Local surgery improves survival in elderly patients with stage IV breast cancer: a population-based retrospective cohort study

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Background: Little is known about the role of local therapy in elderly patients with stage IV breast cancer. This study aimed to evaluate the effect of local therapy including surgery and radiotherapy in this kind of population by using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Eligible patients diagnosed between 2010 and 2015 were selected from the SEER database. Baseline characteristics, way of local therapy and survival information were collected for survival and analysis of prognostic factors. Cause-specific survival (CSS) curves were calculated using the Kaplan-Meier (KM) method and compared by the log-rank test. Cox regression and multivariate competing risk analyses were used to analyze prognosis factors.

Results: A total of 1,900 patients were enrolled with the median age of 71 (range, 65 to 95) years. The 5-year CSS of patients with surgery was significantly better than that of those who did not (36.5% *vs.* 22.4%, P<0.001). Moreover, surgery was an independent protective factor for CSS in both multivariate Cox regression analysis [hazard ratio (HR), 0.588; 95% confidence interval (CI), 0.485–0.643; P<0.001] and multivariate competing risk analysis [subdistribution HR (SHR), 0.620; 95% CI, 0.535–0.718; P<0.001]. Stratified analysis showed that most subgroup patients could benefit from surgery. The 5-year CSS of patients with radiotherapy was comparable to those without radiotherapy (28.9% *vs.* 26.5%, P=0.060), and radiotherapy was not an independent prognostic factor for CSS (SHR, 1.005; 95% CI, 0.846–1.202; P=0.954). However, subgroup analysis found that patients with moderate grade in histopathology, luminal A, or triple-negative breast cancer (TNBC) subtype could benefit from radiotherapy (all P<0.05).

Conclusions: Elderly patients with stage IV breast cancer can benefit from surgical treatment. This study helps to select the appropriate group for local surgery or radiotherapy according to the personal situation of the elderly to obtain the maximum benefit.

Keywords: Breast cancer; surgery; radiotherapy; prognosis; Surveillance, Epidemiology, and End Results program (SEER program)

Introduction

In the United States, breast cancer predominantly affects the elderly. As of 2019, 54% of breast cancer cases are diagnosed in women older than 60 years, and 72% of breast cancer deaths occur in this age group. The median age at which women are diagnosed with breast cancer is 62 years (1). The treatment of stage IV breast cancer is a comprehensive treatment with chemotherapy, targeted, endocrine, and other systemic treatments as the main modalities. The prognosis is poor, and the 5-year overall survival rate is about 38% (2). The role of local therapy in stage IV breast cancer is controversial. The number of prospective studies is limited and the results are inconsistent (3-6). These studies have some flaws. The imbalance of baseline variables, insufficiency of system therapy, and high tumor burden are thought to lead to bias. Whether it improves patient survival and prognosis, or which groups of patients benefit from it, remains to be determined (7). In our previous retrospective analysis of the whole population, local surgery improved 5-year survival in patients with stage IV breast cancer, and radiotherapy seemed to further improve this index (8). However, elderly patients are a special group. The patients had more comorbidities and less desire for active treatment. The disease itself is often of the hormone receptor positive type and sensitive to endocrine

therapy (9). As systematic treatments continue to improve, little is known about the role of local therapy in elderly breast cancer patients. Whether systemic therapy combined with local therapy can benefit, and how to select patients who need local therapy has not been clarified.

Although there was selection bias in the retrospective analysis, it is very difficult to conduct a large prospective study involving elderly patients, especially related to surgery. Surveillance, Epidemiology, and End Results (SEER) database collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population so that it has a rich resource of cases. Hence, we hope to retrospectively analyze data from the it to elucidate the effect of local therapy on the metastatic elderly breast cancer cohort. Through stratified analysis, we hope to further understand which type of elderly patients are more likely to benefit from local therapy. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5124/rc).

Methods

Data source and study population

A retrospective cohort study was performed with data extracted from the SEER 21 registry (November 2020 submission) database using SEER*Stat Software version 8.3.9 software. The inclusion criteria were listed as followed: (I) histologically diagnosed stage IV breast cancer according to the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification between 2010 and 2015; (II) aged 65 years or older; (III) underwent chemotherapy. Patients were excluded for the following reasons: (I) male patients; (II) patients with T0 local disease; (III) cases combined with or secondary to other tumors; (IV) unavailable information about locoregional therapy; (V) information on distant metastatic involvement was missing; (VI) incomplete follow-up data. A total of 1,900 cases entered the final analysis (*Figure 1*). All data obtained included age at diagnosis, race, tumor grade, molecular subtype, TNM stage, metastatic site, treatment (including local surgery and radiotherapy), and follow-up information. SEER data are publicly available, and a signed research data agreement form was required to access the database. Institutional review board approval was waived since it is a medical record-based study. The study was conducted in accordance with the

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Highlight box

Key findings
• Elderly patients with stage IV breast cancer can benefit from surgical treatment.

What is known and what is new?
• The role of local therapy in stage IV breast cancer is controversial. The number of prospective studies is limited and the results are inconsistent. In our previous retrospective analysis of the whole population, local surgery improved 5-year survival in patients with stage IV breast cancer, and radiotherapy seemed to further improve this index.
• Surgical treatment improves the survival of elderly patients with stage IV breast cancer. Notably, patients with moderate grade in histopathology, molecular typing of luminal A, or TNBC can also benefit from radiotherapy.

What is the implication, and what should change now?
• Little is known about the role of local therapy in elderly breast cancer patients. Our study shows that elderly patients with stage IV breast cancer can benefit from surgical treatment. And it helps to select the appropriate group for local surgery or radiotherapy according to the personal situation of the elderly to obtain the maximum benefit.

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n=2,992
• Patients diagnosed with stage IV
  breast cancer from 2010 to 2015
• Older than or equal to 65 years
• Received chemotherapy
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Excluded (n=1,092)
• Male patients (n=59)
• Patients with T0 local disease (n=73)
• Cases combined or secondary to
  other tumors (n=873)
• Unavailable information about
  locoregional therapy (n=36)
• Information on distant metastatic
  involvement was missing (n=17)
• Incomplete follow-up data (n=34)
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Patients included in the study
n=1,900
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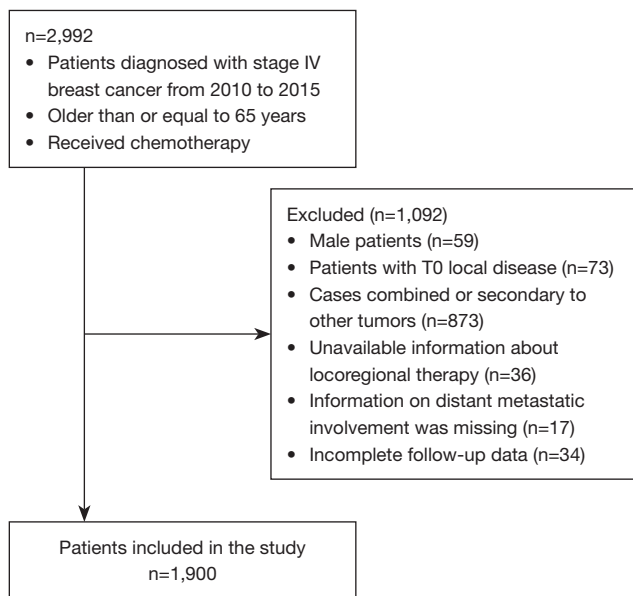
Figure 1 Study flow chart.

Declaration of Helsinki (as revised in 2013).

Statistical analysis

Cause-specific survival (CSS) was defied as the time from the date of diagnosis to the date of death attributed to breast cancer. The CSS was plotted using Kaplan-Meier (KM) curves, and differences between groups were assessed using log-rank test. Variables that significantly affected CSS were investigated by multivariate analyses according to the Cox regression model. Since death from other causes was the competing risk factor for cancer-specific death, Fine and Gray's competing risks regression was also used to identify potential risk factors associated with CSS, with results determined by subdistribution hazard ratio (SHR) and 95% confidence interval (CI). Competing risk analyses were also used to generate cumulative incidence graphs of death probability. All statistical analyses were carried out using R statistical software (version 4.1.2; The R Foundation for Statistical Computing) and Stata (version 13.0; StataCorp LLC, College Station, TX, USA). All tests were two sided, with an priori significance level set at $P<0.05$.

Results

Clinicopathological characteristics

A total of 1,900 patients were enrolled in the study after

screening according to the inclusion criteria. The median age was 71 (range, 65 to 95) years. The White race accounted for 79.7% of cases, followed by the Black race at 14.2%. The primary breast lesions were mostly large masses (T3–4 comprised 52.5%), and regional lymph node metastasis was also common, mainly N1 (43.1%). The main molecular subtypes were luminal type (61.6%). Human epidermal growth factor receptor 2 (HER2) over-expression and triple-negative breast cancer (TNBC) type (10.3% and 19.1%, respectively) were less common. The histopathological grade of tumors was mostly poorly differentiated (45.3%). Bone was the most common site of metastasis (29.5%), followed by the lung (14.4%); brain metastasis was rare (1.1%). The proportion of patients receiving local treatment was low, with 636 patients (33.5%) receiving surgery and 280 patients (14.7%) receiving radiotherapy (*Table 1*).

CSS and cumulative probability

The median follow-up time for all patients was 18 (range, 1–83) months with a 5-year CSS of 27.5%. Patients who underwent local surgery had a higher 5-year CSS than those who did not (36.5% *vs.* 22.4%, P<0.001) (*Figure 2A*). The cumulative mortality curve showed that 5-year tumor-related mortality was lower in patients who underwent local surgery than in those who did not (63.5% *vs.* 77.6%, P<0.001; SHR, 0.628; 95% CI, 0.551–0.717) (*Figure 2B*).

The 5-year CSS of patients who received radiotherapy was comparable to that of those who did not (28.9% *vs.* 26.5%, P=0.060) (*Figure 3A*). The cumulative mortality rates of the two groups were similar (71.1% *vs.* 73.5%, P=0.101; HR, 0.869; 95% CI, 0.736–1.028) (*Figure 3B*). Further subgroup analysis based on clinicopathological data showed that patients of all ages except ≥85 years could benefit from surgery (all P<0.05). In terms of the histopathological grade, all patients except undifferentiated patients could benefit from surgery. Meanwhile, patients with all molecular subtypes could benefit from surgery except for those whose type was unknown (all P<0.05). Besides, only patients with simple bone metastasis could benefit from surgery [P<0.001; hazard ratio (HR), 0.519; 95% CI, 0.394–0.683], but not metastases in other sites (*Figure 4*). Further subgroup analysis based on clinicopathological data showed that only moderately differentiated (P=0.031; HR, 0.672; 95% CI, 0.469–0.964), luminal A (P=0.025; HR, 0.734; 95% CI, 0.560–0.962), and TNBC (P=0.028; HR, 0.700; 95% CI, 0.509–0.962)

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Table 1 Demographic and clinical characteristics of the enrolled patients

Characteristics	Stage IV elderly breast cancer	
	N=1,900 cases	% of patients
Age (years)		
Median [range]	71 [65–95]	
65≤ to <70	803	42.3
70≤ to <75	586	30.8
75≤ to <80	264	13.9
80≤ to <85	172	9.1
≥85	75	3.9
Race		
White	1,515	79.7
Black	269	14.2
Other	114	6.0
Unknown	2	0.1
AJCC 7th, T stage		
T1	205	10.8
T2	469	24.7
T3	288	15.2
T4	708	37.3
Tx	230	12.1
AJCC 7th, N stage		
N0	413	21.7
N1	818	43.1
N2	204	10.7
N3	323	17.0
Nx	142	7.5
Grade		
Well	114	6.0
Moderately	568	29.9
Poorly	860	45.3
Undifferentiated	19	1.0
Unknown	339	17.8
Molecular subtype		
Luminal A	809	42.6
Luminal B	361	19.0
HER2 enriched	196	10.3
TNBC	362	19.1
Unknown	172	9.1

Table 1 (continued)

Table 1 (continued)

| Characteristics	Stage IV elderly breast cancer	
	N=1,900 cases	% of patients
Metastatic site		
Bone	560	29.5
Lung	273	14.4
Liver	137	7.2
Brain	21	1.1
Multiple sites	614	32.3
Other	295	15.5
Surgery		
No	1,264	66.5
Yes	636	33.5
Radiotherapy		
No	1,620	85.3
Yes	280	14.7

AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

can benefit from radiotherapy (*Figure 5*).

Factors associated with CSS

Univariate analysis showed that age ≥75 years, histological grades of poorly differentiated and undifferentiated, molecular subtype of TNBC, lung, liver, brain, and multiple site metastasis, and no surgery or radiotherapy were associated with poor CSS (all P<0.05); luminal B type was associated with better CSS (P=0.005; HR, 0.766; 95% CI, 0.636–0.922). Further multivariate Cox regression analysis confirmed that surgery was an independent protective factor affecting CSS in elderly patients with stage IV breast cancer (P<0.001; HR, 0.558; 95% CI, 0.485–0.643); radiotherapy was not an independent prognostic factor (P=0.822). Other independent prognostic factors included age, histological grade, molecular subtype, and distant metastasis (all P<0.05, *Table 2*).

We also performed a multivariate Gray's competing risk regression model to adjust potential confounding factors (*Table 3*). The results also showed that surgery (P<0.001; SHR, 0.620; 95% CI, 0.535–0.718) was an independent prognostic factor affecting CSS in elderly patients with stage IV breast cancer; radiotherapy was not significantly
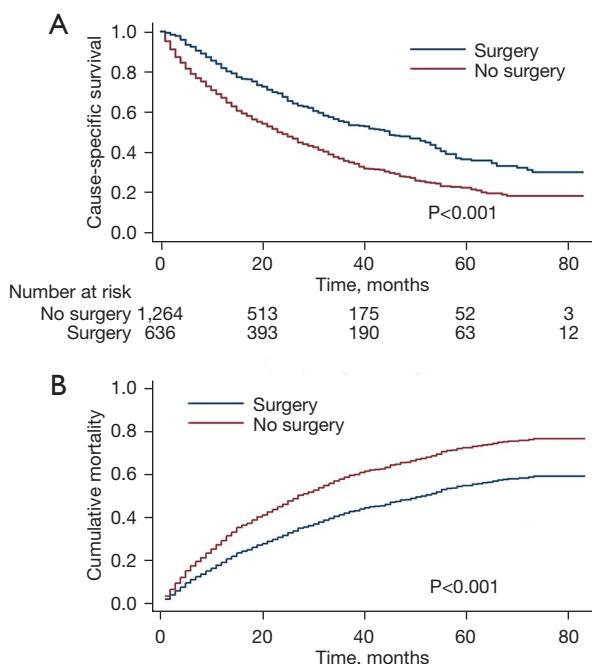
Figure 2 Survival curves of patients with and without surgery. (A) CSS; (B) cumulative mortality. CSS, cause-specific survival.
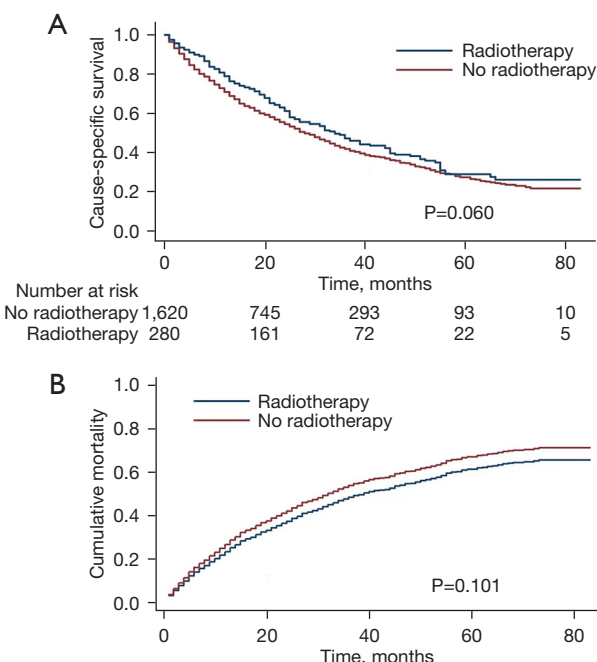
Figure 3 Survival curves of patients with and without radiotherapy. (A) CSS; (B) cumulative mortality. CSS, cause-specific survival.
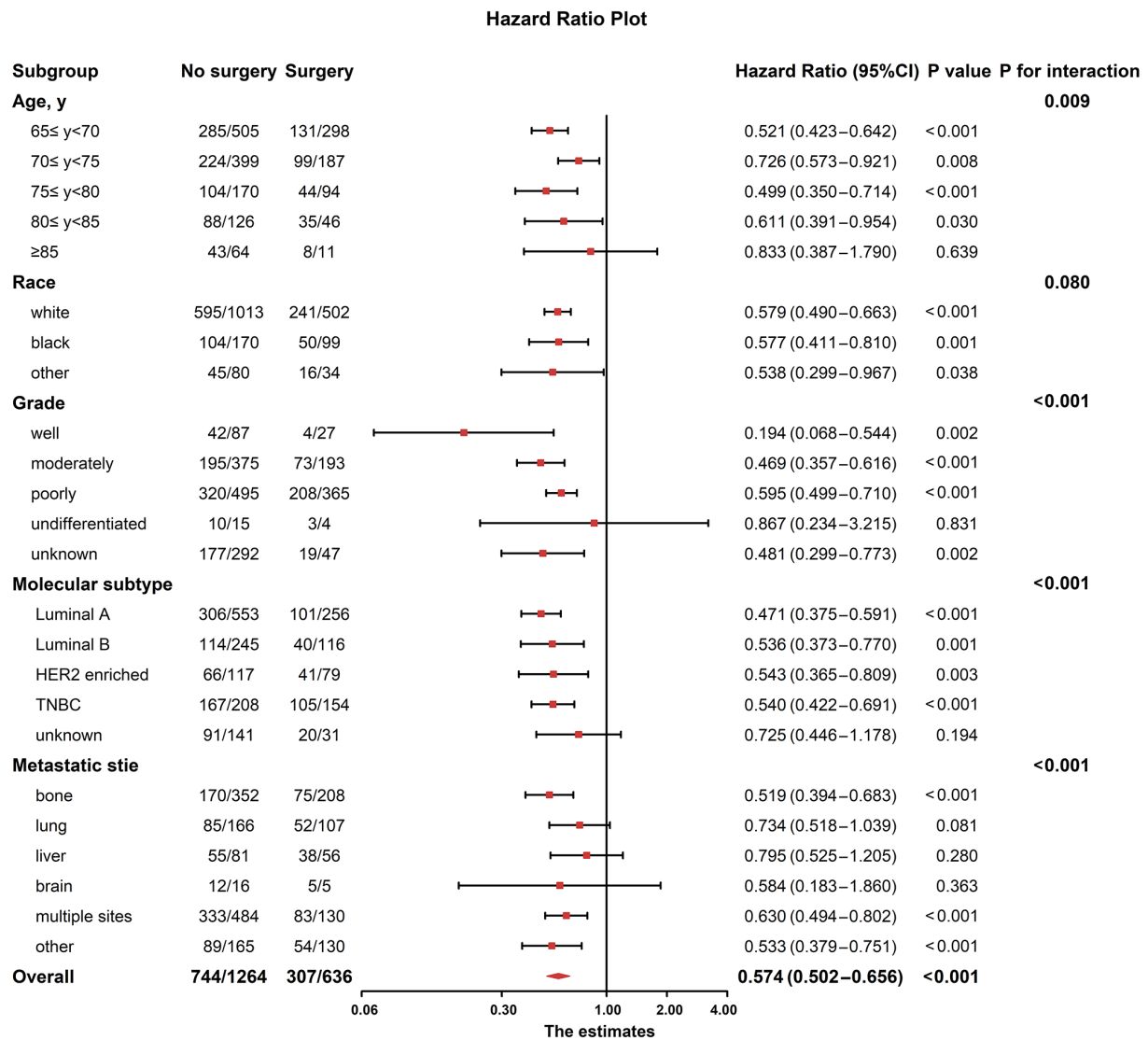
associated with CSS (P=0.954; SHR, 1.005; 95% CI, 0.846–1.202).

Discussion

This study shows that characteristically, elderly breast cancer patients are mainly concentrated between 65 and 75 years. At the time of diagnosis, the diameter of the primary breast mass was larger, and the molecular subtype was more commonly luminal type, and less commonly TNBC. This is consistent with the characteristics of elderly breast cancer reported in previous studies (10,11). In terms of the histopathological grade, moderate and poor differentiation accounted for 75.3%, which may be related to the inclusion of the population with advanced disease, and the presence of selection bias.

The role of local therapy in advanced breast cancer is controversial. This study attempted to elucidate the role of local therapy in stage IV elderly breast cancer. Elderly patients, as a heterogeneous group, are often accompanied by complex complications, poor tolerance of therapy, and more careful choice of invasive treatment. In this study, both the Cox model and risk competition model showed that elderly patients with stage IV breast cancer could benefit from surgery, and age was not an absolute taboo for surgery. However, the risk of surgery increases with age, with the highest risk in patients over 85 years of age (12). This is also consistent with the results of our further subgroup analysis, which found that patients over 85 years of age did not benefit from surgery, and this group should be carefully selected for surgery.

Studies without age limitation suggest that patients with oligometastatic breast cancer, especially those with bone metastasis alone, should more actively choose local therapy to improve survival (13,14). This was also replicated in the subgroup analysis of the present study. Elderly patients with bone metastases may benefit from local treatment, but those with lung, liver, and brain metastases do not. Unfortunately, the SEER database could not obtain the tumor load at the site of metastasis and could not determine whether the metastasis was oligometastasis, which reduced the preciseness of the conclusions we obtained. Tumors and metastases are like seeds and soil. Primary therapy can reduce the possibility of tumor metastasis or re-metastasis at the source, eliminate tumor

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Hazard Ratio Plot

Subgroup	No surgery	Surgery		Hazard Ratio (95%CI)	P value	P for interaction
Age, y						0.009
65≤ y<70	285/505	131/298		0.521 (0.423–0.642)	<0.001	
70≤ y<75	224/399	99/187		0.726 (0.573–0.921)	0.008	
75≤ y<80	104/170	44/94		0.499 (0.350–0.714)	<0.001	
80≤ y<85	88/126	35/46		0.611 (0.391–0.954)	0.030	
≥85	43/64	8/11		0.833 (0.387–1.790)	0.639	
Race						0.080
white	595/1013	241/502		0.579 (0.490–0.663)	<0.001	
black	104/170	50/99		0.577 (0.411–0.810)	0.001	
other	45/80	16/34		0.538 (0.299–0.967)	0.038	
Grade						<0.001
well	42/87	4/27		0.194 (0.068–0.544)	0.002	
moderately	195/375	73/193		0.469 (0.357–0.616)	<0.001	
poorly	320/495	208/365		0.595 (0.499–0.710)	<0.001	
undifferentiated	10/15	3/4		0.867 (0.234–3.215)	0.831	
unknown	177/292	19/47		0.481 (0.299–0.773)	0.002	
Molecular subtype						<0.001
Luminal A	306/553	101/256		0.471 (0.375–0.591)	<0.001	
Luminal B	114/245	40/116		0.536 (0.373–0.770)	0.001	
HER2 enriched	66/117	41/79		0.543 (0.365–0.809)	0.003	
TNBC	167/208	105/154		0.540 (0.422–0.691)	<0.001	
unknown	91/141	20/31		0.725 (0.446–1.178)	0.194	
Metastatic stie						<0.001
bone	170/352	75/208		0.519 (0.394–0.683)	<0.001	
lung	85/166	52/107		0.734 (0.518–1.039)	0.081	
liver	55/81	38/56		0.795 (0.525–1.205)	0.280	
brain	12/16	5/5		0.584 (0.183–1.860)	0.363	
multiple sites	333/484	83/130		0.630 (0.494–0.802)	<0.001	
other	89/165	54/130		0.533 (0.379–0.751)	<0.001	
Overall	**744/1264**	**307/636**		**0.574 (0.502–0.656)**	**<0.001**	

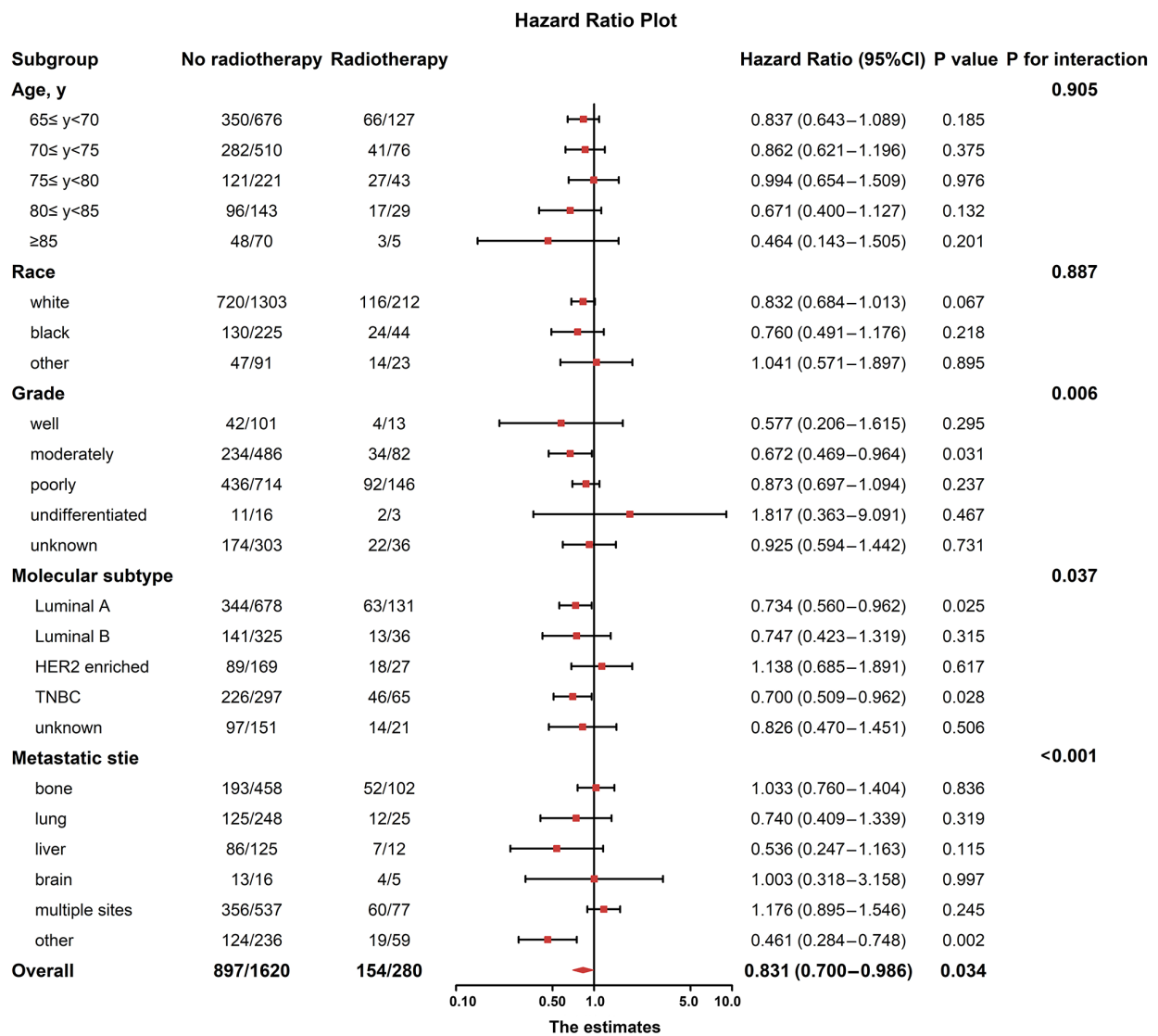0.06   0.30   1.00   2.00   4.00
The estimates

Figure 4 Subgroup analysis of CSS between surgery and no surgery. CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; CSS, cancer-specific survival.

cells and their release of metastatic mediators, thus further controlling the disease (15).

Whether elderly patients can benefit from radiotherapy has been a source of debate. In patients with early-stage breast cancer who are approximately 70 years after breast-conserving surgery, radiation reduces the risk of local recurrence but does not affect long-term survival (16), suggesting that radiation therapy is less effective in elderly breast cancer. The role of radiotherapy in stage IV senile breast cancer has not been described. This study shows that, unlike younger patients (17,18), local radiotherapy does not affect prognosis in older patients with stage IV. However, subgroup analysis suggested that moderately differentiated histological grade seemed to benefit from radiotherapy. There is no literature to support this, and more data are needed. In addition, luminal A and TNBC groups can benefit from radiotherapy. Different researchers have come to different conclusions about whether radiation therapy is better for older patients with luminal A or B. Liu and Chen *et al.* found that patients with luminal A had a better prognosis and the lowest local recurrence rate compared with other subtypes (19,20). However, Zhi *et al.*

Hazard Ratio Plot

Subgroup	No radiotherapy	Radiotherapy		Hazard Ratio (95%CI)	P value	P for interaction
Age, y						0.905
65≤ y<70	350/676	66/127		0.837 (0.643–1.089)	0.185	
70≤ y<75	282/510	41/76		0.862 (0.621–1.196)	0.375	
75≤ y<80	121/221	27/43		0.994 (0.654–1.509)	0.976	
80≤ y<85	96/143	17/29		0.671 (0.400–1.127)	0.132	
≥85	48/70	3/5		0.464 (0.143–1.505)	0.201	
Race						0.887
white	720/1303	116/212		0.832 (0.684–1.013)	0.067	
black	130/225	24/44		0.760 (0.491–1.176)	0.218	
other	47/91	14/23		1.041 (0.571–1.897)	0.895	
Grade						0.006
well	42/101	4/13		0.577 (0.206–1.615)	0.295	
moderately	234/486	34/82		0.672 (0.469–0.964)	0.031	
poorly	436/714	92/146		0.873 (0.697–1.094)	0.237	
undifferentiated	11/16	2/3		1.817 (0.363–9.091)	0.467	
unknown	174/303	22/36		0.925 (0.594–1.442)	0.731	
Molecular subtype						0.037
Luminal A	344/678	63/131		0.734 (0.560–0.962)	0.025	
Luminal B	141/325	13/36		0.747 (0.423–1.319)	0.315	
HER2 enriched	89/169	18/27		1.138 (0.685–1.891)	0.617	
TNBC	226/297	46/65		0.700 (0.509–0.962)	0.028	
unknown	97/151	14/21		0.826 (0.470–1.451)	0.506	
Metastatic stie						<0.001
bone	193/458	52/102		1.033 (0.760–1.404)	0.836	
lung	125/248	12/25		0.740 (0.409–1.339)	0.319	
liver	86/125	7/12		0.536 (0.247–1.163)	0.115	
brain	13/16	4/5		1.003 (0.318–3.158)	0.997	
multiple sites	356/537	60/77		1.176 (0.895–1.546)	0.245	
other	124/236	19/59		0.461 (0.284–0.748)	0.002	
Overall	**897/1620**	**154/280**		**0.831 (0.700–0.986)**	**0.034**	

0.10   0.50 1.0   5.0 10.0
The estimates

Figure 5 Subgroup analysis of CSS between radiotherapy and no radiotherapy. CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; CSS, cancer-specific survival.

reported that patients with luminal A did not benefit from radiotherapy (21). This phenomenon needs further study and confirmation. A study by Zhang *et al.* in the SEER database on the role of radiotherapy in stage IV breast cancer also found that patients with TNBC could benefit from radiotherapy (22). TNBC is considered the most immunogenic subtype of breast cancer (23). It has been shown that radiotherapy may stimulate the immune system, increasing the proportion of antigen-experiential T cells to effector memory T cells (24). Once the immune system is activated, increased concentrations of molecules associated

with pro-inflammatory immune responses, such as tumor necrosis factor (TNF), can promote antigen presentation, stimulate T cells, and lead to activation of the corresponding immune response and tumor cell death in metastatic TNBC patients (25). These effects make radiotherapy a possible way of collaborating with the immune system, leading to metastatic TNBC benefiting from radiotherapy. In addition, some TNBC patients have *BRCA1* gene mutations. The *BRCA1* tumor cells are derived from luminal progenitor cells, and Chiang *et al.* observed that radiotherapy could permanently eliminate luminal ductal epithelial progenitor

Table 2 Univariate and multivariate analyses of CSS in the stage IV elderly breast cancer

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		<0.001*		<0.001*
65≤ to <70	Ref			
70≤ to <75	1.132 (0.979–1.309)	0.095	1.025 (0.886–1.186)	0.740
75≤ to <80	1.250 (1.036–1.508)	0.020*	1.208 (1.00–1.460)	0.050*
80≤ to <85	1.556 (1.264–1.917)	<0.001*	1.510 (1.222–1.865)	<0.001*
≥85	1.801 (1.346–2.410)	<0.001*	1.602 (1.194–2.151)	0.002*
Race		0.771		
White	Ref			
Black	1.081 (0.910–1.284)	0.374		
Other	0.939 (0.724–1/218)	0.636		
Unknown	NA	0.903		
Grade		<0.001*		<0.001*
Well	Ref			
Moderately	1.179 (0.862–1.612)	0.302	1.290 (0.941–1.768)	0.113
Poorly	1.842 (1.362–2.490)	<0.001*	1.897 (1.388–2.593)	<0.001*
Undifferentiated	2.308 (1.247–4.272)	0.008*	1.970 (1.053–3.686)	0.034*
Unknown	1.703 (1.236–2.349)	0.001*	1.499 (1.081–2.077)	0.015*
Molecular subtype		<0.001*		<0.001*
Luminal A	Ref			
Luminal B	0.766 (0.636–0.922)	0.005*	0.639 (0.528–0.773)	<0.001*
HER2 enriched	1.128 (0.912–1.396)	0.268	0.942 (0.764–1.178)	0.603
TNBC	2.089 (1.790–2.438)	<0.001*	1.868 (1.577–2.212)	<0.001*
Unknown	1.536 (1.245–1.895)	<0.001*	1.229 (0.990–1.527)	0.062
Metastatic site		<0.001*		<0.001*
Bone	Ref			
Lung	1.254 (1.018–1.546)	0.034*	1.016 (0.820–1.260)	0.885
Liver	2.227 (1.754–2.829)	<0.001*	2.121 (1.664–2.702)	<0.001*
Brain	3.002 (1.835–4.912)	<0.001*	2.502 (1.520–4.118)	<0.001*
Multiple sites	2.168 (1.851–2.540)	<0.001*	1.965 (1.673–2.308)	<0.001*
Other	1.247 (1.014–1.532)	0.036*	1.129 (0.915–1.392)	0.259
Surgery				
No	Ref			
Yes	0.574 (0.502–0.656)	<0.001*	0.558 (0.485–0.643)	<0.001*
Radiotherapy				
No	Ref			
Yes	0.831 (0.700–0.986)	0.034*		0.822

*, P<0.05. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Table 3 Competing risk SHR for CSS

Variables	SHR	95% CI	P value
Age (years)			
65≤ to <70	Ref		
70≤ to <75	1.024	0.881–1.190	0.755
75≤ to <80	1.099	0.898–1.344	0.358
80≤ to <85	1.300	1.041–1.623	0.021*
≥85	1.402	1.002–1.962	0.049*
Race			
White	Ref		
Black	1.065	0.890–1.274	0.491
Other	0.979	0.752–1.273	0.874
Unknown	NA		
Grade			
Well	Ref		
Moderately	1.442	1.037–2.004	0.029*
Poorly	1.918	1.378–2.669	<0.001*
Undifferentiated	2.209	1.177–4.147	0.014*
Unknown	1.551	1.095–2.195	0.013*
Molecular subtype			
Luminal A	Ref		
Luminal B	0.689	0.570–0.832	<0.001*
HER2 enriched	0.950	0.749–1.206	0.672
TNBC	1.710	1.425–2.053	<0.001*
Unknown	1.033	0.810–1.316	0.795
Metastatic site			
Bone	Ref		
Lung	1.056	0.858–1.230	0.606
Liver	1.849	1.422–2.404	<0.001*
Brain	2.278	1.326–3.913	0.003
Multiple sites	1.756	1.490–2.069	<0.001*
Other	1.114	0.899–1.381	0.322
Surgery			
No	Ref		
Yes	0.620	0.535–0.718	<0.001*
Radiotherapy			
No	Ref		
Yes	1.005	0.846–1.202	0.954

*, P<0.05. SHR, subdistribution hazard ratio; CSS, cancer-specific survival; CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

cells, reducing the risk of recurrence in *BRCA1* mutation carriers (26).

Of course, there are some limitations in this paper. Firstly, this was a retrospective study with inevitable retrospective bias. Secondly, specific chemotherapy regimen, efficacy, recurrence, and other data were not obtained from the SEER database for further analysis. Besides, the information database of radiotherapy site is not specified, but this study can explain the role of radiotherapy in stage IV senile breast cancer, regardless of radiotherapy in primary or metastatic lesions.

In general, elderly patients with stage IV breast cancer can benefit from surgical treatment, especially patients with moderate differentiated, luminal A, or TNBC, who can also benefit from radiotherapy. It is necessary to accurately select appropriate groups for local surgery or radiotherapy based on the individual conditions of the elderly to obtain the greatest benefit.

Conclusions

Surgical treatment improves the survival of elderly patients with stage IV breast cancer. Notably, patients with moderate grade in histopathology, molecular typing of luminal A, or TNBC can also benefit from radiotherapy. This study is helpful in selecting the appropriate group for local surgery or radiotherapy according to the individual circumstances of the elderly for maximum benefit.

Acknowledgments

Footnote

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conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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References

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69:438-51.
2. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475-95.
3. 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.
4. 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.
5. 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.
6. 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. Erratum in: J Clin Oncol 2022;40:1392.
7. Yip CH. Palliation and breast cancer. J Surg Oncol 2017;115:538-43.
8. Xiao M, Zhang P. Conditional cause-specific survival after chemotherapy and local treatment for primary stage IV breast cancer: A population-based study. Front Oncol 2022;12:800813.
9. Lodi M, Scheer L, Reix N, et al. Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review. Breast Cancer Res Treat 2017;166:657-68.
10. Vetter M, Huang DJ, Bosshard G, et al. Breast cancer in women 80 years of age and older: a comprehensive analysis of an underreported entity. Acta Oncol 2013;52:57-65.
11. Grumpelt AM, Ignatov A, Tchaikovski SN, et al. Tumor characteristics and therapy of elderly patients with breast cancer. J Cancer Res Clin Oncol 2016;142:1109-16.
12. de Glas NA, Kiderlen M, Bastiaannet E, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat 2013;138:561-9.
13. Wuerstlein R, Ettl J, Haidinger R, et al. Highlights from ABC4 - Bridging the Gap. Breast Care (Basel) 2017;12:415-9.
14. Gera R, Chehade HELH, Wazir U, et al. Locoregional therapy of the primary tumour in de novo stage IV breast cancer in 216 066 patients: A meta-analysis. Sci Rep 2020;10:2952.
15. Akhtar M, Haider A, Rashid S, et al. Paget's "Seed and Soil" Theory of Cancer Metastasis: An Idea Whose Time has Come. Adv Anat Pathol 2019;26:69-74.
16. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971-7.
17. Kim YJ, Kim SS, Ahn SD, et al. The role of postoperative radiotherapy after primary tumor resection in patients with de novo stage IV breast cancer. Asia Pac J Clin Oncol 2021;17:495-505.
18. Nieder C, Dalhaug A, Pawinski A, et al. Survival After Palliative Radiotherapy in Patients with Breast Cancer and Bone-only Metastases. In Vivo 2016;30:879-83.
19. Liu FF, Shi W, Done SJ, et al. Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy. J Clin Oncol 2015;33:2035-40.
20. Chen HL, Ding A, Wang FW. Prognostic effect analysis of molecular subtype on young breast cancer patients. Chin J Cancer Res 2015;27:428-36.
21. Zhi X, Yang X, Pan T, et al. Correlation of radiotherapy with prognosis of elderly patients with hormone receptor-positive breast cancer according to immunohistochemical subtyping. Chin J Cancer Res 2019;31:471-80.
22. Zhang J, Luo S, Qiu Z, et al. Impact of Postoperative Radiotherapy on Survival of Patients With de novo Stage IV Breast Cancer: A Population-Based Study From the SEER Database. Front Oncol 2021;11:625628.
23. Esteva FJ, Hubbard-Lucey VM, Tang J, et al. Immunotherapy and targeted therapy combinations in

metastatic breast cancer. Lancet Oncol 2019;20:e175-86.

24. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res 2015;3:345-55.

25. Peng C, Chang NT, Chang TW. Identification and characterization of human immunodeficiency virus type 1 gag-pol fusion protein in transfected mammalian cells. J Virol 1991;65:2751-6.

26. Chiang HC, Nair SJ, Yeh IT, et al. Association of radiotherapy with preferential depletion of luminal epithelial cells in a BRCA1 mutation carrier. Exp Hematol Oncol 2012;1:31.

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