Original Article

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Role of Lymphoscintigraphy in Repeat Sentinel Lymph Node Biopsy for cN0 Ipsilateral Breast Cancer Recurrence

cN0 İpsilateral Meme Tümör Nüksünde Tekrar Sentinel Lenf Nodu Biyopsisinde Lenfosintigrafinin Rolü

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Abstract

Objectives: In patients with ipsilateral breast tumor recurrence (IBTR), lymphatic drainage may be altered due to factors such as prior axillary surgery and radiotherapy, thereby increasing the likelihood of sentinel lymph nodes (SLNs) in atypical locations. This study aimed to evaluate patients who underwent surgery for IBTR with lymphoscintigraphy for repeat SLN biopsy (re-SLNB), and to investigate the role of lymphoscintigraphy in re-SLNB in this patient group.

Methods: Patients diagnosed with IBTR who were evaluated using preoperative lymphoscintigraphy and subsequently underwent surgery were included in the study. Patients with systemic or nodal metastases, as well as those who did not undergo lymphoscintigraphy, were excluded. Demographic, clinical, and pathological data of the included patients were analyzed.

Results: A total of 16 patients were evaluated, with a median age of 56 years (range 30-73), all of whom were female. Lymphoscintigraphy successfully localized the SLN in 81.3% of the patients. In eight patients, the SLN was located in the ipsilateral axilla, while in five patients, it was found in the contralateral axilla. Axillary lymph node dissection (ALND) was performed in three patients (all in the contralateral axilla) due to metastatic involvement in the SLN. ALND during first surgery was associated with an increased likelihood of SLN detection in the contralateral axilla or Re-SLNB failure (p=0.043).

Conclusion: In patients undergoing surgery for IBTR, the likelihood of the SLN being in atypical locations is high. Lymphoscintigraphy may enhance the success of Re–SLNB in this patient group.

Keywords: Breast cancer, ipsilateral breast tumor recurrence, lymphoscintigraphy, sentinel lymph node biopsy

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Öz

Amaç: İpsilateral meme tümörü rekürrensi (IMTR) olan hastalarda, geçirilmiş aksiller cerrahi ve radyoterapi gibi faktörler nedeniyle lenfatik drenaj değişebilmekte, buna bağlı olarak da atipik yerleşimlerde sentinel lenf nodları (SLN) olasılığı artmaktadır. Bu çalışmada, IMTR nedeniyle ameliyat edilen hastalarda tekrar SLN biyopsisi (re-SLNB) için lenfosintigrafi kullanımının değerlendirilmesi ve bu hasta grubunda lenfosintigrafinin re-SLNB'de rolünün incelenmesi amaçlanmıştır.

Yöntem: Çalışmaya, preoperatif lenfosintigrafi ile değerlendirilerek ameliyata alınan IBTR tanısı almış hastalar dahil edildi. Sistemik veya lenf nodu metastazları olan hastalar ve lenfosintigrafi yapılmayan hastalar dışlandı. Hastalar demografik, klinik ve patolojik verilerine göre analiz edildi.

Bulgular: Toplam 16 hasta değerlendirildi. Ortalama yaş 56 yıl (aralığı 30-73) ve hastaların hepsi kadındı. Lenfosintigrafi, SLN'yi hastaların %81,3'ünde başarıyla lokalize etti. Sekiz hastada SLN ipsilateral aksillada yer alırken, 5 hastada kontralateral aksillada bulundu. SLN'deki metastatik tutulum nedeniyle üç hastaya (tümü kontralateral aksillada) aksiller lenf nodu diseksiyonu (ALND) yapıldı. İlk ameliyat sırasında ALND, kontralateral aksillada SLN tespiti veya Re-SLNB başarısızlığı olasılığının artmasıyla ilişkiliydi (p=0,043).

Sonuç: IBTR için ameliyat edilen hastalarda SLN'nin atipik yerleşimlerde olma olasılığı yüksektir. Lenfosintigrafi bu hasta grubunda re-SLNB'nin başarısını artırabilir.

Anahtar kelimeler: Meme kanseri, ipsilateral meme tümörü rekürrensi, lenfosintigrafi, sentinel lenf nodu biyopsisi

Introduction

Breast cancer is the most common cancer and the leading cause of cancer-related deaths in women (1). One of the most critical factors in determining the prognosis of breast cancer is the status of the axillary lymph nodes. In early-stage breast cancer, axillary staging is typically performed using sentinel lymph node biopsy (SLNB) (2). However, in patients who have previously undergone breast-conserving surgery (BCS) and develop ipsilateral breast tumor recurrence (IBTR), repeat SLNB (Re-SLNB) becomes challenging. In these cases, lymphatic drainage is often impaired due to previous axillary surgery and treatments such as radiotherapy, increasing the likelihood of a SLN in atypical locations (3,4). The optimal approach to lymphatic staging in this patient group remains controversial in the literature (5). In our study, we aimed to evaluate the outcomes of re-SLNB in patients undergoing surgery for IBTR who were assessed preoperatively with lymphoscintigraphy.

Materials and Methods

Patients over the age of 18 who were diagnosed with IBTR between 2020 and 2023, and underwent surgery after SLN localization using preoperative lymphoscintigraphy, were included in our study. Patients who did not undergo lymphoscintigraphy, had systemic metastases, or were diagnosed with preoperative lymph node metastases, were excluded. Data were evaluated based on age, gender, menopausal status, SLN localization as determined by lymphoscintigraphy, types of breast and axillary surgeries performed for both first and recurrent tumor, histopathological diagnosis, molecular subtype, pathology results, locoregional and systemic recurrences as the third event, and survival. This study was approved by the Istanbul University Istanbul Medical Faculty Clinical Research Ethics committee (decision no: 23, date: 29.11.2024).

Lymphoscintigraphy and Surgical Technique

Lymphoscintigraphy for axillary staging was performed by administering two superficial (periareolar) and one deep (intratumoral) injection of approximately 50 MBq Tc99m-nanocolloid (Senti-Scint, Medicheck). After injection, preoperative imaging was conducted using a dual-head gamma camera (GE Discovery NM 670 SPECT/CT, USA) (Figure 1). If the SLN is localized from these images, its skin projection is marked. Intraoperatively, the SLN is located using a gamma probe and excised. The excised SLN is subsequently re-evaluated with a gamma probe for confirmation. Following SLNB, the axilla is explored again with a gamma probe for the presence of remaining lymph nodes exhibiting radionuclide uptake. If no further involvement is detected, the procedure is concluded. The SLN is evaluated intraoperatively with a frozen section, and if deemed necessary by the surgeon, lymph node dissection is performed.

Outcome Measures

The primary outcome was the effectiveness of lymphoscintigraphy in identifying the SLN in cases of IBTR. The secondary outcome was the localization of the SLN in patients with IBTR.

Statistical Analysis

Statistical analysis was performed using SPSS® version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including numbers, percentages, medians, were used to summarize the study data. The sample size was small, so the data are expressed as median and interquartile range

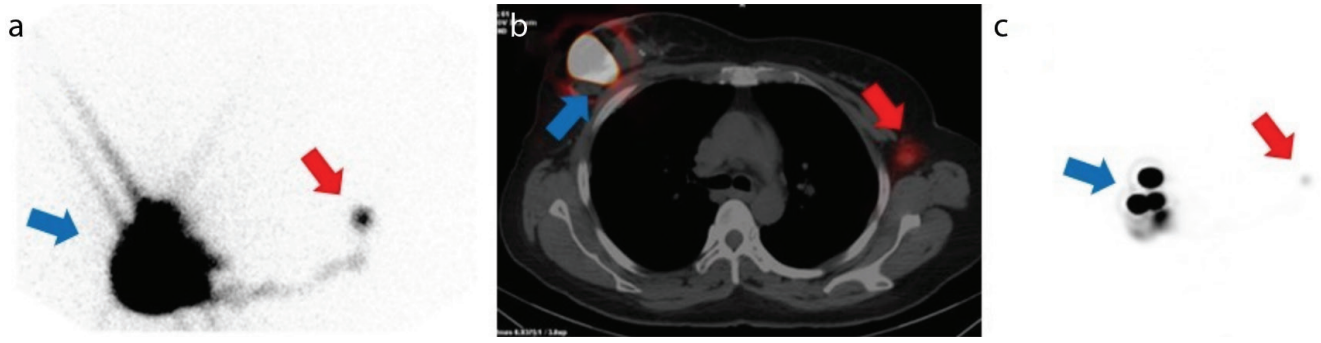

Figure 1. Anterior planar (A), SPECT/CT (B), and maximum intensity projection (C) images of lymphoscintigraphy demonstrate one contralateral axillary sentinel node indicated by the red arrows. The blue arrows indicate the injection site

SPECT: Single photon emission computed tomography, CT: Computed tomography

Table 1. Demographic and clinical features of study participants	
Variables	**All patients (n=16)**
Age (years, median, range)	56 (30-73)
Menopausal status (n, %)	
Premenopausal	6 (37.5%)
Postmenopausal	10 (62.5%)
First breast surgery (n, %)	
BCS	11 (68.7%)
NSM	5 (31.3%)
First axillary surgery (n, %)	
SLNB	12 (75%)
ALND	4 (25%)
Interval time to IBTR (months, median, IQR)	50 (29-58)
Type of breast surgery for IBTR (n, %)	
BCS	4 (25%)
Mastectomy	10 (62.5%)
NSM	2 (12.5%)
Type of axillary surgery for IBTR (n, %)	
No surgery	3 (18.8%)
Re-SLNB	10 (62.5%)
ALND	3 (18.8%)
Localisation of re-SLN (n, %)	
Ipsilateral axilla	8 (50%)
Contralateral axilla	5 (31.3%)
Not found	3 (18.8%)

ALND: Axillary lymph node dissection, BCS: Breast conserving surgery, IBTR: Ipsilateral breast tumor recurrence, IQR: Interquartile range, NSM: Nipple sparing mastectomy, SLN: Sentinel lymph node, SLNB: Sentinel lymph node biopsy, Re-SLNB: Repeat sentinel lymph node biopsy

(IQR), and non-parametric tests were used. Categorical data were compared using Chi-square tests (Pearson Chi-square, continuity correction, Fisher's exact test), and numerical data were compared using the Mann-Whitney U test. Survival analyses included calculating locoregional disease-free survival (LDFS), systemic disease-free survival (SDFS), and overall survival (OS) from the diagnosis of cancer to the first locoregional recurrence, systemic recurrence, last follow-up visit, or death, respectively. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was used to assess the effects of prognostic factors on LDFS, SDFS, and OS. Results were considered significant at $p<0.05$, with a confidence interval of 95%.

Results

Sixteen patients who underwent surgery for IBTR between 2020 and 2023 were included in this single-center retrospective study. The median age was 56 years (range 30-73), and all patients were female. Ten patients (62.5%) were postmenopausal. As the first surgeries for breast cancer, 11 patients (68.7%) underwent BCS, and 12 patients (75%) underwent SLNB. The median interval between the initial surgery and the diagnosis of IBTR was 50 months (IQR 29-58). For IBTR surgery, mastectomy was performed in 10 patients (62.5%). SLN localization via lymphoscintigraphy was achieved in 13 patients (81.3%). In eight patients, the SLN was located in the ipsilateral axilla, while in five patients, it was in the contralateral axilla. Axillary lymph node dissection (ALND) was performed in 3 of the 13 patients, in whom metastatic lymph nodes were detected via SLNB, all in the contralateral axilla (Table 1).

The median pathological diameter of the initial tumors was 21 mm (IQR 17-29), while the median diameter of IBTR was 17 mm (IQR 12-22). Fifteen patients were diagnosed with invasive ductal carcinoma, and one patient was

diagnosed with mucinous carcinoma. Molecular subtyping revealed that 8 patients were classified as luminal B, and 5 as triple-negative. Notably, 76.9% of the patients had grade 3 tumors. Among the 13 patients who underwent Re-SLNB, metastases were detected in 5 (Table 2).

When the factors affecting re-SLN localization were evaluated, no significant relationship was found between the initial tumor diameter, IBTR diameter, and the type of initial breast surgery and re-SLN localization (p=0.365, p=0.320, and p=0.137, respectively). However, it was observed that both the rate of SLN detection in the contralateral axilla and the failure to localize SLNs were significantly higher in patients who underwent ALND during the initial surgery compared to those who underwent SLNB (p=0.043) (Table 3).

During follow-up after surgery for IBTR, a third event (re-recurrence) was observed in four patients. All of these patients experienced locoregional recurrence, with two also having concomitant systemic metastases. Except for one patient who developed systemic metastases, all were alive at the last follow-up. No significant differences were found between patients who experienced a third event and those who did not in terms of menopausal status, type of breast and axillary surgery for IBTR, re-SLN localization, IBTR diameter, IBTR molecular subtype, or re-SLN pathological findings (Table 4).

The median follow-up period for the entire cohort was 27 months. At the end of the follow-up, the median LDFS, SDFS, and OS were not reached for the entire series. LDFS, SDFS, and OS were analyzed based on re-SLN localization and SLN status. No significant differences in survival times were observed according to re-SLN localization (p=0.472, p=0.375, and p=0.223). Among the 13 patients who underwent re-SLNB, LDFS was significantly shorter in those with metastatic SLNs (p=0.037). However, SDFS did not differ significantly between SLN-positive and SLN-negative patients (p=0.429). As all patients in both groups with evaluated SLNs were alive, OS was not compared using Kaplan-Meier analysis (Figures 2 and 3).

Table 2. Histopathological features of study participants

Variables	All patients (n=16)
Tumor diameter in first surgery (mm, median, IQR)	21 (17-29)
IBTR diameter (mm, median, IQR)	17 (12-22)
Histopathologic diagnosis of IBTR (n, %)	
Invasive ductal carcinoma	15 (93.7%)
Mucinous carcinoma	1 (6.3%)
Molecular subtypes of IBTR (n, %)	
Luminal B	8 (50%)
HR+ HER2+	1 (6.3%)
HR- HER2+	2 (12.5%)
Triple negative	5 (31.3%)
Tumor grade for IBTR (n, %)	
G1	0 (0%)
G2	5 (15.4%)
G3	11 (76.9%)
Re-SLN status (n=13, %)	
Negative	8 (61.5%)
Positive	5 (38.5%)

HER2+: Human epidermal growth factor receptor 2 positive, HR+: Hormon receptor positive, IBTR: Ipsilateral breast tumor recurrence, IQR: Interquartile range, SLN: Sentinel lymph node, Re-SLNB: Repeat sentinel lymph node biopsy

Table 3. Factors affecting on re-SLN localisation in IBTR cases

Variables	All patients (n=16)	Ipsilateral axilla (n=8)	Contralateral axilla (n=5)	Not found (n=3)	p-value
Tumor diameter in first surgery (mm, median, IQR)	21 (17-29)	23 (20-29)	16 (14-20)	21 (19-29)	0.365[a]
IBTR diameter (mm, median, IQR)	17 (12-22)	16 (13-19)	10 (10-22)	20 (19-25)	0.320[a]
First breast surgery (n, %)					
BCS	11 (68.7%)	4 (25%)	5 (31.3%)	2 (12.5%)	0.137[b]
NSM	5 (31.3%)	4 (25%)	0 (0%)	1 (6.3%)	
First axillary surgery (n, %)					
SLNB	12 (75%)	8 (50%)	3 (18.8%)	1 (6.3%)	**0.043[b]**
ALND	4 (25%)	0 (0%)	2 (12.5%)	2 (12.5%)	

All p-values less than 0.05 was bold
[a]Kruskal-Wallis Test, [b]Fisher's exact test, ALND: Axillary lymph node dissection, BCS: Breast conserving surgery, IBTR: Ipsilateral breast tumor recurrence, IQR: Interquartile range, NSM: Nipple sparing mastectomy, SLN: Sentinel lymph node, SLNB: Sentinel lymph node biopsy, Re-SLNB: Repeat sentinel lymph node biopsy

Discussion

Currently, conservative methods such as BCS and SLNB are prominent in the treatment of breast cancer, demonstrating survival rates comparable to more invasive procedures, such as mastectomy and ALND, which typically entail higher morbidity (6,7). While local recurrence rates following surgical treatment of breast cancer are generally low, IBTR occurs at a higher rate after BCS compared to mastectomy (7). The optimal treatment approach for cases with IBTR remains controversial in the literature; however, mastectomy and ALND are the most commonly employed surgical interventions (8). Nevertheless, several studies have reported successful outcomes with re-SLNB in this patient population (3,4,5). Re-SLNs were successfully localized in 81.3% of our patients, aligning with the existing literature.

Atypical SLN localizations may occur more frequently in cases of IBTR due to factors that can alter axillary drainage pathways, such as previous ALND and radiotherapy (9). In our study, Re-SLN localization was achieved in 13 out of 16 patients, with 5 of these patients having contralateral axillary Re-SLNs. It was observed that the identification of Re-SLNs in the contralateral axilla or the failure to locate Re-SLNs was significantly more frequent in patients who underwent ALND. Given the high frequency of atypical SLN localizations, preoperative identification of SLN location using techniques such as lymphoscintigraphy may enhance the success of re-SLNB in this patient group.

There is a limited number of studies comparing the applications of re-SLNB and ALND in axillary staging for cases of IBTR. In a retrospective study conducted by Lu et al. (10), it was reported that re-SLNB and ALND yielded similar survival rates in patients with IBTR. In our study, only 3 of the 16 patients underwent ALND. At the last follow-up, 15 patients were alive, and 12 of them were recurrence-free, suggesting that our findings align with the existing literature.

Survival rates after IBTR are reported to be worse than in patients without recurrence (11). However, data on the risk of developing a third event following IBTR remain scarce. While our study did not yield significant findings regarding third-event risk, this may be attributable to the small sample size. Further investigation in larger series is needed to address this gap in the literature.

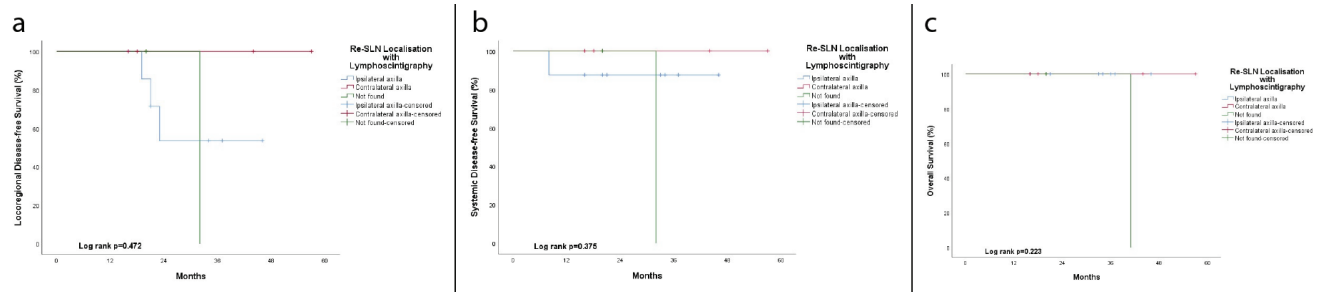

Figure 2. Kaplan-Meier curves illustrating the relationship between Re-SLN localization and survival for: a) LDFS, b) SDFS, and c) OS

Re-SLNB: Repeat sentinel lymph node biopsy, LDFS: Locoregional disease-free survival, SDFS: Systemic disease-free survival, OS: Overall survival

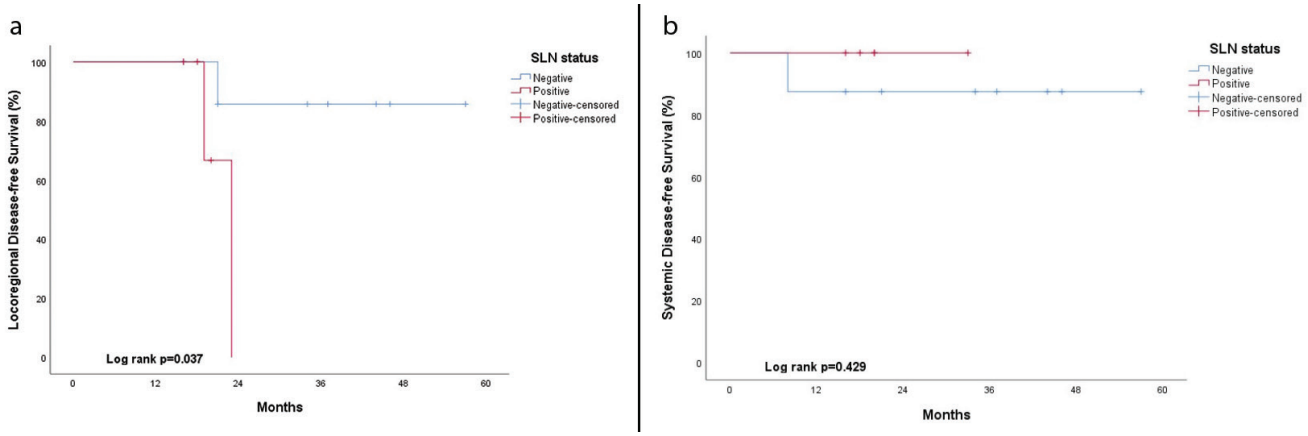

Figure 3. Kaplan-Meier curves illustrating the relationship between SLN status and survival for: a) LDFS, b) SDFS

SLN: Sentinel lymph node biopsy, LDFS: Locoregional disease-free survival, SDFS: Systemic disease-free survival

Table 4. Factors affecting risk of third event				
Variables	**All patients (n=16)**	**No event (n=12)**	**Third event (n=4)**	**p-value**
Menopausal status (n, %)				
Premenopausal	6 (37.5%)	4 (25%)	2 (12.5%)	0.604[a]
Postmenopausal	10 (62.5%)	8 (50%)	2 (12.5%)	
Type of breast surgery for IBTR (n, %)				
BCS	4 (25%)	3 (18.8%)	1 (6.3%)	0.736[a]
Mastectomy	10 (62.5%)	8 (50%)	2 (12.5%)	
NSM	2 (12.5%)	1 (6.3%)	1 (6.3%)	
Type of axillary surgery for IBTR (n, %)				
No surgery	3 (18.8%)	2 (12.5%)	1 (6.3%)	1.000[a]
Re-SLNB	11 (68.8%)	8 (50%)	3 (18.8%)	
ALND	2 (12.5%)	2 (12.5%)	0 (0%)	
Localisation of re-SLN (n, %)				
Ipsilateral axilla	8 (50%)	5 (31.3%)	3 (18.8%)	0.330[a]
Contralateral axilla	5 (31.3%)	5 (31.3%)	0 (0%)	
Not found	3 (18.8%)	2 (12.5%)	1 (6.3%)	
IBTR diameter (mm, median, IQR)	17 (12-22)	17 (12-21)	22 (12-31)	0.627[b]
Molecular subtypes of IBTR (n, %)				
Luminal B	8 (50%)	6 (37.5%)	2 (12.5%)	1.000[a]
HR+ HER2+	1 (6.3%)	1 (6.3%)	0 (0%)	
HR- HER2+	2 (12.5%)	2 (12.5%)	0 (0%)	
Triple negative	5 (31.3%)	3 (18.8%)	2 (12.5%)	
SLN status (n=13, %)				
Negative	8 (61.5%)	7 (53.8%)	1 (7.7%)	0.510[a]
Positive	5 (38.5%)	3 (23.1%)	2 (15.4%)	

[a]Fisher's exact test, [b]Mann-Whitney U test, ALND: Axillary lymph node dissection, BCS: Breast conserving surgery, HER2+: Human epidermal growth factor receptor 2 positive, HR+: Hormon receptor positive, IBTR: Ipsilateral breast tumor recurrence, IQR: Interquartile range, NSM: Nipple sparing mastectomy, SLN: Sentinel lymph node, SLNB: Sentinel lymph node biopsy, Re-SLNB: Repeat sentinel lymph node biopsy

Study Limitations

The main limitations of our study are its retrospective design and the small sample size. Larger studies and prospective trials will aid in determining the optimal approach for the treatment of IBTR.

Conclusion

In cases of IBTR, re-SLNB can be successfully performed, albeit at a lower success rate compared to primary cases. Additionally, lymphoscintigraphy may enhance the success rates of re-SLNB in this patient population by identifying atypical SLN localizations.

Ethics

Ethics Committee Approval: This study was approved by the Istanbul University Istanbul Medical Faculty Clinical Research Ethics committee (decision no: 23, date: 29.11.2024).

Informed Consent: Written informed consent was obtained from participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.D., D.H.Ş., S.E., M.T., M.M., N.C., Concept: B.D., D.H.Ş., N.C., Design: B.D., D.H.Ş., N.C., Data Collection or Processing: B.D., D.H.Ş., S.E., M.T., M.M., N.C., Analysis or Interpretation: B.D., D.H.Ş., N.C., Literature Search: B.D., N.C., Writing: B.D., D.H.Ş., S.E., M.T., M.M., N.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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