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The Effect of Intradermal Methylene Blue Administration on Hemodynamic Stability Under General Anesthesia in Breast Surgery: A Prospective Observational Study

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Abstract

Introduction: Methylene blue (MB) is widely used for sentinel lymph node biopsy (SLNB) in breast cancer surgery, but its potential systemic hemodynamic effects after local administration remain unclear. This study evaluated intraoperative hemodynamic patterns associated with intradermal MB use under standardized general anesthesia.

Materials and Methods: This prospective observational study included 254 adult patients undergoing elective breast surgery, categorized according to intraoperative MB exposure (MB group, n = 137; comparison group, n = 117). General anesthesia was standardized using bispectral index monitoring. Mean arterial pressure (MAP) and heart rate (HR) were recorded via invasive arterial monitoring at baseline and predefined time points up to 60 minutes. Secondary outcomes included intraoperative hypotension incidence and vasopressor requirements.

Results: Baseline characteristics were comparable between groups. The MB group showed higher MAP at 5, 10, 15, and 60 minutes ($p < 0.05$) and higher HR at all post-injection time points ($p < 0.01$). Intraoperative hypotension did not differ significantly between groups (48.9% vs. 60.7%, $p = 0.060$), and vasopressor requirements were comparable. In adjusted linear regression, MB exposure remained associated with higher MAP at 5, 10, 15, and 60 minutes after adjustment for age, BMI, ASA physical status, baseline MAP, and operation duration.

Conclusions: Intradermal MB during SLNB was associated with higher MAP at several time points and higher HR early intraoperatively. However, similar hypotension incidence and vasopressor requirements suggest limited overall clinical relevance under standardized general anesthesia. Because systemic absorption was not assessed, these findings should be interpreted as associations, not evidence of a direct mechanistic or causal effect.

Key words: Methylene blue; sentinel lymph node biopsy; hemodynamics; mean arterial pressure; breast surgery

Introduction

Breast cancer continues to be a leading malignancy worldwide, requiring precise surgical strategies for both treatment and staging. Sentinel lymph node biopsy (SLNB) is currently the gold standard for axillary staging in clinically node-negative patients. By providing a minimally invasive alternative to axillary lymph node dissection, SLNB significantly reduces postoperative complications, most notably lymphedema (1). The success of this procedure depends on accurately identifying the first draining lymph node, which is typically achieved using radioisotopes, vital dyes, or a combination of both. Methylene blue (MB) is frequently used in SLNB because it is cost-effective, readily available, and provides high identification rates. When injected intradermally, MB is rapidly taken up by the lymphatics, allowing for visual mapping (2). However, beyond its role as a diagnostic dye, MB is a pharmacologically active agent. It acts as a potent inhibitor of guanylate cyclase, effectively blocking the nitric oxide (NO) pathway and preventing cGMP-mediated vasodilation (3). Because of these properties, MB has been utilized in critical care as a rescue therapy for refractory hypotension in conditions like septic shock or vasoplegic syndrome after cardiac surgery (4). By inhibiting the NO-cGMP pathway, MB can increase systemic vascular resistance and improve mean arterial pressure (MAP) in patients who do not respond to standard vasopressors. General anesthesia is frequently associated with intraoperative hemodynamic fluctuations, and hypotension remains clinically important because of its potential association with impaired organ

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perfusion and adverse perioperative outcomes. Although methylene blue is administered locally during sentinel lymph node biopsy, limited systemic absorption may still occur. However, intraoperative hemodynamic responses are inherently multifactorial and may be influenced by anesthetic depth, analgesic administration, surgical stimulation, fluid management, and patient-related characteristics. Therefore, the potential hemodynamic relevance of intradermal methylene blue should be interpreted cautiously in the context of these perioperative variables. Accordingly, rather than aiming to establish a direct causal effect, this prospective observational study sought to explore intraoperative hemodynamic patterns associated with intradermal methylene blue exposure in patients undergoing breast surgery under standardized general anesthesia. The primary aim was to evaluate the association between methylene blue exposure and changes in mean arterial pressure (MAP) and heart rate (HR). Secondary objectives were to assess the incidence of intraoperative hypotension and vasopressor requirements.

Materials and Methods

This prospective observational study was conducted at the Anesthesiology and Reanimation Clinic of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between August 2025 and January 2026, following approval from the Institutional Ethics Committee (Approval No: 2025-06/85). The study was performed in accordance with the ethical principles of the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT07040540). This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies. We included 254 adult patients aged 18 to 70 years who were scheduled for elective breast surgery under general anesthesia. Patients were excluded if they had a known allergy to methylene blue, significant pre-existing cardiovascular disease, or were pregnant.

Participants were categorized according to intraoperative exposure to methylene blue used for sentinel lymph node mapping. Patients who received intradermal methylene blue constituted the MB exposure group (n = 137), whereas those in whom alternative mapping methods (e.g., radiocolloid alone) were used formed the comparison group (n = 117). The decision to administer methylene blue was based on the attending surgeon's routine clinical preference and institutional practice, and no randomization or allocation was performed. This approach reflects real-world clinical practice and preserves the observational nature of the study. General anesthesia was standardized across all patients. Induction was achieved using intravenous propofol (2–3 mg/kg), fentanyl (1–2 μg/kg), and rocuronium (0.6 mg/kg), followed by airway management with endotracheal intubation in all cases. Maintenance of anesthesia was provided with sevoflurane in an oxygen–air mixture, titrated to maintain a bispectral index (BIS) value between 40 and 60, in order to ensure a consistent depth of anesthesia. Intraoperative analgesia was provided with intravenous fentanyl administered at induction, with additional boluses given as needed based on clinical judgment and hemodynamic responses. Continuous opioid infusions were not routinely used. Although anesthetic depth was carefully controlled using BIS monitoring, variability in analgesic requirements, surgical stimulation, and individual patient response was recognized as a potential source of hemodynamic variability. Upon arrival in the operating room, standard non-invasive monitoring was applied. Following the induction of anesthesia, invasive arterial blood pressure monitoring was established in all participants via a 20-gauge radial artery catheter to allow precise and continuous hemodynamic measurement. Because methylene blue may interfere with pulse oximetry readings, SpO_2 values after dye administration were interpreted together with the overall clinical context, including arterial waveform quality, invasive blood pressure, heart rate, ventilation parameters, and arterial blood gas assessment when clinically indicated. No persistent clinically relevant desaturation requiring a change in the intraoperative management protocol was documented. This approach enabled real-time recording of mean arterial pressure (MAP) and heart rate (HR), minimizing the limitations associated with intermittent cuff measurements. Baseline hemodynamic values were defined as the average of three consecutive measurements obtained in the preoperative holding area. Methylene blue was used specifically for sentinel lymph node mapping and was not determined by the type of breast surgery itself. Therefore, patients undergoing different breast surgical procedures could receive methylene blue if sentinel lymph node mapping was planned. In the methylene blue exposure group, 5 mL of 1% methylene blue was administered intradermally into the tumor quadrant or subareolar region, followed by gentle massage for approximately 10 minutes to facilitate lymphatic uptake. Hemodynamic parameters were recorded at predefined intraoperative intervals: prior to

induction, immediately before methylene blue injection in the exposure group, and at 5, 10, 15, 30, and 60 minutes following injection. BIS monitoring was used throughout anesthesia maintenance to guide anesthetic depth, with sevoflurane titrated to maintain BIS values within the target range of 40–60. In the comparison group, corresponding measurement time points were defined according to the same intraoperative reference period. Because methylene blue was not administered in this group, control time points were aligned with the average timing of methylene blue injection in the MB group after induction and stabilization of anesthesia. This approach was used to improve temporal comparability between groups during the early intraoperative period. Hypotension was defined as a mean arterial pressure (MAP) below 65 mmHg or a decrease of more than 20% from baseline values. Vasopressor requirement was recorded as the presence or absence of vasopressor administration at each predefined intraoperative time point. The primary outcome of the study was the evaluation of intraoperative hemodynamic patterns, assessed through changes in MAP and heart rate (HR) over time in relation to methylene blue exposure.

Secondary outcomes included the incidence of intraoperative hypotensive episodes and vasopressor requirements at predefined intraoperative time points. The sample size was determined based on preliminary pilot observations, in which a difference of 10 mmHg in mean arterial pressure (MAP) was considered clinically meaningful in the context of intraoperative hemodynamic management (5). To achieve a statistical power of 80% with a two-sided significance level (α) of 0.05 and an anticipated effect size of 0.4, a minimum of 110 patients per group was required. The pilot dataset was not included in the final analysis. To account for potential data loss and enhance the robustness of the study, a total of 254 patients were ultimately enrolled.

Results

The baseline demographic and clinical characteristics of the study population are presented in Table 1. There were no statistically significant differences between the MB and control groups in terms of age, body mass index (BMI), ASA physical status, or duration of surgery.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Groups

		MB Group n=137	Control Group n= 117	p-value
Age (years), mean ± SD		54.37 ± 12.34	52.25 ± 11.39	0.158[a]
BMI (kg/m²), median (Q1–Q3)		27.92 (23-31)	27.24 (23-30)	0.356[b]
Operation Duration (min), median (Q1-Q3)		101 (77-120)	98 (85-120)	0.382[b]
ASA Physical Status, n (%)	I	2 (2)	2 (2)	0.206[c]
	II	99 (72)	95 (81)	
	III	36 (26)	20 (17)	

Values are expressed as mean ± standard deviation (SD), median (interquartile range [Q1–Q3]), or number (percentage) where appropriate. MB: Methylene Blue; BMI: Body Mass Index; ASA: American Society of Anesthesiologists. [a]Independent samples t-test. [b]Mann–Whitney U test. [c]Fisher's exact test. Statistical significance was defined as $p < 0.05$.

Table 2: Intraoperative MAP Trends

Time Point	MB Group (n=137)	Control Group (n=117)	p-value
Baseline	97.74 ± 12.70	97.04 ± 12.52	0.662
5 min	97.37 ± 12.79	88.34 ± 11.62	<0.001
10 min	93.09 ± 12.47	84.69 ± 10.66	<0.001
15 min	85.64 ± 12.66	82.30 ± 11.26	0.029
30 min	81.81 ± 13.41	79.78 ± 12.28	0.213
60 min	83.60 ± 13.33	78.37 ± 14.11	0.003

Values are presented as mean ± standard deviation (SD). MB: Methylene Blue; MAP: Mean Arterial Pressure. Between-group comparisons were performed using the independent samples t-test. Hemodynamic data were obtained via continuous invasive arterial monitoring.

Table 3: Comparison of Intraoperative Heart Rate Between the Methylene Blue and Control Groups Over Time

Time Point	MB Group n=137	Control Group n= 117	p-value
Baseline	83.15 ± 12.53	83.44 ± 12.26	0.857
5 min	88.10 ± 13.11	80.00 ± 12.04	<0.001
10 min	84.80 ± 12.83	76.67 ± 11.96	<0.001
15 min	82.60 ± 12.78	74.72 ± 11.71	<0.001
30 min	80.36 ± 12.01	73.09 ± 10.72	<0.001
60 min	73.67 ± 11.18	69.56 ± 12.21	0.006

Values are presented as mean ± standard deviation (SD). MB: Methylene Blue; HR: Heart Rate. Independent samples t-test. A p-value < 0.05 was considered statistically significant.

Table 4: Intraoperative Hypotension and Vasopressor Requirements

Outcome / Time Point	MB Group (n=137)	Control Group (n=117)	Total (n=254)	p-value
Patients with ≥1 hypotensive episode, n(%)	67 (48.9)	71 (60.7)	138 (54.3)	0.060[b]
Vasopressor requirement at 5 min, n (%)	2 (1.5)	2 (1.7)	4 (1.6)	0.627[a]
Vasopressor requirement at 10 min, n (%)	4 (2.9)	2 (1.7)	6 (2.4)	0.690[a]
Vasopressor requirement at 15 min, n (%)	12 (8.8)	8 (6.8)	20 (7.9)	0.571[b]
Vasopressor requirement at 30 min, n (%)	14 (10.2)	12 (10.3)	26 (10.2)	0.992[b]
Vasopressor requirement at 60 min, n (%)	23 (16.8)	15 (12.8)	38 (15.0)	0.337[b]

Values are presented as number and percentage. Hypotension was defined as MAP <65 mmHg or a decrease of more than 20% from baseline at any predefined intraoperative measurement point. The first row represents patients who experienced at least one hypotensive episode during the intraoperative observation period. Subsequent rows represent patients requiring vasopressor support at each predefined time point. MB: Methylene Blue; MAP: Mean Arterial Pressure. [a] Fisher's exact test, [b] Pearson chi-square test. Statistical significance was defined as $p < 0.05$.

These findings indicate that the two groups were comparable at baseline with respect to the available demographic and clinical variables. Intraoperative MAP measurements are presented in Table 2. Baseline MAP values were comparable between the MB and control groups (97.74 ± 12.70 vs. 97.04 ± 12.52 mmHg, respectively; $p = 0.662$). MAP values were significantly higher in the MB group at 5 minutes (97.37 ± 12.79 vs. 88.34 ± 11.62 mmHg; $p < 0.001$), 10 minutes (93.09 ± 12.47 vs. 84.69 ± 10.66 mmHg; $p < 0.001$), 15 minutes (85.64 ± 12.66 vs. 82.30 ± 11.26 mmHg; $p = 0.029$), and 60 minutes (83.60 ± 13.33 vs. 78.37 ± 14.11 mmHg; $p = 0.003$). No significant difference was observed at 30 minutes (81.81 ± 13.41 vs. 79.78 ± 12.28 mmHg; $p = 0.213$). Intraoperative HR measurements are presented in Table 3. Baseline HR values were comparable between the MB and control groups ($p = 0.857$). HR values were significantly higher in the MB group at all measured time points, including 5, 10, 15, 30, and 60 minutes (all $p < 0.01$). Intraoperative hypotension and vasopressor requirements are presented in Table 4. The

Table 5: Univariable and Multivariable Linear Regression Analyses for Intraoperative MAP Values

Outcome	Univariable β for MB exposure	95% CI	p-value	Adjusted β for MB exposure	95% CI	p-value
MAP at 5 min	9.03	5.99 to 12.07	<0.001	8.70	6.96 to 10.43	<0.001
MAP at 10 min	8.40	5.51 to 11.30	<0.001	8.31	6.08 to 10.54	<0.001
MAP at 15 min	3.34	0.35 to 6.32	0.029	3.14	0.54 to 5.73	0.018
MAP at 30 min	2.03	-1.17 to 5.23	0.213	1.64	-1.41 to 4.69	0.291
MAP at 60 min	5.23	1.84 to 8.63	0.003	4.82	1.54 to 8.11	0.004

Univariable models included only methylene blue exposure as the independent variable. Multivariable models were adjusted for age, BMI, ASA physical status, baseline MAP, and operation duration. MB exposure was coded as 1 for patients receiving methylene blue and 0 for the control group. β values indicate the mean difference in MAP associated with MB exposure. Positive β values indicate higher MAP values in the MB group. CI: Confidence Interval; MAP: Mean Arterial Pressure; MB: Methylene Blue.

incidence of intraoperative hypotension, defined as MAP <65 mmHg or a decrease of more than 20% from baseline at any predefined intraoperative measurement point, was 48.9% (67/137) in the MB group and 60.7% (71/117) in the control group. This difference did not reach statistical significance ($p = 0.060$). Similarly, there were no statistically significant differences between the MB and control groups in vasopressor requirements at 5, 10, 15, 30, or 60 minutes. Univariable and multivariable linear regression analyses for intraoperative MAP values are presented in Table 5. In the univariable analyses, MB exposure was associated with higher MAP at 5, 10, 15, and 60 minutes. After adjustment for age, BMI, ASA physical status, baseline MAP, and operation duration, MB exposure remained associated with higher MAP at 5 minutes (adjusted $\beta = 8.70$ mmHg, 95% CI: 6.96 to 10.43; $p < 0.001$), 10 minutes (adjusted $\beta = 8.31$ mmHg, 95% CI: 6.08 to 10.54; $p < 0.001$), 15 minutes (adjusted $\beta = 3.14$ mmHg, 95% CI: 0.54 to 5.73; $p = 0.018$), and 60 minutes (adjusted $\beta = 4.82$ mmHg, 95% CI: 1.54 to 8.11; $p = 0.004$). No significant association was observed at 30 minutes in either the univariable or multivariable model.

Ethical approval: This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (approval no. 2025-06/85).

Statistical analysis: Statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality and are presented as mean ± standard deviation (SD) or median (Q1-Q3), as appropriate. Between-group comparisons of baseline characteristics were performed using the independent samples t-test or Mann–Whitney U test, depending on data distribution. Categorical variables, including ASA physical status, intraoperative hypotension incidence, and vasopressor requirements, were analyzed using the chi-square test or Fisher's exact test, as appropriate. To further evaluate whether the association between methylene blue exposure and intraoperative MAP values persisted after adjustment for potential confounders, univariable and multivariable linear regression analyses were performed for each predefined MAP measurement time point. In the multivariable models, methylene blue exposure was included as the main independent variable, and the models were adjusted for age, BMI, ASA physical status, baseline MAP, and operation duration. Operation duration was included as an available perioperative variable reflecting surgical time and procedural complexity. Results are presented as β coefficients with 95% confidence intervals. Given the repeated measurement structure of intraoperative hemodynamic data, changes in MAP and heart rate (HR) over time were evaluated using a repeated-measures analytical approach, taking into account within-subject correlations. Post hoc comparisons were performed with appropriate adjustment for multiple testing to reduce the risk of type I error. A two-sided p-value < 0.05 was considered statistically significant. Given the observational design of the study, all statistical findings were interpreted with caution, acknowledging the potential influence of residual confounding.

Discussion

This prospective observational study showed that intradermal administration of methylene blue (MB) during sentinel lymph node biopsy was associated with higher intraoperative MAP values at several predefined time points and higher HR values throughout the observation period. However, the incidence of intraoperative hypotension and vasopressor requirements did not differ significantly between groups. Additional regression analyses showed that the association between MB exposure and higher MAP values persisted after adjustment for age, BMI, ASA physical status, baseline MAP, and operation duration. Nevertheless, given the observational design and the absence of random allocation, these findings should be interpreted as adjusted associations rather than evidence of an independent causal effect. Although MAP and HR differed statistically between groups, the clinical relevance of these differences appears limited in the present cohort. This interpretation is supported by the absence of significant differences in both intraoperative hypotension incidence and vasopressor requirements. In addition, mean MAP values in both groups remained above the commonly used hypotension threshold of 65 mmHg at the predefined measurement points. Therefore, the observed differences may represent measurable hemodynamic variation rather than clinically important instability. However, because postoperative organ outcomes were not assessed, subtle clinical consequences of these intraoperative changes cannot be excluded. The use of MB in sentinel lymph node biopsy is based on local administration to facilitate lymphatic mapping, and this route is expected to result in slower and more limited systemic absorption than intravenous administration (6–8). In the present study, MB exposure was associated with higher

MAP values at several predefined time points. This direction is biologically plausible considering the known pharmacological properties of methylene blue, particularly its inhibitory effect on the nitric oxide–soluble guanylate cyclase pathway and its potential to increase vascular tone (9–12). In septic shock and other vasodilatory states, intravenous MB has been used as an adjunctive therapy to counteract nitric oxide-mediated vasodilation and reduce vasopressor requirements (13,14). However, the doses and routes of administration used in sentinel lymph node biopsy differ substantially from those used in critical care settings. Therefore, although the observed MAP pattern is directionally consistent with the known pharmacology of MB, it should not be interpreted as evidence of a direct vasopressor effect. Because plasma MB concentrations were not measured and systemic absorption was not directly assessed, this explanation remains a biologically plausible interpretation rather than a mechanism demonstrated by the present data. The higher heart rate observed in the MB exposure group, despite standardized anesthesia depth using BIS monitoring, may reflect the combined influence of perioperative sympathetic responses, surgical stimulation, analgesic variability, and individual patient characteristics. Although ephedrine has β-agonist properties that can increase heart rate, vasopressor requirement as a binary variable was comparable between groups. However, because cumulative ephedrine dose was not available, the contribution of vasopressor dosing to the observed HR differences could not be fully assessed. Given the observational design, the relative contribution of these factors could not be fully distinguished. From a clinical perspective, awareness of potential intraoperative changes in MAP and HR during the use of methylene blue for SLNB may assist anesthesiologists in interpreting hemodynamic fluctuations more accurately. Because BIS monitoring was used to guide anesthetic depth throughout anesthesia maintenance, these variations should be interpreted within the broader perioperative context rather than attributed solely to inadequate anesthetic depth or analgesia. Careful interpretation may help avoid unnecessary interventions and support more appropriate intraoperative decision-making. Although the local use of methylene blue is generally considered safe, local adverse effects such as skin and subcutaneous reactions have been reported (6,7). Systemic adverse effects are rare but may be clinically relevant in specific populations, particularly in patients receiving serotonergic medications or those with glucose-6-phosphate dehydrogenase (G6PD) deficiency (14). Accordingly, while methylene blue is widely used in routine practice, its perioperative safety profile should be considered on an individual basis, especially in patients with known risk factors. In addition, methylene blue may transiently interfere with pulse oximetry readings and produce falsely low SpO_2 values. In the present study, SpO_2 values were interpreted together with clinical and hemodynamic parameters, and no persistent clinically relevant desaturation requiring protocol modification was documented.

Study limitations: This study has several important limitations. First, its non-randomized observational design introduces the potential for selection bias, as the decision to administer methylene blue was based on routine clinical preference. Second, detailed surgical procedure subtypes, such as breast-conserving surgery, mastectomy, axillary lymph node dissection, or reconstruction, were not included as separate variables in the present analysis. Although operation duration was included in the adjusted models as an available perioperative variable, residual confounding related to surgical procedure type cannot be excluded. Third, intraoperative hemodynamic parameters are influenced by multiple interacting factors. Although BIS monitoring was used to guide anesthetic depth throughout anesthesia maintenance, detailed BIS values at each predefined time point were not available for quantitative comparison between groups; therefore, between-group comparability of BIS values could not be statistically demonstrated. In addition, vasopressor use was analyzed as a binary variable at predefined time points, and cumulative ephedrine dose was not available for quantitative comparison between groups. Variability in analgesic management, nociceptive stimuli, fluid administration, and individual patient response may also have contributed to residual confounding. Fourth, plasma methylene blue concentrations were not measured, and systemic absorption after intradermal administration was not directly assessed. Therefore, the present study cannot establish a dose–response relationship or confirm a pharmacodynamic mechanism underlying the observed hemodynamic differences. Finally, the analysis was restricted to the first 60 minutes of the intraoperative period, precluding assessment of longer-term hemodynamic effects and clinical outcomes. Future prospective studies with controlled designs, standardized analgesic protocols, detailed surgical characterization, quantitative BIS reporting, cumulative vasopressor dose assessment, and integrated pharmacokinetic

measurements are needed to further clarify the systemic effects of locally administered methylene blue.

Conclusion

In conclusion, intradermal administration of methylene blue during sentinel lymph node biopsy was associated with higher intraoperative MAP values at several time points and higher HR values during the early intraoperative period. However, these differences were not accompanied by significant differences in intraoperative hypotension incidence or vasopressor requirements, suggesting limited clinical relevance under standardized general anesthesia. Given the observational design, these findings should be interpreted as associations rather than evidence of a causal or independent effect. Although the observed hemodynamic pattern may be biologically plausible considering the known pharmacological properties of methylene blue, systemic absorption was not assessed, and no direct mechanistic inference can be made from the present data. Further controlled studies incorporating detailed anesthetic, surgical, and pharmacokinetic measurements are needed to better clarify the systemic hemodynamic relevance of locally administered methylene blue.

Abbreviations: ASA — American Society of Anesthesiologists, BIS — Bispectral Index, BMI — Body Mass Index, cGMP — Cyclic Guanosine Monophosphate, G6PD — Glucose-6-Phosphate Dehydrogenase, HR — Heart Rate, MAP — Mean Arterial Pressure, MB — Methylene Blue, NO — Nitric Oxide, sGC — Soluble Guanylate Cyclase SD — Standard Deviation, SLNB — Sentinel Lymph Node Biopsy, STROBE — Strengthening the Reporting of Observational Studies in Epidemiology

Ethical approval: Ethics approval and consent to participate. This prospective observational study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (IRB No: 2025-06/85). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT07040540) on 19 June 2025. Written informed consent was obtained from all participants prior to inclusion in the study.

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Authors contributions: MKS (Mustafa Kemal Şahin) conceptualized and designed the study, supervised the research process, performed data interpretation, and drafted the manuscript as the corresponding author. EC (Eda Caferoğlu) contributed to data collection, patient follow-up, and manuscript revision. BC (Burak Çalışıcı) participated in methodology development, statistical analysis, and data interpretation. BD (Burak Dinçer) contributed to study implementation, clinical data acquisition, and critical revision of the manuscript. All authors read and approved the final manuscript.

Data availability: The data supporting the findings of this study are not publicly available due to patient confidentiality and ethical restrictions. However, the data can be made available from the corresponding author upon reasonable request and with the approval of the institutional ethics committee.

Consent for publication: Not applicable. This study contains no identifying images or personal or clinical details of individual participants.

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