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ACOSOG Z0011 Çağında Erken Meme Kanseri Hastalarının Aksiller Tedavisi. Tecrübemiz

Axillary Treatment of Early Breast Cancer Patients in The Era of ACOSOG Z0011. Our experience

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ABSTRACT

INTRODUCTION: Z0011 study demonstrated with long-term results that there is no requirement for complete axillary dissection in 1-2 positive axillary lymph nodes in patients who will receive breast-conserving surgery and radiotherapy in early-stage breast cancer. Furthermore, survival outcomes of these patients are not inferior to patients with complete AD. This study aimed to retrospectively evaluate our patients with breast cancer in the era of the Z0011 trial.

METHODS: The study included 89 patients who had not received neoadjuvant chemotherapy with positive SLNB and operated on for breast cancer between 2014 and 2021. Thirty-two of these patients (group I) received only SLNB, and in 57 patients, ALND (group II) was performed after SLNB according to the guidelines. The patients' age, tumor size, hormone, her2 neu, pathological stage, luminal type, grade, and lymphovascular invasion were recorded. In addition, the metastatic LN status after ALND was also evaluated. The data of having radiotherapy were recorded. Finally, patients' follow-up period, locoregional recurrence, and distant metastasis were collected.

RESULTS: The clinicopathologic factors were not different between the two groups. The mean follow-up period were 40 months in goup 1 and 52 months in group 2. In group 1, we did not detect any local recurrence, metastasis, or death. In Group 2, two patients had metastasis (3.5%), and one loss (1.75%) was detected, within no local recurrence.

DISCUSSION AND CONCLUSION: Study z0011 has shown us that low volume axillary disease can be treated with RT without AD. The axillary disease may be evolved to a no-touch technique soon.

Keywords: breast cancer, early breast cancer, axillary dissection, sentinel lymph node biopsy

ÖZ

GİRİŞ ve AMAÇ: Z0011 çalışması erken evre meme kanserinde meme koruyucu cerrahi ve radyoterapi alacak hastalarda 1-2 pozitif aksiller lenf nodunda tam aksiller diseksiyona gerek olmadığını uzun dönem sonuçlarıyla göstermiştir. Ayrıca, bu hastaların sağkalım sonuçları, tam aksiller diseksiyonlu hastalardan daha düşük değildir. Bu çalışma, Z0011 çalışması döneminde meme kanserli hastalarımızı retrospektif olarak değerlendirmeyi amaçladı.

YÖNTEM ve GEREÇLER: Çalışmaya 2014-2021 yılları arasında pozitif SLNB ile neoadjuvan kemoterapi almamış ve meme kanseri nedeniyle opere edilmiş 89 hasta dahil edildi. Bu hastalardan 32'sine (grup I) sadece SLNB, 57'sine ise ALND (grup II) uygulandı.) yönergelere göre SLNB'den sonra yapıldı. Hastaların yaşı, tümör boyutu, hormonu, her2 neu, patolojik evresi, lüminal tipi, derecesi ve lenfovasküler invazyon kaydedildi. Ayrıca ALND sonrası metastatik LN durumu da değerlendirildi. Radyoterapi alma verileri kaydedildi. Son olarak hastaların takip süresi, bölgesel nüks ve uzak metastazlarına ait veriler toplandı.

BULGULAR: Klinikopatolojik faktörler iki grup arasında farklı değildi. Ortalama takip süresi grup 1'de 40 ay ve grup 2'de 52 ay idi. Grup 1'de herhangi bir lokal nüks, metastaz veya ölüm tespit etmedik. Grup 2'de lokal nüks olmaksızın iki hastada (%3,5) metastaz ve bir hastada (%1,75) kayıp saptandı.

TARTIŞMA ve SONUÇ: Çalışma z0011 bize düşük hacimli aksiller hastalığın AD olmaksızın RT ile tedavi edilebileceğini göstermiştir. Aksiller hastalık yakında temassız bir tekniğe dönüşebilir.

Anahtar Kelimeler: meme kanseri, erken meme kanseri, aksiller diseksiyon, sentinel lenf nodu biyopsisi

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INTRODUCTION

The surgical approach to breast cancer has considerably changed since Halstedian mastectomy. In addition to the suitability of breast-conserving surgery, the process to axillary lymph nodes has evolved from complete axillary dissection to the result of not performing axillary dissection despite 1-2 metastatic lymph nodes in early-stage breast cancer patients who did not receive neoadjuvant chemotherapy. Axillary lymph node metastasis is the main prognostic factor for disease-free survival (DFS) and overall survival (OS) in early breast cancer, and its impact is considered when determining treatment modality (1). While axillary lymph node dissection (ALND) revealed the axillary nodal status, it has undesirable comorbidities such as lymphedema, limitation of arm movements, and neuropathy. Precisely at this point, sentinel lymph node (SLN) sampling has become the first-line approach for axillary staging in every appropriate case with the advantage of less morbidity and less invasiveness. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that in clinically node-negative women with T1 or T2 invasive breast cancer, who underwent breast-conserving surgery (BCT) with whole-breast irradiation (WBRT), had excellent local control and survival with sentinel lymph node biopsy (SLNB) alone, even if metastases were found in 1 or 2 SLNs (2). The Z0011 trial indicated that patients who underwent SLNB rather than ALND had no poor prognosis at a mean follow-up of 6.3 years. Furthermore, the nodal recurrence rates were ascertained below 1%. Lately, published 10-year follow-up results of the Z0011 study indicated that the SLNB group prognosis was not inferior to the ALND group, particularly in terms of overall survival (3). Moreover, excellent locoregional control was achieved in patients receiving SLNB with all breast radiotherapy and adjuvant chemotherapy (4). The current study aimed to retrospectively evaluate patients with breast cancer who were operated on in our clinic in the era of the Z0011 and similar trials. We hope this assessment will be a considerable resource for future studies, especially for our country, as there is no complete national database on these issues.

MATERIAL AND METHODS

The study commenced by evaluating the records of 678 patients operated on for breast cancer in our clinic between 2014-2020. After tumor board, while 322 patients received neoadjuvant chemotherapy, 356 did not receive neoadjuvant KT and underwent surgery. Patients who received neoadjuvant chemotherapy and those whose pre-operative axillary nodal status was revealed positive for metastasis by clinical examination, imaging methods (Ultrasonography, Magnetic resonance imaging), or biopsy were excluded. The number of remaining T1-T2 tumors with clinically and radiologically node-negative and had sentinel lymph node biopsy was 236. Of these patients, 89 of them who had sentinel lymph node positivity were enrolled in the study. In addition, patients who underwent mastectomy instead of breast-conserving surgery with early breast cancer were also included in the study. The SLNB positive patients have been classified as the SLNB group of 32 cases (Group 1) and the SLNB following ALND group (Group 2) of 57 patients.

Age, tumor size, estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) status, clinical along with pathological stage and tumor histology, nuclear grade, lymphovascular invasion status of the patients were recorded. In addition, the number of SLNs removed and the number of metastatic LN were also evaluated. Furthermore, the surgical technique (mastectomy or breast-conserving surgery) performed, harvested LN (metastatic and non-metastatic LN count) status in ALND, and the data of radiotherapy received after surgery were recorded. Finally, data of the patients' follow-up period, locoregional recurrence, and distant metastasis were collected.

Statistical analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. The Kolmogorov-Smirnov test evaluated whether the distributions of numeric variables were normal. Accordingly, either independent sample t-tests or Mann-Whitney U tests compared the numeric variables between groups. The numeric variables are represented as mean ± standard deviation. Categorical variables were compared using chi-square tests. Categorical variables are presented as counts and percentages, and a p-value <0.05 was considered to indicate significance. Analyses were performed using SPSS

22.0 statistical software (IBM Corp., Armonk, NY, USA).

RESULTS

The mean age in group 1 was 54.65±11.68 and 54.70±12.62 in group 2. No statistical difference was noted between the age distributions of over 50 and under in both groups. While 37.5% of patients received BCS in Group 1, this ratio was 31.6% in Group 2. Mastectomy was performed at 62.5% and 68.4%, respectively. When the extent of the tumor in the breast was evaluated, there was no significant difference between groups in terms of solitary, multicentric, and multifocality. While all patients in Group 1 had 1-3 lymph node metastases (100%), in Group 2, LN metastases between 1-3 were 78.2%, LN metastases between 4-7 were 10.9%, and more than 7 of LN metastases in Group 2 was 10.9%. Overall, the clinicopathologic variables were not different between the two groups. There was no statistical difference between the two groups when studying the LN status regarding the extranodal invasion and lymphovascular invasions. The mean follow-up period of the patients was 40 months in group 1 (min-max:8-92 months) and 53 months in group 2 (min-max: 22-92 months) respectively (Table 1).

When the harvested LN status after ALND is evaluated, while 58 % of dissected LN was reactive, non-sentinel LN posivity was %42. Furthermore, in our study, less metastatic LN than expected was ascertained in ALND performed after positive SLNB in luminal B subtype tumors, which was statistically significant. But no significant effect was observed on metastatic LN status after ALND in terms of TM size, grade, or clinical stage (Table 2). There was an alteration between the frozen section and final pathology results in 18 of 32 patients who underwent SLNB. Macrometastasis was reported in the pathology results of two patients (6.25%) whose frozen section results were micrometastases. In addition, micrometastasis was identified in 10 of 16 (31.25%) patients without metastasis in the frozen section, and macrometastasis was found in 6 (18.75%) of them (Table 3). Finally, we had no local recurrence, metastasis, or death in group one. In group 2, two patients had metastasis (3.5%) (one brain metastasis operated and one bone metastasis) and one loss after a 48-month follow-up (1.75%) with no local recurrence.

Table 2: The Effect of Clinicopathological Parameters on ALND Metastasis in Group II Patients

		ALND metastasis			
		Metastasis (-)	Metastasis (+)	Sum	P value
Luminal A		20 (%51.3)	19 (%48.7)	39 (%100)	**0.019**
Luminal B		12 (%85.7)	2 (%14.3)	14 (%100)	
Triple negative		1 (%100)	0 (%0)	1 (%100)	
HER2 (+)		0 (%0)	3 (%100)	3 (%100)	
Tumor size					
	0-2 cm	20 (69%)	7 (31%)	25(100%)	0.23
	2-5 cm	13 (44.8%)	17 (55.2%)	29(100%)	
Grade					
	Grade 1	12 (70.6%)	6 (29.4%)	18(100%)	
	Grade 2	18 (58.1%)	14 (41.9%)	32(100%)	0.42
	Grade 3	3 (42.8%)	4 (57.2%)	7 (100%)	
Pathologic stage					
	Stage 1	6(66.6%)	3 (33.4%)	9(100%)	
	Stage 2	26 (63.4%)	15 (36.6%)	41(100%)	0.44
	Stage 3	1 (14.3%)	6 (85.7%)	7 (100%)	

ALND: axillary lymph node dissection, **HER 2**: Human epidermal growth factor receptor 2

Table1. Descriptive Statistics of Categorical Variables

		SLNB	SLNB + ALND	P value
Age				
	<50	12 (37.5%)	23 (40.4%)	0.79
	>50	20 (62.5%)	34 (59.6%)	
Focality				
	Solitary	26 (81.3%)	46 (80.7%)	0.78
	Multifocal	4 (12.5%)	9 (15.8%)	
	Multicentric	2 (6.3%)	2 (3.5%)	
Grade				
	1	18 (56.7%)	18 (30.9%)	0.67
	2	12 (36.7%)	32 (56.4%)	
	3	2 (6.7%)	7 (12.7%)	
Pathologic Stage				
	1	4 (12.5%)	0 (0%)	0.18
	2	24 (75%)	45 (78.8%)	
	3	4 (12.5%)	12 (21.1%)	
Histological type				
	Infiltrative ductal Ca	25 (78.1%)	44 (77.2%)	0.13
	Infiltrative lobular Ca	1 (3.1%)	9 (11.2%)	
	Mikst	2 (6.3%)	1 (3.4%)	
	Other	4 (12.5%)	3 (5.3%)	
Estrogen R				
	No	2 (6.3%)	5 (8.8%)	1.0
	Yes	30 (93.7%)	52 (91.2%)	
Progesteron R				
	No	2 (6.3%)	7 (12.3%)	0.48
	Yes	30 (93.7%)	50 (87.7%)	
Cerb2				
	No	29 (90.6%)	50 (87.7%)	1.0
	Yes	3 (9.4%)	7 (12.3%)	
Luminal				
	Luminal A	20 (62.5%)	39 (68.4%)	0.44
	Luminal B	11 (34.4%)	14 (24.6%)	
	Triple Negative	1(3.1%)	1 (1.7%)	
	Her2 +	0 (0%)	3 (5.3%)	
Ki67				
	<15	20 (62.5%)	29 (50.9%)	0.67
	15-29	8(25%)	20 (35.1%)	
	>29	4 (12.5%)	8 (14%)	
Metastatic LN number				
	1-3	32 (100%)	43 (78.2%)	0.20
	4-7	0	7 (10.9%)	
	>7	0	7 (10.9%)	
Extracapsular invasion				
	No	25 (78.1%)	38 (66.6%)	0.28
	Yes	7 (21.9%)	19 (33.4%)	
Vascular invasion				
	No	22 (68.7%)	34 (59.6%)	0.35
	Yes	10 (31.3%)	23 (40.4%)	
Lymphovascular invasion				
	No	17 (53.1%)	26 (45.6%)	0.74
	Yes	15 (46.9%)	31 (54.4%)	
Neural invasion				
	No	30 (93.7%)	45 (78.9%)	0.11
	Yes	2 (6.3%)	12 (21.1%)	
Intervention				
	BCS	12 (37.5%)	18 (31.6%)	0.35
	Mastectomy Skin Sparing Nipple Sparing	17 (53.1%) 3 (9.4%)	34 (59.6%) 5 (8.8%)	
RT				
	Received	32 (100%)	36 (63%)	<0.05
	Non-Received	0	21 (37%)	
Follow up (month)		40.12 ± 7.02	53.81 ± 5.22	

SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, R: receptor, LN: lymph node, RT: radiotherapy

Table 3. Deviations of SLNB in Frozen Section after Pathology (Group 1)

		Permanent result		
Frozen Section		Metastases	Micrometastases	Sum N (%)
	No metastases	6	10	16 (50%)
	Micrometastases	2	5	7 (21.9%)
	Metastases	9	-	9 (28.1%)
	Sum N (%)	17(53.1%)	15 (46.9%)	32 (100%)

DISCUSSION

ALND was an indispensable step in breast cancer treatment for a long time. However, the clearance of the lymph nodes in the axilla brings with width a spectrum of morbidity. Later on, as a result of the definition of SLNB and its extensive interest and acceptance, the approach to the axilla in breast cancer treatment began to shift. SLNB aims to safely reduce axillary lymph node dissection, specifying negative SLN (5,6). The ACOSOG Z0011 trial has transformed the approach to early breast cancer tremendously. The most remarkable outcomes of this study are that even if 1-2 lymph nodes in SLNB are metastatic, this patient group has similar local recurrence and survival rates with the groups whose axillae were treated with ALND (2,3). ACOSOG Z0011 study, which has achieved such impressive results, includes the patient group consisting of early-stage breast cancer and patients who underwent breast-conserving surgery, planned whole breast radiotherapy, and adjuvant systemic therapy. Similar studies conducted with the Z0011 eligibility criteria supported the results (7–9). In their research, Galimberti et al. evaluated patients after a mean follow-up of 9.7 years with a low axillary burden (micrometastasis). The study provides high-level evidence of not performing an axillary dissection as an adequate treatment due to non-inferiority of the primary outcome of disease-free survival in the no axillary dissection and the axillary dissection group (10). In the current study, the characteristics (tumor grade, pathologic stage, luminal type) of groups 1 and 2 had a similar distribution. All patients in group 1 received post-mastectomy radiotherapy (PMRT). In our study, the similarity of group 1 and 2 draw attention. In study Z0011, hormone-positive patients over 50 years of age are included in the study criteria. The reason for the lack of difference in our study was that in the first years of the Z0011 research, patients who met the inclusion criteria were picked in case selection. In the following years, with the demonstration of the effectiveness of radiotherapy in axillary metastases, we can note that axillary dissection was not performed in patients who did not fully fit the criteria. Beyond the Z0011 trial criteria, as a short-term result of our study, it can be mentioned that performing ALND in triple-negative, Her2-positive, and patients under 50 years of age may not cause axillary recurrence. In a recent study of a 19-year retrospective study published by Sun et al., ALND was not significantly correlated with reduced recurrence or improved OS among patients with cN0, SLN-positive breast cancer treated with mastectomy. Furthermore, ALND was linked considerably with receiving adjuvant systemic therapy, and completion of postmastectomy radiotherapy was associated with improved OS (11). As Galimberti et al. speculated, PMRT can be vital, especially preventing axillary recurrence (10). RT can treat low volume axillary involvement without ALND. In the current study, ALND had also been performed in patients in whom axillary dissection can be avoided despite 1-3 LN metastases; furthermore, we may declare that this effect had come to a fore due to patient choice or the surgeon's preference in the years when the z0011 trial was first implemented in our institute.

The current treatment protocol is to perform ALND in the presence of 3 or more lymph node metastases after SLNB. However, 1-2 metastatic lymph nodes or entirely reactive lymph nodes may be ascertained in the harvested axilla dissected after ongoing ALND. Although there were variations (in terms of metastasis) between the frozen section results and pathology reports of some patients in group 1, these alterations did not change our axillary approach since these diversities were limited to one lymph node (Table

3). Apart from sentinel LN metastasis in the axilla, non-sentinel lymph node (NSLN) metastases may also be present. A recent study reported similar NSLN metastasis in invasive ductal carcinoma, invasive lobular carcinoma, and other subtypes, which did not influence adjuvant chemotherapy or cause an inferior disease outcome (12). In another study, extranodal extension and tumor size were indicated as the essential factors in NSLN metastasis. It states that nomograms may be used to detect NSLN metastases to determine the risk of additional nodal disease in T1-2 tumors and guide treatment (13). The questions that come to mind are, can the metastatic lymph nodes removed after SLNB be sufficient, or can the remaining positive lymph nodes be treated with RT, and what is the impact on LR, DFS, and OS. These queries can only be revealed through randomized trials with broad participation. In this study, no metastasis was found in lymph nodes harvested in 58% of patients who underwent ALND after SLNB. Interestingly, fewer metastatic lymph nodes were found in the ALND group than expected in luminal group B tumors. Although the number of patients is inadequate, this finding may be preliminary data revealing the necessity of evaluating ALNDs after positive SLNB according to tumor subtype.

Clinically node-negative status in the NSABP B-04, ACOSOG Z0011, and IBCSG 23–01 trials was based on negative physical examination of the axilla (3,10,14). One of these studies' criticized aspects is whether it affects their results. The use of imaging modalities and clinical examination during axillary evaluation likely affects the patient groups in the studies and results. An essential factor of the lack of patients included in our study can be explained by the fact that ultrasonography and fine needle aspiration biopsy were performed in addition to clinical examination when evaluating patients with positive the lymph nodes.

Axillary recurrence (AR) has a devastating influence on survival, and the five-year OS for patients with isolated AR has been stated to be between 27% and 49% (15,16). In addition, simultaneous systemic metastases are identified in approximately 30% of patients with axillary recurrence (17). Several studies have evaluated clinicopathological features predisposing to axillary recurrence and proposed factors associated with tumor aggressiveness and metastasis ability. High tumor burden in the ipsilateral axilla, negative ER, young age, size of SLN metastases, lymphovascular invasion, HER2 positivity can be counted among the causes (17–21). These results also indicate that despite applying a conservative or an aggressive axillary treatment, we should remain mindful that some patients will develop AR. The clinicopathologic variables were not different between the two groups in this study. In group 1, we had no local recurrence, metastasis, or death. In group 2, two patients have metastasis (3.5%) (one brain metastasis operated and one bone metastasis), and one loss (1.75%) (After 48 months follow-up) with no local recurrence observed. Although these data can be based on the short-term follow-up of our study, early recurrence may be faced between 24 and 48 months after initial treatment (20,22,23).

Limitations

The weaknesses of our study can be stated as a single-center retrospective study and the small number of patient groups. However, we consider that this effort will create an essential resource on a national basis.

Conclusions

Although these results are based on our study's short-term follow-up, early recurrences may be faced between 24 and 48 months after initial treatment. In addition, as in our research, not performing axillary dissection may not affect the local recurrence of patients in patient groups that are not fully compatible with the Z0011 study. Nevertheless, the study Z0011, similar trials, and our study have confirmed that RT can treat low volume axillary disease without AD. The axillary disease may evolve to a no-touch technique soon.

Ethics Committee Approval: The ethical considerations of the study were evaluated by the Sakarya Univercty Hospital Ethics Board, and ethical approval number E-71522473-050.01.04-39907-364.

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