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Original Research

Locoregional treatment and overall survival of men with T1a,b,cN0M0 breast cancer: A population-based study☆

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Breast conservation;
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Abstract ***Background:*** Male breast cancer (MaBC) is an understudied disease; information about locoregional treatment and outcomes in patients with early stage is unknown. We aimed to analyse patient characteristics, locoregional treatment and overall survival (OS) of T1a,b,cN0M0 male breast cancer.

Methods: We evaluated men with T1a,b,cN0M0 breast cancer reported to Surveillance, Epidemiology, and End Results program from 1988 to 2012. Univariate and multivariate analyses were performed to determine the effect of each variable on OS.

Results: We included 1263 patients. Median age was 66 years (range 27–103). Median follow-up was 62 months (range 1–294). OS at 5 and 10 years were 85.1% and 66.5%, respectively. Distribution according to tumour sub-stage was: T1a 6.5%, T1b 20.7% and T1c 72.8%. Mastectomy was performed in >74% of patients of each tumour size group and overall 44.1% had >5 lymph nodes examined (LNE). Univariate analysis showed that patients with T1c, no surgery and 0 LNE had worse prognosis. In multivariate analysis, older age (hazard ratio [HR] 11.09), grade 3/4 tumours (HR 1.7), no surgery (HR 3.3), 0 LNE (HR 5.1) and unmarried patients (HR 1.7) had significantly shorter OS. There were no differences in OS between breast conservation versus mastectomy and 1–5 LNE versus > 5 LNE.

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Conclusion: Men with early breast cancer have a favourable OS. However, older age, higher grade, no breast surgery, no LNE and unmarried status emerged as poor prognostic characteristics. Efforts to decrease the high rates of mastectomy and extensive LNE should be taken given similar OS observed with breast conservation and 1–5 LNE, respectively.

1. Introduction

Male breast cancer (MaBC) is a rather infrequent disease, representing less than 1% of all breast cancers in the United States [1]. Male patients have been inadequately represented in breast cancer clinical trials, leading to a lack of evidence to guide their management. In particular, no randomised studies have been conducted to evaluate the appropriate locoregional treatment in MaBC.

Breast conserving surgery is a standard treatment in appropriately selected female breast cancer patients, with similar overall survival (OS) compared with mastectomy [2,3]. Sentinel lymph node biopsy has replaced axillary dissection in node-negative women given similar outcomes and decreased morbidity [4]. The implementation of these two surgical techniques in men with breast cancer has been poor. A recent study from our group reported that only 12.8% of men underwent breast conserving surgery over the past ten years [5].

In T1a,b,cN0M0 MaBC—stage I tumours of up to 2 cm of maximum diameter—little information exists about locoregional treatment and outcomes, with most data coming from very small retrospective studies or population studies analysing all stages of disease [6–9]. Given the smaller breast volume in men and the importance of locoregional treatment for early breast cancer, an independent, large scale analysis of these approaches and their outcomes in T1a,b,cN0M0 MaBC would be extremely valuable to improve our treatment recommendations.

The aim of this population-based study was to analyse patient characteristics, locoregional treatment and OS of T1a,b,cN0M0 MaBC.

2. Materials and methods

2.1. Data source and study design

We obtained data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, using the 18 registry (1973–2012) database [10]. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the US population. The SEER program registries routinely collect data on patient demographics, primary tumour site, tumour morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Data on primary tumour size has been collected since 1988, because of this we used that year as the starting point for our study.

We extracted all cases of men with T1a,b,cN0M0 microscopically confirmed invasive breast cancer diagnosed between 1988 and 2012. Patients with another primary malignancy either before or after breast cancer were excluded.

Study variables included age at diagnosis, race, histology, tumour grade, tumour size, oestrogen receptor (ER), progesterone receptor (PR), type of surgery, radiation therapy, number of lymph nodes examined, marital status, survival months and vital status. Four tumour grades were collapsed into 3 grades; with grade 4 merged with grade 3 tumours. Histology codes were grouped according to frequency into six categories using the World Health Organization classification (ductal, lobular, mixed ductal and lobular, mucinous, papillary and other carcinoma). Tumour stage was registered according to the American Joint Committee on Cancer staging system sixth edition. Surgery to the primary site was classified as: no surgery, breast conserving surgery, mastectomy and unknown. We observed inconsistencies between the coding of the surgical procedure to the axilla and the reported number of lymph nodes examined. Therefore, we chose the number of lymph nodes examined as the prognostic variable for the analysis and categorised it as zero, one to five, or more than five lymph nodes examined.

The University of Iowa Institutional Review Board exempted this study from review because patients cannot be identified. This study was approved by Scientific and Ethical Committee of GOCS.

2.2. Statistical analysis

Descriptive statistics, including frequencies, medians and proportions, were used to evaluate characteristics of the patient population. Patient characteristics were compared between tumour sizes using chi-square or Fisher's exact tests, as appropriate.

Within each variable, patients with unknown data were excluded from all comparative analyses, including univariable and multivariable models. OS was the primary end-point chosen to assess prognosis and was defined as the interval from diagnosis of breast cancer until death from any cause or last follow-up for patients that were censored. Survival probabilities were

Table 1
Patient characteristics.

	T1a		T1b		T1c		Total		*P*
	N	%	N	%	N	%	N	%	
All patients	82	6.5%	262	20.7%	919	72.8%	1263	100.0%	
Age at diagnosis, y									
<50	14	17.1%	43	16.4%	113	12.3%	170	13.5%	0.012
50–64	33	40.2%	99	37.8%	290	31.6%	422	33.4%	
>64	35	42.7%	120	45.8%	516	56.1%	671	53.1%	
Race									
White	61	74.4%	208	79.4%	766	83.4%	1035	81.9%	0.07
Black	13	15.9%	35	13.4%	82	8.9%	130	10.3%	
Other	8	9.8%	18	6.9%	64	7.0%	90	7.1%	
Unknown[a]	0	0.0%	1	0.4%	7	0.8%	8	0.6%	
Grade									
I	30	36.6%	68	26.0%	155	16.9%	253	20.0%	<0.0001
II	33	40.2%	131	50.0%	446	48.5%	610	48.3%	
III/IV	11	13.4%	40	15.3%	240	26.1%	291	23.0%	
Unknown[a]	8	9.8%	23	8.8%	78	8.5%	109	8.6%	
Histology									
Ductal	65	79.3%	212	80.9%	771	83.9%	1048	83.0%	0.451
Lobular	2	2.4%	5	1.9%	12	1.3%	19	1.5%	
Mixed ductal and lobular	1	1.2%	6	2.3%	19	2.1%	26	2.1%	
Mucinous	2	2.4%	6	2.3%	26	2.8%	34	2.7%	
Papillary	5	6.1%	8	3.1%	16	1.7%	29	2.3%	
Carcinoma	7	8.5%	25	9.5%	75	8.2%	107	8.5%	
ER									
Negative	6	7.3%	12	4.6%	32	3.5%	50	4.0%	0.345
Positive	68	82.9%	206	78.6%	753	81.9%	1027	81.3%	
Borderline	0	0.0%	1	0.4%	2	0.2%	3	0.2%	
Unknown[a]	8	9.8%	43	16.4%	132	14.4%	183	14.5%	
PR									
Negative	13	15.9%	28	10.7%	94	10.2%	135	10.7%	0.69
Positive	61	74.4%	187	71.4%	672	73.1%	920	72.8%	
Borderline	0	0.0%	1	0.4%	4	0.4%	5	0.4%	
Unknown[a]	8	9.8%	46	17.6%	149	16.2%	203	16.1%	
Surgery									
No surgery	1	1.2%	2	0.8%	12	1.3%	15	1.2%	0.005
Breast conserving surgery	18	22.0%	65	24.8%	139	15.1%	222	17.6%	
Mastectomy	63	76.8%	195	74.4%	767	83.5%	1025	81.2%	
Unknown[a]	0	0.0%	0	0.0%	1	0.1%	1	0.1%	
Radiation									
No	72	87.8%	222	84.7%	808	87.9%	1102	87.3%	0.389
Yes	10	12.2%	40	15.3%	111	12.1%	161	12.7%	
No. of lymph nodes examined									
0	7	8.5%	24	9.2%	84	9.1%	115	9.1%	0.754
1–5	44	53.7%	118	45.0%	418	45.5%	580	45.9%	
>5	31	37.8%	117	44.7%	409	44.5%	557	44.1%	
Unknown[a]	0	0.0%	3	1.1%	8	0.9%	11	0.9%	
Marital status at diagnosis									
Single	13	15.9%	27	10.3%	102	11.1%	142	11.2%	0.729
Married	59	72.0%	187	71.4%	670	72.9%	916	72.5%	
Other	8	9.8%	32	12.2%	106	11.5%	146	11.6%	
Unknown[a]	2	2.4%	16	6.1%	41	4.5%	59	4.7%	
Vital status									
Alive	70	85.4%	214	81.7%	674	73.3%	958	75.9%	0.002
Dead	12	14.6%	48	18.3%	245	26.7%	305	24.1%	
Cause of death									
Alive	70	85.4%	214	81.7%	674	73.3%	958	75.9%	0.01
Breast cancer	5	6.1%	11	4.2%	63	6.9%	79	6.3%	
Other	7	8.5%	37	14.1%	182	19.8%	226	17.9%	

Abbreviations: ER, oestrogen receptor; No, number; PR, progesterone receptor; y, years.
[a] Unknown patients are excluded from the comparative analysis.

estimated using the Kaplan Meier method. Patient and tumour characteristics were individually analysed using log-rank test to determine the effect of each variable on OS. A Cox proportional hazards regression was used to assess the independent association of several variables with OS. Hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were estimated using the Cox model. All study variables previously reported to be associated with prognosis were included in the final Cox model of the present study [5,11]. All P values reported were two sided and P values < 0.05 were considered statistically significant. All statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, TX) and SPSS 20.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient characteristics

A total of 1263 men were diagnosed with T1a,b,cN0M0 breast cancer between 1988 and 2012 and were included in this study. Median age was 66 years (range, 27–103 years). At diagnosis, 83% of tumours were ductal histology. Among patients with known variables, 95.3% were ER positive, 87.2% PR positive and 21.9% grade I. Mastectomy was performed in more than 74% of patients of each tumour size group and overall 44.1% of patients had more than 5 lymph nodes examined. Only 161 patients (12.7%) received adjuvant radiotherapy, of which 94 patients underwent breast conserving surgery and 67 patients total mastectomy. The median number of lymph nodes examined for the overall population was five (range, 1 − 41). Patients who had breast conserving surgery with lymph node examination had a median of three lymph nodes examined (range, 1 − 26), whereas patients who underwent mastectomy had a median of six (range, 1 − 41). A total of 115 patients (9.1%) had no lymph nodes examined (13 patients from the no surgery group, 52 patients from the breast conserving surgery group and 50 patients from the mastectomy group). Eighty-two patients (6.5%; 95% CI, 5.1–7.9%) had T1a tumours, 262 patients (20.7%; 95% CI, 18.5–23%) had T1b tumours and 919 patients (72.8%; 95% CI, 70.3–75.2%) had T1c tumours.

Table 1 shows the distribution of patient characteristics according to tumour size. There were significant differences among patients. Patients with T1c tumours were older ($P = 0.012$), had higher grade ($P < 0.0001$), were more likely to have a mastectomy ($P = 0.005$) and had higher mortality ($P = 0.002$).

3.2. Survival analysis

After a median follow-up of 62 months (range, 1–294 months), 305 deaths were reported (12 in the T1a group, 48 in the T1b group and 245 in the T1c group).

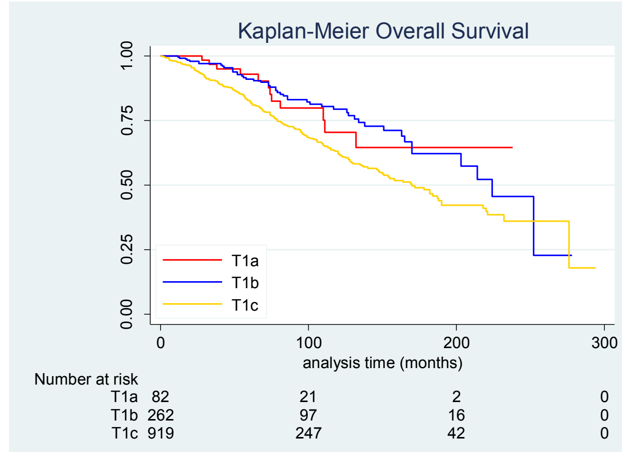

Fig. 1. Kaplan Meier curve for overall survival according to tumour size. Log-rank $P = 0.0003$.

In the overall cohort, the 5- and 10-year OS rates were 85.1% (95% CI, 82.6–87.2%) and 66.5% (95% CI, 62.6–70%), respectively. Analysis of OS according to tumour size showed that patients with T1c tumours had significantly shorter OS (5-year OS 82.6%; 95% CI, 79.6–85.3%; Fig. 1). Fig. 2 shows OS curves by surgery to the primary tumour. There was no difference in OS between breast conserving surgery (5-year OS 80.5%; 95% CI, 72.8–86.3%) and mastectomy (5-year OS 86.4%; 95% CI, 83.8–88.7%); however, patients who did not receive surgery had a significant reduction in OS (5-year OS 42.7%; 95% CI, 14.9–68.3%). Analysis of OS according to the number of lymph nodes examined was also performed, this analysis showed that patients who had no lymph nodes examined had significantly worse OS (5-year OS 46.4%; 95% CI, 35.2–56.8%); however, no difference in OS was seen between patients who had 1–5 lymph nodes examined (5-year OS 89%; 95% CI, 85.3–91.9%) and those who had >5 lymph nodes examined (5-year OS 89%; 95% CI, 85.9–91.5%; Fig. 3).

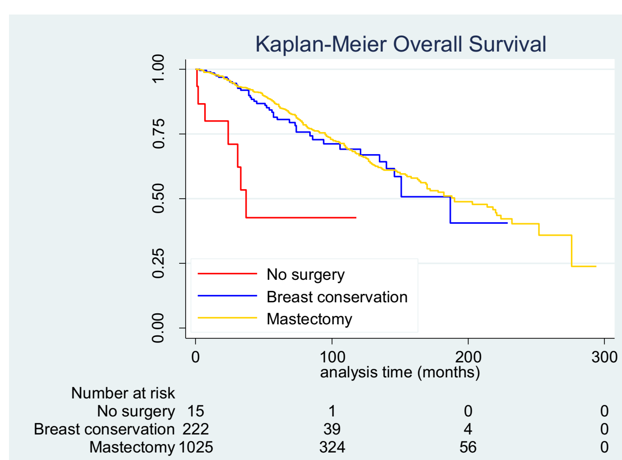

Fig. 2. Kaplan Meier curve for overall survival according to surgery to the primary tumour. Log-rank $P = < 0.0001$.

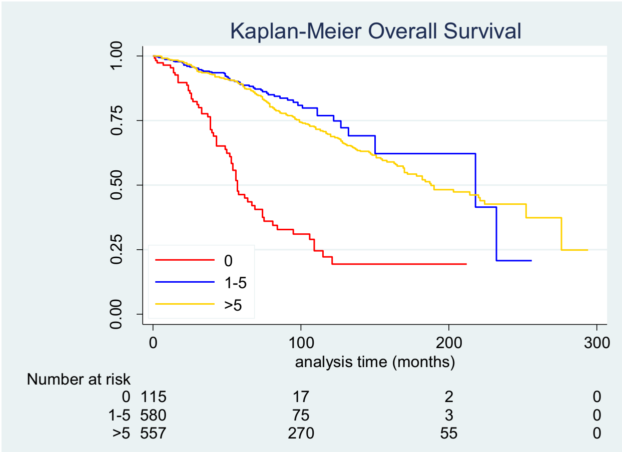

Fig. 3. Kaplan Meier curve for overall survival according to the number of lymph nodes examined. Log-rank $P = < 0.0001$.

Unadjusted models for the overall patient population were consistent with log-rank analysis and revealed a general decrease in OS in those patients who were older, unmarried, had T1c tumours and those who did not receive surgery to the primary tumour or lymph node examination (Table 2). As shown in the table, there were no differences in OS either between breast conserving surgery and mastectomy (hazard ratio 0.8; 95% CI, 0.6 − 1.2) or between 1 and 5 lymph nodes examined and >5 (hazard ratio 1.2; 95% CI, 0.9 − 1.6). Multivariate Cox analyses, conducted among patients with known data in all variables (n = 943), confirmed the independent prognostic significance of age at diagnosis, tumour grade, surgery, number of lymph nodes examined and marital status. Race, histology, tumour size, radiotherapy, ER and PR status did not reach significance with this test. The final Cox model is shown in Table 3.

4. Discussion

The implementation of breast conserving surgery and sentinel lymph node biopsy has significantly shifted the surgical approach of early-stage female breast cancer. However, the use of these techniques in men has lagged behind, in part due to more advanced stages at presentation, smaller breast volume and a lack of data with regards to their efficacy. These gaps in knowledge motivated the conduction of our study. We chose to analyse the specific population of men with T1a,b,cN0M0 breast cancer because this group of patients are likely the best candidates for less extensive approaches.

Our study showed no significant differences in OS between breast conserving surgery and mastectomy. This finding was confirmed both in the unadjusted and in the adjusted analyses. Two previous reports using SEER data to assess outcomes with breast conserving surgery did not specifically examine T1a,b,cN0M0 cases, as a result, they included a very heterogeneous group of patients, most of which were not appropriate candidates for breast conservation due to the presence of advanced disease or large primary tumours in relation with small breast volume [7,9]. In contrast with these reports, the present study analysed a homogeneous cohort of patients with small primary tumours, who might be the most appropriate candidates for breast conservation. Indeed, our results support the use of this treatment modality in this specific group of patients.

A remarkable finding from our study is the high rates of mastectomy seen across all tumour sizes. Even in patients with T1a −tumours 5 mm in size or smaller-in which the relationship between tumour size and breast volume is the best in favour of breast conservation. This suggests that the high rates of mastectomy are likely due to the lack of efficacy data in men. Previous authors have reported similar results [5,11–14]. The present study provides assurance about the efficacy of breast conservation, which could be adopted to decrease the high rates of mastectomy in this group of patients with good prognosis.

Another important component of the locoregional treatment of early breast cancer is the axillary lymph node surgery. Our cohort consisted exclusively of node-negative patients, which provides a unique opportunity to evaluate the impact of the extent of axillary lymph node dissection on outcomes. In this regard, similar to what we observed for the surgery to the primary tumour, there was no significant difference in OS between patients who underwent extensive lymph node dissection (>5 lymph nodes) and those who had only 1–5 lymph nodes examined. On the other hand, patients who had zero lymph nodes examined had significantly worse OS, this could be explained in part by the presence of occult nodal disease. Taken together, our results suggest that men who present with clinically node-negative breast cancer could be good candidates for sentinel lymph node biopsy, as described by previous authors [15–17].

The analysis of nodal examination in our study showed two important results. First, given the similar outcomes seen in both groups who underwent lymph node examination, resecting >5 lymph nodes may represent overtreatment and could be associated with unnecessary morbidity. Second, the lack of axillary nodal examination in men likely represents undertreatment, as the identification of node-positive patients would be valuable not only for accurate prognostic assessment, but also for appropriate systemic therapy recommendations.

The administration of adjuvant radiation therapy in our study did not translate into survival improvements, similar to the findings from other reports [11,18–21]. However, we noticed an underutilisation of this treatment modality in our cohort, only 42.3% of patients

Table 2
Unadjusted overall survival rates.

Variable	5-year OS	Log-rank *P*	HR	95.0% CI for HR	
				Lower	Upper
Age at diagnosis, y					
<50	0.966	<0.0001	Reference		
50–64	0.950		2.167	1.161	4.045
>64	0.756		8.119	4.537	14.527
Race					
White	0.842	0.667	Reference		
Black	0.862		0.983	0.677	1.427
Other (American Indian/ AK Native, Asian/ Pacific Islander)	0.926		0.808	0.506	1.289
Grade					
I	0.900	0.114	Reference		
II	0.859		1.442	1.018	2.041
III/IV	0.815		1.362	0.927	2.001
Histology					
Ductal	0.852	0.563	Reference		
Lobular	0.933		0.507	0.162	1.583
Mixed ductal and lobular	0.795		0.702	0.290	1.700
Mucinous	0.828		0.910	0.468	1.769
Papillary	0.762		1.348	0.635	2.861
Carcinoma	0.871		0.771	0.484	1.229
T					
T1a	0.929	0.0003	Reference		
T1b	0.911		0.935	0.496	1.761
T1c	0.826		1.670	0.935	2.982
Surgery					
No surgery	0.427	<0.0001	4.817	2.160	10.742
Breast conserving surgery	0.805		Reference		
Mastectomy	0.864		0.885	0.639	1.224
Radiation					
No	0.844	0.135	Reference		
Yes	0.902		0.751	0.515	1.095
ER					
Negative	0.859	0.693	Reference		
Positive	0.865		1.130	0.615	2.073
PR					
Negative	0.866	0.543	Reference		
Positive	0.862		1.133	0.756	1.698
No. of lymph nodes examined					
0	0.464	<0.0001	4.924	3.465	6.999
1–5	0.890		Reference		
>5	0.890		1.262	0.939	1.698
Marital status					
Single	0.847	0.0001	Reference		
Married	0.874		0.924	0.636	1.341
Other (separated/ divorced/widowed)	0.720		1.768	1.139	2.744

Abbreviations: AK, Alaska; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; No, number; OS, overall survival; PR, progesterone receptor; y, years.

who underwent breast conserving surgery received adjuvant radiotherapy. The underutilisation of this treatment has also been recently documented in a larger study [5].

We observed significant differences in patient characteristics according to tumour size. Patients with T1c tumours were the most prevalent group and had more high-risk features. This subgroup also experienced shorter OS as seen in the univariate analysis and a trend in the multivariate model. To our knowledge, this is the first study to analyse prognostic differences within T1 tumours in men.

Table 3
Multivariate analysis for overall survival (n = 943).

Variable	*P*	HR	95.0% CI for HR	
			Lower	Upper
Age at diagnosis, y				
<50 years		Reference		
50–64 years	0.011	3.424	1.322	8.863
>64 years	<0.0001	11.092	4.462	27.575
Race				
White		Reference		
Black	0.077	1.576	0.951	2.612
Other (American Indian/ AK Native, Asian/ Pacific Islander)	0.402	0.769	0.416	1.420
Grade				
I		Reference		
II	0.001	2.052	1.333	3.159
III/IV	0.017	1.788	1.110	2.882
Histology				
Ductal		Reference		
Lobular	0.987	0.983	0.129	7.472
Mixed ductal and lobular	0.864	1.083	0.435	2.699
Mucinous	0.462	0.645	0.201	2.076
Papillary	0.792	0.872	0.316	2.411
Carcinoma	0.268	0.690	0.358	1.331
T				
T1a		Reference		
T1b	0.538	1.297	0.567	2.964
T1c	0.076	1.981	0.931	4.218
Surgery				
No surgery	0.032	3.366	1.111	10.196
Breast conserving surgery		Reference		
Mastectomy	0.500	1.170	0.742	1.846
Radiation				
No		Reference		
Yes	0.272	0.765	0.474	1.234
ER				
Negative		Reference		
Positive	0.080	0.503	0.233	1.086
PR				
Negative		Reference		
Positive	0.187	1.409	0.847	2.346
No. of lymph nodes examined				
0	<0.0001	5.137	3.199	8.249
1–5		Reference		
>5	0.695	1.079	0.738	1.576
Marital status				
Single		Reference		
Married	0.022	0.576	0.360	0.924
Other (separated/divorced/ widowed)	0.660	0.879	0.496	1.559

Abbreviations: AK, Alaska; ER, oestrogen receptor; HR, hazard ratio; No, number; PR, progesterone receptor; y, years.

In addition to the prognostic significance of surgery to the primary tumour and number of lymph nodes examined, the multivariate Cox model also showed the independent contributions of age at diagnosis, tumour grade and marital status. These have been traditional prognostic factors in MaBC, regardless of stage, recently confirmed in a large population-based study [5].

We acknowledge that our study has some limitations. The population-based design could include errors in data reporting, in addition, the pathologic data could not be centrally reviewed and was collected from different local pathology laboratories. We do not have information with regards to systemic treatments of this cohort, which may contribute to some of the differences observed in survival according to prognostic variables. SEER currently does not collect information on locoregional and distant recurrences which would assist in the efficacy assessment of each locoregional treatment. However, despite these limitations, our study has several important strengths. To our knowledge, this is the first study to analyse the impact of locoregional treatments on OS in men with T1a,b,cN0M0 breast cancer. In addition, this is the largest study conducted to date to report outcomes according to the number of lymph nodes examined in this group of patients. This population-based cohort is representative of the general population with T1a,b,cN0M0 MaBC, and this confers strong external validity to our results. In the absence of randomised clinical trials for men, the present study provides very relevant clinical information that could be used in clinical practice when considering individual locoregional treatment modalities for appropriately selected MaBC patients.

In summary, in this cohort of male patients with early breast cancer, a favourable OS rate at 5 and 10 years was observed. T1c was the most prevalent subgroup and these tumours had higher-risk features compared with the other sub-stages. Most patients were treated with mastectomy and had >5 lymph nodes resected, regardless of tumour size at presentation. We observed that the use of adjuvant radiotherapy was infrequent. Finally, we identified that older age, higher tumour grade, no breast surgery, no lymph node examination and unmarried status emerged as poor prognostic characteristics. Efforts to decrease the high rates of mastectomy and extensive lymph node dissection should be taken given similar OS observed with breast conservation and resection of 1–5 lymph nodes, respectively.

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None.

Conflict of interest statement

None declared.

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