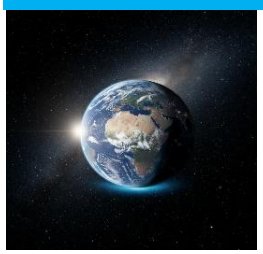
Journal of Education, Health and Sport. 2026;88:68240.
eISSN 2391-8306.

https://doi.org/10.12775/JEHS.2026.88.68240



Journal of Education, Health and Sport. eISSN 2450-3118

Journal Home Page
https://apcz.umk.pl/JEHS/index

BACHURSKA, Dominika, CZACH, Zuzanna, IGNARSKA, Magdalena, IGNARSKA, Justyna and GRYGORCZUK, Oliwia. Hypercalcemia of Malignancy: Diagnostic and Therapeutic Challenges. Journal of Education, Health and Sport. 2026;88:68240. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2026.88.68240

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.01.2026. Revised: 01.02.2026. Accepted: 04.02.2026. Published: 15.02.2026.

Hypercalcemia of Malignancy: Diagnostic and Therapeutic Challenges

BACHURSKA Dominika[1]*, CZACH Zuzanna[2], IGNARSKA Magdalena[3], IGNARSKA Justyna[4], GRYGORCZUK Oliwia[5], MAREK Jakub[6]

Dominika Bachurska[1], https://orcid.org/0009-0008-4298-2301, dominika.bachurska@gmail.com, Central Clinical Hospital in Warsaw, Banacha 1A, 02-097 Warsaw, Poland

Zuzanna Czach[2], https://orcid.org/0009-0009-6154-8022, zuzannamariaczach@gmail.com, National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland

Magdalena Ignarska[3], https://orcid.org/0009-0009-2385-9620, magda.ignarska@gmail.com, University Clinical Hospital No. 4 in Lublin, Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland

Justyna Ignarska[4], https://orcid.org/0009-0009-0340-8240, ignarska.justyna@gmail.com, Faculty of Medicine, Medical University of Lublin, al. Racławickie 1, 20-059 Lublin Poland

Oliwia Grygorczuk[5], https://orcid.org/0000-0003-3089-4546, oliwia.grygorczuk@outlook.com, Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

Jakub Marek[6,] , https://orcid.org/0009-0001-6203-6282, jakubmarek96@gmail.com, 2nd Department of Clinical Radiology, Medical University of Warsaw, Żwirki i Wigury 61

Corresponding author: Dominika Bachurska, dominika.bachurska@gmail.com

Abstract

Background.

Malignancy-associated hypercalcemia (HHM) is a frequent metabolic complication in advanced cancer, often leading to neurological deterioration, cardiovascular disturbances, reduced functional status, and shorter survival. In palliative care, timely diagnosis and management of HHM are essential to improve symptom control and patient comfort.

Aim.

To present a comprehensive, evidence-based review of current diagnostic and therapeutic

approaches to hypercalcemia of malignancy, with a focus on palliative care settings.

Material and methods.

A narrative review was conducted using databases such as PubMed, MEDLINE, Google Scholar, and Europe PMC. Fifty-six articles published between 1994 and 2024 were selected based on clinical relevance and scientific quality.

Results.

Hypercalcemia in malignancy arises predominantly from PTHrP secretion, calcitriol overproduction, or local osteolysis. Diagnostic workup includes calcium profile, PTH/PTHrP levels, and imaging. Management involves intravenous hydration, bisphosphonates, denosumab, glucocorticosteroids, and—occasionally—calcitonin or hemodialysis. Timely treatment improves symptoms and may enable continuation of oncologic therapies. In palliative patients, hypercalcemia often necessitates a shift toward comfort-focused care and underscores the importance of interdisciplinary management.

Conclusions.

Malignancy-associated hypercalcemia significantly worsens prognosis and quality of life in advanced cancer. Individualized treatment—including rehydration, anti-resorptive agents, and symptom control—is essential. Effective calcium regulation alleviates suffering, facilitates supportive care, and should be integrated into comprehensive palliative strategies.

Keywords: Hypercalcemia, Neoplasms, Bisphosphonates, Parathyroid Hormone-Related Protein, Prognosis, Therapeutics

Introduction

Hypercalcaemia, defined as a total serum calcium concentration above 10.4 mg/dL (2.6 mmol/L), is a frequent metabolic disturbance in patients with advanced malignancies [1,2]. Its prevalence in this population reaches 30–44 % and rises with disease progression. Although hypercalcemia is uncommon in early-stage cancers (1–5 %), its development in later phases is linked with a significantly poorer prognosis [3,4]. Epidemiological data indicate that the median

survival of patients with hypercalcemia is often only 40–68 days [3].

In its initial phase, hypercalcemia may be mildly symptomatic, limited to non-specific complaints such as fatigue or loss of appetite. As calcium levels rise, severe complications such as cardiac arrhythmias, renal failure, and encephalopathy emerge [5]. In the context of palliative care, hypercalcemia poses a particular challenge, as electrolyte imbalances further compromise a patient's functional status, worsen prognosis, and increase hospitalisation rates [4,6].

Hypercalcemia of malignancy (HHM) is an important factor influencing the modification, delay, or even discontinuation of anti-cancer treatment—including chemotherapy, radiotherapy, and targeted therapies—which consequently aggravates prognosis [6]. Early detection of hypercalcemia and the implementation of appropriate therapeutic measures improve patient comfort, reduce symptom burden, and limit the risk of life-threatening complications, especially in advanced disease [7]. Comprehensive diagnostics, the identification of risk factors, and effective management of hypercalcemia are therefore crucial at every stage of patient care—from eligibility for anti-cancer therapy, through active treatment, to the palliative phase [8].

Aim

This narrative review aims to critically evaluate and synthesize current evidence on the pathophysiology, clinical presentation, diagnosis, and management of malignancy-associated hypercalcemia (HHM), with a particular focus on palliative care contexts. By integrating data from clinical guidelines, recent studies, and expert consensus, this review seeks to provide a comprehensive and up-to-date resource for clinicians managing hypercalcemia in oncology patients. The synthesis emphasizes individualized therapeutic approaches, prognostic implications, and the role of interdisciplinary care in optimizing patient outcomes and enhancing quality of life in advanced malignancy.

Material and methods

A review of literature was conducted using databases such as PubMed, MEDLINE, Google Scholar. Fifty-six articles published between 1994 and 2024 were selected based on clinical relevance and scientific quality. Studies with outdated data, weak methodology, or limited

relevance to malignancy-associated hypercalcemia were excluded.

Definition and Classification

Under physiological conditions, total serum calcium ranges from 8.5–10.2 mg/dL (2.12–2.55 mmol/L), while ionised calcium is 1.05–1.32 mmol/L [5,7]. Hypercalcaemia is diagnosed when total calcium exceeds 10.5 mg/dL or ionised calcium exceeds 1.35 mmol/L. Depending on severity, hypercalcemia is classified as mild (10.5–12 mg/dL), moderate (12–14 mg/dL), or severe (> 14 mg/dL) [6,9]. Severe hypercalcemia poses a particular threat, potentially leading to acute renal failure, cardiac arrhythmias, and profound consciousness disorders [10]. Assessing the rate of calcium rise is critical for selecting an appropriate treatment strategy and determining the urgency of intervention—patients with rapidly increasing calcium levels are more likely to exhibit neurological and cardiovascular symptoms and require intensive monitoring [7].

Epidemiology and Risk Factors

HHM occurs in 2–30 % of cancer patients, depending on tumour type and stage [11,12]. It is most frequently diagnosed in multiple myeloma (30–40 %) and in breast, lung, and renal cancers, as well as in squamous-cell tumours [5,13]. Risk factors include extensive bone metastases (especially in breast, prostate, lung, and renal cancer), high tumour metabolic activity (neuroendocrine tumours, lymphomas, leukaemias), treatment-related fluid-electrolyte disturbances, co-existing renal failure, diabetes, dehydration, and medications affecting calcium metabolism (loop and thiazide diuretics) [14]. In palliative care, the situation is further complicated by limited possibilities for intensive anti-cancer therapy, particularly in patients with advanced cachexia and disease progression [4].

Pathophysiology

Calcium homeostasis is maintained by a balance between intestinal absorption, renal excretion, and bone turnover. This process is regulated mainly by parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and serum ionised calcium. Disruption of this balance in cancer leads to hypercalcemia, which significantly decreases clinical status and worsens prognosis [7,15].

Several pathophysiological mechanisms underlie malignancy-associated hypercalcemia. The most prevalent is HHM, accounting for approximately 80% of cases [10]. This mechanism involves the ectopic secretion of parathyroid hormone-related peptide (PTHrP) by tumor cells.

PTHrP binds to PTH-1 receptors in bone and kidneys, stimulating osteoclastic bone resorption while simultaneously reducing renal calcium excretion. These actions raise serum calcium levels and suppress endogenous calcitriol synthesis. HHM is most commonly observed in lung, breast, renal, and bladder cancers, as well as in squamous cell carcinomas of the head and neck [16,17].

A second mechanism involves the ectopic overproduction of calcitriol (1,25[OH]$_2$D) due to expression of the enzyme 1α-hydroxylase by malignant cells. This leads to increased intestinal calcium absorption, independent of PTH regulation. Laboratory profiles typically show suppressed or undetectable PTH with concurrently elevated levels of 1,25-dihydroxyvitamin D, a pattern often seen in lymphomas and diagnostically useful in clinical practice [18–20].

The third principal mechanism is local osteolysis, driven by direct activation of osteoclasts through tumor-derived cytokines. Among these, receptor activator of nuclear factor κB ligand (RANKL)—produced by osteoblasts and activated T cells—plays a central role. Its interaction with RANK on osteoclast precursors triggers their activation and promotes bone resorption [21,22]. Other factors exacerbating osteolytic activity include interleukins (IL-6, IL-1β, IL-8, IL-17), tumor necrosis factor alpha (TNF-α), macrophage colony-stimulating factor (M-CSF), and MIP-1α. High serum concentrations of MIP-1α are particularly associated with aggressive osteolysis in multiple myeloma [21,23].

In rare cases, hypercalcemia may result from the ectopic secretion of biologically active PTH, most commonly by neuroendocrine tumors, ovarian carcinoma, lung cancer, or soft tissue sarcomas. These cases closely mimic primary hyperparathyroidism, presenting with elevated serum PTH, hypercalcemia, and concurrent hypophosphatemia [4,11,24].

In the palliative setting, particular attention should be paid to secondary factors that exacerbate hypercalcemia. These include chronic dehydration due to poor oral intake, use of loop or thiazide diuretics, renal dysfunction, and advanced cancer cachexia. Collectively, these factors contribute to reduced intravascular volume and impaired glomerular filtration, thereby limiting renal calcium excretion [25]. Moreover, the catabolic metabolic state typical of advanced malignancy further enhances bone resorption through systemic inflammatory and hormonal pathways [26,27].

Understanding the multifactorial pathophysiology of hypercalcemia of malignancy is essential for timely diagnosis, appropriate therapeutic intervention, and comprehensive patient care—

particularly in advanced stages of cancer, where both biochemical and systemic contributors interact to intensify clinical severity [4].

Clinical Presentation and Consequences

Clinical manifestations vary with the height and rate of calcium increase. In cancer patients, hypercalcemia often rises rapidly, producing more severe symptoms than in non-malignant causes [9]. Early mild hypercalcemia (10.5–11.9 mg/dL) presents with non-specific symptoms: weakness, anorexia, polydipsia, polyuria, constipation, and mood changes (apathy, irritability). Cognitive impairment may appear and may be mistaken for treatment toxicity or cancer progression [6].

With calcium > 12 mg/dL, neurological symptoms progress: disorientation, somnolence, and confusion may evolve into encephalopathy or coma [13,28]. Posterior reversible encephalopathy syndrome (PRES) has been reported in severe cases [29,30].

Cardiovascular effects include QT shortening, potentially progressing to life-threatening arrhythmias such as ventricular fibrillation [31,32]. Gastrointestinal symptoms encompass anorexia, nausea, vomiting, gastroduodenal ulceration, and acute pancreatitis, often misattributed to therapy toxicity [33–35].

Renal effects involve nephrogenic diabetes insipidus (NDI), leading to polyuria, chronic dehydration, and progressive renal failure. Nephrocalcinosis and urolithiasis are less common in HHM [21]. Hypercalcaemia also increases thromboembolic risk due to hyperviscosity and haemostatic disturbances [36]. It accelerates cancer cachexia, causing rapid weight loss and decreased functional capacity [14].

Diagnosis

Diagnosis aims to confirm elevated calcium levels and establish the underlying cause [5]. Elevated total calcium on routine labs prompts assessment of albumin and pH. Ionised calcium should be measured when results are equivocal or in cachectic or patients with paraproteinaemia [37,38]. Elevated calcium should be confirmed on repeat testing to exclude transient dehydration [39].

After the initial confirmation of hypercalcemia, determining its underlying mechanism is crucial. Diagnostic evaluation includes measurement of PTH, PTHrP, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and phosphate levels [21,40]. Suppressed PTH levels suggest a non-parathyroid etiology, with elevated PTHrP indicating HHM [5,41]. Alternatively, increased levels of $1,25(OH)_2D$ may point to lymphoma, where aberrant activation of calcitriol synthesis pathways has been reported [18]. Elevated PTH, on the other hand, suggests primary hyperparathyroidism or, more rarely, parathyroid carcinoma [42]. In familial cases, genetic causes such as calcium-sensing receptor (CaSR) mutations should also be considered [43,44].

When bone metastases are suspected, appropriate imaging—such as plain radiography, bone scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI)—is warranted to evaluate the extent of skeletal involvement [9]. In oncologic patients presenting with hypercalcemia, it is also important to assess parathyroid function and thoroughly review the patient's current medications, particularly thiazide diuretics, vitamin D supplements, and lithium, all of which may contribute to elevated calcium levels [9]. A detailed clinical history is essential, including evaluation of lifestyle factors such as tobacco use and alcohol consumption, which may play a role in the development and progression of malignancy [4].

This comprehensive diagnostic approach—encompassing biochemical analysis, imaging studies, medication review, and clinical history—enables accurate identification of the underlying cause of hypercalcemia. Establishing the etiology is critical for timely initiation of targeted interventions aimed at reducing symptom burden. In the palliative care setting, such measures can directly improve patient comfort and facilitate more effective symptom control strategies [6].

Management

Management is multi-step and aims to achieve both rapid calcium reduction and treatment of the underlying malignancy [6]. In palliative care settings, symptom relief frequently becomes the primary objective. The initial therapeutic priority is correcting dehydration, which is common due to decreased oral intake, nausea, cognitive dysfunction, and nephrogenic diabetes insipidus (NDI) [45]. Intravenous administration of 0.9% saline at a rate of 200–500 mL/h is recommended, with adjustments based on cardiac and renal function [12]. Loop diuretics, such as furosemide, should only be introduced after achieving adequate hydration, in order to avoid

exacerbating fluid depletion [4].

For sustained control of moderate to severe hypercalcemia, anti-resorptive agents are essential. Bisphosphonates remain the first-line treatment, with options including zoledronic acid (4 mg IV over 15–30 minutes) or pamidronate (60–90 mg IV over 2–4 hours) [4]. Zoledronic acid has demonstrated superior efficacy compared to pamidronate, with a more rapid normalization of serum calcium and a longer duration of therapeutic effect [46]. However, bisphosphonate therapy carries the risk of adverse effects, including nephrotoxicity and osteonecrosis of the jaw, particularly with long-term use [47]. Other less common complications include uveitis, hypophosphatemia, hypocalcemia, atypical femoral fractures, and acute phase reactions presenting as flu-like symptoms [48]. Given these risks, close monitoring of renal function is mandatory during bisphosphonate therapy, and dosage adjustments should be made according to estimated glomerular filtration rate values [4].

In cases where bisphosphonates are contraindicated or ineffective, denosumab—a subcutaneously administered monoclonal antibody targeting RANKL (120 mg every 4 weeks)—offers an effective alternative. Compared to bisphosphonates, denosumab is associated with a higher incidence of joint pain, osteonecrosis of the jaw, and hypocalcemia, particularly during the early phases of treatment [4,6].

For severe hypercalcemia requiring rapid yet short-term reduction in serum calcium levels, salmon calcitonin (4–8 IU/kg subcutaneously every 6–8 hours) can be used. However, due to the risk of tachyphylaxis, its use should be limited to a maximum of 48–72 hours [49].

Glucocorticosteroids represent another important therapeutic class, particularly in patients with lymphoma or ovarian germ cell tumors. By inhibiting 1α-hydroxylase activity, they reduce the conversion of 25(OH)D to its active form, thereby lowering intestinal calcium absorption [5,50,51]. In clinical practice, intravenous hydrocortisone (200–400 mg per 24 hours for 3–4 days) is commonly administered, followed by a transition to oral prednisone, either at 10–20 mg/day for 7 days or 40–60 mg/day for up to 10 days. Glucocorticosteroids are expected to reduce serum calcium levels by over 3 mg/dL within the first week. If no therapeutic response is observed after 10 days, discontinuation of treatment is recommended [13]. In cases of partial response, combination therapy with anti-resorptive agents such as bisphosphonates or denosumab should be considered. During glucocorticoid therapy, patients should be closely monitored for potential adverse effects, including hypertension, hyperglycemia, mood disturbances, peptic ulcer disease, and muscle weakness [4].

In rare cases of malignancy-associated hypercalcemia caused by parathyroid carcinoma, surgical resection remains the treatment of choice. In inoperable cases, cinacalcet, a calcimimetic that modulates the CaSR, may be used to suppress PTH secretion and reduce serum calcium levels [52].

In extreme situations—such as severe renal failure or resistance to standard pharmacologic therapy—hemodialysis with a low-calcium dialysate may be indicated. This approach requires access to intensive care resources and is typically reserved for selected patients in whom the primary goal is improving comfort and enabling the continuation of oncologic treatment [53].

Treatment planning should also include regular monitoring of phosphate and magnesium levels, assessment of cancer stage, identification of secreted factors (e.g., PTHrP, calcitriol), evaluation of renal function, and consideration of potential curative oncologic options. A tailored approach addressing both symptom control and underlying pathophysiology may significantly reduce the burden of hypercalcemia and improve quality of life in palliative and non-palliative settings alike [13,19].

Prognostic Significance

HHM is both a metabolic disturbance and a marker of advanced disease and poor prognosis. It often signifies extensive bone marrow infiltration or disseminated metastasis [7,39]. Numerous studies associate HHM with reduced survival—typically weeks to months—depending on disease dynamics and treatment intensity [4]. Severe hypercalcemia ($\geq$ 14 mg/dL) or rapid calcium rise are particularly adverse [21].

Hypercalcemia substantially impairs quality of life by limiting the feasibility of anti-cancer therapy, reducing functional independence, and contributing to neurological complications, anorexia, and cancer cachexia. Symptoms such as fatigue, confusion, dehydration, and renal insufficiency increase the likelihood of hospitalization and the risk of complications later in the disease course. From the palliative care perspective, the primary goal of HHM management shifts toward symptom control and comfort. Effective treatment can facilitate oral fluid intake, optimize pain control, and improve appetite, thus contributing to better overall patient well-being [4,7].

The clinical trajectory of hypercalcemia can influence therapeutic decision-making. In many cases—particularly when calcium levels are persistently rising and no effective oncologic

options remain—hypercalcemia becomes a key determinant in transitioning to comfort-focused, symptom-directed care. Conversely, in patients with less advanced disease, effective management of hypercalcemia may allow the continuation of anticancer therapies, thereby prolonging survival and maintaining quality of life. In clinical practice, short-term stabilization of calcium homeostasis may be undertaken to improve specific symptoms, such as drowsiness, cognitive impairment, or nausea, thereby enhancing patient comfort and communication capacity, even in end-of-life settings [5,34,35].

Acute neurocognitive symptoms pose medical and emotional challenges requiring psychological support and education for patients and caregivers [14,54,55]. Interdisciplinary care is essential, involving physicians, psychologists, dietitians, and physiotherapists to combat cachexia and other effects. Ensuring hydration, laboratory monitoring, and home or hospice-based care improves quality of life in advanced cancer [7,56].

Conclusions

Hypercalcaemia in malignancy remains a significant clinical challenge in oncology and palliative practice. Effective management demands knowledge of pathophysiology, rapid diagnostics, and tailored interventions aligned with calcium kinetics and patient status. While rehydration and anti-resorptives remain the backbone of therapy, emerging options such as cinacalcet and targeted therapies modulating PTHrP and CaSR are gaining importance. These measures should form part of individualised, interdisciplinary care, including home or hospice settings. Maintaining normocalcaemia improves clinical status, alleviates neurological and somatic symptoms, enables continuation of anti-cancer therapy, and reduces hospitalisation risk. Further research into new therapeutic strategies is crucial for improving prognosis and quality of life in advanced cancer.

Author's contribution:

Conceptualization: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska;

Methodology: Dominika Bachurska; Justyna Ignarska; Oliwia Grygorczuk; Jakub Marek

Check: Dominika Bachurska; Zuzanna Czach; Oliwia Grygorczuk; Jakub Marek

Formal analysis: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska; Jakub Marek

Investigation: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska; Justyna Ignarska; Oliwia Grygorczuk; Jakub Marek

Resources: Dominika Bachurska; Zuzanna Czach; Oliwia Grygorczuk; Jakub Marek

Data curation: Dominika Bachurska; Justyna Ignarska; Oliwia Grygorczuk; Jakub Marek

Writing - rough preparation: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska; Justyna Ignarska; Oliwia Grygorczuk; Jakub Marek

Writing - review and editing: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska; Justyna Ignarska; Oliwia Grygorczuk; Jakub Marek

Supervision: Dominika Bachurska; Zuzanna Czach; Magdalena Ignarska;

Project administration: Dominika Bachurska; Zuzanna Czach; Jakub Marek

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

Conflict of Interest Statement: The authors declare no conflict of interests

In preparing this work, the authors used ChatGPT by OpenAI for the purpose of improving language clarity, enhancing readability, and organizing scientific content. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

References

1. Jick S, Li L, Gastanaga VM, Liede A. Prevalence of hypercalcemia of malignancy among cancer patients in the UK: analysis of the Clinical Practice Research Datalink database. Cancer Epidemiol. 2015;39: 901–907. doi:10.1016/j.canep.2015.10.012

2. Mousseaux C, Dupont A, Rafat C, Ekpe K, Ghrenassia E, Kerhuel L, et al. Epidemiology, clinical features, and management of severe hypercalcemia in critically ill patients. Ann Intensive Care. 2019;9: 133.

doi:10.1186/s13613-019-0606-8

3. Gupta S, Rastogi A, Singh P, Chophy A, Roushan R, Krishnan AS, et al. Treatment outcomes and survival in hypercalcemia of malignancy: A grave metabolic emergency. Cureus. 2023;15: e35783. doi:10.7759/cureus.35783

4. Mirrakhimov AE. Hypercalcemia of malignancy: An update on pathogenesis and management. N Am J Med Sci. 2015;7: 483–493. doi:10.4103/1947-2714.170600

5. Asonitis N, Angelousi A, Zafeiris C, Lambrou GI, Dontas I, Kassi E. Diagnosis, pathophysiology and management of hypercalcemia in malignancy: A review of the literature. Horm Metab Res. 2019;51: 770–778. doi:10.1055/a-1049-0647

6. Goldner W. Cancer-related hypercalcemia. J Oncol Pract. 2016;12: 426–432. doi:10.1200/JOP.2016.011155

7. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005;352: 373–379. doi:10.1056/NEJMcp042806

8. Reagan P, Pani A, Rosner MH. Approach to diagnosis and treatment of hypercalcemia in a patient with malignancy. Am J Kidney Dis. 2014;63: 141–147. doi:10.1053/j.ajkd.2013.06.025

9. Zagzag J, Hu MI, Fisher SB, Perrier ND. Hypercalcemia and cancer: Differential diagnosis and treatment. CA Cancer J Clin. 2018;68: 377–386. doi:10.3322/caac.21489

10. Rosner MH, Dalkin AC. Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clin J Am Soc Nephrol. 2012;7: 1722–1729. doi:10.2215/CJN.02470312

11. Almuradova E, Cicin I. Cancer-related hypercalcemia and potential treatments. Front Endocrinol (Lausanne). 2023;14: 1039490. doi:10.3389/fendo.2023.1039490

12. Basso U, Maruzzo M, Roma A, Camozzi V, Luisetto G, Lumachi F. Malignant hypercalcemia. Curr Med Chem. 2011;18: 3462–3467. doi: https://doi.org/10.2174/157340612801216382

13. Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. Ther Clin Risk Manag. 2015;11: 1779–1788. doi:10.2147/TCRM.S83681

14. Bartkiewicz P, Kunachowicz D, Filipski M, Stebel A, Ligoda J, Rembiałkowska N. Hypercalcemia in cancer: Causes, effects, and treatment strategies. Cells. 2024;13: 1051. doi:10.3390/cells13121051

15. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5 Suppl 1: S23–30. doi:10.2215/CJN.05910809

16. Kim W, Takyar FM, Swan K, Jeong J, VanHouten J, Sullivan C, et al. Calcium-sensing receptor promotes

breast cancer by stimulating intracrine actions of parathyroid hormone-related protein. Cancer Res. 2016;76: 5348–5360. doi:10.1158/0008-5472.CAN-15-2614

17. Levine BS, Rodríguez M, Felsenfeld AJ. Serum calcium and bone: effect of PTH, phosphate, vitamin D and uremia. Nefrologia. 2014;34: 658–669. doi:10.3265/Nefrologia.pre2014.Jun.12379

18. Chukir T, Liu Y, Hoffman K, Bilezikian JP, Farooki A. Calcitriol elevation is associated with a higher risk of refractory hypercalcemia of malignancy in solid tumors. J Clin Endocrinol Metab. 2020;105: e1115–e1123. doi:10.1210/clinem/dgz278

19. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: Mechanisms, diagnosis, and treatment. Endocr Rev. 2016;37: 521–547. doi:10.1210/er.2016-1070

20. Sheehan MT, Li Y-H, Doi SA, Onitilo AA. Evaluation of diagnostic workup and etiology of hypercalcemia of malignancy in a cohort of 167 551 patients over 20 years. J Endocr Soc. 2021;5: bvab157. doi:10.1210/jendso/bvab157

21. Tonon CR, Silva TAAL, Pereira FWL, Queiroz DAR, Junior ELF, Martins D, et al. A review of current clinical concepts in the pathophysiology, etiology, diagnosis, and management of hypercalcemia. Med Sci Monit. 2022;28: e935821. doi:10.12659/MSM.935821

22. Maurizi A, Rucci N. The osteoclast in bone metastasis: Player and target. Cancers (Basel). 2018;10. doi:10.3390/cancers10070218

23. Soki FN, Park SI, McCauley LK. The multifaceted actions of PTHrP in skeletal metastasis. Future Oncol. 2012;8: 803–817. doi:10.2217/fon.12.76

24. Neves A, Mendonça I, Cunha Marques JA, Costa J, Almeida JS. Malignant hypercalcemia induced by the ectopic production of intact parathyroid hormone (PTH). Cureus. 2023;15: e34770. doi:10.7759/cureus.34770

25. Cheng C, Kuzhively J, Baim S. Hypercalcemia of malignancy in thymic carcinoma: Evolving mechanisms of hypercalcemia and targeted therapies. Case Rep Endocrinol. 2017;2017: 2608392. doi:10.1155/2017/2608392

26. Solimando DA. Overview of hypercalcemia of malignancy. Am J Health Syst Pharm. 2001;58 Suppl 3: S4–7. doi:10.1093/ajhp/58.suppl_3.S4

27. Song L. Calcium and bone metabolism indices. Adv Clin Chem. 2017;82: 1–46. doi:10.1016/bs.acc.2017.06.005

28. Bushinsky DA, Monk RD. Electrolyte quintet: Calcium. Lancet. 1998;352: 306–311. doi:10.1016/s0140-6736(97)12331-5

29. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264: 1608–1616. doi:10.1007/s00415-016-8377-8

30. Moussawi K, Meltzer EI, Levin SN, Prasad S. Paraneoplastic PRES from lymphoma induced hypercalcemia: Case report and review of the literature. eNeurologicalSci. 2018;13: 24–25. doi:10.1016/j.ensci.2018.11.003

31. Nishi SPE, Barbagelata NA, Atar S, Birnbaum Y, Tuero E. Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. J Electrocardiol. 2006;39: 298–300. doi:10.1016/j.jelectrocard.2005.10.015

32. Chang W-TW, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014;32: 349–366. doi:10.1016/j.emc.2013.12.006

33. Yang L, Lin Y, Zhang X-Q, Liu B, Wang J-Y. Acute pancreatitis with hypercalcemia caused by primary hyperparathyroidism associated with paraneoplastic syndrome: A case report and review of literature. World J Clin Cases. 2021;9: 8906–8914. doi:10.12998/wjcc.v9.i29.8906

34. Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. Curr Opin Endocrinol Diabetes Obes. 2011;18: 339–346. doi:10.1097/MED.0b013e32834b4401

35. Inzucchi SE. Understanding hypercalcemia. Postgrad Med. 2004;115: 69–76. doi:10.3810/pgm.2004.04.1486

36. Duminuco A, Del Fabro V, De Luca P, Leotta D, Limoli MC, Longo E, et al. Emergencies in hematology: Why, when and how I treat? J Clin Med. 2024;13. doi:10.3390/jcm13247572

37. Walker MD, Shane E. Hypercalcemia: A review. JAMA. 2022;328: 1624–1636. doi:10.1001/jama.2022.18331

38. Endres DB. Investigation of hypercalcemia. Clin Biochem. 2012;45: 954–963. doi:10.1016/j.clinbiochem.2012.04.025

39. Kc O, Dahal PH, Koirala M, Al Zaghal E. Unusual case of dehydration leading to severe symptomatic hypercalcemia. Am J Case Rep. 2022;23: e936204. doi:10.12659/AJCR.936204

40. Meng QH, Wagar EA. Laboratory approaches for the diagnosis and assessment of hypercalcemia. Crit Rev Clin Lab Sci. 2015;52: 107–119. doi:10.3109/10408363.2014.970266

41. Wysolmerski JJ, Broadus AE. Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. Annu Rev Med. 1994;45: 189–200. doi:10.1146/annurev.med.45.1.189

42. Markowitz ME, Underland L, Gensure R. Parathyroid disorders. Pediatr Rev. 2016;37: 524–535. doi:10.1542/pir.2015-0076

43. Xie R, Tang B, Yong X, Luo G, Yang S-M. Roles of the calcium sensing receptor in digestive physiology and pathophysiology (review). Int J Oncol. 2014;45: 1355–1362. doi:10.3892/ijo.2014.2560

44. Vahe C, Benomar K, Espiard S, Coppin L, Jannin A, Odou MF, et al. Diseases associated with calcium-sensing receptor. Orphanet J Rare Dis. 2017;12: 19. doi:10.1186/s13023-017-0570-z

45. Body J-J, Niepel D, Tonini G. Hypercalcaemia and hypocalcaemia: finding the balance. Support Care Cancer. 2017;25: 1639–1649. doi:10.1007/s00520-016-3543-1

46. Reid IR, Green JR, Lyles KW, Reid DM, Trechsel U, Hosking DJ, et al. Zoledronate. Bone. 2020;137: 115390. doi:10.1016/j.bone.2020.115390

47. Abrahamsen B. Adverse effects of bisphosphonates. Calcif Tissue Int. 2010;86: 421–435. doi:10.1007/s00223-010-9364-1

48. Coleman RE, Winter MC, Cameron D, Bell R, Dodwell D, Keane MM, et al. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. Br J Cancer. 2010;102: 1099–1105. doi:10.1038/sj.bjc.6605604

49. Maier JD, Levine SN. Hypercalcemia in the intensive care unit: A review of pathophysiology, diagnosis, and modern therapy. J Intensive Care Med. 2015;30: 235–252. doi:10.1177/0885066613507530

50. Lim D, Oliva E. Gynecological neoplasms associated with paraneoplastic hypercalcemia. Semin Diagn Pathol. 2019;36: 246–259. doi:10.1053/j.semdp.2019.01.003

51. Shivnani SB, Shelton JM, Richardson JA, Maalouf NM. Hypercalcemia of malignancy with simultaneous elevation in serum parathyroid hormone--related peptide and 1,25-dihydroxyvitamin D in a patient with metastatic renal cell carcinoma. Endocr Pract. 2009;15: 234–239. doi:10.4158/EP.15.3.234

52. Marcocci C, Chanson P, Shoback D, Bilezikian J, Fernandez-Cruz L, Orgiazzi J, et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab. 2009;94: 2766–2772. doi:10.1210/jc.2008-2640

53. Dellay B, Groth M. Emergency management of malignancy-associated hypercalcemia. Adv Emerg Nurs J. 2016;38: 15–25. doi:10.1097/tme.0000000000000093

54. Delgado-Guay MO, Yennurajalingam S, Bruera E. Delirium with severe symptom expression related to hypercalcemia in a patient with advanced cancer: an interdisciplinary approach to treatment. J Pain Symptom Manage. 2008;36: 442–449. doi:10.1016/j.jpainsymman.2007.11.004

55. Faiman BM, Mangan P, Spong J, Tariman JD, The International Myeloma Foundation Nurse Leadership Board. Renal complications in multiple myeloma and related disorders: survivorship care plan of the International Myeloma Foundation Nurse Leadership Board. Clin J Oncol Nurs. 2011;15 Suppl: 66–76. doi:10.1188/11.CJON.S1.66-76

56. Cherny NI, ESMO Guidelines Working Group. ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation. Ann Oncol. 2014;25 Suppl 3: iii143–52. doi:10.1093/annonc/mdu238