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Combination of ^{125}I brachytherapy and chemotherapy for unresectable recurrent breast cancer

A retrospective control study

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Abstract

Recurrent breast cancer remains an incurable malignancy and cannot be removed by surgery in the majority of cases. This study aimed to explore the feasibility and efficacy of the combination of ^{125}I brachytherapy and chemotherapy for the treatment of unresectable recurrent breast cancer. Patients with unresectable recurrent breast cancer treated between January 2011 and December 2014 with a combination of ^{125}I brachytherapy and capecitabine or gemcitabine were evaluated and outcomes were compared with those of women treated with capecitabine or gemcitabine in conventional dose as a monotherapy. Of 61 patients evaluated, 28 received the combination treatment and 33 received capecitabine or gemcitabine monotherapy. The combination of ^{125}I brachytherapy and chemotherapy resulted in a significant improvement in progression-free survival versus capecitabine or gemcitabine monotherapy (median, 17.8 vs 11.4 months; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.23–0.84; P= 0.013). The objective response rate (ORR) was significantly higher with the combination (82.1%) than with monotherapy (54.5%; P= 0.022), and the rate of pain relief was higher in the combination arm (100% vs 73.6%; P=0.038). There was no significant improvement for overall survival (median, 30.1 vs 27.2 months; HR, 0.82; 95% CI, 0.47–1.44; P=0.496). There were no serious complications detected during the follow-up period, any grade toxicities were comparable between treatment arms. In conclusion, the combination of ^{125}I brachytherapy and second-line chemotherapy is superior to chemotherapy alone and is an effective and safe therapy for unresectable recurrent breast cancer. However, further investigation and much larger scale randomized controlled trials with long-term follow-up are needed.

Abbreviations: AEs = adverse events, CI = confidence interval, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.

Keywords: ^{125}I seed, brachytherapy, recurrent breast cancer, unresectable

1. Introduction

Breast cancer is the most common cancer in women worldwide. Although adjuvant treatment in breast cancer has made much progress, many women still develop tumor relapse. The retreatment of recurrent or metastatic breast cancer after the comprehensive treatment poses a great challenge to physicians. Compared with initial treatment of primary breast cancer, more uncertainties exist regarding the prognosis and salvage therapy of recurrent breast cancer. For metastatic or locally recurrent unresectable breast cancer, first-line treatments for metastatic disease with single-agent hormonal or chemotherapy regimens produce response rates between 20% and 40%.[1,2] In the second-line setting, response rates are only 10% to 20%. Salvage surgery plus radiotherapy followed by systemic chemotherapy could improve the progression-free survival (PFS) and overall survival (OS) for patients with local-regional recurrent breast cancer; however, in some patients recurrent tumor cannot be removed surgically. Besides, limited by radiation tolerance dose, external radiation therapy often cannot be used again. The combination of chemotherapy has demonstrated clinical benefits compared with single-agent regimens, but toxicity was also increased. Thus, the development of new treatment strategies is therefore essential for patients with unresectable recurrent breast cancer.

Currently, ^{125}I brachytherapy has emerged as newly developed local treatment for solid tumors. Because of its ability to offer high precision, little trauma, strong lethality, and fewer complications, ^{125}I brachytherapy has aroused more and more concerns of doctors, and it has been widely applied in clinical

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practice for tumor treatment, such as prostate carcinoma,[3] recurrent gastric cancer,[4] head and neck carcinoma,[5] and others,[6–9] and good curative effects were achieved. Combination of ^{125}I brachytherapy and chemotherapy was also applied to the treatment of locally recurrent lung cancer and pancreatic carcinoma.[10,11] When it comes to breast cancer, brachytherapy has been an important component of radiation therapy for early-stage breast cancer after lumpectomy and in combination with local excision as an alternative to mastectomy for treatment of local recurrences after conservative surgery and radiation therapy.[12] ^{125}I brachytherapy could decrease the local recurrence and may provide adequate local control and acceptable cosmesis in carefully selected patients. Therefore, we hypothesized that ^{125}I brachytherapy combined with second-line chemotherapy may be ideal for the treatment of unresectable recurrent breast cancer after first-line therapy. However, there is little research focus on the applications of ^{125}I brachytherapy for recurrent breast cancer, this combined therapy was uncommonly used and its efficacy and safety remain unclear.

In this study, we performed a systematic assessment on the feasibility and efficacy of the ^{125}I brachytherapy combined with chemotherapy for the treatment of unresectable recurrent breast cancer.

2. Methods

2.1. Patients

Patients with unresectable recurrent breast cancer treated between January 2011 and December 2014 with a combination of ^{125}I brachytherapy and capecitabine or gemcitabine were evaluated, and outcomes were compared with those of women treated with capecitabine or gemcitabine in conventional dose as a monotherapy. Patient inclusion criteria include eligible patients aged 18 years or older with histologically confirmed locally advanced or metastatic disease, and lesions were inoperable; prior surgery, chemotherapy and radiation were performed, hormone therapy or trastuzumab targeted therapy were allowed; and additional eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate bone marrow, liver, and renal function. Patients were excluded if patients had life expectancies of 3 months or less and if patients had active brain metastases, significant risk of major cardiovascular or bleeding events.

All the patients provided informed consent, which was approved by the Ethics Committee of The Affiliated Tumor Hospital of Guangxi Medical University, China. All clinical procedures were conducted in accordance with Good Clinical Practice Guidelines and any related municipal or federal regulations.

2.2. Treatment procedure and study design

This was a retrospective single-institution study. Patients who received a combination of ^{125}I brachytherapy and chemotherapy (capecitabine or gemcitabine) or chemotherapy alone as second-line therapy were divided into 2 groups, and comparative analysis was done. In the combination therapy group (experimental group), the patients received chemotherapy 3 days after ^{125}I seed implantation; in the monotherapy group (control group), the patients received capecitabine or gemcitabine as monotherapy. The dose of capecitabine in each group was 1000 mg/m^2, days 1 to 14, every 3 weeks, and gemcitabine was 1000 mg/m^2, days 1 and 8, every 3 weeks. Treatments were continuously conducted until patients experienced severe adverse events (AEs) (grade 5) or disease progression. Cancer lesions were evaluated by an independent review panel outside the participating institutes every 4 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST). AEs were graded according to the National Cancer Institute' Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

The primary end point was PFS, secondary end points included OS, objective response rate (ORR), pain relief, and safety.

2.3. Implantation of ^{125}I seeds

Radiotherapy treatment planning system (TPS) HGGR-2000 was provided by Zhuhai Hokai Medical Instruments Co., Ltd (Zhuhai, China). ^{125}I seeds and the ^{125}I seed implantation instrument were purchased from Ningbo Junan Pharmaceutical Technology Company (Ningbo, China). The ^{125}I radioactive seeds used in this study had a length of 4.5 mm and a diameter of 0.8 mm, had a half-life of 59.4 days with an average energy of 27.4 keV. Computerized tomography (CT) scans were taken to evaluate the gross tumor volume (GTV) of tumor before ^{125}I seed implantation, and the planning target volume (PTV) included GTV plus 0.5 to 1.0 cm peripheral tissue, acquired CT images were transferred to TPS for treatment plan design. ^{125}I seeds were implanted into the PTV via 18-ga needles and guided by ultrasound, spaced at intervals of 1.0 cm in a parallel array, and extending at least 0.5 to 1.0 cm beyond the margins of the lesions. The ideal position for radioactive seed implantation was determined based on preoperative TPS and tumor location. The initial dose rate was 7 cGy/h prescribed to 1 cm depth, and the prescription dose was 90 to 110 Gy. Based on the classical dosimetry calculating method cited by Memorial Sloan-Kettering Cancer Center, the seed number was determined by the length of 3 dimension axes, which is the distance from the seed to the target. The formula is the following: seed number = ([length + width + thickness/3] × 5)/(seed original activity). Postoperative CT examination was performed, and acquired CT images were then transferred to TPS for the dosimetry evaluation of implanted ^{125}I seeds, supplement implantation was performed if the tumor tissues were outside the scope of irradiation.

2.4. Evaluation of the short-term effects and follow-up

Assessment for tumor response was carried out 4 weeks after treatment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were reported according to RECIST. The ORR was the sum of CR and PR. Pain relief and AEs were also evaluated. AEs were graded according to the NCI-CTCAE, version 3.0 (Bethesda, MD, USA).

Follow-up was performed every 3 months after treatment. Follow-up consisted of physical examination, spiral computed tomography or ultrasonography, and serum biochemistry. All patients were followed up until the date of death or when censored at the latest date (March 30, 2016). OS was defined as the time from the date of treatment to death or when censored at the latest date if patients were still alive. PFS was defined as the length of time from the date of treatment to events such as local progression or the occurrence of a new primary tumor or death without evidence of cancer.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). For time-to-event end points, hazard

ratios (HRs) and 95% confidence intervals (CIs) were estimated with stratified Cox regression with treatment group as a single covariate. *P* values were generated from stratified log-rank tests. Median event-free times were estimated by the Kaplan–Meier method. Chi-square test was used to assess the difference in ORR, pain relief, and AEs between both groups. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients and treatment exposure

From January 2011 to December 2014, 61 patients with recurrence breast cancer were included in our study. The median follow-up period was 28 months, ranging from 6 to 60 months. Of 28 patients who received the combined therapy of ^{125}I brachytherapy and chemotherapy, the median age was 53 years (age range: 42–72 years). Eleven patients presented with chest wall recurrence and sternum metastasis, 13 patients have supraclavicular and neck lymph node metastasis, 4 patients have liver metastasis, and 17 patients with local pain. Nineteen patients received ^{125}I brachytherapy plus capecitabine therapy, and 9 patients received ^{125}I brachytherapy plus gemcitabine therapy. The number of implanted ^{125}I seeds in these patients ranged between 20 and 65, with a median number of 32. After brachytherapy, reimplantation of ^{125}I seeds were required in 3 patients.

Of 33 patients who received chemotherapy alone, the median age was 51 years (age range: 40–68 years). Sixteen patients had chest wall recurrence and sternum metastasis, 9 patients had supraclavicular and neck lymph node metastasis, 3 patients had liver metastasis, and 5 patients had lung and mediastinal lymph node metastasis. Fifteen patients had local pain. Twenty-three patients received capecitabine therapy, and 10 patients received gemcitabine therapy. The characteristics were well balanced between the treatment arms (Table 1).

Table 1

Patient and baseline tumor characteristics.

Characteristic	^{125}I brachytherapy + chemotherapy number of patients, %	Chemotherapy number of patients, %
Age, y		
Median	56.2	54.7
Range	46–69	48–64
ECOG status		
0	26 (92.9)	26 (78.8)
1	2 (7.1)	7 (21.2)
Histology		
Ductal	28 (100)	33 (100)
Other	0 (0.0)	0 (0.0)
Extent of disease		
Metastatic	22 (78.6)	27 (81.8)
Locally recurrent	6 (21.4)	6 (18.2)
Location of metastatic sites		
Nonvisceral	21 (75)	24 (72.7)
Visceral	7 (25)	9 (37.3)
Number of metastatic sites		
≤2	16 (57.1)	19 (57.6)
>2	12 (42.9)	14 (42.4)
Measurable disease		
Yes	28 (100)	33 (100)
No	0 (0.0)	0 (0.0)
Prior neoadjuvant/adjuvant chemotherapy		
Anthracycline	28 (100)	33 (100)
Taxane	20 (71.4)	28 (84.8)
Prior hormonal treatment		
Yes	17 (60.7)	22 (66.7)
No	11 (39.3)	11 (33.3)
Progression-free interval, mo		
≤12	10 (35.7)	19 (57.6)
>12	18 (64.3)	14 (42.4)
Suffering pain		
Yes	17 (60.7)	15 (45.5)
No	11 (39.3)	18 (54.5)

ECOG = Eastern Cooperative Oncology Group.

3.2. Tumor local control and pain relief

In the combination therapy group, 3 months after ^{125}I brachytherapy and chemotherapy, the ORR was 82.1% (23/28). The rates of CR, PR, SD, and PD in this cohort were 32.1% (9/28), 50.0% (14/28), 17.9% (5/28), and 0.0% (0/28), respectively. For the monotherapy group, the ORR was 54.5% (18/33). The rates of CR, PR, SD, and PD in this cohort were 12.1% (4/33), 42.4% (14/33), 36.4% (12/33), and 9.1% (3/33), respectively. The rate of overall response in combination group was higher than the monotherapy group, and the difference was significant ($P = 0.022$).

In the combination group, 60.7% (17/28) of patients were suffering pain before treatment, all patients were pain relief or remission after 2 weeks following ^{125}I seed implantation, the relief rate was 100%, and 82.4% (14/17) of patients achieved a good or medium response. In the monotherapy group, 45.5% (15/33) of patients were suffering pain before treatment. After treatment, the total effective rate was 73.3% (11/15), 53.3% (8/15) of patients achieved a good or medium response. Results show that the rate of pain relief was higher in the combination arm significantly (100% vs 73.3%; $P = 0.038$). Table 2 summarizes the tumor local control and pain relief results.

3.3. Patients' survival

The combination of ^{125}I brachytherapy and chemotherapy resulted in a statistically significant improvement in PFS compared with chemotherapy alone. The median PFS was 17.8 months (95% CI, 13.6–22.1) for the combination and 11.4 months (95% CI, 8.5–14.2) for chemotherapy alone, results achieved statistical significance (HR, 0.44; 95% CI, 0.23–0.84; $P = 0.013$; Fig. 1).

Interim survival data revealed that there was no significant difference for OS between the treatment arms. In combined therapy group, median OS was 30.1 months (95% CI, 24.5–37.7) versus 27.2 months (95% CI, 25.2–30.3) in the monotherapy group (HR, 0.82; 95% CI, 0.47–1.44; $P = 0.496$; Fig. 2).

3.4. Toxicity and complications

There were a few toxicity and complications, and no patients died during the perioperative period. The incidence of side effects was comparable between treatment arms, and these AEs were related to chemotherapy, no obvious side radiotherapeutic effect was observed aside from skin pigmentation that occurred in 3 patients. Table 3 summarizes AE rates occurring in 10% of patients for all grades and 2% for grades 3 to 4 in either treatment arm.

4. Discussion

Breast cancer is the most frequently diagnosed cancer and the second most common cause of cancer deaths in females

Table 2

Tumor local control and pain relief.

Variable	^{125}I brachytherapy + chemotherapy number of patients, %	Chemotherapy number of patients, %	*P* value
Response evaluation			
Overall response	23 (82.1)	18 (54.5)	0.022
Complete response	9 (32.1)	4 (12.1)	0.069
Partial response	14 (50.0)	14 (42.4)	0.554
Stable disease	5 (17.9)	12 (36.4)	0.108
Progressive disease	0 (0.0)	3 (9.1)	0.243
Pain relief			
Total effective rate	17 (100)	11 (73.3)	0.038
Good or medium response	14 (82.4)	8 (53.3)	0.128

worldwide. Breast cancer survival rates vary widely, optimistically heading toward a positive trend. Increased survival is due to the dramatic shift in the screening methods, early diagnosis, and breakthroughs in treatments. For early-stage disease, relapses are most common within the first 5 years after treatment. About 30% of breast cancer cases could appear recurrence or metastasis after surgery.[13,14] Uncontrolled recurrent breast cancer can cause many significant problems that can decrease the quality of life of patients and is the difficult problem for clinical treatment. Many recurrence tumor cannot be removed surgically, and radiotherapy and chemotherapy is the routine therapy for unresectable recurrent breast cancer. However, proposals to administer second radiotherapy treatment have been met with resistance and major concerns regarding side effects have limited the adoption of reirradiation.[15] Besides, the combination of chemotherapy has demonstrated clinical benefits compared with single-agent regimens, but toxicity was also increased.[16] Thus, the development of new treatment strategies is therefore essential for patients with unresectable recurrent breast cancer.

As a minimally invasive treatment technology, radioactive particles implantation has been successfully applied to the treatment of a variety of solid tumors, such as liver cancer, pancreatic cancer, non-small-cell lung cancer, prostate cancer, and others.[17–20] With low activity and short ray distance, radioactive particles increase the dose of irradiation on tumor tissue while minimizing relative exposure to the surrounding normal tissue, therefore significantly decreasing the incidence of the radiation damage. Currently, ^{125}I radioactive seeds are the most common radioactive particles used in clinics. Basic research indicated that ^{125}I seed continuous low-dose rate irradiation could inhibit cancer cells growth, change DNA methyltransferase expression patterns, and induce higher apoptotic rates of cancer cells.[21] Similar biological effects were found in pancreatic, gastric, and lung cancer cell lines.[22–24] The basic research provided evidence for clinical application of ^{125}I radioactive seeds. The available irradiation range of ^{125}I radioactive particles used in our study is 1.7 cm, and the average energy is 27 to 32 keV, so it is easy to protection, clinical application are safe. Besides, ^{125}I radioactive particles have a half-life of 59.6 days and can provide lasting radiation. ^{125}I brachytherapy was administered in a single fraction, the lesion being treated receives a high dose of radiation, with protracted cell-killing effect last for weeks or even months. Taken together, compared to the traditional external radiation therapy, ^{125}I brachytherapy has the following advantages: continuous and high dose of irradiation act directly on the tumor, thus enhance the cell-killing effect on cancer cells. Meanwhile, high conformality index reduces the radiation dose of the surrounding normal tissues, so few adverse reactions of radiation appear.

As previously mentioned, ^{125}I radioactive particles implantation is widely used in the treatment of tumor, especially in the treatment of local recurrent or metastatic solid tumors. In addition, most striking is the fact that ^{125}I radioactive particles implantation combined chemotherapy has been used in patients who cannot receive surgery or radiation therapy and has obtained good curative effect.[10] However, the role of ^{125}I brachytherapy combined chemotherapy in patients with recurrent breast cancer has been rarely reported. In the present study, we performed a retrospective analysis and investigated the clinical efficacy and related complications of ^{125}I brachytherapy combined chemotherapy in the treatment of locally recurrent breast cancer. Our results demonstrated that, compared to chemotherapy alone, ^{125}I brachytherapy in combination with chemotherapy achieved satisfactory efficacy and lack of complications associated with brachytherapy. For the combined therapy, the median PFS was 17.8 months, and the ORR was 82.1% after 3 months, PFS and ORR were significantly higher than those of the control group. Pain is one of the most common clinical symptoms of recurrence or metastasis breast cancer. All patients were pain relief or remission after 2 weeks following ^{125}I seed implantation in the combined group, the relief rate was 100%, while the total effective rate was 73.3% in the control group. Furthermore, no serious complication occurred in these patients at any follow-up time, indicating that ^{125}I brachytherapy combined with second-line chemotherapy is a safe and effective strategy for managing locally recurrent breast cancer.

OS as an end point in advanced breast cancer studies has been a topic of controversy among regulatory authorities and

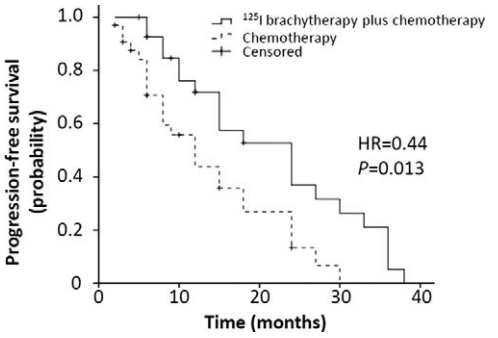

Figure 1. Kaplan–Meier analysis of the primary end point of progression-free survival.

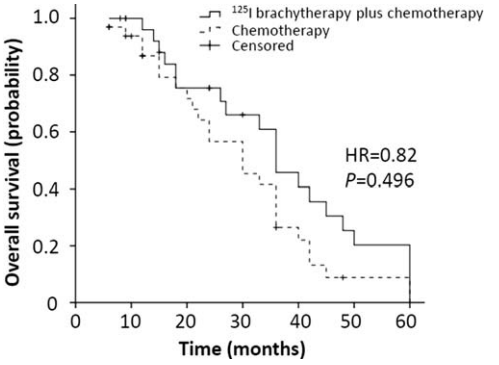

Figure 2. Kaplan–Meier analysis of the secondary end point of overall survival.

Table 3

Treatment-emergent AEs and hematologic toxicity reported in ≥10% of patients for any grade and ≥2% for grades 3 to 4 in the safety population.

	^{125}I brachytherapy + chemotherapy (n = 28)				Chemotherapy (n = 33)			
	Any grade		Grade 3 or 4		Any grade		Grade 3 or 4	
AE	n	%	n	%	n	%	n	%
Neutropenia	23	82.1	3	10.7	25	75.8	4	12.1
Leukopenia	26	92.9	3	10.7	25	75.8	3	9.1
Decreased appetite	18	64.3	4	14.3	22	66.7	2	6.1
Fatigue	13	46.4	1	3.6	13	39.4	0	0.0
Peripheral neuropathy	4	14.3	0	0.0	5	15.2	0	0.0
Vomiting	20	71.4	5	17.9	22	66.7	7	21.2
Dyspepsia	3	10.7	0	0.0	4	12.1	0	0.0
Nausea	15	53.6	2	7.1	18	54.5	2	6.1

AE = adverse event.

clinicians. In the present study, the improvements in PFS and ORR with the combination of ^{125}I brachytherapy and chemotherapy did not translate into prolonged OS. One possibility is that the patient's survival is relatively long in our study, and follow-up time may not be enough. Other possible explanations include the differences of postprogression treatments between groups may confound the OS outcome, statistical chance, or potential imbalances in baseline prognostic factors. Thus, to better define the impact of ^{125}I brachytherapy on OS benefit would probably need a longer follow-up time to observe, and a large clinical trial that possibly defines or controls for subsequent treatment regimens is required. Future studies should also analyze the possible toxicity that may influence the OS after therapies.

Based on our research and experience, compared with other solid tumors, the application value of radioactive particles in recurrent breast cancer is mainly manifested in the following aspects: first, ultrasound-guided particles implantation is safe, convenient, minimally invasive, and economic, and it is recommendable to all kinds of hospitals. Second, chest wall recurrence occurs most often postoperative, the scope of surgical resection again is often limited to a small amount of remaining tissue, and ^{125}I brachytherapy can achieve the same effect with the operation. Further, the incidence of cervical or axillary lymph node metastasis is high, these areas have important blood vessels and nerves, where an operation is risky, and serious radiation complications cannot be ignored if treated with conventional external beam radiotherapy. In these cases, ^{125}I brachytherapy is an effective, reliable, and selective therapeutic method.

Though ^{125}I brachytherapy is an effective and reliable therapeutic method, and there were no serious complications detected during the follow-up period in our study, the limitation of the ^{125}I brachytherapy should not be ignored. The limitations are as follows: the radioactive particles may break off or move through the tissue and result in uneven radiation dose; infection, pain, inflammation, or bleeding may occur in the implanting position, the adjacent skin may develop hyperpigmentation or ulcer. Therefore, the potential complications should be observed during treatment process.

A limitation of our study that cannot be ignored is that the sample size is rather small, further large-sale studies are needed to verify the potential of the combination of ^{125}I brachytherapy and second-line chemotherapy for treatment of locally recurrent breast cancer.

In conclusion, our results demonstrate that the combination of ^{125}I brachytherapy and second-line chemotherapy is superior to chemotherapy alone and is an effective and safe therapy for locally recurrent unresectable breast cancer, but further investigation and much larger scale randomized controlled trials with long-term follow-up are needed.

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