



# Superselective arterial embolization with drug-loaded microspheres for the treatment of unresectable breast cancer

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**Background:** To investigate the short-term efficacy and safety of drug-eluting bead transcatheter arterial chemoembolization (DEB-TACE) using CalliSpheres<sup>®</sup> microspheres in the treatment of unresectable locally advanced breast cancer (LABC).

**Methods:** DEB-TACE using CSM was performed in 15 patients with LABC after failure of medical treatment. The efficacy was evaluated based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The postoperative adverse reactions and complications were analyzed. The changes of white blood cell (WBC) count, creatine kinase isoenzyme-MB (CK-MB), B-type natriuretic peptide (BNP), and carbohydrate antigen15-3 (CA15-3) before and after treatment were compared by using Wilcoxon signed-rank test.

**Results:** The surgeries were successful in all patients. The subjects were followed up for 2–60 months (median: 10 months). According to the mRECIST, no patient achieved complete remission (CR) 1, 3, and 5 months after surgery, and partial response (PR) was achieved in 9, 11, and 11 cases; also, there were 6, 4, and 2 stable disease (SD) cases, and 0, 0, and 2 progressive disease (PD) cases. The postoperative WBC count, CK-MB level, and BNP level were not significantly different from those before surgery, whereas the CA15-3 level significantly decreased. The main postoperative adverse reactions were pain, fever, and gastrointestinal reactions. No severe adverse reactions were observed.

**Conclusions:** DEB-TACE with CalliSpheres<sup>®</sup> microspheres is a safe and feasible treatment for LABC. However, more multi-center studies with larger sample sizes are still warranted.

**Keywords:** Locally advanced breast cancer (LABC); CalliSpheres<sup>®</sup> drug-loaded microspheres; safety; effectiveness; chemoembolization

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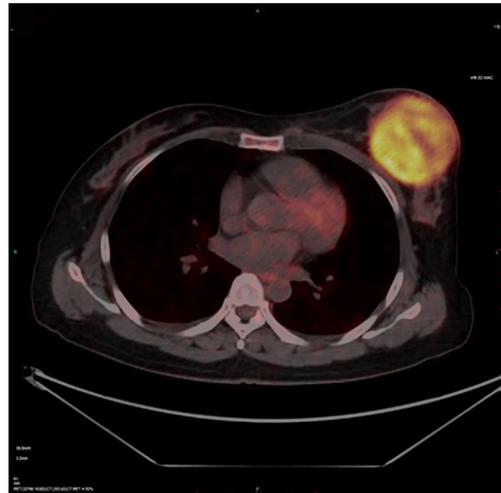
## Introduction

Breast cancer is the most common malignant tumor in Chinese women, with an incidence rate of 28.77 per 100,000 persons and a mortality rate of 6.35 per 100,000 persons (ranking first and second place, respectively, among malignancies in women). Locally advanced breast cancer (LABC) refers to bulky invasive breast tumors without distant metastasis that are difficult to resect. More than 90% of LABC cases are associated with regional lymph node

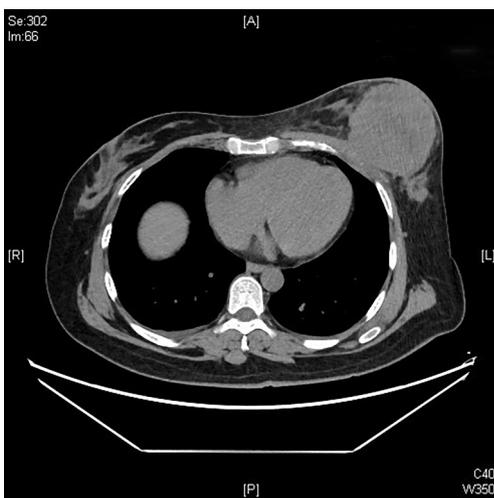
metastasis (1). LABC accounts for about 20–30% of new breast cancer cases in China. It is mainly treated with taxanes and anthracyclines, and the overall prognosis is poor (2). Transarterial chemoembolization with drug-eluting beads (DEB-TACEs) kills tumor cells via the slow release of chemotherapy drugs after embolization of the tumor area. Its efficacy and safety in treating liver cancer has been well demonstrated (3,4). CalliSpheres<sup>®</sup> microsphere is a domestic drug-loading embolization material. While its role in treating



**Figure 1** Case 1: before embolization.



**Figure 3** Case 1: PET-CT performed before embolization.



**Figure 2** Case 1: CT performed before embolization.



**Figure 4** Case 2: before embolization.

liver cancer has been widely described, its application in the treatment of LABC has rarely been reported. In this article, we summarized our recent experience in treating LABC with CalliSpheres® DEB-TACE.

## Methods

### General data

#### Patients

The clinical data of 15 clinically diagnosed LABC patients who had been treated with DEB-TACE in our center from March 2018 to March 2019 were retrospectively analyzed.

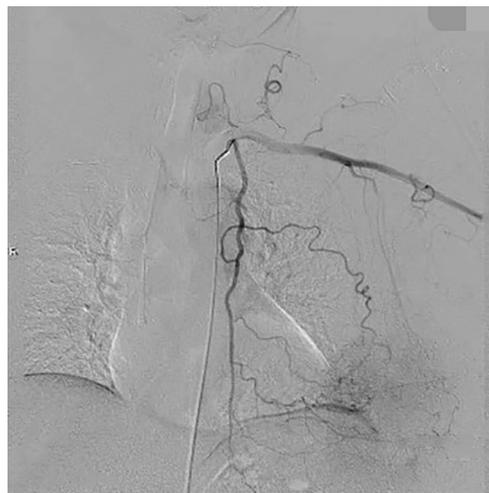
All the subjects were female patients aged 42–81 years (mean:  $60.8 \pm 2.3$  years). The subjects' tumors, located at either the left side ( $n=9$ ) or right side, were sized  $10.7 \pm 2.1$  cm  $\times$   $7.5 \pm 1.1$  cm  $\times$   $4.9 \pm 0.8$  cm (*Figures 1–4*). The tumors were pathologically confirmed as invasive ductal carcinomas, accompanied by axillary lymph node metastasis.

#### Inclusion and exclusion criteria

The inclusion criteria included the following: (I) pathologically confirmed as LABC; (II) unresectable primary lesion that was unresponsive to medical treatment; (III) with an Eastern Cooperative Oncology Group (ECOG)



**Figure 5** Case 1: feeding artery of breast cancer (a branch of subclavian artery).



**Figure 6** Case 1: feeding artery of breast cancer (a branch of the internal thoracic artery).

score of 0–2; and (IV) with a Child-Pugh class of A or B.

The exclusion criteria included the following: (I) cachexia and multiple organ failure; (II) with an expected survival of <3 months; (III) coagulation abnormalities that were difficult to correct; (IV) infection that was difficult to control; and (V) grade 3 or higher bone marrow suppression that was difficult to correct.

### Methodology

#### Equipment and consumables for interventional surgery

The Innova IGS 540 DSA system (GE, USA) was used. The CalliSpheres<sup>®</sup> beads were produced by Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China (production license: Jiangsu Food and Drug Administration Production License for Medical Device No. 20090041; product registration certificate number: National Registration Certificate No. 20153771072; and product standard label: TZB/National 4586-2013).

#### Loading of epirubicin hydrochloride in CalliSpheres<sup>®</sup> beads

After 40–80 mg of epirubicin hydrochloride was dissolved in 4 mL of water for injection or 5% glucose injection, the CalliSpheres<sup>®</sup> drug-loaded beads (100–300 μm) were drawn with a 20-mL syringe. The syringe was left standing for 3 minutes, and then the supernatant was discarded. The epirubicin hydrochloride solution was infused into the 20-mL syringe containing the CalliSpheres<sup>®</sup> beads by a 3-way

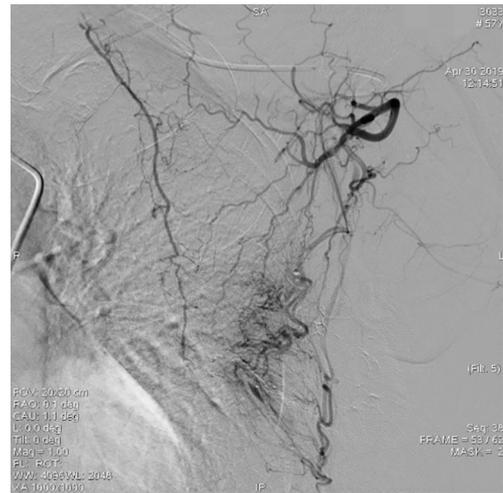
stopcock, and these two materials were well mixed by shaking the syringe. The above operation was repeated after the syringe was placed at rest for 5 minutes, and the total resting time was 30 minutes. Finally, a nonionic contrast agent was mixed with the prepared bead liquid in a ratio of 1:1.

#### Interventional surgical procedure

An intravenous analgesia pump was installed before surgery and was turned on after the patient arrived at the operating room. The bilateral groin areas were routinely disinfected and draped. The Seldinger technique was applied, during which the femoral artery was punctured with a 5 F catheter trocar (Radifocus, Terumo, Japan), and a 5 F Bern or Cobra2 catheter (Boston Scientific, USA) was placed in the internal thoracic artery and the iliac artery at the affected side. Digital subtraction angiography (DSA) was performed with a non-ionic contrast agent iodixanol (Suzhou Hengrui Biomedical Technology Co., Ltd.), with a flow rate of 3 mL/s, a total volume of 12 mL, and a pressure of 300 psi. After the feeding artery of the tumor was located, a 2.7 F torqueable microcatheter (Boston Scientific, USA) was superselected to the tumor-feeding artery and then subtracted, with a flow rate of 3 mL/s, a total volume of 9 mL, and a pressure of 150 psi. The CalliSpheres<sup>®</sup> microspheres loaded with epirubicin hydrochloride were injected to embolize the tumor-feeding artery through the microcatheter. The embolization was terminated when the blood flow in the tumor-feeding artery became stagnant or when vascular casts occurred (Figures 5–12).



**Figure 7** Case 1: after the branch of the subclavian artery was embolized.



**Figure 9** Case 2: feeding artery of breast cancer (a branch of the subclavian artery).



**Figure 8** After the branch of internal the thoracic artery was embolized.



**Figure 10** Case 2: feeding artery of breast cancer (a branch of the internal thoracic artery).

### Postoperative management

After the surgery, the changes in white blood cell (WBC) amount, CK-MB, and BNP were monitored. Analgesia, antiemetic, and symptomatic treatment were offered for 3–5 days; if necessary, antibiotics were used to treat secondary infections.

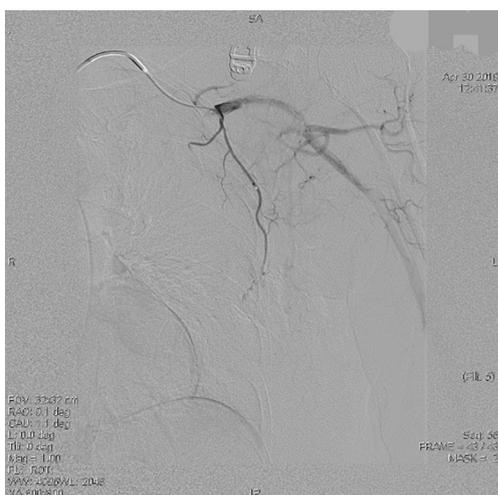
### Follow-up

The changes in CT or PET-CT findings and tumor markers (CA15-3) were compared before and after treatment. The treatment responses were classified as complete

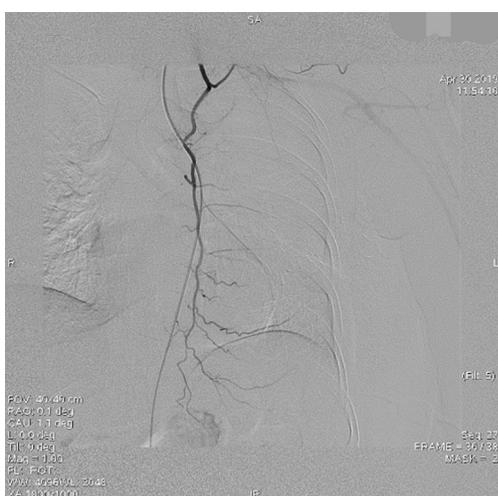
remission (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST), and the evaluation was performed 1, 3, and 5 days after surgery. The adverse reactions and complications that occurred during the treatment were recorded and treated.

### Statistical analysis

The statistical analysis was performed using the SPSS 19.0 software package. The changes of WBC count, and CK-



**Figure 11** Case 2: after the branch of the subclavian artery was embolized.



**Figure 12** Case 2: after the branch of the internal thoracic artery was embolized.

**Table 1** Outcomes of patients during the follow-up period (according to the mRECIST)

Outcome	1 month	3 months	5 months
CR	0	0	0
PR	9	11	11
SD	6	4	2
PD	0	0	2

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease.

MB, BNP, and CA15-3 levels before and after treatment were compared by using Wilcoxon signed-rank test. A P value of <0.05 was considered statistically significant.

## Results

CalliSpheres® DEB-TACE was successfully completed in all 15 patients (100%). The average hospital stay was 7.8 days. The follow-up lasted 2–16 months, and the median follow-up duration was 10 months. According to the mRECIST, no patient achieved CR; 9, 11, and 11 patients achieved PR 1, 3, and 5 months after surgery, respectively; the number of SD cases was 6, 4, and 2, and the number of PD cases was 0, 0, and 2 at the same respective time points (Table 1) (Figures 13–19). All patients survived during the follow-up period. The postoperative WBC count, CK-MB, and BNP were not significantly different from those before surgery, whereas CA15-3 level significantly decreased (Table 2). The main postoperative adverse reactions were pain, fever, and gastrointestinal reactions. All patients suffered from pain in the treatment area: the visual analog scale (VAS) score was 5 in 3 patients and greater than 7 in the remaining 12 patients. All patients experienced fever after surgery, which was moderate in 13 patients and transiently high in 2 patients. The postoperative gastrointestinal reactions were mild in 4 patients and severe in 1 patient. One patient died of heart failure 4 months after surgery.

## Discussion

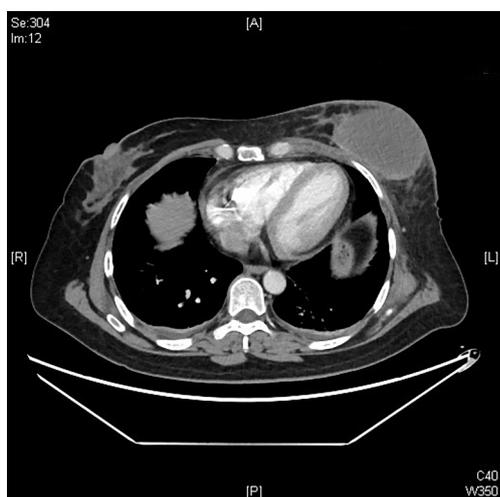
LABC is mainly treated with chemotherapy, endocrine therapy, and targeted therapy to curb the progression of this deadly disease. However, the average survival time is only 18–30 months (5) after treatment, and some patients are unable to adhere to the chemotherapy drugs due to the adverse reactions. In an animal study, compared with transarterial administration alone, the drug-loaded microspheres could embolize the tumor-feeding artery and locally offer a sustained and slow release of the chemotherapy drug; the local peak blood drug concentration was reached on day 3 and maintained for 7–14 days. The systemic blood concentration was reduced by 82% (6), which could effectively reduce the adverse reactions of drugs. Another study showed good safety and a high tumor response rate (7) in liver cancer patients. In recent years, articles on the treatment of liver metastases from breast cancer with DEB-TACE have been published (8,9); however, the application of DEB-TACE for LABC



**Figure 13** Case1: 1 month after embolization.



**Figure 15** Case 1: PET-CT performed 1 month after embolization.



**Figure 14** Case 1: CT performed 1 month after embolization.



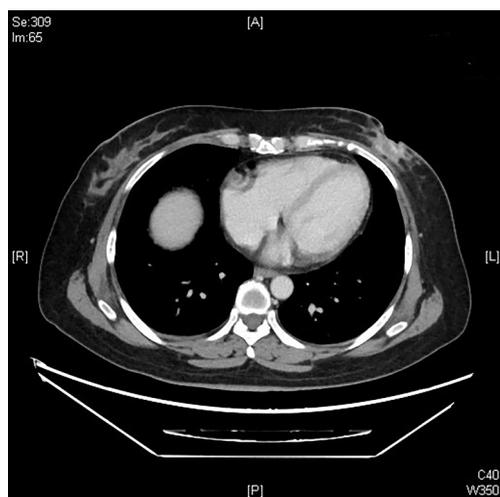
**Figure 16** Case 1: 5 months after embolization.

patients has not been described.

CalliSpheres<sup>®</sup> drug-loaded microsphere is a new made-in-China embolic material. With its main component being the negatively charged polyvinyl alcohol fibers with a diameter of 100–300  $\mu\text{m}$ , it has good compressibility and histocompatibility. The attraction between positive and negative charges can load positively charged antitumor drugs such as anthracyclines (epirubicin, pirarubicin, etc.). In our current series, 40–80 mg of epirubicin hydrochloride was loaded into 15 patients according to body surface area and age.

Special attention must be paid during the surgery.

(I) The tumor-feeding artery should be completely embolized whenever possible. The lesions of LABC are often large and diffuse, and over 90% of such lesions have regional lymph node metastasis (e.g., in the axillary area). Therefore, axillary angiography is often required in addition to the angiography of the internal thoracic artery and intercostal artery. (II) A 5F Bern catheter can be used. After the catheter is placed into the proximal side of the subclavian artery at the affected side, the catheter is inserted upwards (with the head down) and then can directly enter the internal thoracic artery at the affected side. (III) Microcatheters are used for superselective embolization,



**Figure 17** Case 1: CT performed 5 months after embolization.



**Figure 19** Case 2: 3 months after embolization.



**Figure 18** Case 2: 1 month after embolization.

so as to protect normal tissues as much as possible. (IV) For tumors larger than 5 cm, a one-attempt embolization procedure may lead to severe post-embolic syndrome (manifested as severe pain, fever, secondary infection, etc.); therefore, two embolization sessions may be considered to reduce postoperative adverse reactions.

All of our patients suffered from severe pain at the embolization area after surgery, with a VAS score of more than 7 points in most patients. Therefore, the preoperative installation of patient-controlled analgesia (PCA) pump is required. If necessary, an anesthesiologist can be invited to assist the analgesia. Postoperative fever is also common, mainly the absorption fever caused by tumor ischemia

**Table 2** Changes in laboratory indicators ( $\bar{x} \pm SD$ )

Markers	Before operation	3 days after surgery	3 weeks after surgery
WBC count ( $10^9/L$ )	6.6 $\pm$ 1.8	5.8 $\pm$ 1.1	5.0 $\pm$ 1.2
CK-MB (U/L)	10.3 $\pm$ 3.8	13.5 $\pm$ 4.6	14.2 $\pm$ 4.8
BNP (pg/mL)	43.1 $\pm$ 8.6	54.6 $\pm$ 9.9	49.1 $\pm$ 9.4
CA15-3 (U/mL)	77.4 $\pm$ 19.3	69.1 $\pm$ 14.3	35.2 $\pm$ 10.1*

\*,  $P < 0.05$ . WBC, white blood cell; CK-MB, creatine kinase isoenzyme-MB; BNP, B-type natriuretic peptide; CA15-3, carbohydrate antigen 15-3.

and necrosis. The body temperature should be closely observed if it is within 38.5 °C. If the body temperature rises after 3 days, along with continuous increase of the WBC count, antibiotic treatment may be considered. In some patients, tumor necrosis may cause local skin ulceration and exudation, which requires long-term dressing change. Postoperative gastrointestinal reactions are not uncommon. One of our patients experienced severe nausea and vomiting symptoms, which lasted for more than 1 week. After electrolyte imbalance was alleviated, treatment with metoclopramide and tropisetron hydrochloride failed. Luckily, these symptoms disappeared after aprepitant treatment. Epirubicin has been reported to be cardiotoxic, which may lead to myocardial injury and cardiac insufficiency. Fortunately, no chest pain, chest tightness, or abnormal CK-MB and BNP levels were observed in our series during the perioperative period, which might have

been due to the use of epirubicin tailored according to the patient's physical condition and age: patients aged 81 years and older were administered with 40 mg of epirubicin hydrochloride, whereas the remaining patients used a full dose (80 mg) of epirubicin hydrochloride. Of course, the absence of cardiotoxicity might also be explained by the small sample size of our current study. One patient in our series suffered from a large amount of pericardial and pleural effusions due to disease progression and died of cardiac failure 4 months after surgery, which was not necessarily related to the use of epirubicin hydrochloride. Several studies have also confirmed that DEB-TACE can reduce the incidences of postoperative adverse reactions and postoperative complications (10-12).

To summarize, our current study has demonstrated that CalliSpheres® DEB-TACE has definite short-term efficacy and is safe and feasible for the clinical treatment of LABC. It offers a new treatment option for patients who cannot be treated surgically. However, more multi-center studies with larger sample sizes are still warranted.

## Acknowledgments

None.

## Footnote

*Conflicts of Interest:* 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. All patients signed the informed consent forms concerning the use of all case data and figures. The study was approved by the Ethics Committee of our hospital.

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