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De-escalation of axillary surgery in early breast cancer: translating ACOSOG Z0011 study into clinical practice for breast-conserving surgery patients with positive sentinel lymph node biopsy

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Abstract

Purpose This retrospective study aimed to compare patients eligible for the Z0011 study with and without axillary lymph node dissection (ALND) by overall survival (OS), disease-free survival (DFS), and loco-regional recurrence.

Methods We carried out this study with the data from early-stage breast cancer patients (T1, T2, and clinical node-negative) undergoing breast-conserving surgery (BCS) and receiving adjuvant systemic therapy (chemotherapy or endocrine therapy) and adjuvant radiotherapy after sentinel lymph node biopsy (SLNB) at Ankara Oncology Hospital between January 2018–2024. We screened the data from a total of 1,218 patients and selected 126 patients with ALND and 67 patients without ALND. All selected patients satisfied the Z0011 criteria. We excluded mastectomy and metastatic patients, those without SLNB, patients with more than two positive lymph nodes, and those receiving neoadjuvant chemotherapy. Then, we compared groups by OS, DFS, and locoregional recurrence.

Results While the 5-year overall survival was 98.5% (95% CI, 95.8–100.0%) in the Z0011 group, it was 95.2% (95% CI, 92.1–98.3%) in the Z0011-eligible group. The 5-year DFS rate was 97.0% (95% CI, 92.0–99.0%) and 94.4% (95% CI, 91.2–97.0%) in the groups, respectively. We did not discover recurrence in the axial lymph nodes and breast at a mean follow-up of 69 months (67.46–70.43).

Conclusion In summary, the present study demonstrated that the omission of ALND does not exert any significant influence on OS, DFS, and locoregional recurrence among patients satisfying the ACOSOG Z0011 criteria.

Keywords Breast cancer, Sentinel lymph node, ACOSOG Z0011

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Introduction

Surgical treatment of the axilla in breast cancer was regarded as a prognostic indicator of the disease and significantly affected adjuvant therapies. During the era of Halsted radical mastectomy, the axilla was considered a potential point of transition for distant metastases, leading to employing radical dissection procedures. Yet, the advancements in breast cancer research have uncovered that axillary lymph node dissection (ALND) plays a pivotal role in staging and prognosis, rather than serving solely as a preventative measure against distant metastasis.

The NSABP B-04 study, initiated in 1971, sought to ascertain the comparative effectiveness of less extensive axillary surgery and radiotherapy in comparison to Halsted radical mastectomy [1]. With regard to axillary management, patients were randomized to receive complete ALND, axillary radiation, or no axillary treatment. The 25-year follow-up revealed no significant differences in overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS) among participating patients. The subsequent research, the NSABP B-32 study, further investigated the comparative effectiveness of diverse treatment modalities for patients with negative sentinel lymph node biopsy (SLNB). The authors concluded that patients undergoing only SLNB or ALND exhibited equivalent outcomes in terms of OS and DFS [2]. The observations from the NSABP B-04 and NSABP B-32 studies paved the way for the ACOSOG Z0011 study. This randomized controlled trial investigated the safety of the omission of ALND in early-stage breast cancer patients undergoing breast-conserving surgery (BCS) and had 1–2 positive SLNs. The findings suggested that omitting ALND in specific patient groups did not result in a substantial difference in terms of disease control and survival [3]. The groundbreaking results of the Z0011 study have brought a new perspective to the axillary approach, questioning the necessity of axillary dissection and generating great excitement among clinicians. Subsequently, these results were corroborated in diverse populations in several other regions, including the United States, Australia, Europe, Japan, and China [4–6].

This retrospective study builds on the Z0011 trial to compare groups with and without ALND in terms of clinicopathological features, OS, and DFS. It stands out as one of the few studies in the existing literature that validate the findings of the Z0011 trial. Moreover, it represents the most extensive series to date investigating the applicability of the ACOSOG Z0011 criteria in the Turkish context.

Materials & methods

We carried out this study with the data from early-stage breast cancer patients (T1, T2, and clinical node-negative) undergoing BCS and receiving adjuvant systemic therapy (chemotherapy or endocrine therapy) and adjuvant radiotherapy after SLNB at Ankara Oncology Hospital between January 2018–2024. We screened the data from a total of 1,218 patients and selected 126 patients with ALND (Z0011-eligible group) and 67 patients without ALND (Z0011 group). Patients in the Z0011 group did not undergo axillary dissection as they met the Z0011 criteria, whereas patients in the Z0011-eligible group, despite meeting the same criteria, underwent axillary dissection due to the surgeon's preference. All selected patients satisfied the Z0011 criteria [7]. Female patients aged 18 years and over with histologically diagnosed invasive breast cancer, T1 or T2 tumors, a negative axilla confirmed by ultrasonography and biopsy, who underwent lumpectomy, had at most 1–2 positive sentinel lymph nodes, and received whole breast irradiation were included in the study.

We excluded mastectomy and metastatic patients, those without SLNB, patients with more than two positive lymph nodes, and those receiving neoadjuvant chemotherapy or hormonal therapy. Unlike the ACOSOG Z0011 study, routine preoperative axillary nodal ultrasound imaging was performed on all patients, and fine needle biopsy was conducted for suspicious lymph nodes.

We extracted the following patient data from the hospital database: age, T-stage, histopathology, tumor grade, hormone receptor status, Ki-67 and HER2 status, presence of perineural and lymphovascular invasion, tumor localization, adjuvant chemotherapy, adjuvant endocrine therapy, metastasis status and localization, type of surgery, ALND status, surgical margin status, sentinel lymph node count, mean number of positive SLNs, presence of extracapsular invasion in axilla-positive patients, mean number dissected SLNs in ALND patients, and re-excision status. The pathological staging was determined according to the 8th edition of the American Joint Committee on Cancer Staging Manual [8]. SLNs were detected using methylene blue and Tc-99 m pertechnetate, and the pathological diagnosis was performed intraoperatively by examining the surface of 2 mm thick sections of fresh SLN tissues. The precise pathological status of SLN metastases was decided in accordance with the 7th edition of the Tumor Node Metastasis (TNM) Classification of Malignant Tumors [9].

The study flowchart is presented in Fig. 1. The Clinical Research Ethics Committee of Ankara Oncology Hospital granted ethical approval to our study (2024-07/105). All statistical analyses were performed using SPSS 20.0. Overall survival (OS), disease-free survival (DFS), and locoregional recurrence were evaluated using

Fig. 1 Study Flowchart

Kaplan–Meier survival analysis, and survival differences between groups were compared using the log-rank test.

Results

We retrospectively screened the data from a total of 1,218 patients undergoing BCS and SLNB and selected 67 and 126 patients satisfying the Z0011 criteria. The latter group underwent ALND (Z0011-eligible patients).

While Table 1 outlines patients' clinical and pathological characteristics, Table 2 is dedicated to their surgery-specific conditions. In the Z0011 cohort, 70% of patients were 50 years or older, with 62.7% of patients classified as T2 stage. The tumor was localized in the upper outer quadrant in 49% of patients. A subsequent examination of the histopathological subtypes revealed that 88% of patients were no special type (NST), 6% were lobular, and 6% fell into other categories. The majority of them (44%) had Grade 3, and 55% had Grade 1 or 2 carcinoma. Almost all (89%) were hormone receptor-positive. While Ki-67 was detected as >14 in 92%, HER2 negativity was present in 89%. Almost all (91%) underwent oncoplastic surgery, and surgical margin positivity was observed in 16% of them. In this group, 11 patients had a positive surgical margin, and 8 patients had re-excision. Three patients were left to have radiotherapy as they did not provide their consent to re-excision. The majority of patients (80.6%) received nodal radiotherapy, 11.9% were recruited for level 1/2 axillary radiotherapy, and 7.5% received whole breast radiotherapy. The extracapsular invasion rate was found to be 9%. The mean number of dissected SLNs was 3.76 ± 1 [median = 3 (3–6)], while the mean number of positive SLNs was 1.42 ± 0.42 [median = 1 (1–3)]. Lung metastasis was present in only 1 patient at the 12-month follow-up.

Similar to the prior cohort, 70% of patients in the Z0011-eligible group were aged 50 years and older, with 65% classified as T2 stage. The tumor was localized in the upper outer quadrant in 46% of patients. NST, lobular and other histopathological outcomes were detected at rates of 77%, 9.5%, and 10.5%, respectively. In addition, we discovered that 52% of patients had Grade 3, and 48% had Grade 1 or 2 carcinoma. The hormone receptor test yielded a positive result in 89% of cases, 88% had Ki-67 expression levels greater than 14%, and HER2 positivity was found in 84% of cases. Oncoplastic surgery was performed on 69% of patients. While 11% had a surgical margin positivity, re-excision was applied to 12 patients; nevertheless, 3 patients refused re-excision. The distribution of postoperative treatments included 67.5% of patients receiving nodal radiotherapy, 20.6% receiving level 1/2 axillary radiotherapy, and 11.9% receiving whole-breast radiotherapy. The extracapsular invasion rate was 40% among these patients. The mean number of dissected SLNs was 3.33 ± 0.7 [median = 3 (3–6)] while the mean number of positive SLNs was 1.37 ± 0.48 [median = 1 (1–2)]. Four patients were present with distant metastases during the follow-up, including bone metastasis (24 months), vertebral metastasis (30 and 36 months), and lung metastasis (54 months).

We calculated the mean OS and DFS were 67 and 66 months in the Z0011 group, respectively, and 68 and 67 months in the Z0011-eligible cohort, respectively. Our analysis showed statistically insignificant differences between the groups by OS and DFS (Table 3). Besides, the groups exhibited a 5-year OS rate of 98.5% (95% CI, 95.8–100.0%) and 95.2% (95% CI, 92.1–98.3%), respectively (Fig. 2). The 5-year DFS rates were found to be 97.0% (95% CI, 92.0–99.0%) and 94.4% (95% CI, 91.2–97.0%), respectively (Fig. 2). Finally, we concluded no axillary or breast tumor recurrence in the groups during the mean 69-month follow-up (67.46–70.43).

Discussion

The ACOSOG Z0011 study pioneered overreaching developments in breast cancer surgery, as it demonstrated the safety of omitting ALND in early-stage breast cancer patients with positive SLNB. In other words, the study yielded that, compared to patients with ALND, omitting ALND did not affect OS, DFS, and locoregional recurrence among BCS patients with clinical T1 or T2 stage N0 and M0 cancer and 1–2 positive SLNs receiving tangential-field whole-breast radiation therapy and adjuvant systemic therapy.

Following the Z0011 study, numerous regions corroborated the findings within their respective populations [10–13]. In this sense, this study stands out as one of the few in the extant literature that validated the results of the Z0011 study. It also represents the most extensive series to date investigating the applicability of the ACOSOG Z0011 criteria in the Turkish context.

The ACOSOG Z0011 study reported the 5-year OS rate to be 91.8% (95% CI, 89.1-94.5%) in patients with ALND and 92.5% (95% CI, 90.0-95.1%) in those with SLNB. The 5-year DFS rate was reported as 82.2% (95% CI, 78.3-86.3%) and 83.9% (95% CI, 80.2-87.9%), respectively [7]. In the study, only one patient exhibited locoregional lymph node recurrence in the 76th month of the follow-up period [14]. Consistent with these results, we found a low risk of locoregional recurrence and a favorable prognosis in patients with a positive SLN treated with SLNB alone. In this study, we discovered no axillary or breast tumor recurrence at a mean follow-up of 69 months (67.46–70.43). The 5-year OS rate was 98.5% (95% CI, 95.8–100.0%) in the Z0011 group and 95.2% (95% CI, 92.1–98.3%) in the Z0011-eligible patients. We calculated the 5-year DFS rate to be 97.0% (95% CI, 92.0–99.0%) in the Z0011 group and 94.4% (95% CI, 91.2–97.0%) in the Z0011-eligible patients. The survival outcomes found in

Table 1 Patients' clinical and pathological features

Clinicopathological Variables	Z0011 group *n* = 67 (%)	Z0011-eligible group *n* = 126 (%)
Age(years)		
< 50	20(29.9)	37 (29.4)
≥ 50	47(70.1)	89 (70.6)
T-stage		
T1	25 (37.3)	43 (34.1)
T2	42 (62.7)	83 (65.9)
Tumor localization		
Upper Outer Quadrant	33 (49.3)	59 (46.8)
Upper Inner Quadrant	18 (26.9)	25 (19.8)
Lower Inner Quadrant	4 (6.0)	14 (11.1)
Lower Outer Quadrant	5 (7.5)	17 (13.5)
Central	8 (11.9)	11 (8.7)
Histopathological outcome		
NST	59 (88)	97 (77)
Lobular	4 (6)	12 (9.5)
Others	4 (6)	17 (13.5)
Grade		
Grade 3	30 (44.8)	65 (51.6)
Grades 1 and 2	37 (55.2)	61 (48.4)
Hormone receptor		
Negative	7 (10.4)	13 (10.3)
Positive	60 (89.6)	113 (89.7)
ER		
Negative	7 (10.4)	13 (10.3)
Positive	60 (89.6)	113 (89.7)
PR		
Negative	8 (11.9)	16 (12.7)
Positive	59 (88.1)	110 (87.3)
Ki-67 (mean)	35.34 ± 20.13	36.73 ± 22.44
Ki-67		
≤ 14	5 (7.5)	14 (11.2)
> 14	62 (92.5)	111 (88.8)
HER-2 status		
Negative	60 (89.6)	107 (84.9)
Positive	7 (10.4)	19 (15.1)
Presence of perineural invasion		
No	56 (83.6)	94 (74.6)
Yes	11 (16.4)	32 (25.4)
Presence of lymphovascular invasion		
No	46 (68.7)	80 (63.5)
Yes	21 (31.3)	46 (36.5)
Localization		
unifocal	65 (97)	118 (93.7)
multifocal	2 (3)	8 (6.3)
Adjuvant chemotherapy		
No	2 (3)	3 (2)
Yes	65 (97)	123 (98)
Adjuvant endocrine therapy		
No	9 (13)	15 (12)
Yes	58 (87)	111 (88)
RT Localization		
Whole-Breast Alone	5 (7.5)	15 (11.9)
Level I/II	8 (11.9)	26 (20.6)
Nodal Radiotherapy	54 (80.6)	85 (67.5)
Radiotherapy		
No	0	0
Yes	67 (100)	126 (100)

Table 2 Patients' Surgery-Specific conditions

Conditions	Z0011 group *n* = 67 (%)	Z0011-eligible group *n* = 126 (%)
Type of surgery		
Oncoplastic Surgery	61 (91)	87 (69)
Conventional Surgery	6 (9)	39 (31)
ALND		
No	67 (100)	0
Yes	0	126 (100)
Surgical margin status		
Negative	56 (83.6)	111 (88.1)
Positive	11 (16.4)	15 (11.9)
SLN count		
Median	3 (3–6)	3 (3–6)
Number of positive SLNs		
Median	1 (1–2)	1 (1–2)
Presence of extracapsular invasion in axilla-positive patients		
No	61 (91)	76 (60.3)
Yes	6 (9)	50 (39.7)
Mean number of SLNs in ALND patients		
Median	-	32 (5–37)
Re-excision status		
No	59 (88)	114 (90.5)
Yes	8 (12)	12 (9.5)

this study were higher than those reported in the Z0011 study, which may be attributed to the higher proportion of cases with hormone receptor-positive breast cancer in our research (89%) compared to the Z0011 study (75.2%). Moreover, the high rate of HER-2 negativity (89%) in this study might be indicative of a more favorable prognosis. The evolution of adjuvant systemic and radiotherapy therapies over time may have contributed to this improved prognosis among our patient cohort. Alternatively, the relatively smaller sample size of this study may have led to an improvement in patients' observed outcomes. In their ACOSOG Z0011 validation study, Peng et al. reported the 2-year OS to be 100% and DFS to be 99% Similarly, Kittaka et al. reported the 3-year local-regional recurrence-free survival to be 98.7% (95% CI 96.9–100%) and DFS to be 96.8% (95% CI 94.0-99.6%) in the Japanese cohort [5]. In the largest validation series of the literature, Morrow et al. reported the 5-year OS to be 97.6% (95% CI 96.0–99.2%) in the dissection group and 97.5% (95% CI 95.8–99.1%) in the non-dissection group [15]. The previous findings, therefore, overlap with the findings of our study.

The Z0011 study revealed that 52.6% of patients underwent high tangent radiotherapy, and 16.9% received radiotherapy to the supraclavicular region [16]. In the Peng et al. study, 54.5% of the 99 patients treated with only SLNB received nodal radiotherapy, 23.0% received Level I/II radiotherapy, and 22.3% received whole-breast radiotherapy [13]. In contrast, 80.6% of the Z0011 group in this study underwent nodal radiotherapy, 11.9% received Level I/II radiotherapy, and 7.5% received whole-breast radiotherapy. The rate of nodal radiotherapy administered to patients was marginally higher than the respective rates reported in the extant literature, which may be attributed to the heightened vigilance of radiotherapists in opting for more intensive radiotherapy regimens, driven by concerns regarding the potential for recurrence.

In the ACOSOG Z0011 study, 96% of patients in the dissection group and 97% in the sentinel-only group received adjuvant systemic therapy [17]. In our study, this rate is 97% in the Z0011 group and 98% in the Z0011-eligible group. With the application of adjuvant chemotherapy, the risk of both loco-regional and distant recurrence is reduced [18–20]. In hormone receptor-positive, HER2-negative premenopausal women, adjuvant chemotherapy provides a progression-free survival benefit, especially in patients with a recurrence score of 16–25 [21]. Adjuvant chemotherapy is beneficial in women with ER+/HER2- breast cancer with 1–3 positive nodes and a recurrence score of 20–25, regardless of age [22, 23]. Additionally, adjuvant tamoxifen reduces local-regional recurrence rates by 50%, and cytotoxic chemotherapy, aromatase inhibitors, and anti-HER2 therapy reduce local-regional recurrence rates [24–26].

Limitations of the study include the relatively short follow-up period. Since 90% of the patients in the study were hormone receptor-positive, the risk of locoregional and systemic recurrence beyond five years in hormone receptor-positive tumors is significant. As stated in the study by Colleoni et al., the risk of recurrence within the first 5 years is lower in ER-positive patients (9.9%) compared to ER-negative patients (11.5%). However, after 5 years, recurrence rates become higher in ER-positive patients compared to ER-negative patients. Between 5 and 10 years, the annual recurrence rate is 5.4% in ER-positive

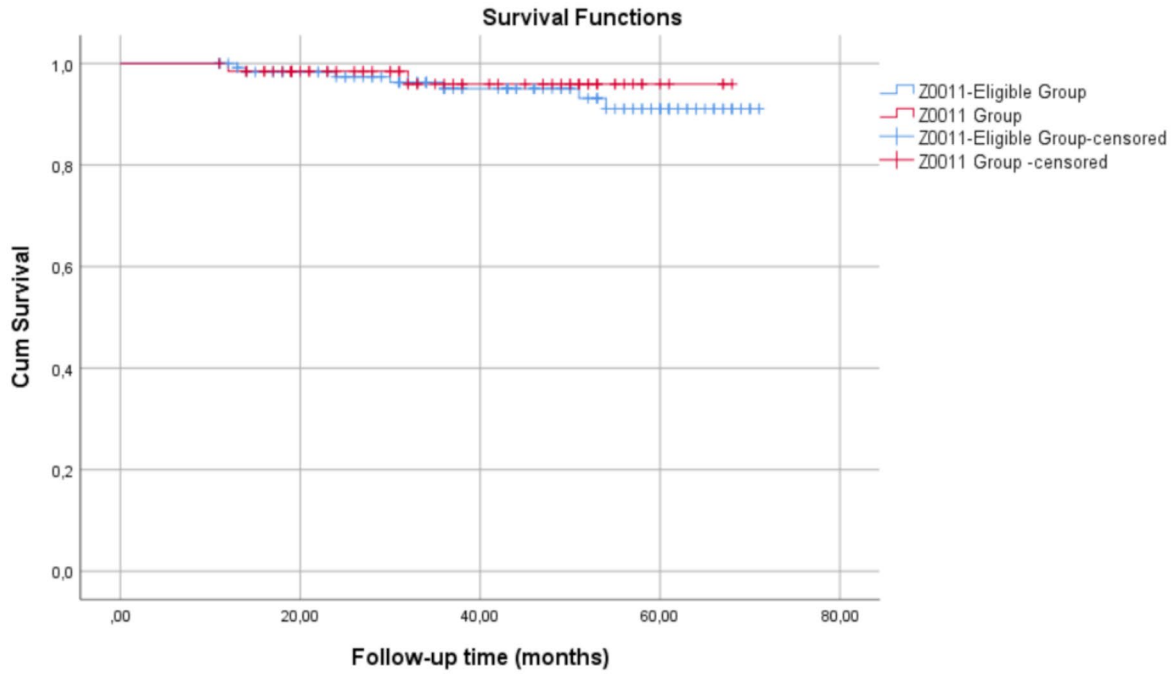
Table 3 OS and DFS of the groups

	Mean OS (95% CI)	SE	Mean DFS (95% CI)	SE
Z0011 group	67.07 (65.29–68.86)	0.91	66.24 (63.85–68.64)	1.22
Z0011-eligible group	68.52 (66.59–70.46)	0.99	67.98 (65.81–70.15)	1.11
Overall OS	68.94 (67.46–70.43)	0.76		

DFS ($p = 0.57$)

OS ($p = 0.40$)

a:



b:

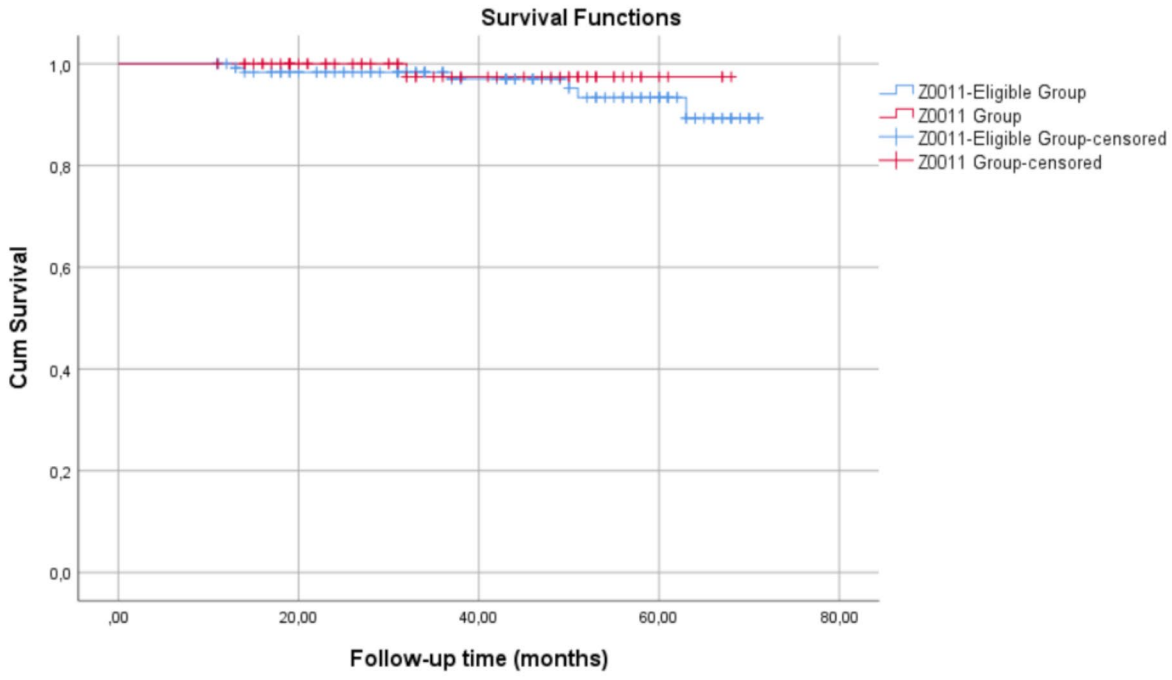


Fig. 2 Kaplan–Meier analysis of distant disease-free survival (**a**) and overall survival (**b**) [$n = 193$ (67 + 126)]

patients, while it is 3.3% in ER-negative patients [27]. Axillary recurrences tend to occur earlier after surgery In the ACOSOG Z0010 study, the median time to axillary recurrence was 19.1 months, whereas in the ACOSOG Z0011 study, the median time to regional recurrence was 48 months [14, 28, 29]. In the study by Greco et al., this period had a median of 30.6 months, while in the study by Martelli et al., it was reported as 33 months [30, 31].

In the 10-year results of the ACOSOG Z0011 study, with a median follow-up of 9.3 years, the 10-year overall survival (OS) was reported as 86.3% in the SLNB group and 83.6% in the ALND group. The 10-year DFS rates were 80.2% for the SLND group and 78.2% for the ALND group. The 10-year loco-regional recurrence rates were 6.2% for the ALND group and 5.3% for the SLND-only group, with no significant difference observed. These results indicate that, for this patient population, SLND alone is not inferior to ALND in terms of both OS and DFS [14].

Similar to the previous findings, ALND was omitted in 68.93% of patients with positive SLNB (upfront group) [10–12, 32, 33]. Although the Z0011 study included an evaluation of the axillary lymph nodes via physical examination, the present study differed in that all patients underwent preoperative ultrasonographic evaluation and biopsy of any suspicious lymph nodes, which may have resulted in enhanced survival outcomes.

The retrospective and single-center design, the relatively brief follow-up period, and the limited sample size represent the principal limitations of this study. Despite its designation as a retrospective validation study, our ultimate objective was to steer the implementation of the same procedures prospectively in mastectomy and neoadjuvant patients and to provide insights for future studies that will question the necessity of SLNB.

Conclusions

In a nutshell, we could corroborate that the omission of ALND has no impact on OS, DFS, or locoregional recurrence among patients satisfying the ACOSOG Z0011 criteria compared to the ALND patients. We believe that our findings may be particularly impactful on the clinical practice of Turkish surgeons.

Abbreviations

ALND	Axillary lymph node dissection
OS	Overall survival
DFS	Disease-free survival
BCS	Breast-conserving surgery
SLNB	Sentinel lymph node biopsy
CI	Confidence interval
RFS	Recurrence-free survival
NST	No special type

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Not applicable.

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by M.F.S and B.D. The first draft of the manuscript was written by M.F.S and C.Ö and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. (Mehmet Furkan Sağdıç, m.f.sagdic@gmail.com)

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Research Ethics Committee of Ankara Oncology Training and Research Hospital, University of Health Sciences (approval number: 2024-07/105). The requirement for informed consent was waived by Research Ethics Committee of Ankara Oncology Training and Research Hospital, University of Health Sciences in accordance with national regulations and institutional policies due to the retrospective nature of the study. All procedures followed the ethical standards of the institutional and national research committee, and the 1964 Helsinki Declaration and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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