Efficacy of Hyperthermia in Treatment of Recurrent Metastatic Breast Cancer After Long-Term Chemotherapy: A Report of 2 Cases

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Case series

Patients: Female, 41-year-old • Female, 42-year-old
Final Diagnosis: Breast cancer
Symptoms: Breast mass
Medication: —
Clinical Procedure: Chemotherapy • hyperthermia • radiotherapy • surgery
Specialty: Oncology

Objective: Unusual clinical course

Background: Breast cancer has a long-term prognosis with various multimodality treatments. This report introduces the effectiveness of radiofrequency (RF) hyperthermia in the long-term treatment for recurrent/metastatic breast cancer.

Case Reports:

In the first case, the patient had bone and liver metastases during the course of chemotherapy, hormone therapy, and radiotherapy for 27 years after curative resection of breast cancer. Finally, she received RF hyperthermia alone for liver metastasis and showed a decrease in tumor markers and reduction in liver metastasis on computed tomography (CT). In the second case, the patient underwent curative resection for multiple occurrences on the left side of the breast. She received postoperative chemotherapy combined with hormone therapy but had metachronous local recurrences. She continued hormone therapy after 2 local recurrence resections; unfortunately, she had bone, liver, and lung metastases and pleural dissemination. Eventually, the patient received RF hyperthermia combined with oral chemotherapy. Her tumor markers decreased, and CT showed disappearance of lung metastasis and improved pleural dissemination. Furthermore, the reduction of chemotherapy adverse events due to hyperthermia allowed the patient to continue chemotherapy and improved her quality of life.

Conclusions: We present 2 cases in which RF hyperthermia had a positive effect despite the presence of a recurrent tumor after various types of surgery, chemotherapy, and radiotherapy. This report suggests that the addition of RF hyperthermia to conventional multidisciplinary therapies may enhance the therapeutic effect of these treatments and improve the quality of life in patients with recurrent breast cancer.

MeSH Keywords: Breast Neoplasms • Drug Therapy, Combination • Hyperthermia, Therapeutic

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Background

Breast cancer is the most common malignancy and the second leading cause of cancer-related death in women, after lung cancer. In the United States, 266,120 new diagnoses and 40,920 deaths due to breast cancer were predicted for 2018 [1]. Postoperative adjuvant treatment for breast cancer is administered in accordance with the recommendations of the National Comprehensive Cancer Network (NCCN) guidelines [2]. Adjuvant regional radiotherapy is recommended for appropriate patients, and the scope and dose of radiotherapy are determined by a radiation oncologist. Additional chemotherapy is administered after the surgery to complete a total of 6–8 cycles. All hormone receptor-positive patients receive endocrine therapy.

Several studies were conducted on preoperative chemotherapy and/or radiotherapy, surgical procedures, postoperative chemotherapy, and hormone therapy for advanced breast cancer [3–14]. Moreover, there are many studies and reports on chemotherapy and radiotherapy for recurrent/metastatic breast cancer [15–18]. Because breast cancer is relatively sensitive to chemotherapy and radiotherapy, long-term postoperative therapy is generally performed in units of 10 years. Currently, new drugs such as molecularly targeted drugs and immune checkpoint inhibitors are being actively developed [6,9,16,18]. However, chemotherapy options are exhausted as the prognosis is prolonged. Additionally, some patients have residual tumor despite the administration of all existing drugs, and some patients experience various adverse events and are unable to continue chemotherapy.

Hyperthermia is thought to be the fifth most common medical treatment after surgery, chemotherapy, radiotherapy, and biological therapy, and plays an important role in the comprehensive treatment of malignant tumors. Radiofrequency (RF) hyperthermia is usually applied as an adjunct to an already established treatment modality, and its treatment effect in breast cancer is well known [19–22].

Case Reports

Case 1

A 41-year-old woman who was diagnosed with right breast cancer in October 1993 underwent mastectomy with axillary lymph node dissection. The Union for International Cancer Control (UICC) TNM classification was stage II A (T2N0M0). Pathological findings included papillotubular adenocarcinoma, estrogen receptor (ER)- and progesterone receptor (Pgr)-positive, and human epithelial growth factor receptor type 2 (HER2)-negative. Figure 1 shows the clinical course after surgery and the notable trend of tumor markers since the appearance of another liver metastasis in October 2018 for this patient. She received oral tamoxifen (an anti-estrogen drug, 20 mg/body/day) therapy as postoperative adjuvant hormone therapy. Sixteen years and 10 months after surgery, computed tomography (CT) revealed a liver mass (Figure 2A) that was diagnosed as liver metastasis of breast cancer based on liver biopsy. Subsequently, the patient received hormone therapy with oral anastrozole (aromatase inhibitor, 1 mg/body/day). As chemotherapy, she received 4 courses of docetaxel hydrate+cyclophosphamide hydrate (TC; docetaxel hydrate, intravenous infusion of 75 mg/m² day 1; cyclophosphamide hydrate, intravenous infusion of 600 mg/m² day 1) every 3 weeks, followed by 4 courses of epirubicin hydrochloride+cyclophosphamide hydrate (EC; epirubicin hydrochloride, intravenous infusion of 60 mg/m² day 1; cyclophosphamide hydrate, intravenous infusion of 500 mg/m² day 1) every 3 weeks. Two years and 2 months after the appearance of liver metastasis, CT revealed a space-occupying lesion in segment 8 of the liver (Figure 2B), but 18F-fluorodeoxyglucose positron emission tomography (PET)/CT (18F-FDG PET/CT) revealed no abnormal accumulation at the same lesion, suggesting that the liver metastasis had lost viability (Figure 2C). However, 21 years and 2 months after surgery, 18F-FDG-PET/CT and magnetic resonance imaging (MRI) revealed bone metastasis in the 3rd lumbar vertebra (Figure 3A, 3B). As a result, she received intensity-modulated radiation therapy (39 Gy/13 Fr) with tomotherapy for the 3rd lumbar metastasis. Oral tamoxifen followed by oral anastrozole were administered as adjuvant hormone therapy. Twenty-five years after surgery, 18F-FDG-PET/CT showed no abnormal accumulation in the 3rd lumbar vertebra that underwent radiation therapy (Figure 3C). However, recurrence was found in the liver at a site that was different from the previous liver metastatic lesion (Figure 4A). Therefore, she was treated with a palbociclib (CDK4/6 inhibitor) as chemotherapy combined with hormone therapy using letrozole (aromatase inhibitors) every 4 weeks (oral palbociclib, 125 mg/body/day for 21 consecutive days followed by a 7-day rest; oral letrozole, 2.5 mg/body/day for 28 consecutive days). Two months later, the tumor marker CEA/CA15-3 level was elevated; therefore, the hormone therapy was changed to oral medroxyprogesterone acetate (progestin, 1200 mg/body/day), but the antitumor effect
Figure 1. Detailed clinical history and notable trend of tumor markers since October 2018 in Case 1. AI – aromatase inhibitor; EC – epirubicin hydrochloride+cyclophosphamide hydrate; EM – eribulin mesylate; MA – medroxyprogesterone acetate; Rad – radiation therapy; RF-HT – radiofrequency hyperthermia; TAM – tamoxifen; TC – docetaxel hydrate+cyclophosphamide hydrate; CEA – carcinoembryonic antigen (<5.0 ng/mL); CA15-3 – cancer antigen 15-3 (<25 U/mL).

Figure 2. Changes in liver metastasis on enhanced computed tomography (E-CT) and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) imaging. Liver metastasis (white arrowhead) found on E-CT 16 years and 10 months after surgery (A) were recognized as space-occupying lesions (white arrowhead) on E-CT 2 years later (B). 18F-FDG PET/CT showed no abnormal accumulation (white arrowhead) in that area (C).
Figure 3. Changes in bone metastasis on $^{18}$F-FDG-PET/CT imaging, magnetic resonance imaging (MRI), and bone scintigraphy. $^{18}$F-FDG-PET/CT (A) and MRI (B) revealed bone metastasis in the 3rd lumbar vertebra (white arrowhead) in December 2014. Three years and 10 months later, $^{18}$F-FDG-PET/CT (C) showed no abnormal accumulation in the 3rd lumbar vertebra (white arrowhead). Bone scintigraphy in June 2019 showed no abnormal accumulation in the 3rd lumbar vertebra and no other bone metastases (D).
was poor. One month later, the patient received eribulin mesylate (intravenous infusion of 1.4mg/m^2 days 1 and 8) every 3 weeks as chemotherapy because of a continued increase in tumor marker levels. Administration of eribulin mesylate for 8 months showed some decrease in tumor markers, but no reduction in liver metastasis (Figure 4B). Bone scintigraphy in June 2019 showed no apparent abnormal accumulation in the 3rd lumbar vertebra (Figure 3D), and no further bone metastases were observed thereafter. In November 2019, the patient refused to continue chemotherapy because there was no decline in tumor marker levels and owing to continued adverse events such as weakness, fatigue, and hair loss. Subsequently, she requested RF hyperthermia. RF hyperthermia was performed once a week with 40-min irradiation with 8-MHz RF capacitive heating equipment (Thermotron RF-8; Yamamoto Vinita Co., Ltd., Japan). The output was increased until complications such as pain occurred, following which output was decreased and subsequently increased when pain subsided. The patient underwent 30 cycles of RF hyperthermia without noticeable adverse events, and a CT scan revealed reduction of liver metastasis (Figure 4C). Tumor markers gradually decreased after the initiation of RF hyperthermia and remained low. THEREAFTER, she had no evidence of tumor metastasis or recurrence.

Case 2

A 42-year-old woman who was diagnosed with left breast cancer in July 2007 underwent quadrantectomy with axillary lymph node dissection. Figure 5 shows the postoperative clinical course and notable trend of tumor markers of the patient since the appearance of lung metastasis and pleural dissemination in January 2019 for this patient. The stage of UICC TNM classification was stage IIB (T2N1M0), and ER, PgR, and HER2 were highly positive, moderately positive, and negative, respectively (Figure 6A, preoperative CT image). Since histopathologically the surgical margin was positive, a modified radical mastectomy was performed as an additional operation. Histopathological examination revealed 4 isolated tumors in the additionally excised specimen. The final pathological diagnosis was scirrhous carcinoma and papillotubular adenocarcinoma of the breast. As postoperative chemotherapy, she received 6 courses of EC (epirubicin hydrochloride, intravenous infusion of 60 mg/m^2 day 1; cyclophosphamide hydrate, intravenous infusion of 500 mg/m^2 day 1) every 3 weeks followed by 2 courses of paclitaxel (PTX, intravenous infusion of 80 mg/m^2 days 1, 8, and 15) every 4 weeks until February 2008. Simultaneously, oral tamoxifen was administered as an adjuvant hormone therapy, followed by oral anastrozole. However, local recurrences of the chest wall were observed twice: 3 years and 8 months and 4 years and 4 months after the first surgery (Figure 6B, 6C). Therefore, the recurrent lesions were resected; thereafter, she received anastrozole hormone therapy postoperatively. Six years and 9 months after the first surgery, CT (Figure 7A) revealed liver metastasis (segment 6); therefore, she was treated with fulvestrant (a 17β-estradiol analog, intramuscular administration of 500 mg/body days 1, 15, and 29, and every 28 days thereafter). Six months later, CT revealed bilateral multiple lung metastases in addition to enlarged liver metastasis (Figure 7B), and bone scintigraphy showed hyperaccumulation image in the right 6th rib (Figure 7C), which

Figure 4. Changes in newly developed liver metastasis on E-CT imaging. Twenty-five years after surgery, E-CT (A) revealed newly developed liver metastasis (white arrowhead). E-CT after administration of eribulin mesylate for 8 months showed no reduction in liver metastasis (B). E-CT images after receiving 30 cycles of RF hyperthermia (C) (white arrowheads) showed liver metastasis that gradually reduced.
Figure 5. Detailed clinical history and the notable trend of tumor markers since January 2019 in Case 2. AI – aromatase inhibitor; Bv – bevacizumab; EC – epirubicin hydrochloride+cyclophosphamide hydrate; EM – eribulin mesylate; FUL – fulvestrant; GEM – gemcitabine; PTX – paclitaxel; RF-HT – radiofrequency hyperthermia; TAM – tamoxifen; XC – capecitabine+cyclophosphamide hydrate; CEA – carcinoembryonic antigen (<5.0 ng/mL); CA15-3 – cancer antigen 15-3 (<25 U/mL).

Figure 6. Primary breast cancer and recurrent lesions on E-CT imaging. E-CT on July 2007 (A) showed the primary breast cancer (white arrowhead). E-CT at 3 years and 8 months (B) and 4 years and 4 months (C) after the first surgery revealed the recurrent lesions (white arrowheads) in the left chest wall.
was diagnosed as bone metastasis. For these multiple metastases, the anticancer treatment was switched to oral S-1 (an oral 5-fluorouracil prodrug) chemotherapy (twice daily at a dose of 100 mg/body/day for 28 consecutive days followed by a 14-day rest). Two years and one month after switching the chemotherapy to oral S-1, CT revealed the disappearance of liver and lung metastases (Figure 7D), and bone scintigraphy showed no abnormal accumulation of bone metastasis (Figure 7E). Although CT showed no new liver or lung metastases 6 months after becoming disease free, she was diagnosed with left pleural dissemination because left pleural thickening and pleural effusion were observed (Figure 8A). Subsequently, her chemotherapy had been changed from oral S-1 to eribulin mesylate (intravenous infusion of 1.4 mg/m² days 1 and 8) every 3 weeks. Five months later, CT revealed disappearance of left pleural effusion and pleural thickening (Figure 8B), and no new metastatic lesions; hence, chemotherapy with eribulin mesylate was continued for 20 months.

Figure 7. Changes in liver metastasis on E-CT and bone metastasis on bone scintigraphy. E-CT 6 years and 9 months after the first surgery (A) revealed liver metastasis (white arrowhead). Six months later, E-CT (B) showed the enlargement of liver metastasis (white arrowhead), and bone scintigraphy (C) showed bone metastasis in right 6th rib (black arrow). After 2 years and one month with oral S-1 chemotherapy, both liver and bone metastases disappeared on CT (D) and bone scintigraphy (E).
One year and 3 months after becoming disease-free for the second time, CT revealed left pleural effusion again and a nodular shadow in the lingular division of the left lung (Figure 8C). Chemotherapy was changed to PTX (intravenous infusion of 90 mg/m² days 1, 8, and 15) and bevacizumab (vascular endothelial growth factor, intravenous infusion of 10 mg/kg days 1 and 15) every 4 weeks. After 6 courses of PTX + bevacizumab chemotherapy, CT showed increase in left pleural effusion, enlargement of the nodular shadow in the lingular division of the left lung, and thickening of the left visceral pleura on a contrast-enhanced image (Figure 8D). Based on these CT findings, she was diagnosed with recurrent pleural dissemination.

The subsequent chemotherapy was changed to gemcitabine (GEM, intravenous infusion of 1250 mg/m² days 1 and 8) every 3 weeks, but she was unable to continue GEM chemotherapy for even a single course because of adverse events, including severe poor appetite and malaise. Two months later, her chemotherapy was changed to combined oral capecitabine (a prodrug that is metabolized to 5-fluorouracil) and cyclophosphamide hydrate (XC; capecitabine 1800 mg/body/day for 14 consecutive days followed by a 7-day rest; cyclophosphamide hydrate, 100 mg/body/day for 14 consecutive days followed by a 7-day rest). RF hyperthermia (once a week with 40 min irradiation with 8 MHz RF capacitive heating equipment) was...
started simultaneously. The output was increased until complications such as pain occurred, after which the output was decreased and subsequently increased when pain subsided. CT performed after receiving 25 cycles of RF hyperthermia without noticeable adverse events revealed disappearance of lung metastasis and decrease in pleural effusion (Figure 8E). CEA and CA15-3 gradually decreased after the initiation of RF hyperthermia and XC chemotherapy, and these tumor markers remained low after RF hyperthermia. Thereafter, she had no evidence of tumor metastasis or recurrence.

**Discussion**

Hyperthermia exploits the heat sensitivity of cancer cells by exposing the body to temperatures of 42°C or higher. Although cancer cells may not die outright because of hyperthermia, they may become more susceptible to radiotherapy or to certain chemotherapy drugs, which may allow such therapy to be administered in reduced doses [23]. Hyperthermia is usually added to radiotherapy, chemotherapy, or chemoradiotherapy, and recently to gene therapy and immunotherapy. Recent studies have demonstrated the efficacy of hyperthermia in treating breast cancer [24–26]. Furthermore, some reports have demonstrated the efficacy of RF hyperthermia for advanced cancer concomitant with chemotherapy and chemoradiotherapy [27,28]. Similarly, we applied 8 MHz RF hyperthermia equipment introduced in our hospital in October 2019 in combination with chemotherapy, and the patients received the combination therapy without major adverse events.

Many postoperative patients with recurrent breast cancer have received numerous other treatments, including radiotherapy and chemotherapy. These prior treatments increase the risk of adverse events and lead to treatment resistance in cancer cells [29]. Previously, hyperthermia was shown to improve tumor control by sensitizing cancer stem-like cells to radiation [30–33]. In their meta-analysis of recurrent breast cancer patients treated with hyperthermia and radiotherapy, Datta et al. reported that the complete response rate was 66% for patients who were previously irradiated [34]. Moreover, recent reports demonstrated that modulation of oxidative stress is exploited for therapeutic benefits [35]. Increase in oxidative stress in the tumor and its microenvironment significantly enhances hyperthermia-induced apoptosis, and oxidative stress plays a key role in cell signaling pathways, including immune pathways in anticancer therapy [36]. Regarding the immune response by hyperthermia, there are interesting reviews that locally heating tumors with hyperthermia can elicit antitumor immune responses by enabling tumor cells to stimulate the immune system through increased surface expression of MHC class I chain-related gene A (MICA) or MHC class I and release of heat shock proteins and/or exosomes. In addition, this review concluded that antitumor immune responses can be induced by directly activating intra-tumoral immune cells such as natural killer cells, CD8+ T cells, and dendritic cells [37]. These reports suggest that hyperthermia enhances susceptibility to anticancer treatments by stimulating the immune system of cancer patients.

In this report, we described 2 cases in which hyperthermia demonstrated a certain effect, although the patients continued to have cancer despite various types of surgery, chemotherapy, and radiotherapy. In the first case, the patient had bone metastasis and liver metastasis during postoperative chemotherapy, hormone therapy, and radiotherapy for 27 years after curative resection of breast cancer. Eventually, she could not tolerate the multiple adverse events from chemotheraphy and ended up receiving hyperthermia. She received RF hyperthermia alone, which showed a reduction in tumor markers and liver metastasis on CT image. In the second case, the patient underwent curative resection for a special form of breast cancer with multiple recurrences. She received several kinds of chemotherapy combined with hormone therapy, but had 2 metachronous local recurrences and multiple metastases. Eventually, she received RF hyperthermia combined with chemotherapy for the last remaining lung metastasis and pleural dissemination. At present, her tumor markers continue to decline, and CT revealed disappearance of lung metastasis and improved pleural dissemination. Although she had adverse events, including anorexia, malaise, and loss of motivation due to chemotherapy, after receiving RF hyperthermia, her appetite recovered and her range of activities and ambition increased. Thus, her quality of life was significantly improved by RF hyperthermia combined with chemotherapy.

**Conclusions**

In conclusion, breast cancer can persist for a long time despite multimodality treatments such as surgery, chemotherapy, and radiotherapy. However, the longer the treatment, the more limited the treatment method. This report suggests that the addition of RF hyperthermia to conventional multidisciplinary therapies can enhance the therapeutic effect of these treatments and lead to new therapeutic strategies. Moreover, hyperthermia combined with chemotherapy plays an important role in improving the treatment efficacy of antitumor drugs and quality of life in patients with recurrent breast cancer.

**Department and Institution where work was done**

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