SPINAL METASTASES IN THE MOST COMMON CANCERS

Ruxandra Vatavu[1,2], Ş. Şelaru[1], Anca Sava[2,4], Ana Maria Dumitrescu[1], Gabriela Florența Dumitrescu[4], B. Costăchescu[2,4], C. I. Stan[2], L. Eva[4], Andreia Mereuță [5], Ana Nemțoi[3], Ioana Sadiye Scripcariu[2], Diana Tatarciuc[2], D. A. Chiran[2], A. Knieling[2,6]

"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

1. Doctoral School
2. Faculty of Medicine
3. Faculty of Dental Medicine
4. "Prof. Dr. N. Oblu" Emergency Clinical Hospital, Iasi, Romania
5. "Sf. Spiridon" County Clinical Emergency Hospital Iasi, Romania
6. Institute of Forensic Medicine

*Corresponding author. E-mail: cristi_stan00@yahoo.com

SPINAL METASTASES IN THE MOST COMMON CANCERS (Abstract): The **aims** of this study are to identify the underlying causes of spinal injuries and the molecular subtypes which are involved in the production of these pathologies. **Materials and methods**: This study is a retrospective one, which covered a period of four months (from January 1st to April 30th, 2015), and involved a total of 50 patients who were diagnosed with non-traumatic spinal cord injuries. These patients received treatment at the "Prof. Dr. N. Oblu" Emergency Clinical Hospital in Iași. **Results**: Despite having a group of just 50 patients we also managed to identify several key factors implicated in bone dissemination of the primary tumor: skeletal homotropism, vertebral bone composition, genetic and epigenetic alterations, bone remodeling imbalance. **Conclusions:** The study highlights the need for a multidisciplinary approach to manage spinal metastases effectively. The interplay between cancer progression, bone health, and patient's quality of life, can help healthcare providers to develop more comprehensive management strategies for individuals affected by metastatic disease. **Keywords**: BREAST CANCER, SPINAL METASTASES, PRIMARY TUMORS, BRONCHOPULMONARY CANCER.

INTRODUCTION

According to alarming data published by the World Health Organization (WHO), the rate of spinal bone metastases in the structure of cancer morbidity has increased significantly over the last 10 years, exceeding 70%, and in the last 2 years has even reached 85%.

This worrying trend places bone metastases in third place in terms of frequency among metastases, second only to lung and liver metastases. It is also worth noting that bone metastatic tumors occur 35-40 times more frequently than primary bone tumors. Metastatic cancer of the spine is an increasingly common problem due to significant advances in the treatment of primary cancers (1-3).

In cases of spinal metastases, the thoracic region is most frequently affected,

accounting for nearly 70% of cases, with a predilection for the T10 vertebral level. Approximately 25% of spinal metastases are found in the lumbosacral region, particularly around the L3 level. The cervical spine is less commonly involved, representing only about 15% of cases. At the vertebral level, the areas most commonly impacted by metastases are the vertebral body and pedicles, which are involved in 85% of cases. The paravertebral space (10-15%) and the epidural and intramedullary/intraspinal spaces (less than 5%) are less frequently affected.

Notably, the posterior part of the vertebra tends to be affected first, followed by the anterior part (2). Metastatic lesions in the spine can present as osteolytic, osteoblastic, or mixed. Spinal tumors are clinically manifested by significant pain, which is the primary reason for referral, along with neurological signs of spinal cord compression by the tumor mass and local or regional spinal deformity. The location of the pain corresponds to the site of the tumor and varies in intensity, progressively worsening over time, influenced by a number of intrinsic and extrinsic factors (2-5). Severe bone destruction can cause pathological fractures, spinal instability, and deformities, which may lead to the most serious complication-spinal cord compression. The onset of neurological symptoms is influenced by factors such as the location of the metastatic tumor on the spine, its position relative to the spinal cord, the speed at which compression occurs, and the vascular anatomy of the spinal cord in the affected area (3). These symptoms usually appear in the later stages and are marked by motor or sensory deficits, along with issues related to sphincter control. Spinal metastases, which affect approximately 70% of cancer patients, are a leading cause of mortality. Autopsy studies reveal alarming statistics, with spinal metastases present in 90% of prostate cancer cases, 75% of breast cancer cases, 55% of melanoma cases, 45% of lung cancer cases, and 30% of kidney cancer cases. Clinically, spinal metastases are most commonly associated with lung (21%), prostate (19%), and breast (12%) cancers, necessitating targeted medical interventions (4). Spinal metastases from breast cancer, like those from other cancers, can cause local pain, spinal instability, pathological vertebral fractures, spinal cord compression, neurological damage, and paralysis, all of which significantly impact patients' quality of life and reduce their lifespan. Accurate histopathological diagnosis is critical to identify the cancer subtype and the genetic mutations involved, guiding the selection of targeted therapies and specific immunotherapy. Percutaneous biopsy is a safe and effective method for obtaining tissue samples needed for diagnosis. The success of this procedure depends on several factors, including the suspected diagnosis, the size and location of the lesion, the imaging guidance used, the operator's experience, the available equipment, and the chosen approach (2-8).

This study aims to identify the underlying causes of spinal cord injury and the molecular subtypes involved in causing these pathologies.

Spinal injuries affect a significant number of people and significantly limit their quality of life.

MATERIALS AND METHODS

This retrospective study, conducted over a four-month period (January 1st - April 30th, 2015), included 50 patients with spinal cord or spine non-traumatic injuries who were

treated at the "Prof. Dr. N. Oblu" Emergency Clinical Hospital in Iași. Initially, the study sample consisted of 58 patients diagnosed with spinal tumors. However, 8 patients were excluded based on the following criteria: lack of surgical treatment due to clotting disorders; severely compromised general health status; life expectancy of less than 3 months; severe associated comorbidities. Data collection and statistical evaluation were based on electronic medical records. Collected data included patient demographics (such as age at breast metastasis (BM) diagnosis), and morphological features of the primary cancer (location, cytopathological features, histopathological subtype (HP), and immunohistochemical (IHC) characteristics). Cytopathological examination was conducted on intraoperative smears, using small specimens obtained during surgery. A small sample (1-2 mm^3) of the biopsy specimen was placed on one edge of a clean, dry, labeled slide, then crushed with the edge of another clean, dry slide, applying sufficient pressure to spread the tissue into a thin film on both slides. The slides were immediately stained with 1% toluidine blue. The remaining biopsy sample was processed for fixation. Surgical specimens were fixed in a 10% neutral buffered formalin solution for 24 hours, dehydrated using acetone and xylene, and embedded in paraffin. Paraffin blocks were sectioned into 3-µm-thick histological slices, which were stained with Hematoxylin-Eosin (HE) for microscopic examination. Additional 3-µm-thick sections were prepared for IHC staining, following a standard immunohistochemical protocol.

RESULTS

The study showed a gender ratio of approximately 1.17: 1 (female to male), with an average age of 57.04 years and a range from 12 to 79 years. Regarding background classification, 52% of patients were from urban areas, while 48% were from rural areas. Ethnic distribution included 82% Romanians and 18% Roma individuals. In terms of education, 20% of patients had postgraduate degrees, 62% had university degrees, 14% had secondary education, and 4% had primary education. The study also examined the duration from the onset of pain to surgery. Surgery was performed within 1 month of pain onset for 56% of patients, between 1 and 3 months for 36%, between 3 and 6 months for 4%, and after more than 6 months for the remaining 4%. Additionally, the study analyzed the type of tumor and its location at various spinal levels. Classification by tumor type shows that 9 patients (18%) had primary tumors and 41 patients (82%) presented secondary tumors. According to tumor site in the spine, 8 patients had cervical (16%), 31 patients (62%) had thoracic, and 11 patients (22%) had lumbar localizations. Our study revealed specific preoperative clinical features of spinal tumor pathology such as spinal pain, paravertebral muscle contracture, radicular pain, paresis or paralysis of a limb, paraplegia and sphincter disorders. Results were categorized by gender.

In male patients, the most common source of metastasis was bronchopulmonary cancer (fig. 1), representing 70% of the analyzed subjects.

One spinal metastasis of small cell bronchopulmonary carcinoma was identified in the selected group of patients (fig. 2), a common cancer in smokers with a 5-year survival prognosis of less than 1% (9).

The incidence of prostate cancer ranks it second among the primary cancers we

encountered as the starting point for spinal metastases diagnosed in the analyzed males (figs. 3, 4). The biopsy revealed metastatic adenocarcinoma. The neoplastic cells were organized in cords and nests, with some areas exhibiting a cribriform growth pattern. These cells had hyperchromatic small nuclei, a few of which contained prominent nucleoli. Immunohistochemical staining showed positive results for prostate-specific antigen and prostate acid phosphatase, while the tumor was negative for CK 7, CK 20, TTF-1, and chromogranin.

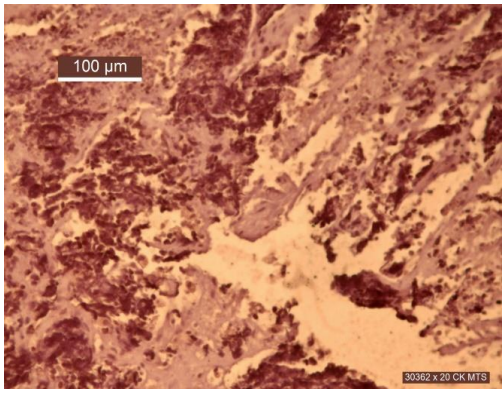

Fig. 1. Metastasis of undifferentiated bronchopulmonary carcinoma. Cytokeratin immunostaining, x200.

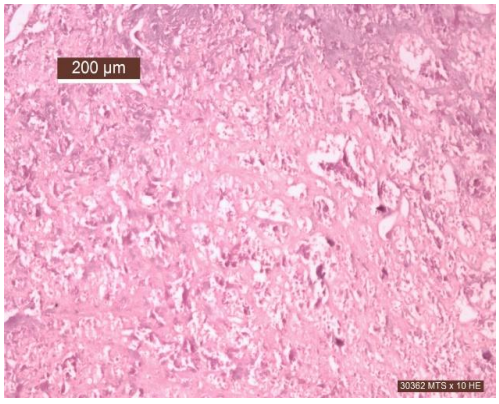

Fig. 2. Osteolytic metastasis of small cell carcinoma. HE staining x100.

After the surgery, the patient was referred to radiation oncology, where he received a total radiation dose of 20 Gy in five fractions, targeting the region from L4 to S3. During the three-month follow-up visit, the patients reported increased strength in his legs and noted improvements in his ability to walk.

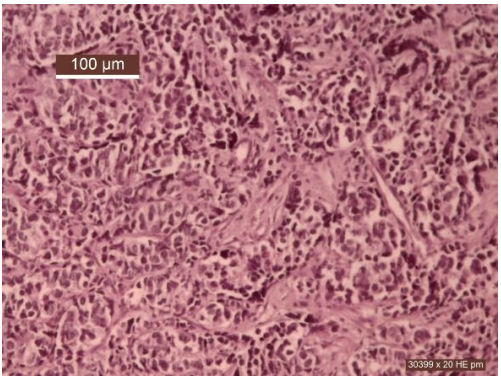

Fig. 3. Metastasis of moderately differentiated prostatic adenocarcinoma in a 68-year-old man. The preserved tubular structure is noted. HE staining, x200.

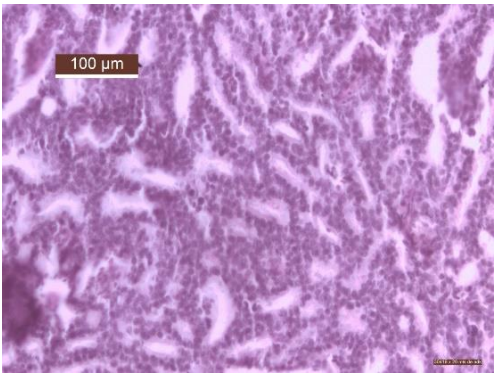

Fig. 4. Metastasis of prostatic adenocarcinoma. HE staining, x200.

As for the female group, breast cancer was the most frequent cancer and 60% of them were over 60 years old (figs. 5, 6, 7). No breast cancer was identified in the male group.

We present in figure 5 a metastasis of ductal breast carcinoma in a 60-year-old woman.

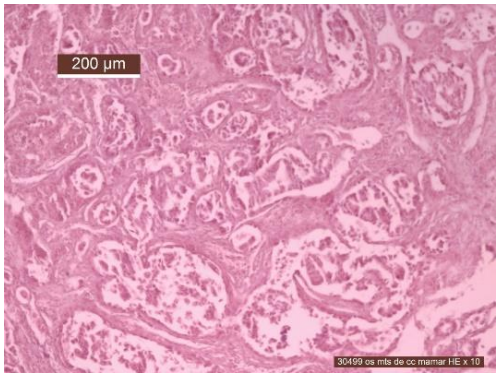

Fig. 5. Osteolytic metastasis of ductal carcinoma. HE staining, x100.

In figure 6 we can see the same metastasis at a higher magnification to note the partially preserved ductal architecture.

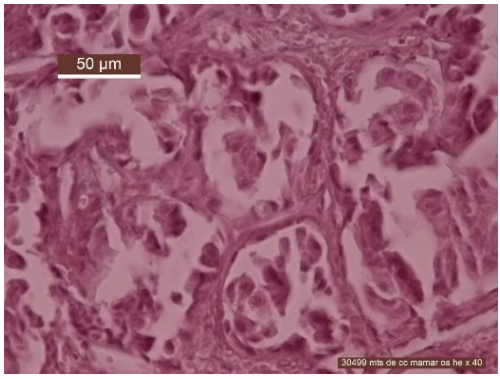

Fig. 6. Spinal metastasis of ductal breast carcinoma in a 60-year-old woman. HE staining, x400.

We considered it appropriate to analyze the parameters recorded in relation to the molecular subtype. For this purpose, we divided the total number of patients into 4 groups according to molecular subtype.

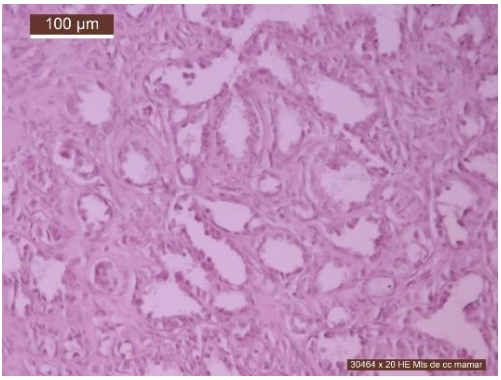

Fig. 7. Spinal metastasis of tubular breast carcinoma in a 68-year-old woman. HE staining, x200.

Based on molecular markers, breast cancer can be classified into molecular subtypes as follows (4, 11):

- Luminal type A is the most common subtype and is characterized by strong ER+ and/or PR+ but HER2- immunostaining. In terms of HP, it has a lower grade (low Ki67 LI) and is hormone responsive with a good prognosis. Type A luminal disease generally only requires endocrine therapy.
- Luminal type B is characterized by ER+ and/or PR+ and HER2+ immunolabels. It correlates with higher grade tumors (high Ki67 LI) and has a worse outcome compared to luminal type A, but also like luminal type A, this type B could be treated with endocrine therapy and chemotherapy.
- HER2+, but ER- is less common, being diagnosed at a younger age. Such cases have a high-grade histopathology and an aggressive outcome, but this outcome could be improved with Herceptin.
- Basal-like type breast cancer (BC) or triple negative breast cancer (TNBC) is an aggressive subtype characterized by high-grade histopathology, propensity for metas-

tasis and a poorer prognosis. Young women are at risk of developing this subtype of BC. Targeted therapies are currently under investigation, but chemotherapy appears to be indicated for most patients.

• Triple-positive BC with ER+/PR+ and HER2+ is a new subtype that can be treated with anti-HER2 agents and chemotherapy.

In the studied group of 27 patients, a number of 16, representing 59.25% were classified in the Luminal A molecular type, while a number of 7 patients, representing 25.92% were classified in the Luminal B type. The fewest patients were classified as HER2 type, 4 patients representing 14.81%.

The distribution of patients according to histopathological type shows a majority number representing 73% classified as ductal, 18.1% as lobular, and 8.9% as mixed.

The second most common cancer in patients is bronchopulmonary cancer as the origin of cancer for the spinal metastases. Figure 8 shows a spinal metastasis with bronchopulmonary origin at the T8 vertebral body in a 61-year-old woman.

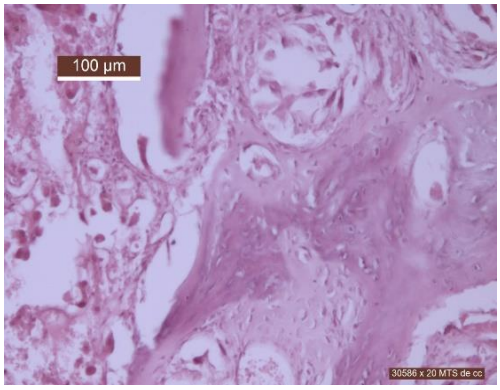

Fig. 8. Osteolytic and osteolytic metastasis of bronchopulmonary carcinoma. HE staining, x200.

DISCUSSION

Human bones are constantly in a state of self-renewal, undergoing a process known as remodeling. This intricate process involves a harmonious interplay between two types of cells: osteoblasts and osteoclasts. Under normal circumstances, these cells work in concert to maintain the bone strength and integrity of our bones (11-13).

However, in the case of metastatic lesions, this delicate balance is disrupted. The presence of cancer disrupts the bone's microenvironment, in favor of the osteoclasts. This disruption triggers a vicious cycle, where the weakened bones provide a favorable environment for tumor growth, which further accelerates bone destruction (12).

This disruption of the bone remodeling process can have serious consequences, leading to bone pain, fractures, and even loss of mobility. Other frequent dissemination sites are represented by lungs or liver (11-14).

Spinal metastasis is a common complication in advanced stages of malignant disease (9). Cadaveric studies reveal that 30% to 90% of cancer patients have spinal metastases at the time of death (10-15). In literature, the average patient age was 63.6 years. This aligns with data showing that the highest incidence of spinal metastases occurs between the ages of 40 and 65, a period when cancer risk is at its peak (15-16).

Spinal metastases typically affect the epidural space and/or vertebral column, while intradural extramedullary and intramedullary metastases are much rarer, accounting for only 5% to 6% and 0.5% to 1% of cases, respectively. The most common histological type involved is adeno-

carcinoma, most frequently originating from the breast and lung. The incidence of bone metastases is notably high in specific cancers.

Prostate adenocarcinoma, which affects up to 70% of men over 80, is the second leading cause of cancer-related death in men. Skull and spinal metastases occur in approximately 10% of prostate cancer patients, though intradural spinal cord tumors from prostate cancer are exceedingly rare. Spinal metastases represent a critical complication of advanced cancers, often leading to severe outcomes such as spinal cord compression, fractures, and neurological deficits. In our study, we analyzed the patterns and characteristics of spinal metastases in a cohort of patients, focusing on primary tumor types, clinical presentation, and outcomes following surgical interventions. The results were further examined in relation to broader literature on spinal metastases, specifically focusing on prostate and breast cancers, which are among the most frequent sources of bone metastasis (14-16).

Approximately 10% of patients with prostate cancer may experience spinal cord compression due to vertebral metastasis. Focal intradural metastasis of the prostate to the spinal cord, however, is extremely rare. An extensive search of English literature on *PubMed* revealed only nine documented cases of patients with intradural spinal cord metastasis (ISCM) from prostate cancer who underwent surgery.

In our study, prostate cancer was identified as the second most common primary tumor responsible for spinal metastasis in male patients. This aligns with established research, which indicates that approximately 10% of patients with prostate cancer develop spinal cord compression due to vertebral metastasis. The clinical presentation in our cohort often included back pain, paraparesis, or sphincter dysfunction, typical signs of vertebral involvement. Biopsy results revealed metastatic adenocarcinoma, with the neoplastic cells exhibiting hyperchromatic small nuclei and positive immunohistochemical staining for prostate-specific antigen (PSA) and prostate acid phosphatase. Following surgical intervention, many patients demonstrated notable improvements in strength and mobility, underscoring the importance of early detection and timely treatment (14).

Interestingly, while our study focused on extradural metastases, it is important to note that prostate cancer can also, though rarely, lead to intradural spinal cord metastasis (ISCM). Extensive reviews of English literature have found only nine documented cases of ISCM from prostate cancer, indicating the extreme rarity of this phenomenon. In contrast, extradural metastases are more common and are a significant cause of spinal cord compression in prostate cancer patients. This finding from the broader literature correlates with our study's emphasis on extradural vertebral metastases as a key cause of spinal pathology in men with prostate cancer. Thus, while ISCM remains a rare presentation, vertebral metastasis leading to spinal cord compression is a frequent and serious concern in prostate cancer patients (10-19).

In our female cohort, breast cancer was the most frequent primary tumor causing spinal metastases, particularly among women over 60 years old. This finding is consistent with data showing that 60-75% of women with advanced breast cancer develop bone metastases. This cancer type is the most frequent cause of bone metastases in women globally. Studies show that

60-75% of women with advanced breast cancer develop bone metastases, with a higher risk in certain subtypes (19). Our study revealed that breast cancer metastases were commonly localized in the thoracic spine, leading to clinical presentations such as spinal pain, radicular symptoms, and in severe cases, paraplegia. The molecular subtype classification in our study provides further insight, with the majority of breast cancer metastases (59.25%) falling under the Luminal A category, followed by Luminal B and HER2-positive subtypes.

A large study analyzing electronic records from various cancer centers in the US found that breast cancer was the leading cause of bone metastases (36%), followed by lung cancer (16%) and colorectal cancer (12%) (20-22).

The identification of molecular subtypes in breast cancer plays a crucial role in understanding metastatic behavior. For example, Luminal A breast cancer is known for a slower progression and a better prognosis, which may explain its prevalence in older women in our study, while HER2-positive breast cancer, though less common, tends to exhibit more aggressive metastatic patterns.

In our study, the majority of women with spinal metastases from breast cancer had ductal carcinoma, which is known for its tendency to metastasize to bones, further reinforcing the connection between this cancer type and bone involvement.

Breast cancer's invasion to bones disrupts the osseous tissue natural rebuilding process, leading to osteolytic lesions. Cancer cells trigger this process by releasing molecules that activate osteoclasts and, interestingly, osteoblasts are also involved, as they also produce factors that stimulate bone breakdown (19). Breast cancer cells initiate the destructive process in the bone by secreting factors such as parathyroid hormone-related protein (PTHrP), which directly affect bone cells. PTHrP, a powerful activator of osteoclasts, is found at elevated levels in an overwhelming 90% of bone metastasis samples. (20). It is the impact of the cancer cells that seems to shift the balance toward tissue breakdown.

Key factors, including parathyroid hormone-related protein (PTHrP) and transforming growth factor-β (TGF-β), play crucial roles in the process of bone destruction associated with metastatic cancer. PTHrP acts as a potent stimulator of osteoclast activity, contributing to bone resorption and further tumor progression. Additionally, TGF-β, released during osteoclast activation, exacerbates the situation by promoting increased production of PTHrP, creating a vicious cycle that accelerates both bone breakdown and cancer advancement.

PTHrP's influence extends beyond bone breakdown. It can directly promote tumor cell growth and angiogenesis through autocrine signaling (21, 22). However, PTHrP's role in prognosis remains a controversy. While some studies suggest its presence in early breast cancer indicates a poorer outcome (22), others show a potential link to improved survival and fewer bone metastases (19-21).

For adding another layer of complexity, the transforming growth factor-β (TGF-β) is responsible. Released by activated osteoclasts, TGF-β further increases PTHrP production in cancer cells (19). This creates a vicious cycle: PTHrP stimulates osteoclasts, leading to bone breakdown and the release of more TGF-β, which in turn increases PTHrP production.

CONCLUSIONS

Cancer metastasis to bones represents a significant challenge in oncology, fundamentally disrupting the natural balance of bone remodeling. This disruption is primarily driven by the interplay between osteoblasts, which build bone tissue, and osteoclasts, which reabsorb it. In cases of metastatic disease, this balance is tipped toward bone breakdown, leading to weakened skeletal structures that further facilitate tumor growth.

In our study, we observed that prostate cancer is the second most common primary tumor responsible for spinal metastases in male patients. This finding aligns with the understanding that among the various sites affected by metastatic disease, spinal metastases are particularly prevalent, especially in advanced stages of cancer. The thoracic and lumbar regions are frequently involved, corroborating existing literature that highlights these areas as common sites for metastatic lesions.

The complications associated with spinal metastases, including spinal cord compression (SCC), fractures, and debilitating pain, pose significant challenges to patient care. The presence of SCC is particularly concerning, as it not only leads to severe neurological deficits but also substantially impacts the functional prognosis and overall quality of life. Our findings indicate that early detection and timely intervention are crucial for mitigating these risks and improving patient outcomes.

Given the serious complications associated with bone metastases, especially the risk of SCC, there is an urgent need for enhanced diagnostic strategies and effective treatment modalities. Interventions that focus on preserving bone integrity and preventing complications can lead to substantial improvements in patient well-being. For instance, surgical interventions aimed at alleviating SCC, followed by radiation therapy, have shown promise in restoring neurological function and enhancing mobility in patients with metastatic disease.

Furthermore, our study emphasizes the importance of understanding the underlying mechanisms of bone metastasis. As we unravel the complex interactions between cancer cells, bone remodeling processes, and the tumor microenvironment, we can better identify therapeutic targets. This deeper understanding is essential for developing innovative treatment approaches that not only address the metastatic lesions themselves but also mitigate the bone-related complications that arise.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

REFERENCES

1. Patel A. Benign *vs* malignant tumors. *JAMA Oncol* 2020; 6(9): 1488.
2. Şelaru Ş, Sava A, Scripcariu DV, *et al*. Epidemiological and pathological characteristics of spinal metastases from gastrointestinal cancers: a series of 40 cases. *Rom J Morphol Embryol* 2023; 64(2): 225-234 / doi: 10.47162/RJME.64.2.13.
3. Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2014 / doi: 10.1002/ijc.29210.

4. Litak J, Czyżewski W, Szymoniuk M, *et al*. Biological and clinical aspects of metastatic spinal tumors. *Cancers (Basel)* 2022; 14(19): 4599 / doi: 10.3390/cancers14194599.
5. Ziu E, Viswanathan VK, Mesfin FB. *Spinal metastasis*. In: StatPearls (Internet). StatPearls Publishing; Treasure Island, FL, USA; 2023.
6. Wewel JT, O'Toole JE. Epidemiology of spinal cord and column tumors. *Neurooncol Pract.* 2020; 7-9 / doi: 10.1093/nop/npaa046.
7. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends: an update. *Cancer Epidemiol Biomarkers Prev* 2016; 25: 16-27 / doi: 10.1158/1055-9965.Epi-15-0578.
8. Wang X, Romero-Gutierrez CW, Kothari J, Shafer A, Li Y, Christiani DC. Prediagnosis smoking cessation and overall survival among patients with non-small cell lung cancer. *JAMA Netw Open* 2023; 6(5) / doi: 10.1001/jamanetworkopen.2023.11966.
9. Khalil A, Abd El Rahman A, Rahman EA. Place de l'IRM dans le cancer bronchopulmonaire. *J Radiol Diagn Interv* 2016; 97(4): 411-424.
10. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006; 12(20): 6243s-6249s / doi: 10.1158/1078-0432.CCR-06-0931.
11. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004; 350(16): 1655-1664 / doi: 10.1056/NEJMra030831.
12. Fisher JL, Brown SA, Sorkin JD. Osteoclasts and osteoblasts in bone metastasis. *Bone* 2006; 38(3): 363-372 / doi: 10.1016/j.bone.2005.09.024.
13. Mundy GR. Metastasis to bone: Causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002; 2(8): 584-593 / doi: 10.1038/nrc867.
14. Bubendorf L, Schöpfer A, Wagner U, *et al*. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol* 2000; 31(5): 578-583 / doi: 10.1053/ hp. 2000.6698.
15. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: The Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005; 23(9): 2028-2037 / doi: 10.1200/JCO.2005.00.991.
16. Sundaresan N, Digiacinto GV, Hughes JE, Cafferty M. Treatment of neoplastic spinal cord compression: results of a prospective study. *Neurosurgery* 1991; 29(5): 645-650 / doi: 10.1227/00006123-199111000-00003.
17. Kwon ED, Drake CG, Scher HI, *et al*. Future directions in the treatment of prostate cancer. *Mayo Clin Proc* 2011; 86(10): 1031-1042 / doi: 10.4065/mcp.2011.0148.
18. Engelhard HH, Villano JL, Porter KR, *et al*. Clinical presentation, histology, and treatment of intradural spinal cord tumors: The University of Illinois at Chicago experience. *Neurosurgery* 2010; 67(2): 422-429 / doi: 10.1227/01. NEU.0000371988.73584.97.
19. Guisse TA, Mohammad KS, Clines G, *et al*. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. *Clin Cancer Res* 2006; 12: 6213s-6216s.
20. Iowa S, Shimo T, Ibaragi S, *et al*. PTHrP regulates angiogenesis and bone resorption via VEGF expression. *Anticancer Res* 2010; 30(7): 2755-2767.
21. Kang Y, Siegel PM, Shu W, *et al*. A multigenic program mediating breast cancer metastases to bone. *Cancer Cell* 2003; 3: 537-549.
22. Henderson MA, Danks JA, Slavin JL, *et al*. Parathyroid hormone-related protein localization in breast cancers predict improved prognosis. *Cancer Res* 2006; 66: 2250-2256.