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PALLIATIVE REIRRADIATION WITH AN ACCUMULATED DOSE OF 80 GY FOR PAINFUL BRACHIAL PLEXUS METASTASIS AFTER 60 GY IRRADIATION FOR LYMPH NODE METASTASIS OF BREAST CANCER : A CASE REPORT

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Abstract

The rare condition of brachial plexus metastasis (BPM) from malignant carcinoma causes extreme pain and can limit activities of daily living. A few reports have indicated that palliative irradiation is an effective and safe treatment for BPM ; however, the efficacy and safety of reirradiation for BPM are not well-known. In the present report, we describe the case of a patient with BPM of breast cancer who had a history of receiving 60 Gy of irradiation in 30 fractions to bilateral subclavian areas to treat lymph node metastases, developed extremely painful BPM in the primary irradiated area, and underwent further irradiation with 20 Gy in five fractions. This palliative reirradiation initially resulted in significant pain relief, and the tumors reduced in size immediately after the treatment. Regrowth of the tumors and recurrence of the pain occurred five months after irradiation ; however, further irradiation was not administered as it could be associated with a high risk of plexopathy or myelopathy. This case report describes the tolerability and effectiveness of reirradiation for BPM, the decision process of reirradiation, and the usefulness of modern diagnostic imaging for deciding radiation field and technique to deliver safe and effective reirradiation.

Key words : brachial plexus metastasis, repeat irradiation, breast cancer, palliative radiation

Introduction

Brachial plexus metastasis (BPM) of malignant carcinoma is rare[1)]. It causes severe pain around the neck, shoulder, and upper extremities and can be accompanied by weakness and wasting of the shoulder along with sensory impairment of upper limb muscles along the distribution of brachial plexus nerves[2)]. This can impose limits on activities of daily living. Palliative irradiation, which is generally administered at a lower radiation dose to avoid severe complications that may occur with definitive irradiation administered at a higher radiation dose to treat cancer, is known to be an effective therapy for painful bone metastasis, and some studies have found that palliative irradiation is a useful and tolerable treatment for BPM as well[3,4)]. Reirradiation for painful bone metastasis is reported to be safe and effective[5,6)] ; however, to the best of our knowledge, no reference is available about reirradiation for BPM.

Herein, we describe the case of a woman who present-

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ed with extremely painful BPM from breast cancer. She had undergone definitive salvage irradiation with a dose of 60 Gy in 30 fractions for bilateral subclavian lymph node recurrence followed by curative surgical treatment for the primary breast tumor, and BPM occurred in the irradiated area three years after salvage radiation therapy. Since the pain due to BPM was resistant to medications and prevertebral nerve blocks, reirradiation was administered to the patient at 20 Gy in five fractions after explaining the details about reirradiation and could achieve a relief of the pain. In this report, we describe this case and discuss the tolerability and effectiveness of reirradiation for BPM by referring to the decision process for reirradiation dose and the usefulness of modern diagnostic images for deciding radiation field and technique, which have the potential to deliver safe and effective reirradiation.

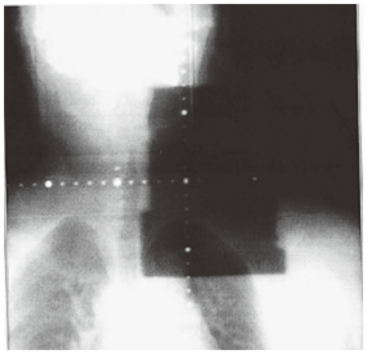

Figure 1. Linacgram of initial radiation plan for left subclavicular lymph node metastases.
Anterior view of the left neck and subclavian area five years before repeat irradiation. Anteroposterior doses of 60 Gy in 30 fractions to bilateral areas were prescribed.

Case description

A 44-year-old woman presented with left BPM, which caused extreme pain in the left shoulder and weakness of the left upper extremity. She had undergone left mastectomy for breast cancer (pathological T2N2a according to the UICC 8^{th} edition[7], luminal HER2-positive) seven years ago. Two years later, follow-up computed tomography (CT) detected recurrence in the lymph nodes at bilateral neck and subclavicular areas, which was treated by definitive radiation at a dose of 60 Gy in 30 fractions (Figure 1). She achieved complete remission with definitive irradiation ; however, three years later, multiple metastatic lesions occurred in the lung and liver. Systemic chemotherapy was initiated ; however, the treatment resulted in a partial response. Three months later, the patient presented with severe pain in the left shoulder. Contrast-enhanced CT, magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) revealed enhanced lesions along the left cervical (C) 4-6 nerve roots and an intraspinal canal mass at the C4 level ; these were diagnosed as BPM based on the radiologic images and clinical symptoms (Figure 2A-C). Despite treatment with opioids and prevertebral nerve blocks, the pain became more intense, and the left upper limb became weak. She then presented to our institution from another institution for reirradiation for the BPM.

The patient was given a detailed explanation of the possible effects and risks of reirradiation for the BPM and provided written informed consent for the procedures. Three-dimensional conformal radiation therapy based on CT simulation scans was planned with reference to contrast-enhanced CT and MRI, and ^{18}FDG-PET findings of BPM as enhanced lesions along the cervical nerve roots (Figure 3A, B). We defined the target volume of radiation as the area expanding these enhanced lesions by 5 mm in all directions. We selected a prescribed dose of 20 Gy in five fractions, according to the data of previous reports[8,9]. The details of the dose decision process are described in the discussion section ; in brief, we used the concept of biological effective dose (BED) to determine the prescribed dose. We modified the radiation dose to meet the two criteria : 1) BED at $\alpha/\beta = 10$ Gy (BED_{10}), which is thought to be related to the treatment effect, is near to 30 Gy_{10}[8], and 2) total BED at $\alpha/\beta = 2$ Gy (BED_2) of two irradiation cycles, which is thought to be related to late toxicity to the brachial plexus, is less than 190 Gy_2[9]. Thus, a dose of 20 Gy in five fractions met these criteria with a BED_{10} of 28 Gy_{10} and a total BED_2 of 180 Gy_2. Pain and weakness improved subjectively and objectively at four days after starting palliative radiation therapy. Furthermore, contrast-en-

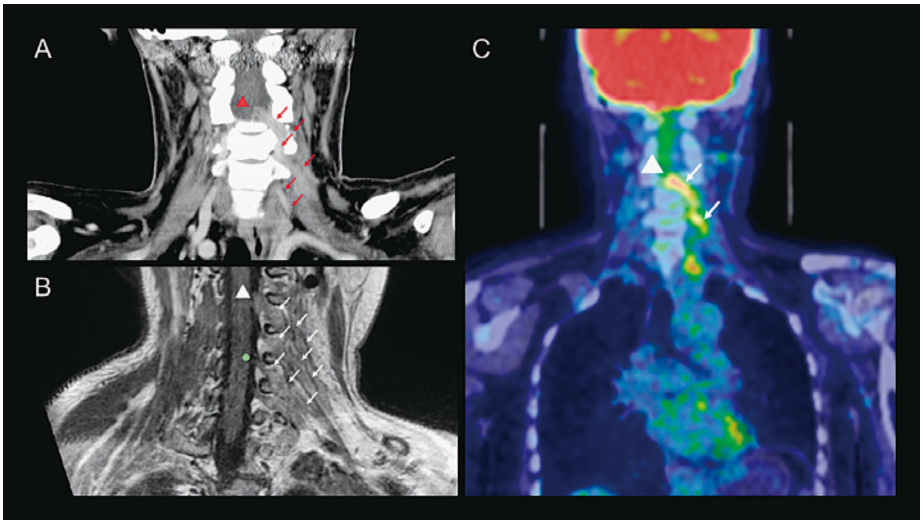

Figure 2. Diagnostic images before repeat irradiation.
Pretreatment contrast-enhanced CT (A), T1-weighted MRI (B), and ^{18}FDG-PET (C) images show enhanced lesions along the left cervical 4-6 nerve roots (arrows) and enhanced mass in the spinal canal at the cervical 4 level (arrowhead).

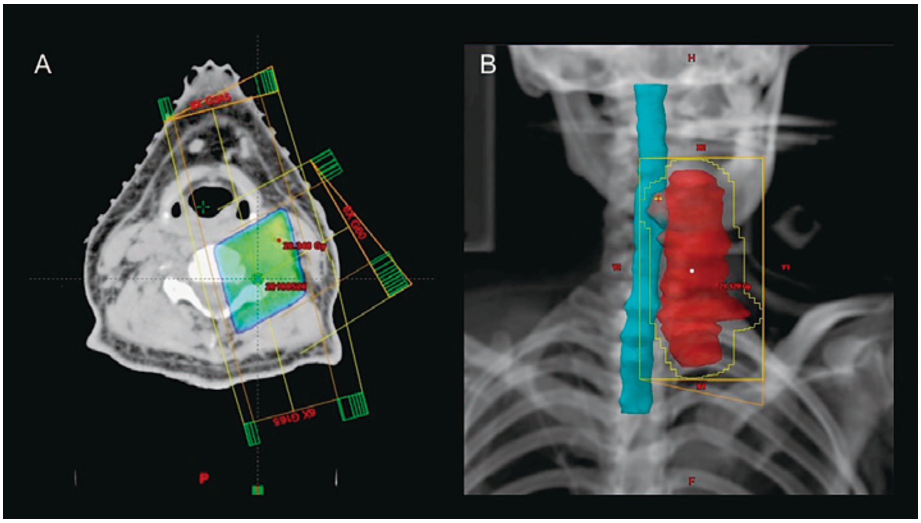

Figure 3. Repeat irradiation planning.
Anterior view (A) and dose distribution in the axial image (B). An irradiation field from the left side was added to the anteroposterior fields to reduce the irradiated dose to the spinal cord and ensure the prescribed dose to BPM.

hanced CT performed two months later (Figure 4A) revealed reductions in the sizes of the tumors, and the weakness of the shoulder reduced. However, five months after completion of palliative irradiation, left shoulder pain recurred, and regrowth of the tumors was revealed on contrast-enhanced CT (Figure 4B). T2-weighted MRI also revealed a tumor at the C4 level. These images indicated that pain recurrence was associ-

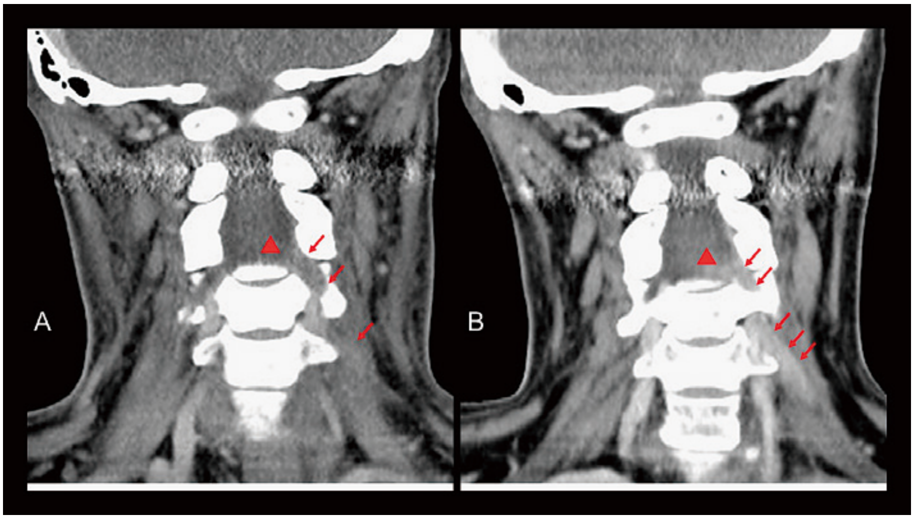

Figure 4. Contrast-enhanced CT imaging findings after repeat irradiation.
Two months after repeat irradiation (A), the intracanal mass is smaller (arrowhead) and contrast enhancement of the brachial plexus is weak (arrows). After five months, when the patient presented with recurrent left shoulder pain (B), the size of the intracanal mass has increased (arrowhead) and increased contrast enhancement along the left brachial plexus is observed (arrows).

ated with progression of the growth of the tumors and not related to late toxicities of radiation. Further irradiation avoiding the spinal cord was difficult and included the risk of severe plexopathy and myelopathy; thus, the medication for the pain of BPM was continued.

Discussion

In the present report, we describe the case of a patient in whom repeat irradiation performed for painful BPM resulted in good pain relief for five months without severe toxicity. Some studies have reported the efficacy of palliative radiation for BPM[3,4]; however, information about the efficacy and tolerability of repeat irradiation for BPM is scarce. Our experience indicated that repeat irradiation for symptomatic BPM might generate satisfactory results for at least a limited period. In addition, diagnostic imaging modalities, including contrast-enhanced CT, MRI, and ^{18}FDG-PET were useful for identifying BPM lesions and defining the irradiation target in the present case. Appropriate target delineation, which was not too wide or too narrow according to these images, might have contributed to the favorable treatment results.

Palliative radiation therapy for symptomatic BPM in patients with no history of irradiation to the same area is reportedly useful and can provide significant pain relief in approximately 50% of patients[3,4]. One study[10], published in 1973, found that the prescribed radiation dose to treat BPM was from 35 Gy in 10 fractions to 50 Gy in 20 fractions. Because the radiation treatment effect is related not only to the total dose but also to the dose per fraction, the BED, which is calculated as "total dose × (1+ dose per fraction/[α/β])" based on the linear-quadratic equation, is used to compare the effects and toxicities of radiation between different doses per fraction regimens[11]. When calculating the effect of treatment on the tumor, BED at $\alpha/\beta = 10$ (BED_{10}) is used in this formula, and the unit of the result of this calculation is described as "Gy_{10}."[11] When calculating late toxicities at normal organs, BED at $\alpha/\beta = 2$ or 3 (BED_2 or BED_3) is used in this formula, and the unit of the result of this calculation is described as "Gy_2" or "Gy_3." According to the formula, the BED_{10}, which is thought to reflect the anti-tumor effect of radiation, of 35 Gy in 10 fractions to 50 Gy in 20 fractions equals 47.25 Gy_{10} to 62.5 Gy_{10}. Another recent study published in 2009 suggested that a $BED_{10} > 30$ Gy_{10} was related to a good pain relief rate[8]. This radiation dose was lower than that previously reported[10]. Regardless of initial irradiation or reirradiation, a higher dose may increase the risk of complications, and knowing the minimum dose required for palliation is important to decide the radiation dose schedule. In the present patient, radiation treatment at high doses seemed to be highly risky due to a history of irradiation in the same area; however, according to these data, we attempted to deliver a radiation dose near 30 Gy_{10}.

Little is known about the tolerability of reirradiation for symptomatic BPM. The toxicities and effects of the treatment should be considered when determining the radiation dose for reirradiation. It is often difficult to prescribe a high dose as initial irradiation due to the risk of late toxicity to irradiated normal organs and tissues. It is important to balance between the sufficient dose to achieve pain relief and the tolerable dose to avoid severe late toxicities. One study[12] found that 60 Gy in 2 Gy per fraction with BED_2 equivalent to 120 Gy_2 would cause brachial plexopathy in < 5% of patients within five years after completion of radiation. Because the present patient had a history of irradiation with 60 Gy in 2 Gy per fraction, we could not reduce the risk for brachial plexopathy by more than 5%. Another study found that the prevalence of one-year freedom from brachial plexus-related neuropathy was 66% and 87% for patients with head and neck cancer who received cumulative maximum doses of > 95 Gy and < 95 Gy in 2 Gy per fraction, respectively[9]. The BED_2 of 95 Gy in 2 Gy per fraction was equivalent to 190 Gy_2, and this was thought to be one of the threshold doses for reducing late brachial plexus-related neuropathy by approximately 10%-15% at one year after irradiation. In the present case, the cumulative total BED_2 dose of previous definitive radiation and the present palliative radiation was 180 Gy_2 (120 Gy_2 of 60 Gy in 30 fractions plus 60 Gy_2 of 20 Gy in five fractions), and this could achieve a maximum BED_2 limit of 190 Gy_2 in addition to 28 Gy_{10}, which was almost near to the reported effective dose of 30 Gy_{10}, as described in the previous paragraph. The present patient could achieve pain relief without severe toxicities; however, further studies are needed to determine the radiation dose of reirradiation for BPM.

Radiation planning involves two important factors: radiation dose and irradiation target. In addition to considering the radiation dose schedule, it is important to decide the appropriate area to irradiate and achieve good pain relief. Moreover, in cases of patients with brachial plexus-related symptoms who have a history of irradiation to the brachial plexus area, it is important to differentiate BPM from radiation injury to the brachial plexus related to the previous irradiation; in other words, it is important to determine whether the symptoms are caused by metastatic lesions and not by late toxicity of previous irradiation. In the discrimination of BPM and radiation injury, the presence of severe pain, lower trunk lesions (C7-8, T1), and Horner syndrome were reported to be evidence to suspect BPM rather than radiation injury[3,13]. Enhancement of gadolinium contrast and mass formation on MRI[11-16] and FDG uptake on ^{18}FDG-PET[17] have also been reported to be more frequently seen in cases of BPM than radiation injuries. In the present case, abnormal findings were observed in the radiographic images of the upper trunk (C4-6), and Horner syndrome was absent; however, the patient had extremely severe pain, and mass formation and enhancement on MRI and uptake of FDG on ^{18}FDG-PET were observed. Thus, we could diagnose BPM. Contrast-enhanced CT, MRI, and ^{18}FDG-PET findings were also helpful not only for differential diagnosis but also for determining where to irradiate. In the present case, the BPM lesion was clearly delineated in all these images. However, a previous study showed the possibility of false-negative results for each imaging modality[17], and therefore, it may be useful to combine these modalities to confirm the spread of BPM. Physical assessment, as well as diagnostic images, are important to determine where to irradiate during palliative irradiation treatment[18]. In the present case, we confirmed that the dermatomes of the patient's symptoms matched the findings in diagnostic images, and the symptoms were caused by the lesions of BPM that were identified on diagnostic images.

Especially in cases of reirradiation, shrinking the area of irradiation and avoiding extra radiation exposure to normal organs and tissues are thought to be important to avoid severe toxicities. High-precision radiation therapies such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy can improve dose distribution and coverage for treatment targets and decrease radiation exposure to surrounding normal organs. Clinical advantages of IMRT in reducing radiation toxicities for palliative radiation therapy have been reported overseas. For example, whole-brain radiation therapy using the IMRT technique could preserve cognitive function and patient-reported symptoms by avoiding bilateral hippocampi[19], thoracic irradiation using the IMRT technique could reduce dysphagia by avoiding the esophagus[20], and palliative irradiation for head and neck cancer using proton beam radiotherapy technique could reduce toxicities[21]. These modern radiation techniques are also thought to have merit in palliative reirradiation cases ; however, the use of these techniques is limited to definitive intent irradiation in the Japanese insurance system for medical treatment. Therefore, in the present case, we used a three-dimensional conformal radiation therapy technique, which is the same technique used in other cases for palliative reirradiation such as cases of painful bone metastases. Life expectancies of patients with a history of palliative irradiation have been improved due to the evolution of systemic therapy, and opportunities to consider repeat palliative irradiation should be increased. Further studies and evidence regarding the use of high-precision radiation therapies in the palliative setting are desirable.

In conclusion, this case report describes a patient in whom the outcome of repeated irradiation for painful BPM was good. Although careful follow-up for late complications is needed, we consider that reirradiation could be a useful treatment strategy to relieve extreme, intractable pain in patients with severe, symptomatic BPM.

Conflict of interest

The authors have no conflicts of interest to declare.

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