

Is Axillary Reverse Mapping Oncologically Safe in Breast Cancer Surgery?

Meme Kanseri Cerrahisinde Ters Aksiller Haritalama Onkolojik Olarak Güvenli midir?

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Abstract

Objective: Axillary reverse mapping (ARM) has been described to protect against lymphedema. This study aimed to explore the oncological safety of ARM in terms of tumor characteristics and other factors.

Methods: The study included 81 patients who received mastectomy or breast-conserving surgery for diagnosis of breast cancer and undergo ARM as clinically axillary positive disease.

Results: No axillary reverse mapping lymph node (ARMLN) was found for 26 patients (32%). Of the 55 patients with ARMLN, 19 (34%) were malignant and 36 (66%) were benign. A statistically significant relationship was found between ARMLN and the number of lymph nodes dissected (p=0.004). The larger the size of ARMLN dissected, the more likely it is that the lymph nodes will be malignant (p=0.001).

Conclusion: Our study suggests that the higher the axillary burden, the more likely it is for ARMLN to be malignant and the less safe its preservation. Additional randomized prospective studies with a focus on patient survival time and recurrence are warranted to verify the potential feasibility of the ARM technique and confirm the reliability of the reported protocols.

Keywords: Axillary dissection, axillary reverse mapping, breast cancer, lymphedema

Öz

Amaç: Aksiller ters haritalama lenfödemi önlemek için tarif edilmiştir. Bu çalışma, tümör özellikleri ve diğer faktörler açısından aksiller ters haritalamanın onkolojik güvenliğini araştırmayı amaçlamaktadır.

Yöntem: Çalışmaya meme kanseri tanısı ile mastektomi veya meme koruyucu cerrahi uygulanan ve klinik olarak aksiller pozitif hastalık nedeniyle aksiller ters haritalama uygulanan 81 hasta dahil edildi.

Bulgular: Yirmi altı hastada (%32) aksiller ters haritalama lenf nodu (ATHLN) bulunamadı. ATHLN 55 hastanın, 19'u (%34) malign, 36'sı (%66) benigndi. ATHLN sayısı ile disseke edilen lenf nodu sayısı arasında istatistiksel olarak anlamlı ilişki bulundu (p=0,004). Disseke edilen ATHLN'nin boyutu ne kadar büyükse, lenf nodlarının malign olma olasılığı da o kadar yüksektir (p=0,001).



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Öz

Sonuç: ATHLN malignitesi açısından, hastaların aksiller yükünün fazla olması, intraoperatif olarak seviye III diseksiyon yapılması, aksiller lenf nodu diseksiyonu (ALND) ile 20'den fazla lenf nodu rezeksiyonu yapılması, ekstrakapsüler invazyonun olması ve ATHLN'leri 1 cm'den büyük olmasının malignite ile istatistiksel olarak anlamlı bir bağlantısı vardır. Çalışmamız, koltuk altı yükü ne kadar yüksekse, ATHLN'nin malign olma ihtimalinin o kadar yüksek olduğunu ve korunmasının daha az güvenli olduğunu ileri sürüyor.

Anahtar Kelimeler: Aksiller diseksiyon, ters aksiller haritalama, meme kanseri, lenfödem

Introduction

Although the surgical approach to the axilla in patients with a low axillary tumor burden is changing, axillary dissection remains a frequently used procedure in clinical practice. One of the most serious complications associated with axillary dissection is lymphedema. 5-20% of patients undergoing axillary dissection are reported to experience lymphedema, and this figure can go up to 50% for patients undergoing adjuvant radiotherapy. The search for prevention of lymphedema for treating breast cancer continues. Among the techniques used is axillary reverse mapping (ARM), which enables the preservation of arm lymphatic vessels⁽¹⁾. This procedure, in which lymph nodes (LN) considered to be located within the arm lymphatic drainage area are not dissected intraoperatively, needs to be tested for oncological safety. This study explores the oncological safety of ARM in terms of tumor characteristics and other factors.

Materials and Methods

This prospective study was approved by the Ethical Board of the Institutional Ethics Committee of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey (2016-12/02). Informed consent was obtained from all participants included in the study.

The study included 81 patients who were to undergo mastectomy or breast-conserving surgery for having been diagnosed with breast cancer and who were clinically axillary-positive. Three minutes before skin incision for mastectomy, 3-5 cc of isosulfan blue dye was injected into the inner aspect of the ipsilateral arm using intradermal injections. The patients then underwent axillary dissection. No extra or inadequate dissections were performed as part of the study. Level III axillary dissection was left to the discretion of the surgeon. Following the completion of axillary dissection and collection of specimens, all blue LN marked with ARM were removed from the specimens and were separately sent to pathology. Patients undergoing sentinel lymph node biopsy

(SLNB) (due to the risk of interfere between blue dyes) and neoadjuvant chemotherapy were excluded from the study. The data about the patients were recorded, including age, body mass index (BMI), comorbidities, type of biopsy, level of axillary dissection, type of surgery and tumour characteristics [tumour location, grade, Ki-67 proliferative index, Cerbb2, estrogen receptor (ER) and progesterone receptor (PR), lymphovascular invasion (LVI), extracapsular invasion].

Statistical Analysis

IBM SPSS Statistics 20.0 was used for data analysis. The relationship between the categorical variables and ARM lymph node status was analyzed using Mantel-Haenszel chi-square test, while Pearson correlation was used in the analysis of this relationship with rank order variables. P<0.05 was used as a cut-off for statistical significance.

Results

All patients included in the study were females with a mean age of 53.2+/-12.2. Sixty-one (75%) patients were diagnosed with trucut biopsy, 18 (22.5%) with excisional biopsy, and 2 (2.5%) with incisional biopsy. Seventy-two (89%) of the patients underwent mastectomy, and nine patients underwent breast-conserving surgery. Fifty-five (68%) patients received levels I and II axillary dissection, while 26 (32%) patients received level III axillary dissection intraoperatively at the surgeon's discretion. Tumor location was in the upper outer quadrant for 49 (60%) patients, in the upper inner quadrant for 11 patients, in the lower outer quadrant for 9 (11%) patients, in the lower inner quadrant for 6 (7%) patients, and in the central region for 6 (7%) patients. Table 1 presents the clinicopathological characteristics of patients. The pathology of all patients was invasive ductal carcinoma. Mean tumor size was 3.8+/-2.2 cm. Tumor grade for 67 patients (83%) was 3. Regarding hormone receptor status, 66% were ER positive, 44% were PR positive, and 26% were Cerbb2 positive. The Ki-67 proliferative index was between 0-14% for 20%, 15-30% for 16%, and above 30% for 63%. Fifty-two patients (65%) had LVI, and 42 patients

(52%) had extracapsular invasion. Table 2 presents tumor characteristics.

The mean number of LN resected with axillary dissection was 23.1+/-7.1 (9-42). Fify-one patients (63%) had more than 20 LN resected. On average, 7 (0-38) LN dissected contained malignancy. The mean number of LNs resected with axillary reverse mapping lymph node (ARMLN) was 2.7+/-2.3 (1-9). No ARMLN was found in 26 patients (32%). Of the 55 patients (68%) with ARMLN, 19 (34%) were malignant and 36 (66%) were benign.

The relationship between ARMLN malignancy rates and patients' clinicopathological characteristics was analyzed, and no significant differences were found in relation to age, BMI, comorbidities, type of biopsy, type of surgery, and tumor location. In patients who received level III axillary dissection intraoperatively at surgeon discretion because of a high axillary burden, the more frequent presence of malignant ARMLN was found to be statistically significant (p=0.03) (Table 3).

An analysis of ARMLN malignancy rates and tumor characteristics found no significant relationship in relation to tumour size, grade, ER, PR, Cerbb2, Ki-67 and LVI. The more frequent presence of positive ARMLN in patients with extracapsular invasion was found to be significant

Table 1. Clinicopathological characteristics of patients			
Age	≤50	32 (40%)	
	>50	49 (60%)	
ВМІ	≤25	28 (35%)	
	>25	53 (65%)	
Comorbidity	Yes	31 (38%)	
	No	50 (62%)	
Type of biopsy	Tru-cut	61 (75%)	
	Excisional	18 (22.5%)	
	Incisional	2 (2.5%)	
Type of surgery	Mastectomy	72 (89%)	
	Lumpectomy	9 (11%)	
Axillary dissection	Level I, II	55 (68%)	
	Level I, II, III	26 (32%)	
Location	Upper outer	49 (60%)	
	Upper inner	11 (13.5%)	
	Lower outer	9 (11%)	
	Lower inner	6 (7%)	
	Central	6 (7%)	
BMI: Body mass index			

Table 2. Pathologic characteristics of tumours				
Tumour size	≤3 cm	40 (50%)		
	>3 cm	40 (50%)		
Grade	1-2	14 (17%)		
	3	67 (83%)		
ER	+	53 (66%)		
	-	27 (34%)		
PR	+	35 (44%)		
	-	45 (56%)		
0.110	+	21 (26%)		
Cerbb2	-	59 (74%)		
Ki-67	0-14	16 (20%)		
	15-30	13 (16%)		
	>30	51 (63%)		
Lumphoupooular invasion	Yes	52 (65%)		
Lymphovascular invasion	No	25 (31%)		
	Yes	42 (52%)		
Extracapsular invasion	No	37 (46%)		
ER: Estrogen receptor, PR: Progesterone receptor				

		ARMLN	ARMLN	
Characteristic		benign (%)	malignant (%)	p-value
Age	≤50	15 (68%)	7 (32%)	0.93
	>50	21 (64%)	12 (36%)	
BMI	≤25	15 (68%)	7 (32%)	
BIMI	>25	21 (64%)	12 (36%)	0.30
Comorbidity	No	26 (68%)	12 (32%)	0.11
	Yes	10 (58%)	7 (42%)	
Type of biopsy	Tru-cut	23 (59%)	16 (41%)	
	Excisional	11 (78%)	3 (22%)	
	Incisional	2 (100%)	0	0.23
Type of surgery	Mastectomy	33 (66%)	17 (34%)	0.68
	Lumpectomy	3 (60%)	2 (40%)	
Axillary dissection	Level I, II	30 (73%)	11 (27%)	0.02
	Level I, II, III	6 (43%)	8 (57%)	0.03
	Upper outer	24 (68%)	11 (32%)	
	Upper inner	2 (33%)	4 (67%)	
Location	Lower outer	5 (71%)	2 (29%)	
	Lower inner	3 (60%)	2 (40%)	0.38
	Central	2 (100%)	0	
ARMLN: Axillary	reverse mapping ly	mph node, BN	II: Body mass in	dex

Table 3. The relationship between ARMLN involvement and clinicopathological characteristics

(p=0.001) (Table 4). Of the 14 patients who had less than 20 LN resected with ALND, 3 contained malignancy, whereas of the 41 patients who had more than 20 LN resected, ARMLN in 16 was found to be positive for malignancy. A statistically significant relationship was found between ARMLN and the number of LNs dissected (p=0.004). The more the number of ARMLN resected, the more likely it is for ARMLN to overlap with breast lymphatics and become malignant. A statistically significant relationship between the number of ARMLN identified and ARLMN malignancy was found (p=0.001). The larger the size of ARMLN dissected, the more likely it is for LN to be malignant (p=0.001) (Table 5).

Discussion

The ARM procedure is based on the assumption that both the upper extremity and breast have separate pathways of lymphatic drainage. Studies have also found that they are not as distinct as once thought, though, with the reporting of interconnections between these pathways⁽²⁾.

There are different views on the oncological safety of ARM. A research study conducted by Bedrosian et al.⁽¹⁾ with 30

		ARMLN	ARMLN	
Characteristic		benign (%)	malignant (%)	p-value
Tumour size	≤3 cm	21 (72%)	8 (28%)	0.44
	>3 cm	14 (56%)	11 (44%)	
Grade	1-2	6 (75%)	2 (25%)	0.60
Grade	3	30 (64%)	17 (36%)	
ER	-	12 (60%)	8 (40%)	0.54
	+	24 (68%)	11 (32%)	
PR	-	18 (67%)	9 (33%)	0.21
	+	18 (64%)	10 (36%)	
Cerbb2	-	27 (67%)	13 (33%)	0.64
	+	9 (60%)	6 (40%)	
	0-14	7 (63%)	4 (37%)	
Ki-67	15-30	5 (71%)	2 (29%)	0.69
	>30	24 (65%)	13 (35%)	0.69
Lymphovascular invasion	No	17 (89%)	2 (11%)	0.07
	Yes	18 (54%)	15 (46%)	
Extracapsular invasion	No	27 (93%)	2 (7%)	0.001
	Yes	8 (33%)	16 (67%)	

patients found that the rate of identifying axillary reverse mapping ARMLN with the use of blue dye injected in the upper inner ipsilateral arm was 50%. Because 20% of ARMLN cases were identified in patients with pathologically evidenced LN containing malignancy, preservation of ARMLN was not considered oncologically safe⁽¹⁾. Nos et al.⁽³⁾ found that 14% of ARMLN cases were malignant and that there was a statistically significant relationship between N3 and ARMLN positivity. Kang et al.⁽⁴⁾ identified ARMLN in 101 (78%) of 129 patients. ARMLN was identified in 55 (68%) of the 81 patients included in our study and ARMLN malignancy rate was 34%.

Some studies have employed radioisotopes to increase ARMLN identification rates. In a series that included 172 patients, the patients were injected in the ipsilateral hand on the day of surgery, and ARMLN was identified in all patients. It was reported that 92% of the ARMLN identified occurred in the area referred to as zone D, above the second intercostobrachial nerve and lateral to the lateral thoracic vein. This study reported the rate of ARM malignancy as 31%⁽⁵⁾. Arm lymphatics overlap with breast lymphatics more frequently in the radioisotope technique than in the blue dye technique^(6,7). ARM-preserving selective ALND does not seem safe oncologically due to this relationship; thus, the involvement of ARM according to its location was taken into account, and 9.4% of ARMLN in zone D were found to be positive for malignancy. Because of low involvement in zone D, it was suggested that emphasis should be placed on the preservation of LN in zone D⁽⁸⁾. Ikeda et al.⁽⁹⁾ found that the ARM LN were located between the second intercostobrachial nerve and the axillary vein. The mean number of ARMLN resected is 2. In patients undergoing ALND on the grounds of having clinically positive nodes, 24% of ARMLN patients had positive ARM nodes, whereas 3% of patients with SLNB had metastasis⁽⁹⁾. Other studies have reported that preservation

LN characteristics					
Characteristic		ARMLN benign (%)	ARMLN malignant (%)	p-value	
ALND number of LN resected	≤20	11 (78%)	3 (22%)	0.004	
	>20	25 (61%)	16 (39%)	0.004	
ARMLN number	≤2	24 (61%)	15 (39%)	0.001	
	>2	4 (25%)	12 (75%)		
ARMLN size	≤l cm	22 (100%)	0	0.001	
	>1 cm	13 (40%)	19 (60%)	0.001	
ARMLN: Axillary reverse mapping lymph node, LN: Lymph nodes, ALND: Axillary lymph node dissection					

Table 5. The relationship between ARMLN involvement and

of ARMLN in SLNB-positive patients undergoing ALND is safe⁽¹⁰⁾.

as the axillary tumor burden increases, the malignancy rates in ARMLN also increase. In a series, two-thirds of the subjects consisted of patients with a low axillary burden (N1), ARMLN were less likely to have metastasis compared with N2-3⁽¹¹⁾. A low malignancy rate of 6% was found in zone D ARMLN in patients who were considered axillary-negative following clinical and radiological classifications and underwent ALND because of malignancy after SLNB. It was reported that it is theoretically possible to perform ARM-preserving ALND with these patients as well, which could be regarded as a good example of the selection of the right patients using preoperative axillary USG.

Lymphedema often occurs as a result of damage to the lymphatic system, and several risk factors have been associated with its development. Some of these risk factors: Extensive surgery, chemotherapy especially taxane-based regimens, and radiation therapy. However, there is also a risk of lymphedema in patients who undergo SLNB due to breast cancer; lymphedema can be seen in 4-6%⁽¹²⁾.

When examining the effectiveness and safety of ARM, it is necessary to determine the long-term results of axillary recurrence and arm lymphedema. In the study evaluating patients who underwent selective dissection with reverse axillary mapping, nanocoll containing 5 MBq technetium 99 was intradermally administered to the patients from the dorsal hand on the same side 6-24 hours before surgery. During axillary dissection, nodules close to the axillary vein with high uptake were preserved. During the 51-month follow-up of 100 patients included in the study, ipsilateral axillary recurrence was detected in only 1 patient⁽¹³⁾.

The effectiveness of ARM was also investigated in patients receiving neoadjuvant therapy. In a meta-analysis of published studies on this subject examining nearly 5000 patients, there was no statistically significant reduction in the risk of metastases in the ARMLN for patients who underwent neoadjuvant chemotherapy compared with those who did not. In other words, neoadjuvant chemotherapy did not appear to have a meaningful impact on reducing the risk of metastasis in this context. It is clear that this result is closely related to the biological characteristics of the tumors due to the response to neoadjuvant therapy. As the response to treatment increases, the rate of ARMLN will decrease⁽¹⁴⁾.

In a randomized controlled study conducted on clinically node-negative breast cancer patients, ALND was performed in 98 patients because of SLNB positivity. While ARMLNpreserving axillary dissection was performed in 49 patients, whereas conventional axillary dissection was performed in 49 patients. In the group that underwent conventional ALND, metastasis in ARMLN was detected in only 1 patient. During the 24-month follow-up, lymphedema was detected in only 3 patients (6.5%) in the ARMLND preserved group, whereas lymphedema was detected in 9 patients (20.9%) in the conventional axillary dissection group (p=0.04). This approach to ALND in early breast cancer patients is seen as a way to achieve a better balance between reducing the risk of arm lymphedema, a quality of life concern, and ensuring the oncological safety of the treatment, which is critical for cancer control⁽¹⁵⁾.

In another randomized controlled study, the combination of ARM and ALND resulted in fewer reported complaints of lymphedema at 6, 12, and 24 months after the surgery (p<0.05). Importantly, no axillary recurrence was found in either group. This suggests that the combination of ARM-ALND did not compromise the oncological safety of the procedure, as there were no instances of cancer recurrence in the axillary LN⁽¹⁶⁾.

Study Limitations

The limitations of our study were restricted study population, not comparing the patients with control group and lack of postintervention follow-up evaluation.

Conclusion

The need for axillary dissection in the surgical treatment of breast cancer has rapidly decreased. SLNB has become a sufficient procedure for the regional treatment of many patients. The increased effectiveness of neoadjuvant therapy has also reduced the need for ALND. Our study did not find the ARM procedure safe in patients with a heavy burden of axillary metastasis. ARM may protect patients from lymphedema in patients without a heavy burden of axillary metastasis but are indicated for ALND. Considering that SLNB is not completely immune to lymphedema, ARM may improve the quality of life by preventing lymphedema in early stage breast cancer.

Ethics

Ethics Committee Approval: This prospective study was approved by the Ethical Board of the Institutional Ethics

Committee of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey (2016-12/02).

Informed Consent: Informed consent was obtained from all participants included in the study.

Authorship Contributions

Surgical and Medical Practices: M.O.K., A.K., İ.B.Ç., Concept: B.A., L.D., İ.B.Ç., A.U.B., Design: M.O.K., A.K., L.D., C.Ö., İ.B.Ç., A.U.B., Data Collection or Processing: Z.M.B., C.Ö., Analysis or Interpretation: N.K., C.Ö., Literature Search: B.A., N.K., Writing: M.O.K., L.D., A.U.B.

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