Editorial | Symptom Management in Palliative Medicine and Palliative Care

Increased pain after palliative radiotherapy: not only due to cancer progression

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Radiotherapy plays an important role in cancer treatment and is an important curative modality for uncomplicated locoregional tumors, sometimes in combination with other treatment strategies, such as pre- and postoperative adjuvant therapy and chemotherapy (1). Radiotherapy technology is advancing, based on the development of radiotherapy equipment, radiobiology, and computational planning systems (2). Owing to the rising incidence of cancer and the aging of cancer patients, the demand for radiotherapy is expected to increase.

The prevalence of debilitative pain in cancer patients remains high (3,4). Such pain negatively affects human quality of life (QOL), including the impairment of daily life and social interactions of the patients (5). Opioids, such as fentanyl, hydromorphone, oxycodone, morphine, and methadone, have been indicated for the management of moderate-to-severe cancer-related pain (3).

Radiotherapy is a curative and palliative treatment option that relieves cancer symptoms, and combinations of opioids and radiotherapy can be used to treat cancer pain. Research indicates pain relief rates in patients ranging from 59% to 73% and complete response rates ranging from 23% to 34% (6-8). Palliative radiotherapy is an effective modality for managing pain and other cancer-related symptoms (9), but to our knowledge, no study has reported on how this modality affects opioid prescription patterns. Here, we summarize the current relationship between palliative radiotherapy and changes in pain intensity in patients with cancer.

Radiotherapy can be broadly classified into two types based on its therapeutic purpose: (I) curative and (II) palliative radiotherapy (*Table 1*). The aim of curative radiotherapy is to cure the cancer or drive it into remission (making pain undetectable for a long time). The aim of palliative radiotherapy is to maintain and improve the patients' QOL by reducing cancer pain and various symptoms caused by the cancer itself. Palliative radiotherapy can help patients continue with their main cancer treatment (curative radiotherapy, chemotherapy, etc.), and it is used throughout the treatment period in many cancer patients (6-8).

Palliative radiotherapy can be used not only to address pain or numbness but also for symptoms such as severe dyspnea, dysphagia, and bleeding (*Table 2*). It is commonly used to treat cancer pain due to bone metastases (6-8). Research has indicated relief from pain due to bone metastases in approximately 70% of the patients and complete elimination of pain in approximately 30% of the treated patients. Therefore, palliative radiotherapy may be beneficial for painful bone metastases.

In palliative radiotherapy, a minimum amount of radiation is needed to suppress symptoms; it also has a shorter treatment period with fewer side effects than curative radiotherapy, and in some cases, the same site can be re-radiated.

Table 1 Aim of radiotherapy

Type	Aim of therapy
(I) Curative radiotherapy	Cure the cancer or drive it into remission (or making pain undetectable for a long time)
(II) Palliative radiotherapy	Maintain and improve the patients' QOL by reducing cancer pain and various symptoms caused by the cancer itself

QOL, quality of life.

Table 2 Indication of palliative radiotherapy

Symptom	Cause, site
Pain (somatic pain)	Bone metastasis
Numbness, paralysis, and gait disturbance	Spinal cord compression
Dyspnea	Stenosis or obstruction of bronchial tube
Dysphagia	Due to esophageal cancer
Vision loss	Compression of optic nerve
Headache, nausea, and vomiting	Brain metastasis
SVC syndrome	Lung cancer
Bleeding	Intestinal cancer, skin metastasis, and invasion of skin

SVC, superior vena cava.

Recently, stereotactic body radiation therapy (SBRT) and high-precision radiotherapy have been attempted as palliative therapy, with possibilities for future use (10).

Although the mechanism underlying the analgesic effect of radiotherapy has not been fully elucidated, it may act in various stages of cancer pain development. Radiotherapy may ameliorate cancer pain in some cases. If pain increases after radiotherapy, the factors could be cancer progression, effect of central/peripheral sensitization, pain flare following palliative radiotherapy, and patient characteristics.

Tumor growth is painless, but the tumor cells may stimulate sensory nerve receptors in the bone and/or periosteum due to the production of pain-inducing substances. In addition, increased internal bone pressure, decreased bone mechanical strength, and direct invasion or compression of nerve roots by tumors can increase cancer pain.

Peripheral sensitization represents a reduction in the threshold and/or an increase in the magnitude of responsiveness at the peripheral ends of the sensory nerve fibers (11,12). This occurs in response to chemical mediators released by nociceptors and/or non-neuronal cells at sites of tissue injury or inflammation.

Recent research findings indicate that central sensitization (CS) influences chronic pain conditions and the transition from acute to chronic pain (13-16). The International Association for the Study of Pain defines CS as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input". CS is studied as a mechanism of cancer pain because it caused pain in approximately 40% of the breast cancer survivors (17,18). Continuous exposure to nociceptive stimuli due to cancer induces peripheral and CS, resulting in an increase in pain.

Pain flares are a common side effect of radiopharmaceutical and hormonal therapies. The incidence of pain flares due to external beam radiotherapy is reported to range from 2% to 44% (19,20). Hird *et al.* reported an overall pain flare incidence rate of 40% (the incidence of pain flare in patients treated with a single dose of 8 Gy was 39%); pain flares occurred within the first 5 days following radiotherapy in 80% of all evaluable patients (21). Pain flares may be due to the release of inflammatory cytokines; therefore, dexamethasone may prevent or attenuate the occurrence of pain flares through its anti-inflammatory action. Chow *et al.* showed that compared with placebo, dexamethasone reduced the incidence of pain flares and nausea as well as improved functional activity and appetite without serious

adverse effects (22).

Depression is a common condition that may accompany cancer pain. It is unclear whether pain stress causes depression or whether depression causes pain as a physical symptom. Cook *et al.* showed that pain catastrophizing is related to pain-related fear, depression, and disability; pain-related fear is related to depression and disability, and both depression and disability are related to pain severity (23). The fear-avoidance model is a cognitive-behavioral model, and this model explains why a minority of patients with acute low back pain develop chronic pain (24). As per the fear-avoidance model of pain, patients often engage in pain catastrophizing when the pain becomes intractable, leading to symptoms such as disability, disuse syndrome, and impairment in activities of daily living. Therefore, depression considered as a risk factor for intractable pain.

In addition, if pain increases after radiotherapy, it is necessary to consider the possibilities due to non-cancer pain. As a result, non-cancer pain may exist as a complication, or that non-cancer pain may worsen during radiotherapy unexpectedly. Regard less of assumption that pain is due to cancer, it is important to consider various factors to worsen pain.

Arabandi *et al.* investigated the association between palliative radiotherapy and opioid prescription patterns of patients with metastatic cancer (25). The results showed that patients receiving palliative radiotherapy may require higher opioid doses after radiotherapy, particularly those who are younger or have comorbid depression; hence, these patients require careful treatment planning.

These findings contribute to knowledge of the risk factors of cancer pain after palliative radiotherapy and ameliorative action, and may form the basis of further research.

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