.	2.735(2.243–3.226)	1.678(0.457–2.898)	0.832
Mean distant disease-free survival (DDFS)(95%CI); yrs.	2.714 (2.166–3.262)	2.466 (1.194–3.738)	0.712
Mean breast cancer-specific survival (BCSS) (95%CI); yrs.	3.619(3.158–4.081)	2.921*	0.157

*only one case of death

Author contributions
P.B - Writing – first author, original draft, Conceptualization, Data curation, MethodologyV.V - Writing – review & editing, Formal analysis, MethodologyB.L– Software, SupervisionS.M.– Validation, VisualizationK.T. - Formal analysisP.V- ConceptualizationN.T. - Data curation, SoftwareM.V.– Corresponding author, Supervision, Writing – review & editing, Project administration.

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Data availability
The Datasets generated and/or analyzed in the current study are not publicly available due to the individual's privacy issue but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was certified by the Institutional Review Board of the faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the study in compliance with the international guidelines for human research protection as declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP). The certified Expedited Review approval is COA No. 1530/2023.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Center MSKC. About Your Sentinel Lymph Node Biopsy, in Memorial Sloan Kettering Cancer Center. 2023.
2. Dogan NU, et al. The basics of Sentinel Lymph Node Biopsy: anatomical and pathophysiological considerations and clinical aspects. J Oncol. 2019;2019:p3415630.
3. Heerdt AS. Lymphatic mapping and Sentinel Lymph Node Biopsy for breast Cancer. JAMA Oncol. 2018;4(3):431–431.
4. Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. Lancet Oncol. 2014;15(8):e351–62.
5. Allweis TM, et al. Current controversies in sentinel lymph node biopsy for breast cancer. Breast. 2003;12(3):163–71.
6. Galimberti V, et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. Eur J Surg Oncol. 2014;40(10):1203–8.
7. Caruso G, et al. Lymphoscintigraphy with peritumoral injection versus lymphoscintigraphy with subdermal periareolar injection of technetium-labeled human albumin to identify sentinel lymph nodes in breast cancer patients. Acta Radiol. 2014;55(1):39–44.
8. Engel J, Emeny RT, Hölzel D. Positive lymph nodes do not metastasize. Cancer Metastasis Rev. 2012;31(1–2):235–46.
9. Ferrucci M, Franceschini G, Douek M. New techniques for sentinel node biopsy in breast cancer. Translational Cancer Res, 2018: p. S405–17.
10. Krag DN, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
11. Bianchi P, et al. Different sites and modes of Tracer Injection for Mapping the Sentinel Lymph Node in patients with breast Cancer. Tumori J. 2000;86(4):307–8.
12. Veronesi U, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010;251(4):595–600.
13. Reimer T, et al. Is Axillary Sentinel Lymph Node Biopsy required in patients who undergo primary breast surgery? Breast Care (Basel). 2018;13(5):324–30.
14. Kavallaris A, Camara O, Runnebaum IB. Subareolar blue dye only injection sentinel lymph node biopsy could reduce the numbers of standard axillary lymph node dissection in environments without access to nuclear medicine. J Cancer Res Clin Oncol. 2008;134(6):667–72.
15. Vongsaisuwon M, Pongpirul K, Chatamara K. Clinical outcomes and surgical preferences for breast-conserving surgery and mastectomy: a propensity score-matched analysis. Asian Biomed. 2019;13(3):95–100.
16. Klimberg VS, et al. Subareolar Versus Peritumoral Injection for Location of the Sentinel Lymph Node. Ann Surg. 1999;229(6):860.
17. Malhotra C, et al. Efficacy of Periareolar Versus Peritumoral Injection of TC99-Labelled Sulphur Colloid and Methylene Blue Dye for Detection of Sentinel Lymph Node in patients with early breast Cancer: a comparative study. Indian J Surg Oncol. 2021;12(1):119–23.
18. Noguchi M, Inokuchi M, Zen Y. Complement of peritumoral and subareolar injection in breast cancer sentinel lymph node biopsy. J Surg Oncol. 2009;100(2):100–5.
19. Yap RV, De La FM, Serna. Outcomes of Sentinel Lymph Node Biopsy using Blue Dye Method for early breast Cancer - A single-Institution experience in the Philippines. Breast Cancer (Dove Med Press). 2020;12:37–44.
20. Skandalakis JE, Shiffman MA. 2009, Springer Berlin Heidelberg: Berlin, Heidelberg. 3–24.
21. Suami H, Pan WR, Taylor GI. Historical review of breast lymphatic studies. Clin Anat. 2009;22(5):531–6.
22. de Moraes FCAd G, Alves VFC, Priantti JN, Gomes GC, Carnevalli SVB, Madeira T, Vilbert M, Stecca C, Figueroa Magalhães MC, et al. Cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone for HR-Positive, HER-2-Negative early breast Cancer: Meta-Analysis of Phase III randomized clinical trials. J Personalized Med. 2024;14(5):464. https://doi.org/10.3390/jpm14050464.

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