American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e926647
DOI: 10.12659/AJCR.926647

Received: 2020.06.07
Accepted: 2020.09.17
Available online: 2020.09.24
Published: 2020.11.03

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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Hirozumi Sawai
ABCD 1 Masaaki Kurimoto
BCD 2 Yuka Suzuki
BCD 2 Yoshimi Yamaguchi
BCD 2 Akemi Murata
BCD 2 Enami Suganuma
ABCD 2 Kazuya Yamamoto
BCDF 1 Hiromasa Kuzuya
BCDF 1 Shuhei Ueno
ABCF 1 Shuji Koide
BCDF 1 Hajime Koide
ABCF 1 Atsushi Kamiya

1 Department of Surgery, Narita Memorial Hospital, Toyohashi, Aichi, Japan
2 Department of Medical Technique (Radiological Technology), Narita Memorial Hospital, Toyohashi, Aichi, Japan

Corresponding Author: Hirozumi Sawai, e-mail: sawai@meiyokai.or.jp
Conflict of interest: None declared

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

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926647

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

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].

Here, we report 2 cases in which RF hyperthermia was administered after multimodality treatments, including surgery, chemotherapy, and radiotherapy, because of recurrent and progressive metastatic breast cancer. The first patient underwent RF hyperthermia alone as she was unable to continue chemotherapy owing to severe adverse events 27 years after surgery. The second patient received RF hyperthermia combined with oral chemotherapy as the tenth regimen after surgery.

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 IIA (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/m^2 day 1; cyclophosphamide hydrate, intravenous infusion of 600 mg/m^2 day 1) every 3 weeks, followed by 4 courses of epirubicin hydrochloride+cyclophosphamide hydrate (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. 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 ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-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, ^{18}F-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, ^{18}F-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

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

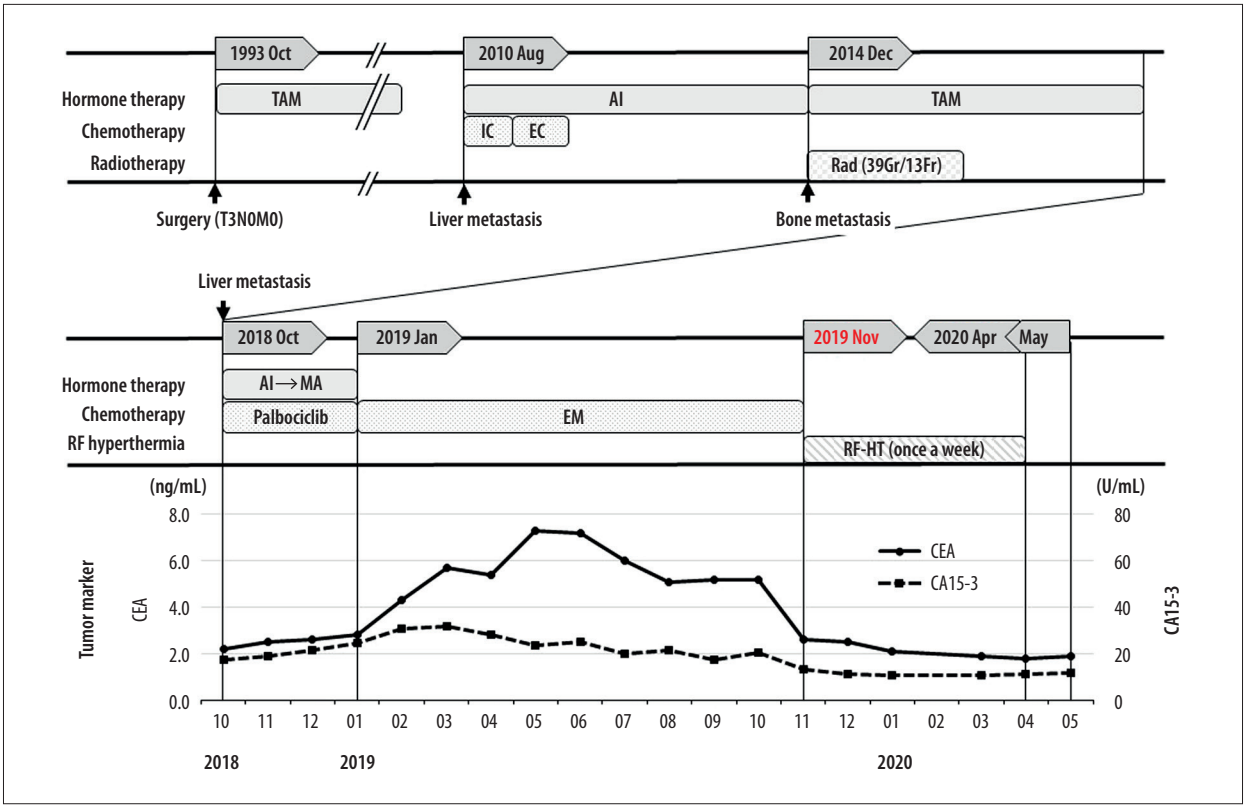

Figure 1. Detailed clinical history and notable trend of tumor markers since October 2018 in Case 1. AI – aromatase inhibitor; EC – epirubicin hydrochloride+cyclophosphamide hydrate; EM – eribulin mesylate; MA – medroxyprogesterone acetate; Rad – radiation therapy; RF-HT – radiofrequency hyperthermia; TAM – tamoxifen; TC – docetaxel hydrate+cyclophosphamide hydrate; CEA – carcinoembryonic antigen (<5.0 ng/mL); CA15-3 – cancer antigen 15-3 (<25 U/mL).

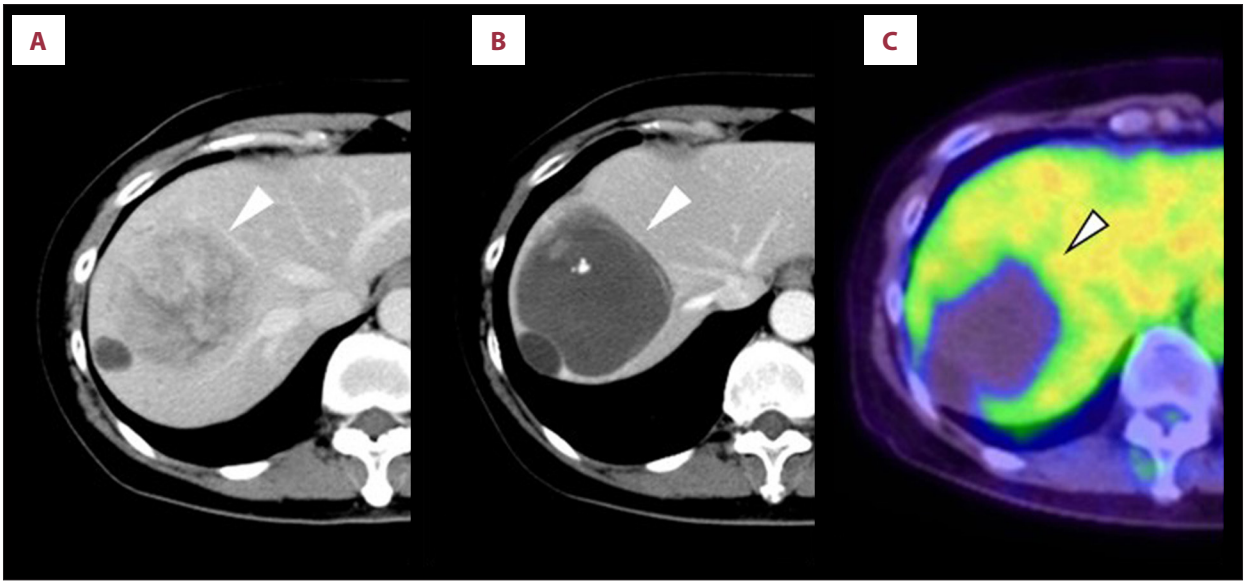

Figure 2. Changes in liver metastasis on enhanced computed tomography (E-CT) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging. Liver metastasis (white arrowhead) found on E-CT 16 years and 10 months after surgery (**A**) were recognized as space-occupying lesions (white arrowhead) on E-CT 2 years later (**B**). ^{18}F-FDG PET/CT showed no abnormal accumulation (white arrowhead) in that area (**C**).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

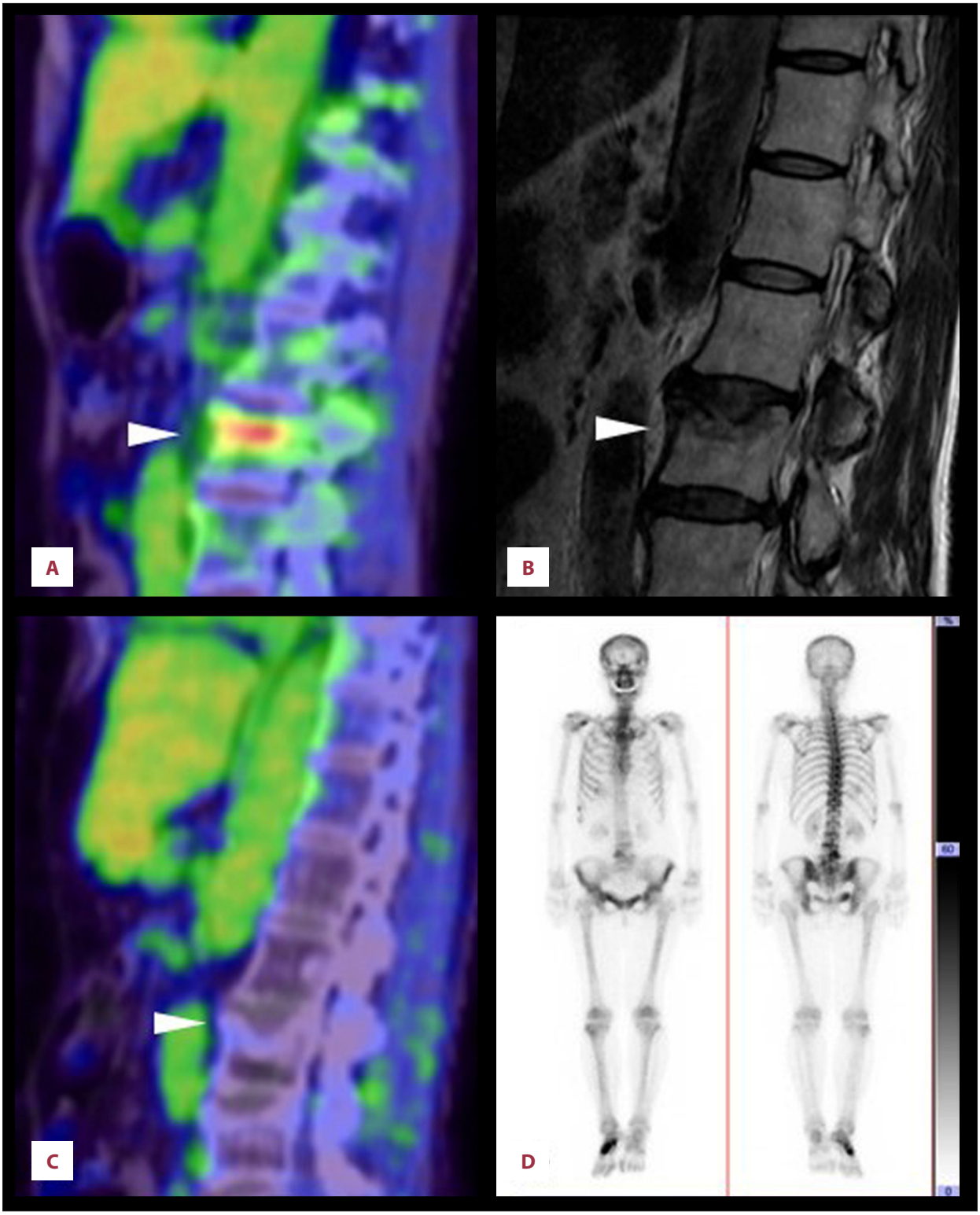

Figure 3. Changes in bone metastasis on ^{18}F-FDG-PET/CT imaging, magnetic resonance imaging (MRI), and bone scintigraphy. ^{18}F-FDG-PET/CT (**A**) and MRI (**B**) revealed bone metastasis in the 3rd lumbar vertebra (white arrowhead) in December 2014. Three years and 10 months later, ^{18}F-FDG-PET/CT (**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**).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

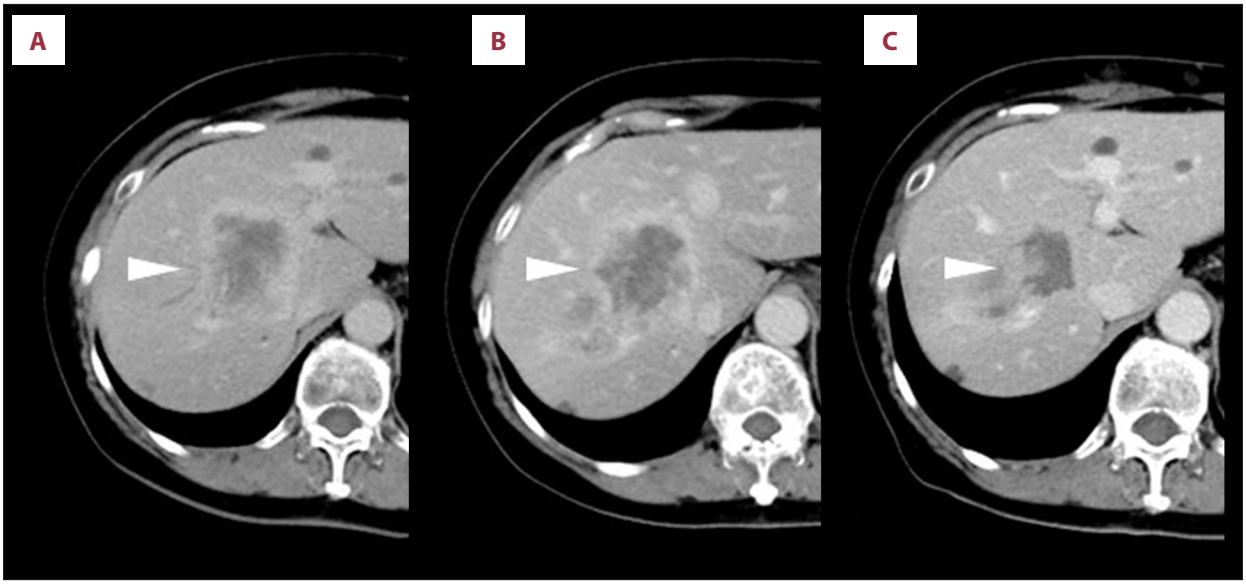

Figure 4. Changes in newly developed liver metastasis on E-CT imaging. Twenty-five years after surgery, E-CT (**A**) revealed newly developed liver metastasis (white arrowhead). E-CT after administration of eribulin mesylate for 8 months showed no reduction in liver metastasis (**B**). E-CT images after receiving 30 cycles of RF hyperthermia (**C**) (white arrowheads) showed liver metastasis that gradually reduced.

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

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

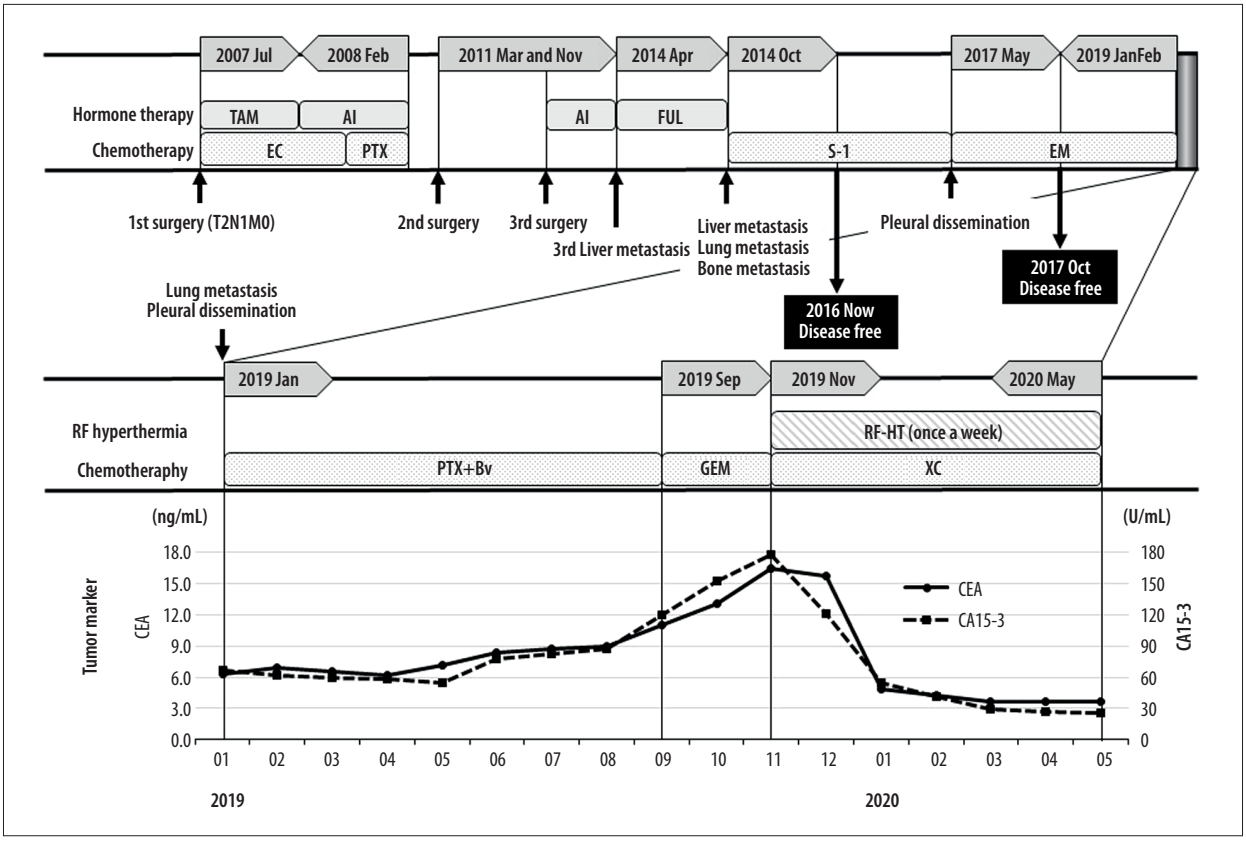

Figure 5. Detailed clinical history and the notable trend of tumor markers since January 2019 in Case 2. AI – aromatase inhibitor; Bv – bevacizumab; EC – epirubicin hydrochloride+cyclophosphamide hydrate; EM – eribulin mesylate; FUL – fulvestrant; GEM – gemcitabine; PTX – paclitaxel; RF-HT – radiofrequency hyperthermia; TAM – tamoxifen; XC – capecitabine+cyclophosphamide hydrate; CEA – carcinoembryonic antigen (<5.0 ng/mL); CA15-3 – cancer antigen 15-3 (<25 U/mL).

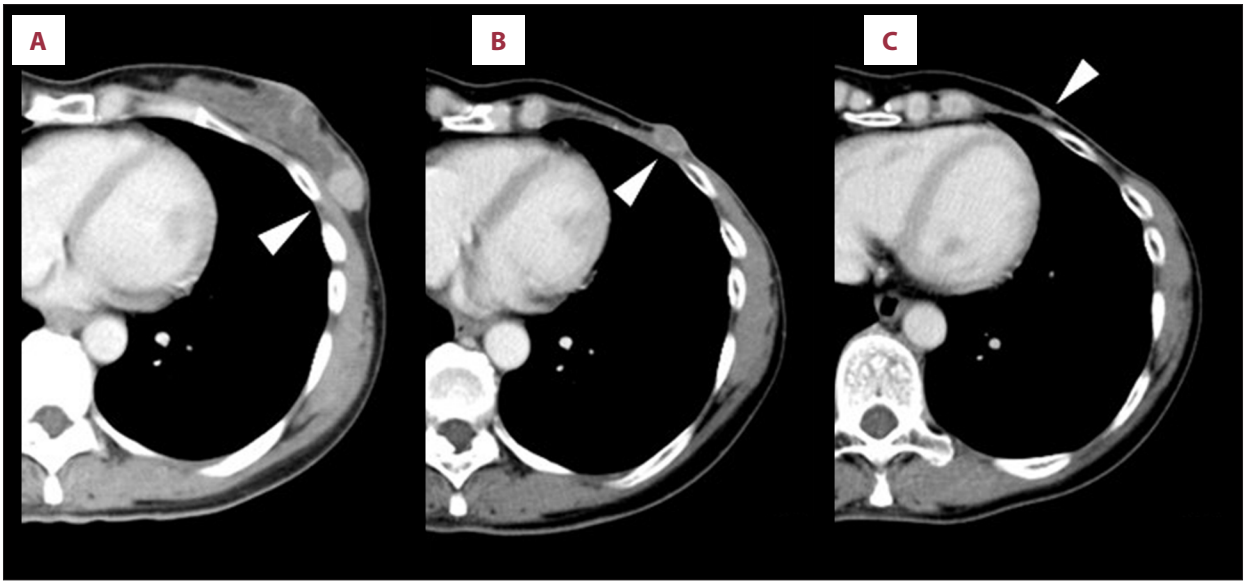

Figure 6. Primary breast cancer and recurrent lesions on E-CT imaging. E-CT on July 2007 (**A**) showed the primary breast cancer (white arrowhead). E-CT at 3 years and 8 months (**B**) and 4 years and 4 months (**C**) after the first surgery revealed the recurrent lesions (white arrowheads) in the left chest wall.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

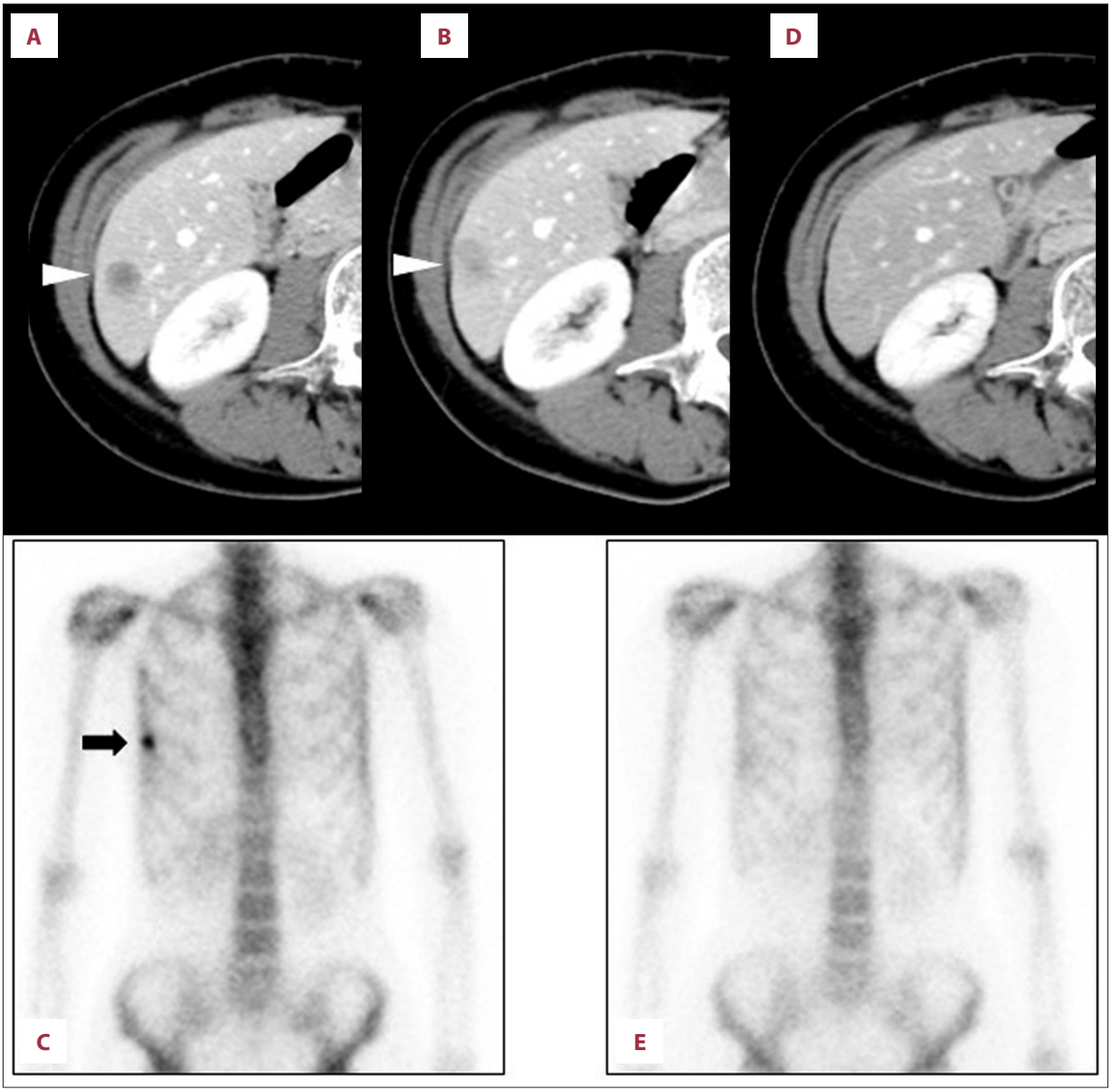

Figure 7. Changes in liver metastasis on E-CT and bone metastasis on bone scintigraphy. E-CT 6 years and 9 months after the first surgery (**A**) revealed liver metastasis (white arrowhead). Six months later, E-CT (**B**) showed the enlargement of liver metastasis (white arrowhead), and bone scintigraphy (**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**).

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 1 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/m^2 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.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

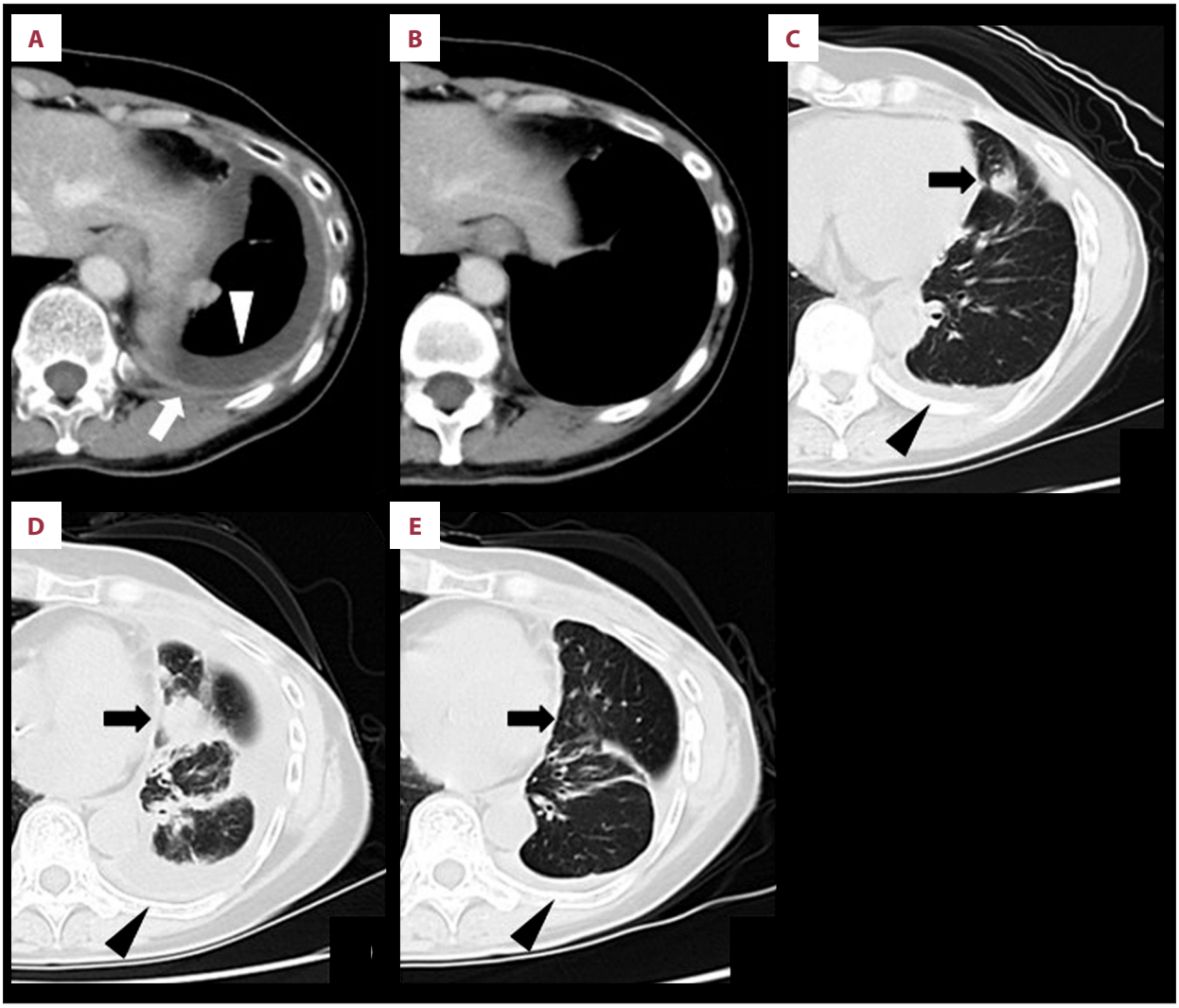

Figure 8. Changes in the pleural effusion, pleural thickening, and lung metastasis on CT. E-CT in May 2017 (**A**) showed the pleural effusion (white arrowhead) and pleural thickening (white arrow). E-CT 5 months later (**B**) revealed disappearance of pleural effusion and pleural thickening. On CT in January 2019 (**C**), left pleural effusion was observed again (black arrowhead) and a nodular shadow appeared in the lingular division of the left lung (black arrow). CT in September 2019 (**D**) revealed increased pleural effusion (black arrowhead) and an enlarged nodular shadow (black arrow). E-CT performed after receiving of RF hyperthermia (**E**) showed disappearance of lung metastasis (black arrows) and decrease in pleural effusion (black arrowheads).

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/m^2 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/m^2 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

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

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 chemotherapy 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

Department of Surgery, Narita Memorial Hospital, Department of Medical Technique, Narita Memorial Hospital, Toyohashi, Aichia, Japan

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

References:

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. Cancer J Clin, 2018; 68: 7–30
2. National Comprehensive Cancer Network. Breast cancer version 4. 2018. *https://doi.org/10.6004/jnccn.2018.0012*
3. Fisher B, Bryant J, Wolmark N et al: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol, 1998; 16: 2672–85
4. Hennessy BT, Hortobagyi GN, Rouzier R et al: Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol, 2005; 23: 9304–11
5. McAndrew N, DeMichele A: Neoadjuvant chemotherapy considerations in triple-negative breast cancer. J Target Ther Cancer, 2018; 7: 52–69
6. Schmid P, Salgado R, Park YH et al: Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: Results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol, 2020; 31: 569–81
7. Li J, Yu K, Pang D et al: Adjuvant capecitabine with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial. J Clin Oncol, 2020; 38: 1774–84
8. Li Q, Qin T, Bi Z et al: Rac1 activates non-oxidative pentose phosphate pathway to induce chemoresistance of breast cancer. Nat Commun, 2020; 11: 1456
9. Greenwell K, Hussain L, Lee D et al: Complete pathologic response rate to neoadjuvant chemotherapy increases with increasing HER2/CEP17 ratio in HER2 overexpressing breast cancer: Analysis of the National Cancer Database (NCDB). Breast Cancer Res Treat, 2020; 181: 249–54
10. Veronesi U, Paganelli G, Viale G et al: A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med, 2003; 349: 546–53
11. Pilewskie M, Morrow M: Axillary nodal management following neoadjuvant chemotherapy. A review. JAMA Oncol, 2017; 3: 549–55
12. Cohen BL, Collier AL, Kelly KN et al: Surgical management of the axilla in patients with occult breast cancer (cT0 N+) after neoadjuvant chemotherapy. Ann Surg Oncol, 2020; 27: 1830–41
13. Riogi B, Sripadam R, Barker D et al: Management of the axilla following neoadjuvant chemotherapy for breast cancer – a change in practice. Surgeon, 2020 [Epub ahead of print]
14. Rueth NM, Black D, Limmer AR et al: Breast conservation in the setting of contemporary multimodality treatment provides excellent outcomes for patients with occult primary breast cancer. Ann Surg Oncol, 2015; 22: 90–95
15. McKenzie HS, Maishman T, Simmonds P et al: Survival and disease characteristics of *de novo* versus recurrent metastatic breast cancer in a cohort of young patients. Br J Cancer, 2020; 122: 1618–29
16. Wu Q, Wang X, Zhang M et al: Cost-effectiveness analysis of bevacizumab plus paclitaxel versus bevacizumab plus capecitabine for HER2-negative locally recurrent or metastatic breast cancer. Oncol Res Treat, 2020; 43: 153–59
17. Li CH, Karantza V, Aktan G, Lala M: Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: A systematic literature review. Breast Cancer Res, 2019; 21: 143
18. Tan AR, Wright GS, Thummala AR et al: Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: A multicentre, randomised, open-label, phase 2 trial. Lancet Oncol, 2019; 20: 1587–601
19. Linthorst M, Baaijens M, Wiggenraad R et al: Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Radiother Oncol, 2015; 117: 217–22
20. Klimanov MY, Syvak LA, Orel VE et al: Efficacy of combined regional inductive moderate hyperthermia and chemotherapy in patients with multiple liver metastases from breast cancer. Technol Cancer Res Treat, 2018; 17: 1–7
21. Yang Z, Cheng R, Zhao C et al: Thermo- and pH-dual responsive polymeric micelles with upper critical solution temperature behavior for photoacoustic imaging-guided synergistic chemo-photothermal therapy against subcutaneous and metastatic breast tumors. Theranostics, 2018; 8: 4097–115
22. Oei AL, Korangath P, Mulka K et al: Enhancing the abscopal effect of radiation and immune checkpoint inhibitor therapies with magnetic nanoparticle hyperthermia in a model of metastatic breast cancer. Int J Hyperthermia, 2019; 36(Suppl.): 47–63
23. Hegyi G, Szigeti GP, Szász A: Hyperthermia versus oncothermia: Cellular effects in complementary cancer therapy. Evid Based Complement Alternat Med, 2013; 2013: 672873
24. Hadi F, Tavakkol S, Laurent S et al: Combinatorial effects of radiofrequency hyperthermia and radiotherapy in the presence of magneto-plasmonic nanoparticles on MCF-7 breast cancer cells. J Cell Physiol, 2019; 234: 20028–35
25. Ware MJ, Krzykawska-Serda M, Chak-Shing HJ et al: Optimizing non-invasive radiofrequency hyperthermia treatment for improving drug delivery in 4T1 mouse breast cancer model. Sci Rep. 2017; 7: 43961
26. Luo J, Wu X, Zhou F et al: Radiofrequency hyperthermia promotes the therapeutic effects on chemotherapeutic-resistant breast cancer when combined with heat shock protein promoter-controlled HSV-TK gene therapy: Toward imaging-guided interventional gene therapy. Oncotarget, 2016; 7: 65042–51
27. Li Z, Sun Q, Huang X et al: The efficacy of radiofrequency hyperthermia combined with chemotherapy in the treatment of advanced ovarian cancer. Open Med (Wars), 2018; 13: 83–89
28. Shoji H, Motegi M, Takakusagi Y et al: Chemoradiotherapy and concurrent radiofrequency thermal therapy to treat primary rectal cancer and prediction of treatment responses. Oncol Rep, 2017; 37: 695–704
29. Luo M, Clouthier SG, Deol Y et al: Breast cancer stem cells: Current advances and clinical implications. Methods Mol Biol, 2015; 1293: 1–49
30. Huang H, Yu K, Mohammadi A et al: It's getting hot in here: Targeting cancer stem-like cells with hyperthermia. J Stem Cell Transplant Biol, 2017; 2: 113–21
31. Oei AL, Vriend LEM, Krawczyk PM et al: Targeting therapy-resistant cancer stem cells by hyperthermia. Int J Hyperthermia, 2017; 33: 419–27
32. Atkinson RL, Zhang M, Diagaradjane P et al: Thermal enhancement with optically activated gold nanoshells sensitizes breast cancer stem cells to radiation therapy. Sci Transl Med, 2010; 2: 55ra79
33. Man J, Shoemake JD, Ma T et al: Hyperthermia sensitizes glioma stem-like cells to radiation by inhibiting AKT signaling. Cancer Res, 2015; 75: 1760–69
34. Datta NR, Puric E, Klingbiel D et al: Hyperthermia and radiation therapy in locoregional recurrent breast cancers: A systematic review and meta-analysis. Int J Radiat Oncol Biol Phys, 2016; 94: 1073–87
35. Gurer-Orhan H, Ince E, Konyar D et al: The role of oxidative stress modulators in breast cancer. Curr Med Chem, 2018; 25: 4084–101
36. Tabuchi Y, Ahmed K, Kondo T: Induction of oxidative stress by hyperthermia and enhancement of hyperthermia-induced apoptosis by oxidative stress modification. In: Kokura S, Yoshikawa T, Ohnishi T (eds.). Hyperthermic Oncology from Bench to Bedside. Singapore, Singapore: Springer, 2016; 7–15
37. Toraya-Brown S, Fiering S: Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia, 2014; 30: 531–39

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]