GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Targeting bone cancer: Emerging therapies and treatment strategies

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GSC Biological and Pharmaceutical Sciences, 2025, 32(03), 049–058

Publication history: Received on 23 June 2025; revised on 30 August; accepted on 02 September 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.32.3.0308

Abstract

Bone cancer is a serious medical condition that affects millions of people worldwide. It is characterized by the uncontrolled growth of abnormal cells in the bone tissue, leading to tumors that can cause pain, swelling, and limited mobility. Despite advances in treatment, bone cancer remains a challenging disease to manage, with a high risk of recurrence and metastasis. This review aims to provide an overview of the current understanding of bone cancer, its types, causes, symptoms, diagnosis, and treatment options. Here also discuss the challenges and limitations of current treatments and explore potential future directions for improving patient outcomes.

Keywords: Cancer; Bone; Osteosarcoma; Therapy; Sarcoma; Tumor

1. Introduction

Bone cancer is still a serious medical issue. Tumor excision is the most often used therapeutic therapy approach today. Although it is mostly successful, there are a number of possible drawbacks, including the need for several surgeries, extended hospital stays, and the possibility of recurrence due to insufficient cancer cell removal [1]. Malignant bone tumors, often known as bone cancer, are tumors that develop in the bone or its supporting tissues. It is separated into primary bone cancer and bone metastases [2]. Changes in cellular DNA that result in unchecked cell division are the cause of cancer. In 2020 alone, there were 18.1 million instances of cancer globally, according to the World Cancer Research Fund [3]. Since 1995, the annual death rate from cancer has been declining because of improvements in early identification and treatment. However, in 2020 and 2021, cancer was the second leading cause of death in the US and still killed more people than COVID-19. One important element that may contribute to the failure of cancer therapies is the existence of cancer stem cells (CSCs) [4]. Because bone cancer significantly impairs a patient's quality of life, a multidisciplinary approach is essential to ensuring optimal care [5]. An uncommon but dangerous kind of cancer that arises in bone tissue is called bone cancer [6]. The primary cause of cancer is a loss of genomic stability. Certain DNA-damaging chemicals from carcinogens primarily change the stability of cells' genomes [7]. Tumors of the soft tissues and bones are conditions that pose a major threat to human life and health. Primary malignant bone tumors have increasingly become more common in recent years. Most primary malignant bone tumors, such as osteosarcoma, Ewing sarcoma, chondrosarcoma, malignant fibrous histiocytoma, chordoma, and others, occur in adolescents and middle-aged adults between the ages of 10 and 30 [8].

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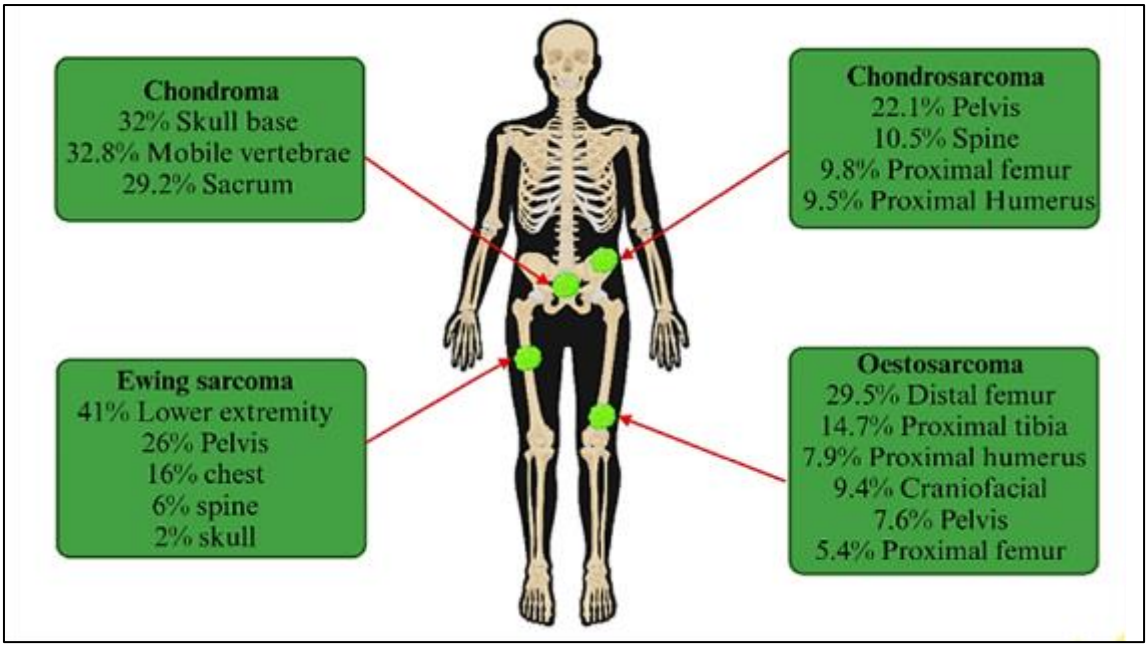

Figure 1 Anatomical distribution of Bone Cancer [6]

1.1. Cancer

Genetic or epigenetic changes in somatic cells cause cancer, a condition characterized by aberrant cell development that can spread to other body areas [9]. Cancer is characterized by the unregulated growth and division of abnormal cells. Tumors, which appear as aberrant tissue masses, can develop from the accumulation of these abnormal cells [10]. Cancer is a category of diseases that can affect any region of the body. It is characterized by a group of cells that are resistant to regulatory signals, grow continuously, and escape from the body's control [11]. Therefore, either inhibition of T-cell activation or cancer cell escape from immune surveillance may be the cause of the proliferation of cancer cells [12]. Mineralized connective tissue, bone is made up of cell types such as osteocytes, osteoblasts, osteoclasts, and bone lining cells as well as extracellular matrix. About 40% of the body weight is made up of the skeletal system, which performs a variety of vital tasks for immune system and blood production, as well as for mobility, tissue protection, and physical support [13]. The accumulation of genetic changes that cause a healthy cell to change into its malignant counterpart is the cause of cancer [14]. The growing availability and integration of many data types, such as genomic, transcriptomic, and histopathologic data, is facilitating the transition of cancer care towards precision healthcare [15]. Over the past century, cancer immunotherapy has continuously drawn interest as a treatment for neoplastic disease. About 10% of hematologic malignancies are multiple myeloma (MM), a cancer of clonal plasma cells. The immune cell components and the bone marrow (BM) microenvironment play a key role in the etiology and progression of multiple myeloma [12]. Multiple myeloma, chondrosarcoma, and giant cell tumors of bone are examples of primary malignant bone tumors in addition to OS [16]. With an expected 10 million deaths from the disease in 2022, cancer is the world's top cause of death. The cancers of the stomach, breast, liver, colon, and lung were the mostdeadly [11]. Globally, cancer is the major cause of illness and mortality, and its prevalence varies significantly by race and ethnicity. The disparity is multifaceted and may be related to access to high-quality healthcare, obesity, genetic predisposition to cancer, and alcohol or tobacco use [17]. About 65–80% of metastases in individuals with metastatic breast cancer occur in the bones and skeletal system, making it the most prevalent location of breast cancer metastasis, along with the lungs, liver, and brain [18]. Medication-related osteonecrosis of the jaw (MRONJ) is a danger linked with the use of bone-modifying drugs (BMA), such as denosumab and bisphosphonates (BP) [19].

1.2. Bone

The body needs bones for stability and support, which guarantees good posture and mobility. They provide the structural support for muscles, organs, and tissues, enabling both effective mobility and defense against outside influences. Numerous variables, including mechanical stress, hormonal fluctuations, and metabolic demands, cause bone tissue to constantly remodel, grow, and heal [20]. Myeloma cells live in bone, which is also a major factor in the development and recurrence of MM. Drug delivery that targets bone is a successful tactic [21]. A common occurrence in many tumor types, bone metastasis is a dangerous consequence of advanced cancer [22]. Even after attaining maturity,

bone, a highly active structure, continues to remodel throughout life. Osteoclasts and osteoblasts work together to drive the process of bone remodeling [23].

Improvements in diagnosis and therapy brought about by a greater understanding of cancer biology have extended the life expectancy of cancer patients [24]. With incidence rates of 19% and 12.9%, respectively, anxiety and sadness are frequent side effects of cancer. Cancer patients quality of life, adherence to therapy, and survival may all be impacted by these diseases [25].

1.3. Bone pains

Bone pain is a common problem among individuals with unlocalized bone metastatic tumors. These aches may be inflammatory or mechanical in nature, and they get worse at night. Intraosseous nerves, periosteal irritation, and inflammatory-based symptoms are caused by the production of inflammatory mediators by tumor cells in the bone marrow [26].

1.4. Cancer pain

About 30 to 50% of cancer patients experience persistent pain while undergoing clinical therapy, making it a prevalent complaint among cancer patients. With a 75% frequency, bone cancer pain (BCP) is one of the most prevalent forms of chronic pain that patients with late-stage cancer encounter [27].

1.5. Causes of Cancer

Numerous factors can lead to cancer in various body parts. For example, tobacco use accounts for 22% of deaths, while poor diet, obesity, inactivity, excessive alcohol consumption, and other factors like exposure to ionizing radiation, environmental pollutants, and infections account for 10% of deaths [9].

2. Cancer Growth

When cancer cells behave differently from healthy ones, a cancer can spread. Normal cells and cancer cells have the same requirements [9].

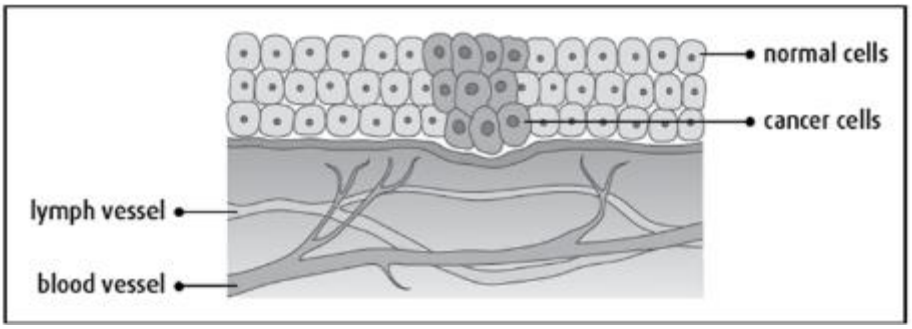

Figure 2 Growth of cancer [9]

3. Types of the sites for cancer to metastasis

Table 1 Type of the cancer to their sites of metastasis[26]

Type of cancer	Sites of metastasis
Metastatic prostate cancer	Bone (84%) Distant lymph nodes (10.6%) Liver (10.2%) Thorax (9.1%)
Metastatic lung cancer and adenocarcinoma	Nervous system (47%) Bone (39%)

	Liver (35%)
Recurrent endometrial carcinoma	Pelvic and para-aortic lymph nodes Peritoneum Lungs Vagina Other atypical sites such as bones, abdominal wall, muscle, intra-abdominal organs, and brain
Metastatic renal cell carcinoma	Bone metastasis (10%–49%) Brain (2%–16%)
HCC	The most common metastatic site: Lungs Infrequent extrahepatic metastatic sites Abdominal regional lymph nodes Bones Diaphragm Pancreas Gallbladder Stomach, colon Pleura Peritoneum Cervical lymph nodes Shoulder soft tissue Adrenal gland
Breast cancer (TNBC, nonbasal, HER2enriched, basal-like, luminal/HER2, luminal A, and luminal B)	All breast cancer sub types excluding basal-like tumors: Bone Compared with luminal A tumors, luminal/HER2andHER2-enriched tumors were associated with: Brain Liver Lung Basal-like tumors: Brain •Lung •distant nodal are markably lower rate of metastasis to bone and liver TNCB non basal tumors disclosed similar metastatic sites; nonetheless, they were not accompanied by fewer liver metastases
Colorectal cancer	43% of patients with right colon cancer, 54% with left colon cancer, and52% of patients with rectal cancer: Liver 33% of patients with right colon cancer: Peritoneal metastases 28% of patients with rectal cancer
Head and neck squamous cell carcinoma	Pulmonary metastases (66%) Bone (22%) Liver (10%) Other sites: • Mediastinum • BM • Skin
Metastatic urothelial carcinoma of the urinary bladder	Lymph node (25%) Bone (24%) Urinary (23%) Lung (23%) Liver (3%)

4. Types

4.1. Osteosarcoma

Calcium, as the most abundant element of bone and an essential element for various physiological processes, plays crucial roles in both osteosarcoma and bone biology, influencing secretion, proliferation, mineralization, and gene expression [28]. Osteosarcoma, an uncommon yet highly aggressive malignancy, predominantly affects children and adolescents, with a notable prevalence in those aged10–20years [29]. Osteosarcoma (OS) mainly affects children and is characterized by abnormal formation of bone tissue and spindle cells. It originates from primitive bone-forming cells in the mesenchyme. Typically, the tumor forms near the growth plate in the long bones of the limbs, such as the shinbone, upper arm bone, and thigh bone [30]. Osteosarcoma, a primary malignant tumor which originates from mesenchymal tissue, commonly affects children and adolescents [10]. Osteosarcoma, the most common primary bone cancer in both children and young adults, typically manifests in the distal femur, with typical hallmarks including pain and bone swelling [28]. Osteosarcoma (OS) is the most common primary malignant sarcoma in clinical practice at present. The age of onset is bimodally distributed the highest incidence rate is among children and adolescents, followed by the elderly (over 60 years old) [31]. Osteosarcoma (OS) is the most common malignant bone tumor affecting children and adolescents [32]. Osteosarcoma (OSA) shows the highest morbidity among primary malignant bone tumor among children and young adults. It exhibits the typical feature of formation of immature osteoid by tumor cells. All OSA patients have a median age of 20 years [33].

4.1.1. Hydrogels for Osteosarcoma Therapy

In osteosarcoma, combination medication therapy is frequently used to cause cancer cell death. However, a high dosage can cause toxicity and harm surrounding tissues, and only a tiny percentage of intravenously delivered medications can reach their organ target in vivo [34].

4.1.2. Application of calcium biomaterials for osteosarcoma therapy: [28]

- calcium phosphate (CaP)
- Calcium carbonate (CaCO3)
- Calcium-based bioactive glasses (Ca-BG)

4.1.3. Drawbacks

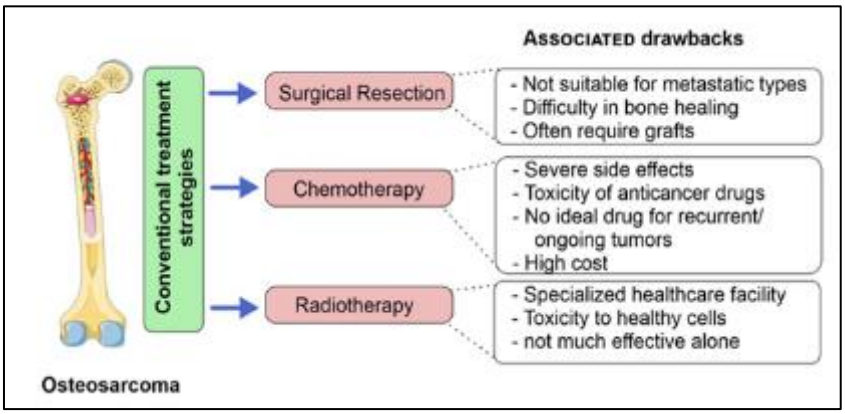

Figure 3 Associated drawbacks of osteosarcoma [35]

4.2. Chondrosarcoma:

Endogenous cartilage ossification inside the tumor tissue is a characteristic of chondrosarcoma, a rather frequent malignant bone tumor that arises from chondrocytes [36]. Although it is the most prevalent in adults, EphA2 in chondrosarcoma CS is a malignant mesenchymal tumor and the third most frequent bone sarcoma in all age groups [37]. The most prevalent malignant bone tumor that affects kids and teenagers is osteosarcoma (OS). A primary malignant bone tumor that starts in cartilaginous tissue is called chondrosarcoma. It is the second most common malignant bone tumor after osteosarcoma and accounts for around 20% of all bone tumors [38].

4.2.1. Common treatment methods for chondrosarcoma [37]

- Surgical resection
- Radiation therapy
- Chemotherapy
- Chemoresistance and radio resistance in chondrosarcoma

4.2.2. Application in OS drug therapy

One major obstacle to patient treatment is OS's well-known resistance to chemotherapy. The possibility of medication delivery using nanoparticles to overcome OS treatment resistance was shown in another investigation [39].

4.3. Ewing sarcoma

Ewing's sarcoma, an aggressive bone and soft tissue cancer affecting children and young adults, constitutes approximately 2% of childhood cancers and ranks as the second most frequent bone cancer in children [10].

4.3.1. Current standard of care:[40]

First-line therapy: Until recently, there was no internationally accepted chemotherapy treatment for Ewing sarcoma, and individuals with newly diagnosed illness in the US and Europe were treated with diverse regimens.

Recurrent disease: The median overall survival for patients with recurrent or refractory disease is around 12 months, which is a bad prognosis. In this context, several regimens are employed, however the research supporting them has generally been of low quality.

4.4. Multiple myeloma

With an annual incidence of around 4.5-6 cases per 100,000 people, multiple myeloma (MM) is the second most frequent hematologic malignancy, making up around 10% of all hematologic tumors [41]. With an average diagnostic age of almost 70 years, multiple myeloma (MM), a plasma cell-based cancer, disproportionately affects older persons [42]. Due to growing genetic instability, multiple myeloma (MM), an incurable hematologic malignancy, progresses step-by-step in both initiation and evolution [14]. Numerous correlations between race and ethnicity and the prevalence and prognosis of multiple myeloma have been shown [43].

5. Treatment

when melphalan and corticosteroids were introduced as the first viable therapy option for MM, the management of the condition has advanced significantly [44].

Ewing lesions when surgical margins indicate a residual tumor, when spinal tumors cause neurologic impairment, when lung metastases are evident, or when the tumor location or size precludes surgical removal. [45].

5.1. Chemotherapy [46]

Neoadjuvant chemotherapy regimens are used to minimize the size and quantity of lung metastases, induce tumor necrosis, and shrink the main tumor. Currently available chemotherapeutic options include ifosfamide, cisplatin, high-dose methotrexate, and doxorubicin. By interfering with the cell cycle in one or more ways, cytotoxic medications all work against tumor cells.

5.2. Radiotherapy [46]

The physical method of treating cancer cells is called radiotherapy. The radiation that is administered is known as ionization radiation because it creates electrically charged particles and gives the cells it enters energy. The tumor cells' genetic material may be damaged or killed directly by the high-energy radiation, which would prevent them from proliferating and dividing further.

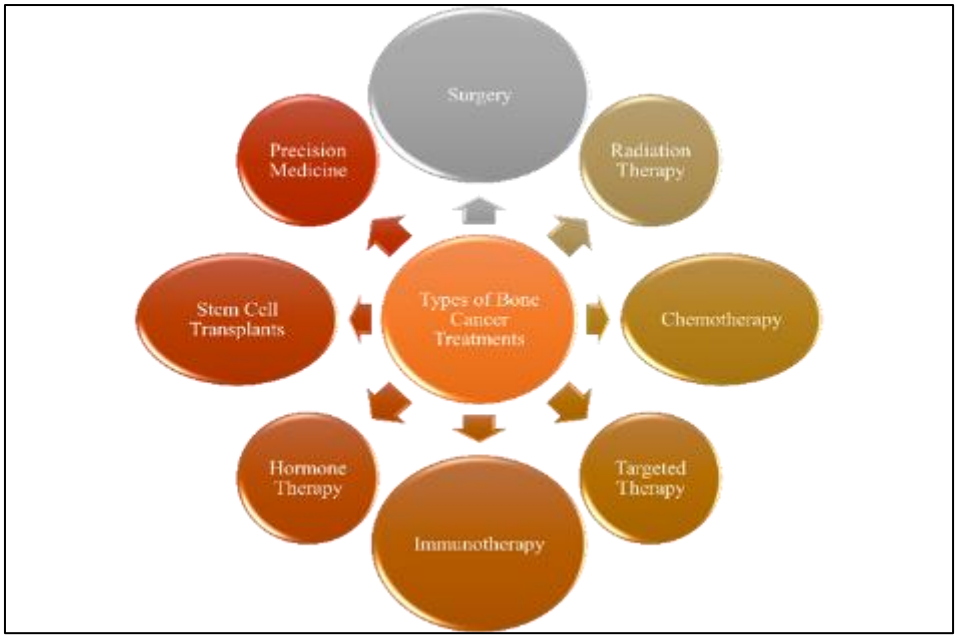

Figure 4 Treatment types of bone cancer [9]

6. Side Effect

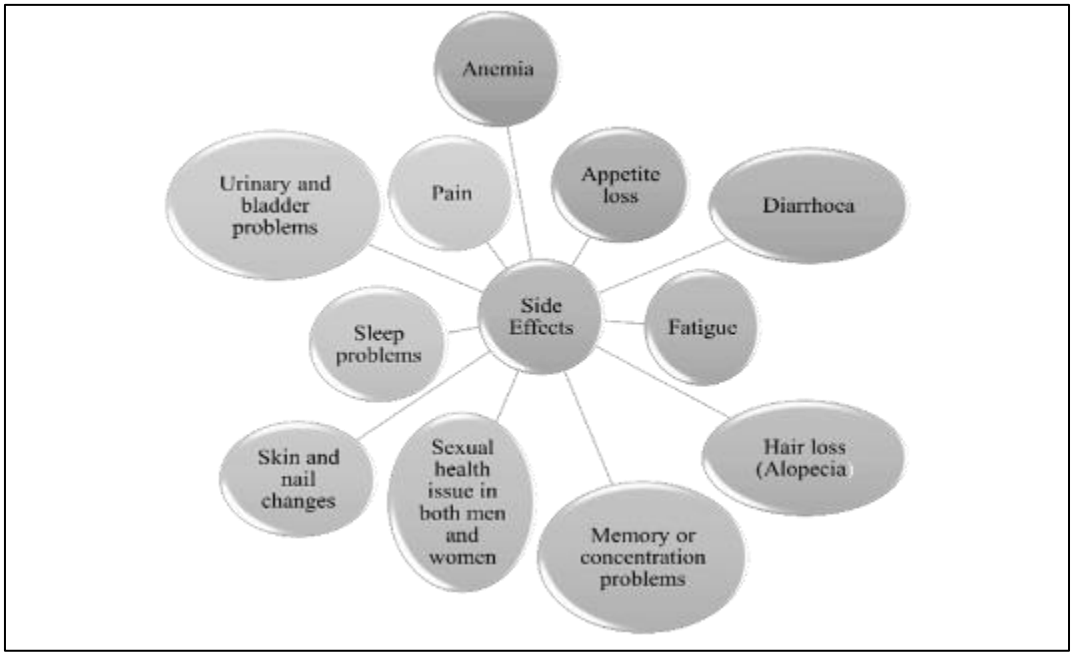

Figure 5 Side Effect of bone cancer [9]

7. Conclusion

Bone cancer is a complex and multifaceted disease that requires a comprehensive approach to management. While significant progress has been made in understanding the biology of bone cancer and developing effective treatments, there is still much to be learned about this disease. Further research is needed to improve our understanding of the causes and mechanisms of bone cancer, as well as to develop more effective and targeted treatments. By working together, we can improve patient outcomes and enhance the quality of life for those affected by bone cancer.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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