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Short-term clinical outcome of early onset colorectal cancer and bone metastasis progression: Evaluation of zoledronic acid effectivity in controlling the skeletal related events

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Abstract: The incidence of early-onset colorectal cancer (EOCRC), which affects people under 50 worldwide, has increased by nearly 30% over the past 20 years, particularly in high-income nations. Fifty percent of patients will experience metastases following surgical treatment of the primary tumor, and 20% have metastatic disease at the time of diagnosis. The main factors associated with patient morbidity are skeletal-related events (SREs), which frequently manifest as spinal cord compression, bone pain, pathological fractures, and hypercalcemia. This study aims to evaluate the short-term clinical outcomes of pharmacologic treatment options for bone metastasis related to early-onset colorectal cancer undergoing definitive surgical resection and adjuvant chemotherapy, which progresses to skeletal-related events. The study will include both resectable colorectal adenocarcinomas. Patients with a prior history of neoadjuvant chemotherapy will be excluded. The primary clinical outcome to be assessed is pain reduction associated with bone metastasis after zoledronic acid treatment over six months. From January 2023 to January 2025, we reported 15 cases of early-onset colorectal cancer that progressed to bone metastasis after resection and adjuvant treatment. Seven cases involved sigmoid adenocarcinoma. The most common symptom was chronic pain. Pain levels, measured by the Visual Analog Scale (VAS), improved after six cycles of zoledronic acid treatment, with no further reports of worsening skeletal-related events. Early diagnosis of colorectal cancer is crucial, as early-onset cases have a higher likelihood of spreading to the bones. Pharmacologic therapy demonstrates a favorable clinical outcome in controlling symptoms related to skeletal-related events.

Keywords: *Bone metastasis, Clinical outcome, Early Onset colorectal cancer, Zoledronic acid.*

1. Introduction

According to Fornetti, et al. [1] the incidence of early-onset colorectal cancer (EOCRC) has climbed by nearly 30% in the past 20 years, particularly in high-income nations such as the US, Australia, and Canada, and it affects individuals under the age of 50 all over the globe.

These incidence rates of EOCRC have been increasing at a pace of about 2% per year since 1994. Although colorectal cancer incidence and mortality rates have been on the decline, the fact that EOCRC is more common in older adults is cause for grave concern, as indicated by Holladay, et al. [2]. Additionally, Suresh, et al. [3] agree that the features of EOCRC, including its disease patterns, causes, body structure, metabolism, and biological behaviour, set it apart from late-onset colorectal cancer (LOCRC), which usually occurs in people over 50.

Most EOCRC cases localise in the rectum. The distal colon is a close second, and when these cancers are diagnosed, more than 70% of them are found on the left side of the colon. Cancers on the left side of the body follow different treatment protocols, are smaller, and have longer periods of disease-free

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survival than cancers on the right side. They also have lower recurrence rates, according to Fornetti, et al. [1] and Suresh, et al. [3].

When it comes to nonspecific clinical symptoms, younger patients are more likely to be dismissive. Most people don't pay much attention to common ones that are linked to colorectal cancer, like a loss of appetite, stomach pain, and weight loss. This procedure delays the diagnosis by approximately 6 to 9 months. Colorectal cancer symptoms typically signal a more advanced stage of the disease, which is associated with a worse prognosis. A study by Assi, et al. [4] found that more than 61% of EOCRC patients had metastatic disease, which is higher than in LOCRC patients.

Finally, Holladay, et al. [2] reported on the treatment aspect. EOCRC and LOCRC are very similar; the only difference is that patients under the age of 50 are more likely to receive and have better postoperative tolerance of treatment. The goal of the international multidisciplinary team known as Direct was to help clinicians treat patients with EOCRC by compiling evidence-based guidelines.

Compared to cancers of the prostate or breast, colorectal cancer has a far lower incidence of bone metastasis (less than 10% of patients). The most common places for bone metastasis caused by colorectal cancer to occur are the spine (65%), pelvis or hip (34%), long bones (26%), and other bone sites (17%), as indicated by Park, et al. [5].

Furthermore, according to Li, et al. [6] individuals under the age of 60 may also face an elevated risk, although the increase may be linked to a more aggressive form of colorectal cancer rather than solely to age. Research indicates that the emergence of bone metastasis is associated with resistant lung metastasis. Risk factors include rectal cancer, signet-ring cell carcinoma, the size of CRC tumours, and spread to lymph nodes, liver, and brain, as well as high levels of carcinoembryonic antigen (CEA).

A patient's morbidity is mainly influenced by skeletal-related events (SREs). Compression of the spinal cord, bone pain, pathologic nail fractures, and hypercalcemia are common symptoms of SREs in the metastasis of colorectal cancer. These occurrences are all associated with a decline in quality of life, the need for supportive care, a drop in survival rate, and the end of systemic chemotherapy. Nerves close to a bone tumour may overreact to stimuli, leading to excruciating pain, because the tumour alters the environment around it. Kawamura, et al. [7] state that the initial indication of bone metastasis is usually the presence of pain.

Osteolytic, osteoblastic, and mixed metastatic bone lesions are the three main types. Typically, osteolytic lesions are found in cases of colorectal cancer. Osteoclasts cause these lesions. Increased numbers of osteoclasts and progenitor osteoclast cells, a process known as osteoclastogenesis, exacerbate bone resorption.

Patients whose cancer has spread to their bones can receive treatment based on either systemic or local control. Reducing skeletal-related events (SREs) and controlling the progression of metastasis are the goals of systemic treatment. Patients with a prognosis of at least six weeks can benefit from localised treatment, which focusses on stabilising bones and seeks to improve localised lesions. A patient's prognosis, pain management capabilities, life expectancy, tumour localisation, staging, and other relevant factors should inform treatment decisions, as indicated by Kawamura, et al. [7]; Ma, et al. [8] and Li, et al. [9].

2. Methods

The Surgery Department of Moewardi General Hospital in Indonesia conducted this observational study. We collected data from January 2023 to 2025.

The inclusion criteria are both resected adenocarsinoma colon and rectum and patients younger than 50 years old who progressed to bone metastasis after curative resection and adjuvant treatment.

This study will exclude cases with a history of neoadjuvant chemotherapy.

Patients with adenocarsinoma colon and rectum already diagnosed with bone metastasis from the clinical symptom of pain and already confirmed by a bone survey exam will be recorded and categorised based on the visual analogue score (VAS) pain scoring system.

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Both patients were included in this study and treated with 6 cycles of intravenous zoledronic acid infusion at 4-week intervals. VAS scores of each patient will be reported and compared with the post-treatment after finishing the 6 cycles of ZA.
The clinical symptom which is to be evaluated is the decreasing of the VAS score after the ZA treatment.

3. Results

During the course of our research, we documented fifteen instances of colorectal cancer with an early onset that developed bone metastasis following resection and adjuvant treatment. It has been reported that there have been seven cases of sigmoid adenocarcinoma. There are two other sites, which are the rectum and the ascending colon. Chronic and persistent pain is the most typical symptom. Following the completion of six cycles of treatment with zoledronic acid, the VAS was found to have improved, and there have been no further reports of skeletal-related events becoming more severe.

The average of the VAS scores of the patients with bone metastasis is 6, and those who were previously already treated with NSAIDs before being diagnosed had 4 mg of intravenous zoledronic acid administered at 4-week intervals.

During the follow-up of these cases, all of the patients had improvement of the chronic pain regarding the decreasing of the VAS score to 1-2 after completing the 6 cycles of zoledronic acid.

No patients required opioid analgesia, and no patient has experienced progressive disease or skeletal-related events associated with the bone metastasis of colorectal cancer.

Even in the early onset of the colorectal cancer, both of the patients could tolerate well these treatments, and there were no side effects to be reported.

Table 1.
Data Characteristic.

Characteristics	**n**	**Percentage (%)**
Sex		
Male	7	47%
Female	8	53%
Tumor Location		
Ascending	1	7%
Transverse	1	7%
Descendens	1	7%
Sigmoid	7	47%
Rectum	5	33%
VAS	**Score (mean)**	**p value**
VAS Pre	6	0.000[a]
VAS Post	2	

Note: [a]paired t-test.

4. Discussion

Li, et al. [6] and Ma, et al. [8] state that metastatic bone lesions are classified into three categories: osteolytic, osteoblastic, and mixed. Osteolytic lesions are predominantly observed in cases of CRC. Osteoclasts are responsible for the formation of these lesions. The process of osteoclastogenesis, characterised by an increase in osteoclasts and progenitor osteoclast cells, exacerbates bone resorption. CRC cells disseminate to bone tissue through the expression of CCL3, a chemokine that directly promotes osteoclastogenesis, thereby facilitating the progression of the malignancy, as indicated by Li, et al. [6] and Ma, et al. [8].

As state by Li, et al. [9] skeletal-related events (SREs) are primarily associated with a patient's morbidity. Bone metastasis of colorectal cancer (CRC) frequently manifests as spinal cord compression, bone pain, pathologic fractures, and hypercalcemia. The events are associated with diminished quality of life, increased need for supportive care, reduced survival rates, and discontinuation of systemic

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chemotherapy. Bone tumours can influence the surrounding environment, leading to heightened sensitivity of nearby nerves and resulting in significant pain. Pain is often the initial symptom that indicates the presence of bone metastasis. There is a concern that the rise in colorectal cancer survivability may lead to an increase in the incidence of bone metastasis associated with this disease.

Treatment strategies for patients with colorectal cancer bone metastasis focus on systemic or local control methods. Systemic treatment seeks to manage the advancement of metastasis and diminish skeletal-related events (SREs). Localised treatment seeks to enhance localised lesions in patients with a minimum life expectancy of six weeks, emphasising the stabilisation of bone. Treatment methods must take into account a patient's prognosis, pain management capabilities, life expectancy, tumour staging, and localisation, among other factors.

Individuals with colorectal cancer metastasising to the bone exhibit an increased risk of skeletal-related events (SREs) as indicated by Baek, et al. [10].

As state by Kawamura, et al. [7] and Liu, et al. [11]. Patients may exhibit compromised bone integrity, resulting in spinal cord compression and pathological fractures. The process of bone resorption releases calcium into the bloodstream, which may result in hypercalcemia associated with malignancy. The results support the application of pharmacological interventions to suppress osteoclast activity, including bisphosphonates (BPs) and denosumab. Bisphosphonates inhibit farnesyl pyrophosphate synthase, thereby suppressing osteoclast proliferation and promoting their apoptosis. Zoledronic acid (ZA) is a widely used bisphosphonate for the prevention of skeletal-related events (SREs) and the correction of hypercalcemia associated with malignancy. The systemic treatment of bone metastases may involve the supplementation of vitamin D and calcium to prevent drug-induced hypocalcaemia associated with bisphosphonates and denosumab. Dexamethasone, a glucocorticoid that inhibits inflammatory processes, is also employed for the prophylaxis of bone pain resulting from radiation exposure.

5. Conclusion

Although it might be to early , from this observational study it will be decided that the administration of zoledronic acid 4 weekly for another 6 cycles as adjuvant treatment could prevent the future skeletal related events and these the patients could tolerated well with these treatment.

Institutional Review Board Statement:

This case study has already been approved the Institutional Review Board by Health Research Ethic Committee of Moewardi General Hospital, Surakarta, Indonesia.

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Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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