Original Article

Axillary lymph node removal in *de novo* metastatic breast cancer

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Background: Several prospective studies have found that local surgical resection did not improve the survival of patients with *de novo* metastatic breast cancer (dnMBC). However, a significant portion of dnMBC patients still undergo local surgery, and the role of axillary lymph node dissection (ALND) in dnMBC patients remains unclear. This study aimed to investigate the effect of ALND in patients with dnMBC.

Methods: We included patients diagnosed with dnMBC between 2010 and 2020 using the data from the Surveillance, Epidemiology, and End Results program. The Chi-square test, binomial logistic regression, propensity score matching (PSM), Kaplan-Meier method, and multivariate Cox proportional models were employed for statistical analysis.

Results: A total of 6,838 patients were identified, with 5,562 (81.3%) in the ALND group and 1,276 (18.7%) in the non-ALND group. Being diagnosed in later years emerged as an independent predictive factor related to the receipt of ALND (P=0.003). Before PSM, the 5-year breast cancer-specific survival (BCSS) was 51.1% and 38.2% in those with and without ALND, respectively (P<0.001). The 5-year overall survival (OS) was 45.9% and 32.3% in those with and without ALND, respectively (P<0.001). ALND was identified as an independent prognostic factor related to better BCSS (P<0.001) and OS (P<0.001) compared to the non-ALND group. Similar findings were observed after PSM. The outcomes were significantly better in the ALND group than in the non-ALND group in most subgroups. However, the number of removed lymph nodes did not show a significant association with BCSS (P=0.27) and OS (P=0.29).

Conclusions: Our study suggests that ALND is associated with improved survival outcomes in dnMBC patients. These findings advocate for a re-evaluation of the role of surgical interventions in dnMBC, emphasizing the need for personalized treatment strategies that consider the potential benefits of ALND.

Keywords: Metastatic breast cancer; surgery; lymph node dissection; survival analysis; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Breast cancer (BC) remains a significant health concern worldwide, with a substantial impact on morbidity and mortality in women (1). The incidence of BC has increased by 0.5% per year annually and the incidence of *de novo* metastatic BC (dnMBC) is increasing despite widespread mammography screening (2,3). While advancements in BC screening and treatment modalities have improved outcomes for many patients, dnMBC presents a distinct challenge due to its advanced metastatic nature at initial diagnosis. dnMBC is characterized by the spread of BC beyond the breast and regional lymph nodes to distant sites, such as the bones, lungs, liver, or brain, at the time of diagnosis. It is a relatively rare condition, affecting approximately 5–10% of all BC patients. However, its prognosis is generally poor, with a median survival time of only 2–3 years (4-7).

Several retrospective studies have indicated that women diagnosed with dnMBC may experience enhanced survival rates following the surgical removal of the primary tumor. However, the interpretation and generalizability of these findings are limited due to potential selection bias. Four clinical trials have evaluated the impact of local surgical resection of the primary lesion in dnMBC (8-11). Three of these trials demonstrated improved locoregional control, yet they did not reveal any statistically significant difference in overall survival (OS). The fourth trial reported an improvement in 5-year OS, but this finding drew criticism due to concerns that patients in the surgery group may have been in a more favorable prognostic category before the intervention (11). However, there were still 26.8–57.2% of patients receiving local surgery in the real world and the results found that local surgical resection of the primary lesion was associated with better survival outcomes in this population (12-15).

Historically, the primary goal of axillary lymph node dissection (ALND) in non-metastatic BC has been to accurately stage the disease and guide adjuvant treatment decisions. Additionally, ALND is believed to provide local control by removing potentially cancerous lymph nodes in the axilla. However, its role in dnMBC patients has been a subject of debate and investigation. In light of this, the objective of our study was to examine the trends and impact of ALND in patients diagnosed with dnMBC using a population-based cohort. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-130/rc).

Highlight box

Key findings

- The receipt of axillary lymph node dissection (ALND) was associated with better breast cancer-specific survival and overall survival in patients with *de novo* metastatic breast cancer (dnMBC) before and after propensity score matching.

What is known and what is new?

- The role of ALND in dnMBC patients who underwent local surgery remains unclear.
- Limited studies have reported the effect of ALND in dnMBC. We examined the trends and impact of ALND in patients diagnosed with dnMBC using a population-based cohort.

What is the implication, and what should change now?

- ALND is associated with improved survival outcomes in dnMBC patients. Our study advocates for a re-evaluation of the role of surgical interventions in dnMBC.

Methods

Patients

This retrospective study utilized data from the Surveillance, Epidemiology, and End Results (SEER) program to include patients diagnosed with dnMBC between 2010 and 2020 (16). The SEER program, a resource by the National Cancer Institute, is a comprehensive source of cancer statistics providing data on cancer incidence, demographics, clinicopathological variables, treatment, and vital status from 18 cancer registries across the United States. The analysis included women who met the following criteria: (I) diagnosed with dnMBC aged 18 years or above; (II) underwent local surgery including breast-conserving surgery or mastectomy; (III) with or without additional ALND during local surgery. Patients were excluded from the analysis if they had missing data on tumor (T) stage, nodal (N) stage, estrogen receptor (ER) status, progesterone receptor (PR) status as well as human epidermal growth factor receptor 2 (HER2) status. In addition, those with unavailable sites of distant metastasis (DM) were also excluded from the analysis. As the SEER program only contains anonymized data, our study was exempt from the approval process by the ethics committee. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables

The analysis incorporated the following variables: years of diagnosis, age, race, tumor grade, histology, T stage, N stage, ER status, PR status, HER2 status, receipt of chemotherapy, surgical procedure, and sites of DM. The definition of DM sites included bone, brain, liver, lung, or distant lymph nodes. The primary outcomes of this study were breast cancer-specific survival (BCSS) and OS. BCSS was calculated from the time of dnMBC diagnosis to the time of death specifically due to BC or the follow-up cutoff. OS was measured from the time of dnMBC diagnosis to the time of death from any cause or the follow-up cutoff.

Statistical analysis

The Chi-square test was utilized to compare the demographic and clinicopathological variables between the groups that underwent ALND and those that did not. Binomial logistic regression was carried out to identify the independent predictors associated with the receipt of ALND. To mitigate selection bias between the ALND and non-ALND cohorts, a 1:1 propensity score matching (PSM) was implemented. BCSS and OS curves were plotted by the Kaplan-Meier method and the log-rank test was employed to compare the differences between these curves. Multivariate Cox proportional analysis was applied to determine the independent prognostic factors significantly related to survival outcomes. Sensitivity analyses were conducted after stratifying the demographic and clinicopathological variables to verify the robustness of the results. All statistical analyses were carried out using the SPSS statistical software (version 25.0, IBM Corporation, Armonk, NY, USA). P values less than 0.05 were defined as statistical significance.

Results

Patient baseline characteristic

A total of 6,838 patients were included in the study (*Figure 1*), of which 5,562 (81.3%) were in the ALND group and 1,276 (18.7%) in the non-ALND group. The baseline characteristics of patients are listed in *Table 1*. The median age of diagnosis was 58 years. There were 4,372 (63.9%) who were of White race, 3,428 (50.1%) had an undifferentiated disease, 5,217 (76.3%) had invasive ductal carcinoma, and 5,440 (79.6%) had nodal-positive disease. Regarding BC subtype (BCS), 3,880 (56.7%), 1,157 (16.9%), 699 (9.8%), and 1,132 (16.6%) patients had hormone receptor (HoR)$^+$/HER2$^-$, HoR$^+$/HER2$^+$, HoR$^-$/HER2$^+$, and HoR$^-$/HER2$^-$, respectively. Bone (n=4,082, 59.7%) was the most common site of DM, followed by distant lymph nodes (n=1,805, 26.4%), lung (n=1,645, 24.1%), liver (n=1,329, 19.4%), and brain (n=241, 3.5%). There were 5,144 (75.2%), 1,232 (18.0%), 364 (5.3%), 88 (1.3%), and 10 (0.1%) patients who had one, two, three, four, and five sites of DM, respectively. There were significant differences in age, race, tumor grade, histology, T stage, N stage, surgical procedure, chemotherapy receipt, and the sites of DM between those with and without ALND (all P<0.05) (*Table 1*). However, a similar distribution in BCS (P=0.70) was found between those with and without ALND. A total of 396 pairs of patients were completely matched using PSM (*Table 1*).

Trends of ALND during the study period

The trends of ALND in dnMBC patients between 2010 and 2020 are shown in *Figure 2*. There were 79.1% of patients received ALND in 2010 and 83.4% of patients received ALND in 2020. The probability of ALND increased slightly between 2010 and 2020, but there was no statistically significant difference (P=0.15).

Binomial logistic regression was performed to determine the independent predictors of ALND receipt (*Table 2*). The results showed that patients with Hispanic race [*vs.* White, odds ratio (OR) 1.336, 95% confidence interval (CI): 1.082–1.650, P=0.007], diagnosed in later years (OR 1.026, 95% CI: 1.004–1.048, P=0.02), received mastectomy (*vs.* breast-conserving surgery, OR 3.915, 95% CI: 3.389–4.523, P<0.001), received chemotherapy (*vs.* no chemotherapy, OR 1.606, 95% CI: 1.394–1.850, P<0.001) were the independent predictive factors associated with the receipt of ALND. However, those with advanced T stage (T4 *vs.* T1, OR 0.470, 95% CI: 0.381–0.581, P<0.001), lung metastasis only (*vs.* bone metastasis only, OR 0.709, 95% CI: 0.569–0.882, P=0.002), and multiple metastases (*vs.* bone metastasis only, OR 0.568, 95% CI: 0.483–0.667, P<0.001) were associated with non-receipt of ALND.

Survival

The median follow-up was 33 months. A total of 3,679 patients died, including 3,162 patients died with BC (85.9%). Those treated with ALND had better BCSS and OS compared to those without ALND. Before PSM,

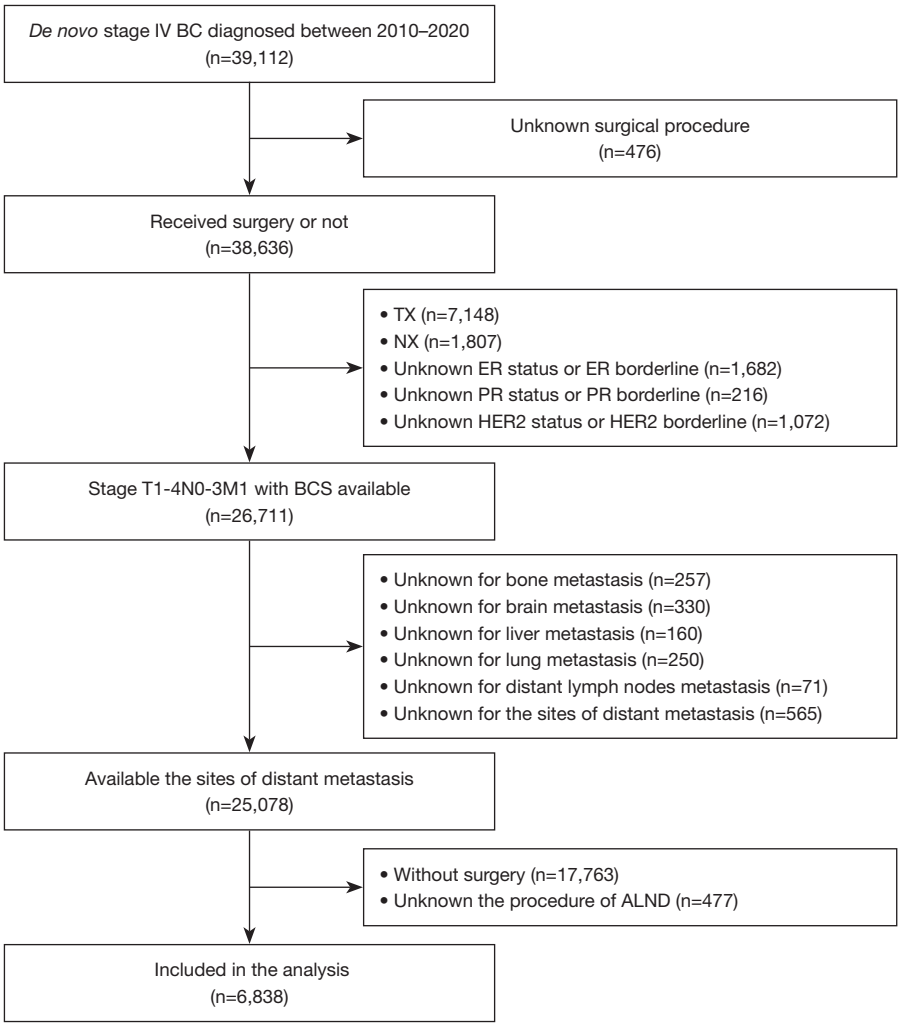

Figure 1 The flow chart of the cohort selection. BC, breast cancer; T, tumor; N, nodal; X, unknown; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast cancer subtype; M, metastasis; ALND, axillary lymph node dissection.

Table 1 Patient baseline characteristics before and after PSM

Variables	Before PSM				After PSM			
	n	ALND (%)	Non-ALND (%)	P	n	ALND	Non-ALND	P
Age (years)				<0.001				>0.99
<65	4,464	3,697 (66.5)	767 (60.1)		534	267	267	
≥65	2,374	1,865 (33.5)	509 (39.9)		258	129	129	
Race/ethnicity				0.048				>0.99
Non-Hispanic White	4,372	3,518 (63.3)	854 (66.9)		618	309	309	
Non-Hispanic Black	1,014	830 (14.9)	184 (14.4)		86	43	43	
Hispanic (all races)	834	703 (12.6)	131 (10.3)		52	26	26	
Others	618	511 (9.2)	107 (8.4)		36	18	18	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Before PSM				After PSM			
	n	ALND (%)	Non-ALND (%)	P	n	ALND	Non-ALND	P
Grade				<0.001				>0.99
Well-differentiated	455	376 (6.8)	79 (6.2)		28	14	14	
Moderately differentiated	2,399	1,958 (35.2)	441 (34.6)		304	152	152	
Poorly/undifferentiated	3,428	2,811 (50.5)	617 (48.4)		440	220	220	
Unknown	556	417 (7.5)	139 (10.9)		20	10	10	
Histological subtype				0.048				>0.99
Invasive ductal carcinoma	5,217	4,230 (76.1)	987 (77.4)		716	358	358	
Invasive lobular carcinoma	647	549 (9.9)	98 (7.7)		22	11	11	
Others	974	783 (14.1)	191 (15.0)		54	27	27	
T stage				<0.001				>0.99
T0/T1	981	771 (13.9)	210 (16.5)		302	151	151	
T2	2,520	2,120 (38.1)	400 (31.3)		336	168	168	
T3	1,338	1,177 (21.2)	161 (12.6)		54	27	27	
T4	1,999	1,494 (26.9)	505 (39.6)		100	50	50	
N stage				<0.001				>0.99
N0	1,398	753 (13.5)	645 (50.5)		302	151	151	
N1	2,525	2,121 (38.1)	404 (31.7)		336	168	168	
N2	1,298	1,205 (21.7)	93 (7.3)		54	27	27	
N3	1,617	1,483 (26.7)	134 (10.5)		100	50	50	
BCS				0.70				>0.99
$HoR^+/HER2^-$	3,880	3,167 (56.9)	713 (55.9)		472	236	236	
$HoR^+/HER2^+$	1,157	938 (16.9)	219 (17.2)		134	67	67	
$HoR^-/HER2^+$	669	549 (9.9)	120 (9.4)		64	32	32	
$HoR^-/HER2^-$	1,132	908 (16.3)	224 (17.6)		122	61	61	
Surgical procedure				<0.001				>0.99
Breast-conserving surgery	1,921	1,303 (23.4)	618 (48.4)		274	137	137	
Mastectomy	4,917	4,259 (76.6)	658 (51.6)		518	259	259	
Chemotherapy				<0.001				>0.99
No/unknown	1,838	1,375 (24.7)	463 (36.3)		216	108	108	
Yes	5,000	4,187 (75.3)	813 (63.7)		576	288	288	
Sites of distant metastases				<0.001				>0.99
Bone only	2,792	2,340 (42.1)	452 (35.4)		342	171	171	
Brain only	79	66 (1.2)	13 (1.0)		0	0	0	
Liver only	583	508 (9.1)	75 (5.9)		34	17	17	
Lung only	722	568 (10.2)	154 (12.1)		58	29	29	
Distant lymph nodes only	968	826 (14.9)	142 (11.1)		68	34	34	
Multiple metastases	1,694	1,254 (22.5)	440 (34.5)		290	145	145	

PSM, propensity score matching; N, nodal; T, tumor; BCS, breast cancer subtype; HoR, hormone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection.

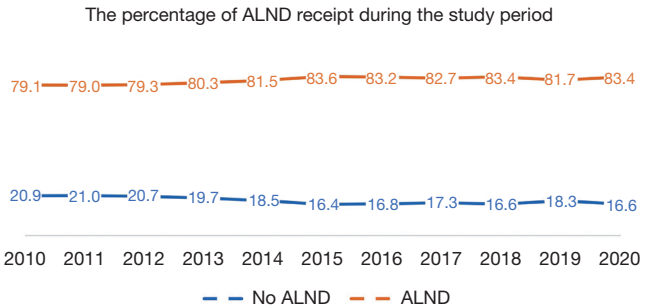

Figure 2 The trends of ALND during the study period. ALND, axillary lymph node dissection.

Table 2 Independent predictive factors associated with the receipt of ALND

Variables	OR	95% CI	P
Year of diagnosis (continuous variable)	1.026	1.004–1.048	0.02
Age (years)			
<65	1		
≥65	0.947	0.822–1.092	0.46
Race/ethnicity			
Non-Hispanic White	1		
Non-Hispanic Black	1.082	0.897–1.306	0.41
Hispanic (all races)	1.336	1.082–1.650	0.007
Others	1.036	0.821–1.309	0.76
Grade			
Well-differentiated	1		
Moderately differentiated	0.859	0.649–1.137	0.29
Poorly/undifferentiated	0.929	0.702–1.229	0.61
Unknown	0.622	0.446–0.869	0.005
Histological subtype			
Invasive ductal carcinoma	1		
Invasive lobular carcinoma	1.111	0.866–1.425	0.41
Others	1.017	0.845–1.223	0.86
T stage			
T0/T1	1		
T2	1.225	1.005–1.494	0.045
T3	1.223	0.961–1.558	0.10
T4	0.470	0.381–0.581	<0.001
BCS			
$HoR^+/HER2^-$	1		
$HoR^+/HER2^+$	0.871	0.724–1.049	0.15
$HoR^-/HER2^+$	0.904	0.714–1.145	0.40
$HoR^-/HER2^-$	0.840	0.693–1.019	0.08
Surgical procedure			
Breast-conserving surgery	1		
Mastectomy	3.915	3.389–4.523	<0.001
Chemotherapy			
No/unknown	1		
Yes	1.606	1.394–1.850	<0.001
Sites of distant metastases			
Bone only	1		
Brain only	1.042	0.553–1.960	0.90
Liver only	1.207	0.918–1.587	0.18
Lung only	0.709	0.569–0.882	0.002
Distant lymph nodes only	0.964	0.776–1.198	0.74
Multiple metastases	0.568	0.483–0.667	<0.001

ALND, axillary lymph node dissection; T, tumor; BCS, breast cancer subtype; HoR, hormone receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval.

the 5-year BCSS was 51.1% and 38.2% in those with and without ALND, respectively (P<0.001) (*Figure 3A*). The 5-year OS was 45.9% and 32.3% in those with and without ALND, respectively (P<0.001) (*Figure 3B*). Similar results were found after PSM (*Figure 3C,3D*).

Prognostic analyses

The results of multivariate Cox proportional analysis revealed that patients who underwent ALND exhibited significantly improved BCSS [hazard ratio (HR) 0.657,

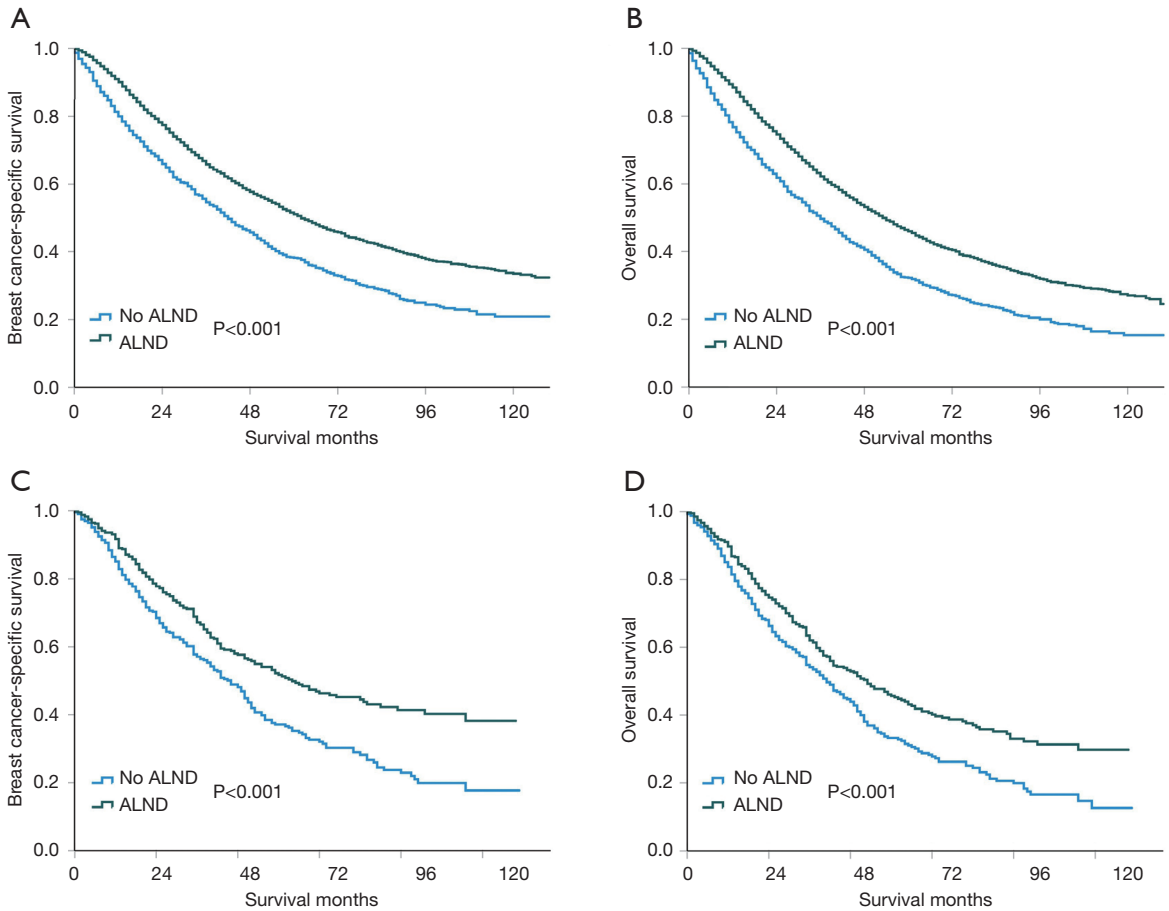

Figure 3 Comparison of BCSS and OS between those with and without ALND. (A) BCSS before propensity score matching. (B) OS before propensity score matching. (C) BCSS after propensity score matching. (D) OS after propensity score matching. ALND, axillary lymph node dissection; BCSS, breast cancer-specific survival; OS, overall survival.

95% CI: 0.598–0.722, P<0.001] and OS (HR 0.685, 95% CI: 0.628–0.746, P<0.001) compared to those who did not before PSM (*Table 3*). Furthermore, age, race, grade, histology, T stage, N stage, BCS, surgical procedure, chemotherapy, and the sites of DM were also identified as independent prognostic factors associated with BCSS and OS. In the cohort balanced by PSM, the addition of ALND was still significantly associated with improved BCSS (HR 0.63, 95% CI: 0.517–0.771, P<0.001) and OS (HR 0.694, 95% CI: 0.577–0.835, P<0.001) compared to those who did not (*Table 4*).

Sensitivity analyses

We used stratified analysis to characterize the patients who might be expected to benefit from the ALND in the PSM cohort (*Figure 4*). The results of the multivariate Cox proportional analysis showed that in most subgroups, BCSS and OS were significantly higher in the ALND group than in the non-ALND group. However, patients with early T stage, N0 disease, $HoR^-/HER2^-$ disease, receipt of breast-conserving surgery, no chemotherapy, live metastasis only, lung metastasis only, and distant lymph node metastasis only did not benefit from the ALND.

The effect of the number of removed lymph nodes on survival outcomes

In those with ALND (n=5,562), the median number of removed lymph nodes (RLNs) was 9 (25th percentile 4, 75th percentile 16; range, 1 to 60). In the four categories of the RLNs (1–4, 5–9, 10–16, and >16), the number of RLNs

Table 3 Multivariate prognostic analysis before PSM

Variables	BCSS			OS		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
<65	1			1		
≥65	1.258	1.165–1.358	<0.001	1.408	1.313–1.511	<0.001
Race/ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	1.161	1.053–1.281	0.003	1.185	1.083–1.297	<0.001
Hispanic (all races)	1.059	0.947–1.184	0.32	1.030	0.927–1.144	0.58
Others	0.792	0.689–0.910	<0.001	0.772	0.678–0.880	<0.001
Grade						
Well-differentiated	1			1		
Moderately differentiated	1.306	1.095–1.558	0.003	1.150	0.986–1.341	0.08
Poorly/undifferentiated	2.042	1.709–2.440	<0.001	1.739	1.488–2.031	<0.001
Unknown	1.747	1.428–2.136	<0.001	1.497	1.226–1.755	<0.001
Histological subtype						
Invasive ductal carcinoma	1			1		
Invasive lobular carcinoma	1.288	1.136–1.459	<0.001	1.236	1.100–1.389	<0.001
Others	1.116	1.011–1.232	0.03	1.123	1.025–1.230	0.01
T stage						
T0/T1	1			1		
T2	1.164	1.031–1.315	0.01	1.153	1.032–1.288	0.01
T3	1.247	1.088–1.429	0.001	1.230	1.086–1.392	0.001
T4	1.478	1.298–1.683	<0.001	1.527	1.360–1.716	<0.001
N stage						
N0	1			1		
N1	1.085	0.975–1.207	0.14	1.061	0.961–1.170	0.24
N2	1.256	1.112–1.419	<0.001	1.221	1.091–1.367	<0.001
N3	1.435	1.277–1.612	<0.001	1.365	1.225–1.520	<0.001
BCS						
$HoR^+/HER2^-$	1			1		
$HoR^+/HER2^+$	0.584	0.520–0.656	<0.001	0.631	0.568–0.702	<0.001
$HR^-/HER2^+$	0.751	0.654–0.862	<0.001	0.810	0.714–0.920	0.001
$HoR^-/HER2^-$	2.344	2.124–2.586	<0.001	1.258	2.058–2.477	<0.001
Surgical procedure						
Breast-conserving surgery	1			1		
Mastectomy	1.087	0.998–1.184	0.06	1.068	0.986–1.155	0.11

Table 3 (*continued*)

Table 3 (*continued*)

Variables	BCSS			OS		
	HR	95% CI	P	HR	95% CI	P
Chemotherapy						
No/unknown	1			1		
Yes	0.647	0.595–0.704	<0.001	0.634	0.587–0.685	<0.001
Sites of distant metastases						
Bone only	1			1		
Brain only	1.376	1.018–1.859	0.04	1.447	1.097–1.907	0.009
Liver only	1.359	1.178–1.566	<0.001	1.420	1.246–1.619	<0.001
Lung only	1.013	0.894–1.149	0.84	1.057	0.942–1.186	0.35
Distant lymph nodes only	0.681	0.599–0.773	<0.001	0.747	0.665–0.838	<0.001
Multiple metastases	1.671	1.529–1.827	<0.001	1.657	1.525–1.801	<0.001
ALND						
No	1			1		
Yes	0.657	0.598–0.722	<0.001	0.685	0.628–0.746	<0.001

PSM, propensity score matching; T, tumor; N, nodal; BCS, breast cancer subtype; HoR, hormone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection; BCSS, breast cancer-specific survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

Table 4 Multivariate prognostic analysis after PSM

Variables	BCSS			OS		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
<65	1			1		
≥65	1.222	0.965–1.546	0.10	1.248	1.004–1.551	0.046
Race/ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	0.929	0.667–1.293	0.66	1.062	0.785–1.437	0.70
Hispanic (all races)	0.899	0.587–1.377	0.63	0.914	0.611–1.366	0.66
Others	0.681	0.385–1.27	0.19	0.753	0.455–1.248	0.27
Grade						
Well-differentiated	1			1		
Moderately differentiated	2.237	0.972–5.148	0.06	1.291	0.705–2.365	0.41
Poorly/undifferentiated	3.511	1.504–8.197	0.004	1.974	1.058–3.683	0.03
Unknown	4.000	1.464–10.930	0.007	1.928	0.844–4.401	0.12

Table 4 (*continued*)

Table 4 (*continued*)

Variables	BCSS			OS		
	HR	95% CI	P	HR	95% CI	P
Histological subtype						
Invasive ductal carcinoma	1			1		
Invasive lobular carcinoma	1.418	0.780–2.577	0.25	1.282	0.734–2.238	0.38
Others	0.750	0.477–1.178	0.21	0.947	0.645–1.389	0.78
T stage						
T0/T1	1			1		
T2	1.386	0.937–2.050	0.10	1.317	0.928–1.869	0.12
T3	1.603	1.001–2.567	0.05	1.439	0.938–2.207	0.10
T4	1.966	1.305–2.963	0.001	1.749	1.207–2.527	0.003
N stage						
N0	1			1		
N1	1.224	0.942–1.590	0.13	1.180	0.924–1.507	0.19
N2	1.564	1.041–2.352	0.03	1.474	1.007–2.159	0.046
N3	1.255	0.848–1.858	0.26	1.188	0.823–1.714	0.36
BCS						
$HoR^+/HER2^-$	1			1		
$HoR^+/HER2^+$	0.523	0.369–0.742	<0.001	0.577	0.421–0.792	<0.001
$HoR^-/HER2^+$	0.625	0.385–1.013	0.06	0.829	0.549–1.250	0.37
$HoR^-/HER2^-$	2.591	1.929–3.478	<0.001	2.392	1.804–3.173	<0.001
Surgical procedure						
Breast-conserving surgery	1			1		
Mastectomy	0.934	0.728–1.199	0.59	0.951	0.753–1.200	0.67
Chemotherapy						
No/unknown	1			1		
Yes	0.654	0.505–0.846	0.001	0.656	0.515–0.834	<0.001
Sites of distant metastases						
Bone only	1			1		
Brain only	–	–	–	–	–	–
Liver only	0.804	0.435–1.486	0.49	0.794	0.449–1.406	0.43
Lung only	0.738	0.488–1.116	0.15	0.844	0.580–1.230	0.38
Distant lymph nodes only	0.622	0.404–0.960	0.03	0.805	0.548–1.181	0.27
Multiple metastases	1.339	1.060–1.690	0.01	1.408	1.129–1.757	0.002
ALND						
No	1			1		
Yes	0.631	0.517–0.771	<0.001	0.694	0.577–0.835	<0.001

PSM, propensity score matching; T, tumor; N, nodal; BCS, breast cancer subtype; HoR, hormone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection; BCSS, breast cancer-specific survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

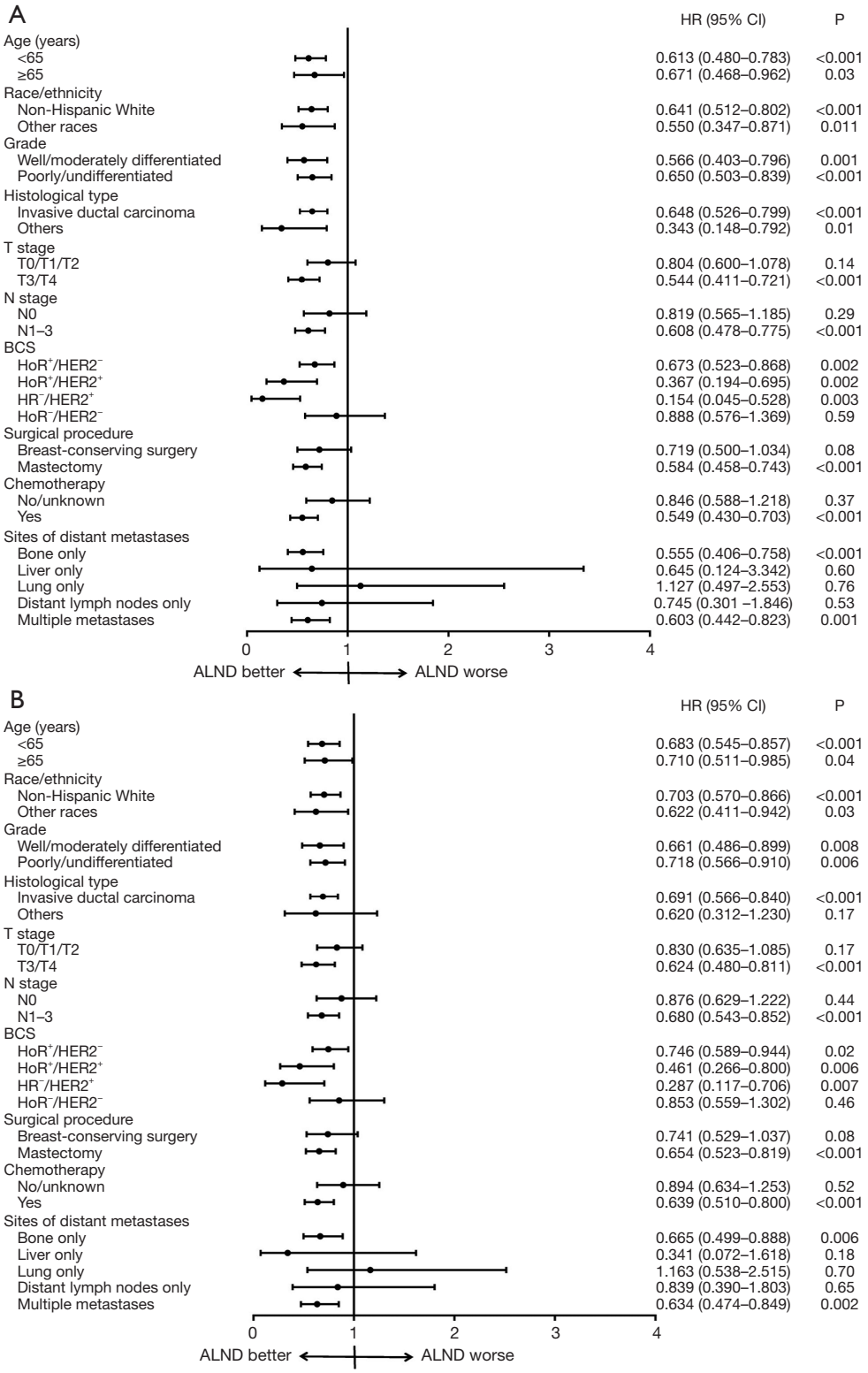

Figure 4 Adjusted hazard ratios for breast cancer-specific survival (A) and overall survival (B) between those with and without ALND after stratifying by the demographic and clinicopathological variables. T, tumor; N, nodal; BCS, breast cancer subtype; HoR, hormone receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval; ALND, axillary lymph node dissection.

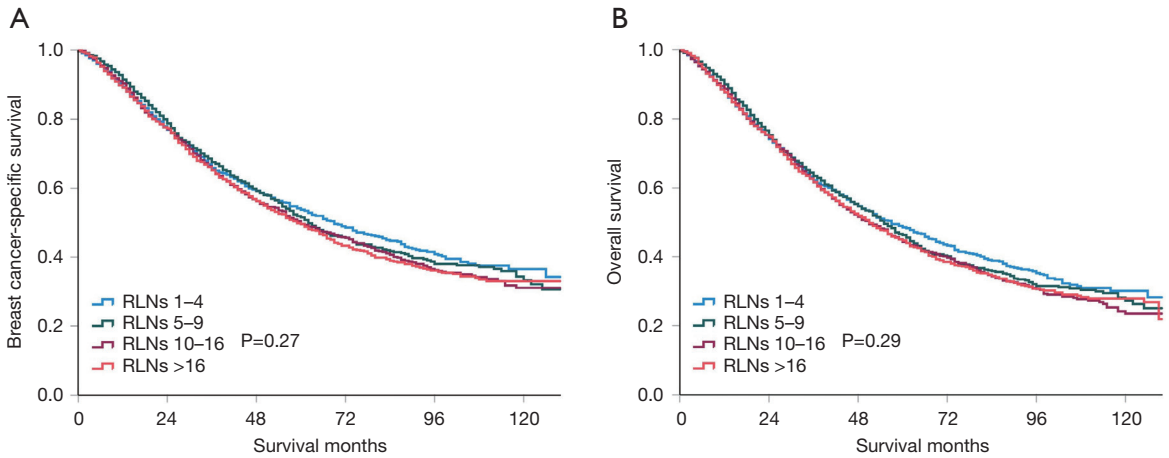

Figure 5 Comparison of breast cancer-specific survival (A) and overall survival (B) among the four categories of the number of RLNs. RLNs, removed lymph nodes.

was not significantly associated with BCSS and OS. The 5-year BCSS was 53.8%, 51.6%, 49.6%, and 49.5% in those with RLNs 1–4, 5–9, 10–16, and >16, respectively (P=0.27) (*Figure 5A*). The 5-year OS was 48.5%, 46.3%, 44.3%, and 44.7% in those with RLNs 1–4, 5–9, 10–16, and >16, respectively (P=0.29) (*Figure 5B*).

Discussion

The role of ALND in dnMBC patients remains a subject of debate and investigation. This study aimed to investigate the effect of ALND in patients with dnMBC and our study found that 81.3% of patients with dnMBC had ALND during their surgery at the local site. Moreover, the receipt of ALND was associated with better survival outcomes in this population.

Several prospective studies have found that local surgical resection did not improve the survival of patients with dnMBC (8-11). In addition, two recent meta-analyses included randomized control trials to investigate the effect of locoregional therapy on survival and quality of life in dnMBC, the results showed that breast surgery may benefit locoregional control but does not improve OS and quality of life in dnMBC patients (17,18). However, there were still 26.8–57.2% of patients undergoing local surgical treatment in the real world, and studies have found that local surgery could further improve the survival of patients (12-15,19). As an important part of BC surgery, ALND or sentinel lymph node biopsy (SLNB) plays a crucial role in the staging and treatment decisions for non-metastatic BC. However, the value of ALND for dnMBC patients following local surgery remains unclear. In this study, we found a higher proportion of undergoing ALND following local surgery (81.3%), which is higher than our previous study involving patients diagnosed from 1990 to 2010 (63.2%) (20). In the prospective studies, ALND or SLNB was performed in dnMBC patients who received local surgery (8,9,11). In a retrospective study, there were also 55–79% of patients receiving ALND (21,22). A higher proportion of the receipt of ALND in this population may reflect a belief among some clinicians that ALND can provide more accurate staging information and guide adjuvant therapy decisions, even in the context of metastatic disease. In addition, the lack of clear guidelines or consensus on the management of the axilla in dnMBC may also lead to variability in practice (23,24). Moreover, it may also be driven by patient preference, as some patients may opt for more aggressive surgical approaches with the hope of achieving better disease control. The results of the multivariable analysis showed that those diagnosed in later years were having a higher proportion of patients undergoing ALND. This trend is noteworthy given the ongoing debate about the role of ALND in this patient population and reflects the complexity of decision-making in managing the axilla in dnMBC.

In our study, patients with smaller tumor sizes were more likely to receive ALND. Therefore, it is hypothesized that healthier patients or those with less extensive disease are more likely to undergo ALND. However, our results showed that patients with multiple sites of DM was the

independent predictive factor associated with no receipt of ALND in this population. This trend may reflect evolving attitudes in clinicians and patients towards the role of ALND in dnMBC management. As axillary surgery may further decrease the potential tumor burden in dnMBC, it may reduce its potential for dissemination to new metastatic localizations (25). However, it is critical to balance these potential benefits with the potential risks and complications of ALND, including lymphedema, shoulder dysfunction, and postoperative pain.

In patients with early-stage BC, SLNB is sufficient for axillary staging assessment and guiding treatment decisions (26). In our study, 79.6% of patients had nodal-positive disease, which is similar to the results of several prospective and retrospective studies (77–94.2%) (9,15,27,28). Moreover, we also found that more extensive ALND did not increase the survival of patients. Therefore, SLNB may also be sufficient for patients with dnMBC without lymphadenopathy in preoperative assessment. For patients with non-metastatic BC who need ALND, a minimum of 10 lymph nodes removed for a complete ALND is recommended by numerous trials (29,30). However, several studies also found that the removal of more than 10 lymph nodes did not result in a significant survival benefit even in high-risk nodal-positive BC patients (31,32). It is crucial to remember that the decision to perform ALND should be made individually, considering the patient's overall health, the extent and characteristics of the disease, and the potential benefits and risks of the procedure. This decision should be made as part of a multidisciplinary discussion that includes the patient's preferences and values.

Several studies have explored the efficacy of ALND in dnMBC. A previous study from ours included patients diagnosed between 1990 and 2010, and the results showed that patients who underwent ALND had better BCSS and OS (20). The findings from De Wit *et al.* also showed survival benefits with the addition of ALND in dnMBC (21). However, a meta-analysis included 16 studies and found that ALND could not improve the OS of patients (22). We should note that the above studies have been grouped for a long time, and cannot reflect the current clinical treatment practice of dnMBC. The treatment of advanced BC has made substantial progress in the past decade (33-35). In this study, we included patients diagnosed between 2010 and 2020, which reflected contemporary clinical practice. Our study showed that patients who underwent ALND had better BCSS and OS, and this was observed across various clinicopathological subgroups.

The observed survival benefit associated with ALND in our study may be attributed to various factors that reflect the complex interplay of tumor biology, patient characteristics, and treatment modalities. First, ALND provides valuable information about the extent of axillary nodal involvement, which can help guide adjuvant systemic therapy decisions. Accurate staging may allow for more personalized treatment strategies, potentially leading to improved outcomes. Second, ALND may have a direct therapeutic effect by reducing the total tumor burden. The removal of axillary lymph nodes could decrease the likelihood of disease recurrences, which might contribute to better survival outcomes. Third, patients selected for ALND are likely to be in better overall health or have fewer comorbidities, which could contribute to improved survival outcomes. Moreover, patients who undergo ALND might be more compliant with adjuvant therapies and follow-up visits due to their engagement with the healthcare system, which could indirectly contribute to better survival outcomes. Finally, there is growing interest in the potential immunomodulatory effects of surgical interventions such as ALND. By removing immunosuppressive tumor-draining lymph nodes, ALND could potentially enhance the body's immune response to cancer, and the immunity was restored after tumor surgery (36).

While our study adds valuable insights to the role of ALND in managing dnMBC, it is not without limitations. First, the retrospective nature of our study and the reliance on PSM to control for confounding factors highlight the need for caution in interpreting the results. Second, the information regarding chemotherapy regimens, endocrine therapy, target therapy as well as immunotherapy was not included in the SEER database. Third, comorbidities, treatment compliance, and quality of life between the two groups were not recorded in the SEER program. Finally, the presence of metastasectomy and the precise timing of surgery following a diagnosis of dnMBC were not recorded in the SEER database.

Conclusions

In conclusion, our study suggests that ALND is associated with improved survival outcomes in dnMBC patients. These findings advocate for a re-evaluation of the role of surgical interventions in dnMBC, emphasizing the need for personalized treatment strategies that consider the potential benefits of ALND. Further research is essential to validate

these findings and to explore the mechanisms of ALND conferring a survival advantage in this population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-130/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-130/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study did not require approval from the institutional review board due to the de-identified information in the SEER program. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
2. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
3. Heller DR, Chiu AS, Farrell K, et al. Why Has Breast Cancer Screening Failed to Decrease the Incidence of de Novo Stage IV Disease? Cancers (Basel) 2019;11:500.
4. Berg T, Jensen MB, Rossing M, et al. Development and Methodological Validation of a Modified Staging System for de Novo Metastatic Breast Cancer. JAMA Netw Open 2024;7:e242174.
5. Plichta JK, Thomas SM, Hayes DF, et al. Novel Prognostic Staging System for Patients With De Novo Metastatic Breast Cancer. J Clin Oncol 2023;41:2546-60.
6. Miyashita M, Balogun OB, Olopade OI, et al. The optimization of postoperative radiotherapy in de novo stage IV breast cancer: evidence from real-world data to personalize treatment decisions. Sci Rep 2023;13:2880.
7. Merloni F, Palleschi M, Gianni C, et al. Locoregional treatment of de novo stage IV breast cancer in the era of modern oncology. Front Oncol 2023;13:1083297.
8. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015;16:1380-8.
9. Fitzal F, Bjelic-Radisic V, Knauer M, et al. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial. Ann Surg 2019;269:1163-9.
10. Khan SA, Zhao F, Goldstein LJ, et al. Early Local Therapy for the Primary Site in De Novo Stage IV Breast Cancer: Results of a Randomized Clinical Trial (EA2108). J Clin Oncol 2022;40:978-87.
11. Soran A, Ozmen V, Ozbas S, et al. Primary Surgery with Systemic Therapy in Patients with de Novo Stage IV Breast Cancer: 10-year Follow-up; Protocol MF07-01 Randomized Clinical Trial. J Am Coll Surg 2021;233:742-751.e5.
12. Lane WO, Thomas SM, Blitzblau RC, et al. Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer: Contemporary Practice Patterns and Survival Analysis. Ann Surg 2019;269:537-44.
13. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002;132:620-6; discussion 626-7.
14. Rahmani J, Elhelali A, Yousefi M, et al. Locoregional therapy containing surgery in metastatic breast cancer: Systematic review and meta-analysis. Surgeon 2024;22:43-51.

15. Hotton J, Lusque A, Leufflen L, et al. Early Locoregional Breast Surgery and Survival in de novo Metastatic Breast Cancer in the Multicenter National ESME Cohort. Ann Surg 2023;277:e153-61.
16. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020) - Linked To County Attributes - Time Dependent (1990-2021) Income/Rurality, 1969-2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.
17. Ren C, Sun J, Kong L, et al. Breast surgery for patients with de novo metastatic breast cancer: A meta-analysis of randomized controlled trials. Eur J Surg Oncol 2024;50:107308.
18. Reinhorn D, Mutai R, Yerushalmi R, et al. Locoregional therapy in de novo metastatic breast cancer: Systemic review and meta-analysis. Breast 2021;58:173-81.
19. Kim KN, Qureshi MM, Huang D, et al. The Impact of Locoregional Treatment on Survival in Patients With Metastatic Breast Cancer: A National Cancer Database Analysis. Clin Breast Cancer 2020;20:e200-13.
20. Wu SG, Li FY, Chen Y, et al. Therapeutic role of axillary lymph node dissection in patients with stage IV breast cancer: a population-based analysis. J Cancer Res Clin Oncol 2017;143:467-74.
21. De Wit A, Arbion F, Desille-Gbaguidi H, et al. Role of surgery in patients with synchronous metastatic breast cancer: Is there a need for axillary lymph node removal? J Gynecol Obstet Hum Reprod 2021;50:101771.
22. Lisboa A FCAP, Silva RB, de Andrade KRC, et al. Axillary surgical approach in metastatic breast cancer patients: a systematic review and meta-analysis. Ecancermedicalscience 2020;14:1117.
23. Al Sukhun S, Temin S, Barrios CH, et al. Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource-Stratified Guideline. JCO Glob Oncol 2024;10:e2300285.
24. Sakai T, Kutomi G, Shien T, et al. The Japanese Breast Cancer Society Clinical Practice Guidelines for surgical treatment of breast cancer, 2022 edition. Breast Cancer 2024;31:1-7.
25. Hosseini H, Obradović MMS, Hoffmann M, et al. Early dissemination seeds metastasis in breast cancer. Nature 2016;540:552-8.
26. Tauber N, Bjelic-Radisic V, Thill M, et al. Controversies in axillary management of patients with breast cancer - updates for 2024. Curr Opin Obstet Gynecol 2024;36:51-6.
27. Huang Z, Tan Q, Qin Q, et al. Impact of Primary Site Surgery on Survival of Patients with de novo Stage IV Breast Cancer. Cancer Manag Res 2021;13:319-27.
28. Choi SH, Kim JW, Choi J, et al. Locoregional Treatment of the Primary Tumor in Patients With De Novo Stage IV Breast Cancer: A Radiation Oncologist's Perspective. Clin Breast Cancer 2018;18:e167-78.
29. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415-8.
30. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-75.
31. Ebner F, Wöckel A, Schwentner L, et al. Does the number of removed axillary lymphnodes in high risk breast cancer patients influence the survival? BMC Cancer 2019;19:90.
32. Ebner F, Wöckel A, Janni W, et al. Personalized axillary dissection: the number of excised lymph nodes of nodal-positive breast cancer patients has no significant impact on relapse-free and overall survival. J Cancer Res Clin Oncol 2017;143:1823-31.
33. Swaminathan H, Saravanamurali K, Yadav SA. Extensive review on breast cancer its etiology, progression, prognostic markers, and treatment. Med Oncol 2023;40:238.
34. Wang J, Wu SG. Breast Cancer: An Overview of Current Therapeutic Strategies, Challenge, and Perspectives. Breast Cancer (Dove Med Press) 2023;15:721-30.
35. Ziyeh S, Wong L, Basho RK. Advances in Endocrine Therapy for Hormone Receptor-Positive Advanced Breast Cancer. Curr Oncol Rep 2023;25:689-98.
36. Danna EA, Sinha P, Gilbert M, et al. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004;64:2205-11.

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