



Percutaneous microwave ablation combined with endocrine therapy versus standard therapy for elderly patients with HR-positive and HER2-negative invasive breast cancer: a propensity score-matched analysis of a multi-center, prospective cohort study

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Background: There is a growing trend to apply minimally invasive local treatments for elderly patients with early-stage breast cancer. As a minimally invasive thermal therapy, microwave ablation (MWA) has been attempted to treat breast cancer of small lesions, but its long-term local efficacy on elderly patients has seldom been reported. In this study, we aimed to compare outcomes of MWA combined with endocrine therapy to standard surgery combined with adjuvant therapy in the treatment of hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative invasive breast cancer for elderly patients.

Methods: This prospective multi-center cohort study enrolled patients over 70 years old diagnosed with HR-positive and HER2-negative early-stage invasive breast cancer between January 2016 and July 2021. Patients chose either non-randomized to undergo MWA combined with endocrine therapy (MWA group) or standard surgery combined with adjuvant therapy (surgery group). Endpoints for the comparisons were disease-free survival (DFS), overall survival (OS) and length of hospital stay (LOS) after adjusting for previously reported risk factors using propensity score matching (1:3).

Results: Of the enrolled 132 patients, 33 were in the MWA group and 99 were in the surgery group. MWA was successfully performed in all cases, and technical effectiveness was achieved in all cases. With a median follow-up of 31 months, only one case had local recurrence 23 months after MWA. MWA combined with endocrine therapy and standard surgery combined adjuvant therapy for elderly patients with breast cancer achieved similar DFS [hazard ratio, 0.536; 95% confidence interval (CI): 0.128–2.249] and OS (hazard ratio, 0.537; 95% CI: 0.089–3.235). Besides, MWA had much shorter LOS than standard surgery (7.1 versus 13.0 days, $P < 0.001$).

Conclusions: MWA combined with endocrine therapy and standard surgery combined with adjuvant

therapy for elderly breast cancer patients achieved similar outcomes. MWA combined with endocrine may be a feasible treatment strategy for elderly patients with HR-positive and HER2-negative invasive breast cancer.

Keywords: Microwave ablation (MWA); breast cancer; elderly patients; endocrine therapy; survival

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Introduction

Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases in 2020 (1). And approximately 30% of breast cancer cases occur in women aged 70 years and older (2). Compared with young patients, less aggressive treatment has been performed for elderly patients (3-5), due to their physiologic alterations, presumed short life expectancy, comorbid diseases, and inability to tolerate active therapy. But locoregional surgery cannot be omitted for these elderly patients because of a very high rate of local progression and presumed shorter life expectancy without local-regional treatment (3,6). Locoregional surgery has undergone a dramatic evolution over the past several decades from radical mastectomy to breast-conserving surgery (BCS)

and sentinel lymph node biopsy (SLNB), providing less aggressive treatment for patients with early-stage breast cancer (7).

Apart from these surgeries, minimally invasive therapies, including radiofrequency ablation (RFA), microwave ablation (MWA), laser therapy, and cryotherapy, have been attempted to treat breast cancer of small lesions in several ablation-resection feasibility studies (8-13). However, the relatively long-term local efficacy of ablation in the treatment of breast cancer has only been reported in limited case series (14,15) with small sample sizes. The ICE3 study has shown that cryoablation is effective for breast cancer of small lesions ≤ 1.5 cm (16). MWA shows several advantages compared to other minimally invasive therapies (8,17-19), including larger ablation volumes, shorter ablation times and improved convection profile. Only one retrospective comparative study with a small sample size reported MWA of breast cancer ≤ 5 cm without subsequent excision in comparison to nipple sparing mastectomy (20). However, all of the 21 patients treated with MWA included different molecular subtypes; and the efficacy analysis has been influenced by comprehensive treatments, including chemotherapy, endocrine therapy, radiotherapy and targeted therapy.

For elderly patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer, usually receive endocrine therapy only, and there is a trend to omit chemotherapy for these patients (3,4,6,21,22). Additionally, there is a growing trend to apply minimally invasive local treatments for elderly patients with early-stage breast cancer (23), such as omit SLNB (24) and radiotherapy after lumpectomy for elderly patients with low risk of recurrence (25). The precise and optimal treatment strategy remains unknown for elderly patients with early-stage breast cancer, especially for HR-positive and HER2-negative breast cancer.

In this multi-center prospective cohort study, we aimed to determine the efficacy of MWA combined with endocrine therapy (MWA group) versus standard surgery

Highlight box

Key findings

- MWA combined with endocrine therapy and standard surgery combined with adjuvant therapy for elderly breast cancer patients achieved similar outcomes.
- MWA combined with endocrine therapy may be a feasible treatment strategy for elderly patients with HR-positive and HER2-negative invasive breast cancer.
- MWA had much shorter length of hospital stay than standard surgery.

What is known and what is new?

- As a minimally invasive thermal therapy, MWA has been attempted to treat breast cancer of small lesions.
- The precise and optimal treatment strategy remains unknown for elderly patients with early-stage breast cancer, especially for HR-positive and HER2-negative breast cancer.

What is the implication, and what should change now?

- MWA combined with endocrine therapy and standard surgery combined with adjuvant therapy for elderly breast cancer patients achieved similar outcomes. MWA combined with endocrine may be a feasible treatment strategy for elderly patients with HR-positive and HER2-negative invasive breast cancer.

combined with adjuvant therapy (surgery group) in the treatment of primary tumors (≤ 3 cm) for elderly patients diagnosed with HR-positive and HER2-negative invasive breast cancer. To the best of our knowledge, this is the first study to compare these two groups for elderly patients with HR-positive and HER2-negative early-stage breast cancer. We present this article in accordance with the STROBE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gc-23-33/rc>).

Methods

Study design

This prospective, non-randomized, multi-center study was conducted with the approval from the Institutional Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (No. 2010-SR-003), and all patients had given written informed consent for participation. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). From January 2016 to July 2021, elderly female patients diagnosed with invasive breast cancer were included in this study from three hospitals, The First Affiliated Hospital with Nanjing Medical University, Sir Run Run Hospital Nanjing Medical University, and The Fourth Affiliated Hospital of Nanjing Medical University.

The inclusion criteria included the following: (I) female patients with the age over 70 years old diagnosed with HR-positive and HER2-negative invasive breast cancer; (II) a solitary mass confirmed by using both US and mammography; (III) a tumor outside the nipple-areola area with any distance to the skin and chest wall but not infiltrated to the skin and pectoralis major muscle; (IV) estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67 were determined by using immunohistochemical analysis of tissue from a core-needle biopsy specimen; (V) breast cancer 3.0 cm or less in greatest diameter confirmed by using ultrasonography (US); (VI) clinical negative axillary lymph node status confirmed by using US. Exclusion criteria were patients who received any previous surgery, radiotherapy or systemic anti-tumor treatment before enrollment or with distant metastasis.

Allocation of treatments

This prospective cohort study was based on patients' self-selected treatments: patients who chose to undergo MWA

combined with endocrine therapy or standard surgery followed by chemotherapy, radiotherapy or endocrine therapy if necessary. Patients who chose MWA, would be arranged for MWA under local anesthesia without axillary lymph node surgery (biopsy or dissection). No patient received radiotherapy or chemotherapy in the MWA group. All of the included patients received aromatase inhibitors (AIs) for endocrine therapy. Patients who chose surgery, would receive standard surgeries under general anesthesia, including mastectomy or BCS for breast, and axillary lymph node dissection (ALND) or SLNB for axillary lymph node. And radiotherapy and chemotherapy were recommended after surgery according to operation procedures (BCS or mastectomy), clinical-pathological characteristics, patients' physical conditions and decisions. And endocrine therapy was recommended for all patients.

MWA procedure

All MWA procedures were performed by one surgeon with 10 years of experience in breast intervention. After enrollment, MWA was performed to targeted tumor under local anesthesia. US was used to guide MWA and monitor the procedure. Local anesthesia was induced with 10 mL of 1% lidocaine. And about 20 mL of 0.5% lidocaine was injected into both subcutaneous space and retromammary space and hydrodissection was performed (26). The antenna (14 G) was placed into the tumors along the largest axis. The microwave irradiation frequency of the system (Nanjing Yigao Microwave Electric Institute, Nanjing, China) was 2,450 MHz with the output power set at 40 W. After testing the cycling system with cold water, MWA was started immediately to cover the entire tumor.

According to our previous experiences, MWA for at least 2 minutes was recommended to achieve complete ablation for tumor larger than 2 cm, and at least 1 min for tumor smaller than 2 cm (27). Complete ablation was defined as the tumor disappearing completely on US. The whole MWA procedure was completed in half an hour. After ablation, patients were monitored for half an hour in the hospital where they received therapy for immediate complications. Technical effectiveness of MWA was defined as complete ablation at follow-up enhanced imaging 1 month after MWA.

Follow-up

All the patients were followed completely in the outpatient

clinic. For the MWA group, breast US was recommended 1 week after ablation, breast magnetic resonance imaging (MRI) and contrast-enhanced US (CEUS) were recommended 1 month after ablation and then every year during follow-up. Complete ablation was defined as no focal enhancement within or at the periphery of the tumor confirmed by CEUS or MRI during follow-up (14). For both groups, breast US was recommended at 3-month intervals during the first year after treatment and then at 6-month intervals thereafter. Laboratory and other imaging examinations (e.g., chest and abdominal computed X-ray tomography, abdominal ultrasound, gynecological ultrasound) for metastases screening were performed at 6-month intervals within 2 years after treatment and then every year.

Clinical outcomes

Endpoints for the comparisons between the two groups were disease-free survival (DFS), overall survival (OS) and length of hospital stay (LOS) of the first hospitalization. The LOS was calculated as the difference between admittance and discharge dates, including pre-treatment examination, core-needle biopsy, waiting for pathological results and primary treatment (MWA or surgery). The post-operation LOS was calculated as the difference between primary treatment (MWA or surgery) and discharge dates.

Statistical analysis

Median, percentiles, range, mean and standard deviation were analyzed for numerical data as appropriate. In order to avoid potential selection bias and reduce the influence of confounding factors, propensity score matching analysis was performed. The proportion of included patients in the surgery group and MWA group is 3:1. According to the previous studies, the variables used for this procedure were date of diagnosis, age, tumor histology, tumor size, ER status, PR status and Ki-67 (28-30). Differences between the two groups were analyzed with the chi-square test or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. Wilcoxon test was used to compare the difference of LOS and postoperative hospital stay between the two groups. Hazard ratios and 95% confidence interval (CI) were calculated using a stratified Cox proportional hazards model. The median follow-up and survival were analyzed with the Kaplan-Meier method.

All P values were two-tailed with 5% significance levels. All statistical analyses were performed by using software STATA version 13.0 (StataCorp, College Station, TX, USA) or R version 4.1.1.

Results

Basic characteristics

From January 2016 to July 2021, 246 patients were finally eligible for inclusion in the study. A flow diagram of the study participants is shown in *Figure 1*. Of these included 246 patients, 33 patients underwent MWA combined with endocrine therapy (MWA group), and other 213 patients underwent standard surgeries combined with standard adjuvant therapies (surgery group) (*Table 1*). To avoid potential selection bias and reduce the influence of confounding factors, propensity score matching analysis was performed. After 1:3 propensity score matching for date of diagnosis, age, histology, tumor size, ER status, PR status and Ki-67, 99 patients were finally identified as control in the surgery group.

The mean age of the patients was 77.9 (range, 70–94) years for the overall patients; and 79.4 (range, 70–94), 77.4 (range, 70–92) years old for patients in the MWA group and in the surgery group, respectively. The baseline characteristics of patients in two groups are summarized in *Table 2*.

Treatments

In the MWA group, MWA was successfully performed to all 33 cases under local anaesthesia (*Table 3*). The mean ablation time was 2.64 ± 0.59 minutes, with a range from 1.67 to 4.5 minutes. The exact duration of MWA for each patient is shown in *Table 4*. After the first assessment 1 week after ablation, second ablation was given to one case for a little residual on the edge of the lesion under ultrasound. The remaining 32 cases received ablation only once, and ultrasound 1 week later showed no residual lesions. One month after ablation, no enhancement of the ablated tumor was observed by using MRI (*Figure 2*) and CEUS (*Figure 3*) in all cases. Of these 33 cases, technical effectiveness (complete ablation at follow-up enhanced imaging 1 month after MWA) was achieved in all 33 cases (100%; 95% CI, 89.4–100.0%). No skin burn, haematoma, infection or other ablation-related adverse events were observed during or after the procedure.

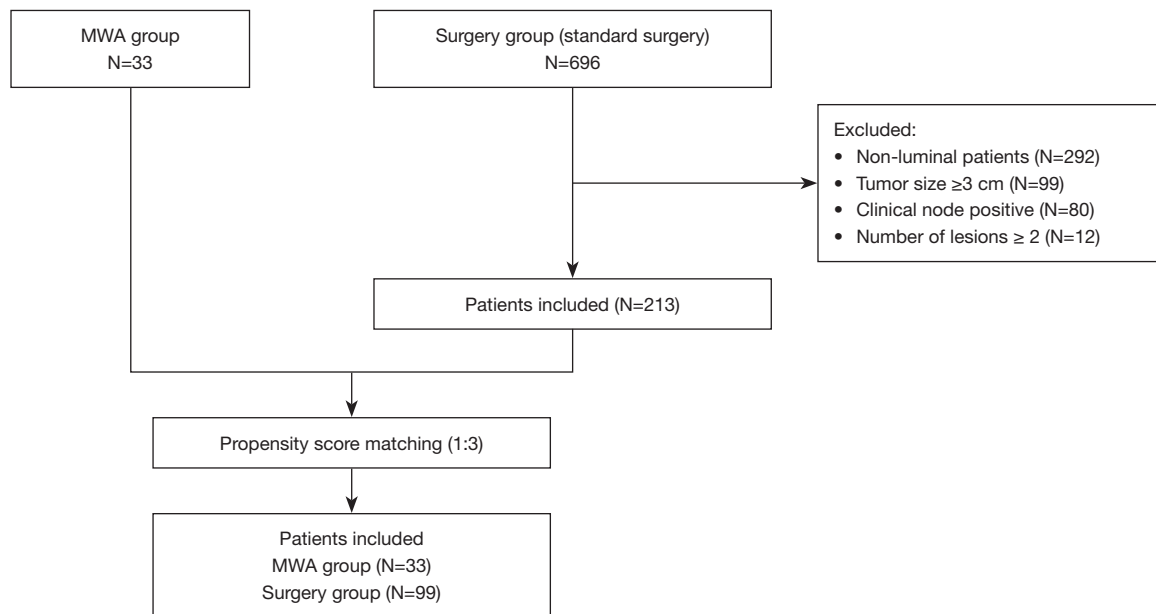


Figure 1 Patient flow diagram. Patients in the MWA group underwent MWA combined with endocrine therapy. Patients in the surgery group underwent standard surgery followed by chemotherapy, radiotherapy if necessary, and all of them received endocrine therapy. MWA, microwave ablation.

Table 1 The baseline characteristics of 213 elderly patients with HR-positive and HER2-negative invasive breast cancer received standard surgery

Characteristic	N
Age, years	
≤75	129
>75	84
Histology	
Invasive ductal carcinoma	173
Invasive lobular carcinoma	16
Other invasive carcinoma	24
Clinical tumor size, cm	
T1	116
T2	95
T3	2
Estrogen receptor	
<80%	14
80–90%	130
>90%	69
Progesterone receptor	
<20%	45
≥20%	168

Table 1 (continued)

Table 1 (continued)

Characteristic	N
Ki67 status	
≤14%	50
>14%	163
Breast surgery	
Breast-conserving surgery	15
Mastectomy	198
Axillary surgery	
SLNB	154
ALND	59
Radiotherapy	
Yes	6
No	207
Chemotherapy	
Yes	33
No	180
Endocrine therapy	
Yes	207
No	6

HR, hormone receptor; HER2, human epidermal growth factor receptor2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 2 Basic characteristics of enrolled patients in MWA and surgery groups

Characteristic	MWA group (n=33)	Surgery group (n=99)	P value
Age (years), mean \pm SD	79.4 \pm 7.6	77.4 \pm 5.5	0.103 [†]
Histology, n			0.147 [‡]
Invasive ductal carcinoma	31	80	
Invasive lobular carcinoma	1	4	
Other invasive carcinoma (mucinous carcinoma)	1	15	
Clinical tumor size (cm), n			0.948 [‡]
<1	2	7	
1–2	18	57	
>2	13	35	
Estrogen receptor, n			1.000 [‡]
<90%	2	8	
\geq 90%	31	91	
Progesterone receptor, n			0.619 [‡]
<20%	8	19	
\geq 20%	25	80	
Ki67 status, n			0.681 [‡]
\leq 14%	13	35	
>14%	20	64	

[†], Student's *t*-test; [‡], Fisher's exact test. MWA, microwave ablation; SD, standard deviation.

Table 3 The treatment in MWA and surgery groups

Variables	MWA group (n=33)	Surgery group (n=99)	P value
The procedure of MWA			–
MWA time (minutes), mean \pm SD	2.64 \pm 0.59	–	
Complete ablation after 1 week, n	32	–	
Complete ablation after 1 month, n	33	–	
Breast surgery, n			–
Breast-conserving surgery	–	8	
Mastectomy	–	91	
Axillary surgery, n			<0.001 [‡]
SLNB	0	76	
ALND	0	23	
No	33	0	
Radiotherapy, n			0.200 [‡]
Yes	0	8	
No	33	91	
Chemotherapy, n			0.200 [‡]
Yes	0	8	
No	33	91	
Endocrine therapy, n			–
Yes	33	99	
No	0	0	

[‡], Fisher's exact test. MWA, microwave ablation; SD, standard deviation; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 4 The exact duration of MWA for each patient

Case	Tumor size	Ablation duration
1	2.6 cm	3 min
2	2.7 cm	3.5 min
3	1.7 cm	3 min
4	1.5 cm	2.5 min
5	1.7 cm	3 min
6	2.1 cm	3.5 min
7	1.7 cm	2.5 min
8	2.3 cm	2.25 min
9	1.33 cm	2 min
10	2.3 cm	3 min
11	0.7 cm	1 min 40 s
12	1.2 cm	2.5 min
13	2.4 cm	2 min
14	3.0 cm	2 min 40 s
15	2.3 cm	2 min
16	1.3 cm	2 min
17	1.7 cm	4.5 min
18	1.7 cm	2 min 20 s
19	1.8 cm	2.5 min
20	1.5 cm	2 min 10 s
21	1.4 cm	3 min
22	2.2 cm	3.5 min
23	2.6 cm	2.5 min
24	1.5 cm	2.5 min
25	2.91 cm	2 min 20 s
26	1.8 cm	2 min 20 s
27	0.7 cm	2 min
28	1.5 cm	3 min
29	1.4 cm	2 min 20 s
30	2.3 cm	2.5 min
31	1.9 cm	2 min 20 s
32	2.9 cm	3 min 37 s
33	2.0 cm	2 min 40 s

MWA, microwave ablation.

In the surgery group, 8 (8.1%) patients received BCS, 91 (91.9%) patients received mastectomy, 76 (76.8%) patients received SLNB, and 23 (23.2%) patients received ALND. Besides, 8 (8.1%) patients received radiotherapy, and 8 (8.1%) patients received chemotherapy. All of the patients in the two groups received AIs for endocrine therapy (*Table 3*).

DFS and OS

With a median follow-up of 31 months (range, 2–74 months), DFS among patients in the MWA group and surgery group was not significantly different (hazard ratio, 0.536; 95% CI: 0.128–2.249; $P=0.38$) (*Figure 4*). Only 1 (1/33) patient in the MWA group had local recurrence 23 months after MWA, to whom modified radical mastectomy was performed. This patient was alive without any second recurrence at the end of follow-up. No patient in the MWA group developed distant metastasis. For the surgery group, tumor progression occurred in 3 (3/99) patients. One patient developed recurrent breast cancer involving chest wall at 23 months and was treated with further surgery. And this patient died 34 months after surgery. One patient was diagnosed with lung metastasis at 12 months after surgery and a third patient developed liver metastasis at 31 months after surgery. These two patients have received first-line endocrine therapy and still alive at the last follow-up.

No significant difference in OS was observed between the two groups of patients treated with MWA combined endocrine therapy and standard surgery combined with adjuvant therapies ((hazard ratio, 0.537; 95% CI: 0.089–3.235; $P=0.49$) (*Figure 4*).

The 1-, 3-year OS rates were 97.0% and 92.6% for patients in the MWA group and 100.0% and 96.1% for patients in the surgery group, respectively.

LOS

Among patients in the MWA group, there were 9 patients received MWA on an outpatient basis without hospitalization. In comparison to LOS for patients received standard surgeries, the mean LOS for patients received MWA was approximately 5 days shorter (7.1 versus 13.0 days, $P<0.001$) (*Figure 5*). And the post-operative LOS was still shorter for patients in the MWA group than those in the surgery group

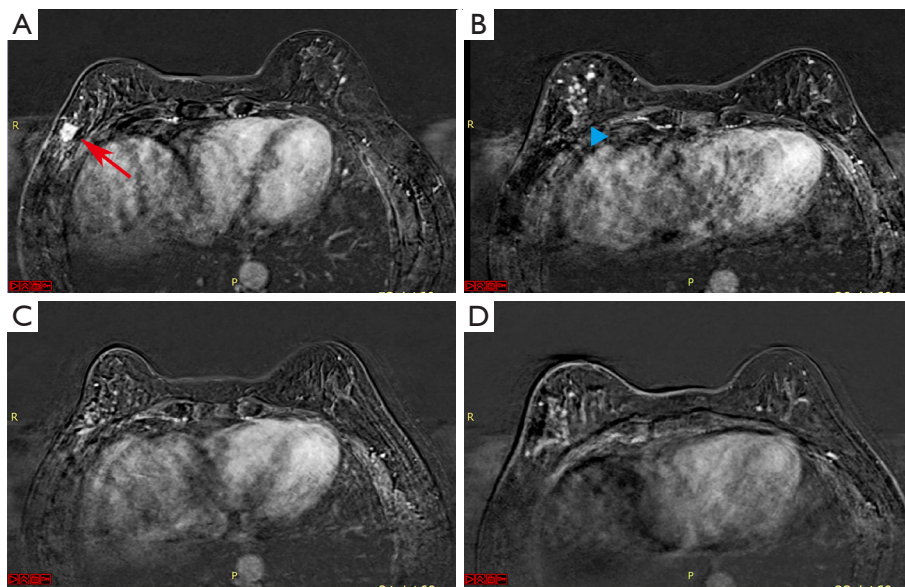


Figure 2 Contrast-enhanced subtracted MRI in a 51-year-old woman diagnosed with invasive ductal carcinoma before and after MWA. (A) The tumor (arrow) is clearly identified. (B) One week after MWA, the tumor is not enhanced, and the ablation zone (arrowhead) can be identified. 7 (C) and 14 months (D) after MWA, no enhancement is found. MRI, magnetic resonance imaging; MWA, microwave ablation.

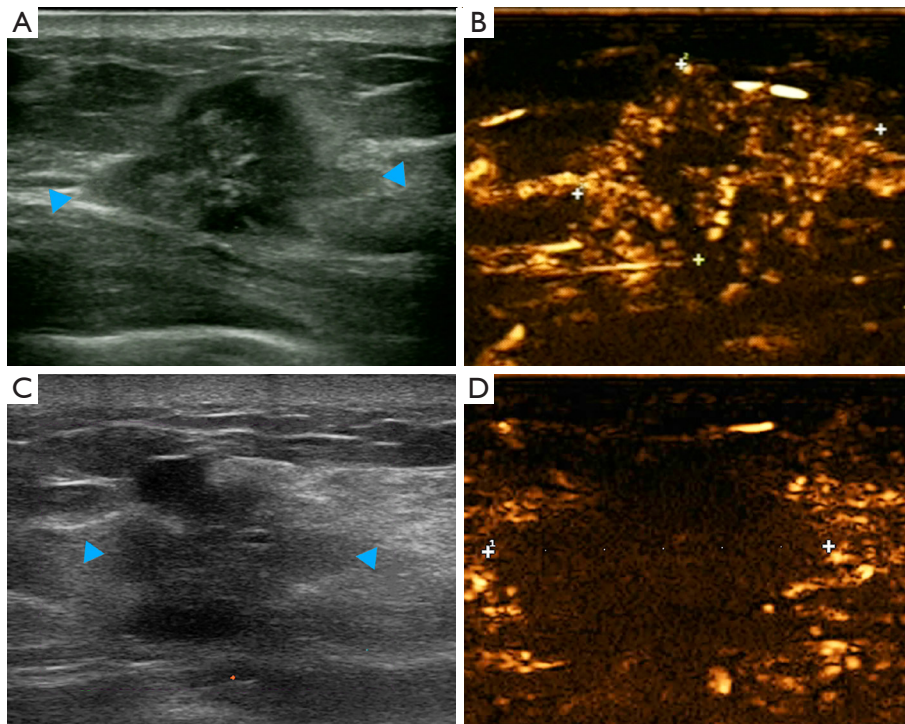


Figure 3 Conventional US and CEUS in an 83-year-old woman diagnosed with invasive ductal carcinoma before and 1 week after MWA. The tumor (arrowheads) is clearly identified (A) and enhanced in CEUS (B) before ablation. After MWA, the tumor (arrowheads) became deformed (C) and is not enhanced in CEUS (D). US, ultrasonography; CEUS contrast-enhanced US; MWA, microwave ablation.

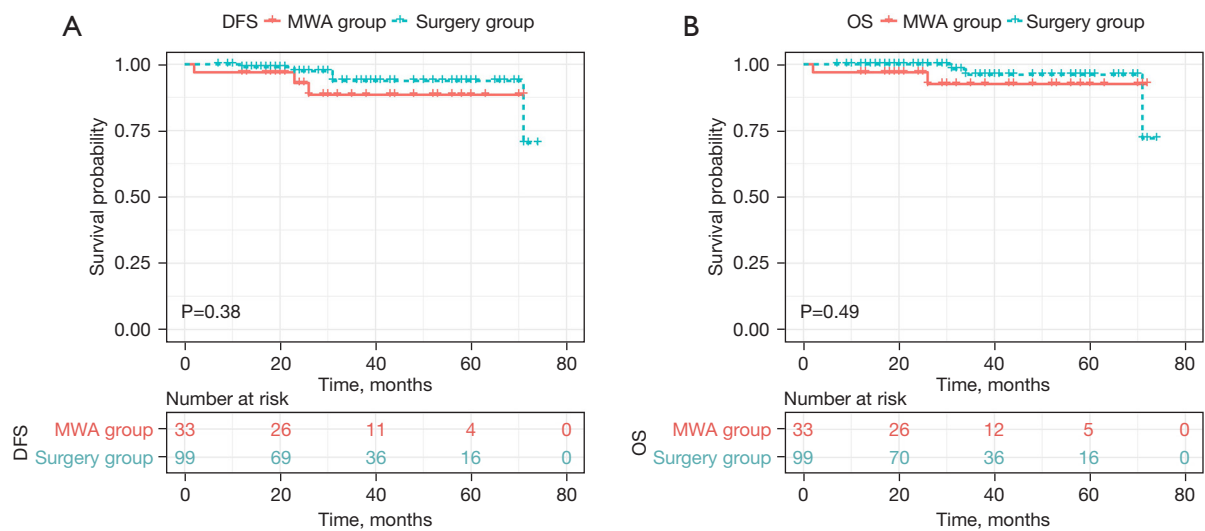


Figure 4 Kaplan-Meier curves for (A) DFS and (B) OS. DFS, disease-free survival; MWA, microwave ablation; OS, overall survival.

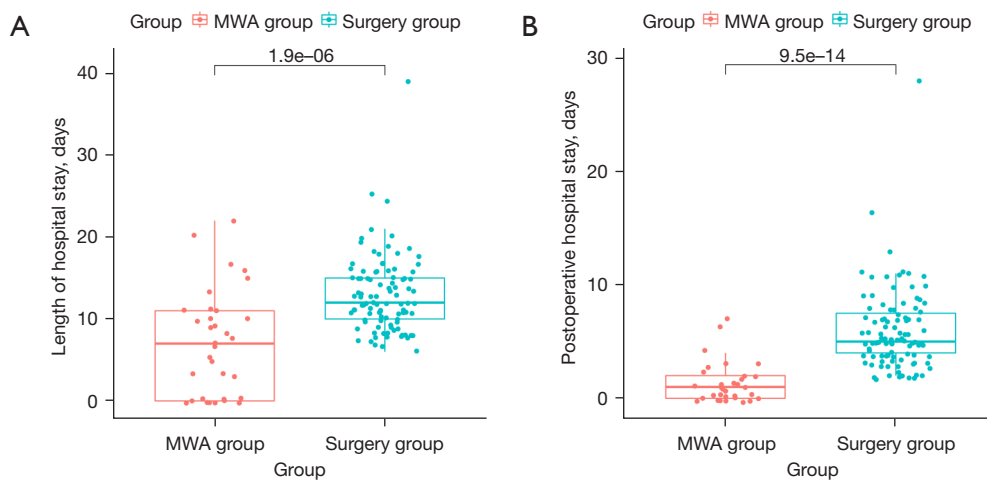


Figure 5 LOS (A) and post-operative LOS (B) for patients in the MWA group and standard surgery group. MWA, microwave ablation; LOS, length of hospital stay.

(1.3 versus 6.1 days, $P < 0.001$) (Figure 5).

Discussion

We firstly report follow-up outcomes of MWA combined with endocrine therapy in the treatment of HR-positive and HER2-negative invasive breast cancer with small lesions. We found that the local efficacy and survival of patients received MWA were not significantly different from patients receiving standard surgeries. Among 33 cases during follow-up, local recurrence was observed in only one case 23 months after MWA, which might be attributed

to endocrine therapy resistance. Our results suggested that MWA might be a reliable local therapy for elderly patients with breast cancer of small lesions. And MWA combined with adjuvant endocrine therapy may be a feasible treatment strategy for elderly patients with HR-positive and HER2-negative early-stage invasive breast cancer. In addition, MWA can be performed under local anesthesia, with less invasiveness, shorter operative time and hospitalization time compared with standard surgical approach. And it is of feasibility and safety to perform MWA on outpatient basis, resulting in potential cost savings and perhaps a higher quality of life.

For elderly patients, there is a trend to treat early-stage breast cancer with less aggressive therapies (4). However, local surgery cannot be omitted for elderly patients treated with adjuvant endocrine therapy (6,31). Minimally invasive therapies have been attempted to treat early breast cancer (14,15). MWA in the treatment of breast cancer has been reported in several feasibility studies (8,19), and a high rate of complete ablation has been found. Different from the margin status assessment of BCS (23), MRI and CEUS were applied to assess the ablation efficacy of MWA in the treatment of breast cancer in previous studies (11,14,15,32), which were effective and convenient approaches for follow-up after MWA. In the current study, we found excellent efficacy dependent on MRI or CEUS and favorable survival among patients receiving MWA with low risk of local recurrence.

Radiotherapy is also indispensable for local control after BCS, even for old patients at low risk of local recurrence (25), and sentinel node biopsy is the standard therapy for early breast cancer with a clinically negative axilla (33,34). Importantly, there is a trend to omit radiotherapy and SLNB for early breast cancer with very low risk of local-regional recurrence (24,25). In the current study, no patient received axillary lymph node surgery or radiotherapy in the MWA group. Moreover, no patient received chemotherapy in this study, even for patients with a high Ki67 index. Only one local recurrence was observed, and then radical mastectomy was performed on this patient, who was alive without any recurrence after surgery. For these elderly patients with HR-positive and HER2-negative breast cancer, minimally invasive thermal therapies such as MWA should be proposed to patients who have contraindication for surgery or who decline the surgical treatment even with comprehensive explanations.

Limitations

Several limitations existed in the current study. First, the current study was not a randomized study. Thus, propensity score matching analysis was performed to avoid potential selection bias and imbalance of clinical characteristics of patients in two groups. Second, the ablation efficacy after MWA was not evaluated by surgery. MRI or CEUS was applied to confirm the efficacy of MWA for all of the patients during follow-up, in which accumulative experience is needed in the judgment. Besides, follow-up was with imaging alone and hence microscopic tumor cannot be

excluded, albeit probably rare. Third, because of limited participating patients and follow-up, future randomized clinical trials with large sample size are needed to test this treatment strategy.

Conclusions

Of all patients enrolled, very few (one patient in the MWA group, and three in the surgery group) experienced recurrence or died within the observed time frame. MWA combined with adjuvant endocrine therapy and standard surgery combined with adjuvant therapies for elderly patients with breast cancer achieved similar outcomes. MWA of breast cancer of small lesions is efficient in elderly patients. MWA combined with adjuvant endocrine therapy may be a feasible treatment strategy for elderly patients with HR-positive and HER2-negative breast cancer, although future studies with long-term follow-up are still needed for adoption into everyday practice.

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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-23-33/rc>

Data Sharing Statement: Available at <https://gs.amegroups.com/article/view/10.21037/gS-23-33/dss>

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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-23-33/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. The study was conducted in accordance with Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of the First Affiliated Hospital with Nanjing Medical University (No. 2010-SR-003) and informed consent was taken from all individual participants.

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