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Review article

Hypercalcemia of Malignancy and Malignancy-Associated Kidney Damage: A Comprehensive Narrative Review with Clinical Relevance

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Abstract
Hypercalcemia of malignancy (HCM) is a common paraneoplastic syndrome occurring in 10–30% of patients with advanced cancer. It is associated with significant morbidity and poor prognosis. This narrative review examines the mechanisms of HCM, its clinical presentation, diagnostic approach, and current management strategies, with particular emphasis on the interplay with kidney damage. Renal impairment both results from and exacerbates hypercalcemia, creating a vicious cycle that complicates therapy. Evidence-based recommendations, including those from the 2023 Endocrine Society Clinical Practice Guideline, highlight the role of hydration, antiresorptive agents (bisphosphonates and denosumab), and treatment of the underlying malignancy. Multidisciplinary collaboration between oncologists and nephrologists is essential for optimizing outcomes in patients with concurrent acute kidney injury or chronic kidney disease. Early recognition and mechanism-specific therapy can reverse renal dysfunction in many cases and improve quality of life.
Keywords. Hypercalcemia, Malignancy, Parathyroid Hormone-Related Peptide, Acute Kidney Injury.

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Introduction

Hypercalcemia of malignancy (HCM), also known as malignancy-associated hypercalcemia (MAH), represents one of the most frequent metabolic complications in oncology. It develops in approximately 10–30% of patients with advanced solid tumors (particularly squamous cell carcinomas of the lung, head and neck, esophagus, and breast cancer) and hematologic malignancies such as multiple myeloma and lymphoma [1,2]. Among hospitalized cancer patients, malignancy is the leading cause of hypercalcemia, surpassing primary hyperparathyroidism in frequency [3,4]. Severe HCM is an oncologic emergency that correlates with shortened survival, often 2–6 months in untreated or refractory cases [1,2].

Beyond its direct effects on bone, neurologic, and gastrointestinal systems, HCM frequently induces kidney damage, which further elevates serum calcium by impairing excretion [5]. This bidirectional relationship underscores the clinical relevance of onco-nephrology in managing these patients [5]. The kidneys are both a target and a mediator of HCM: hypercalcemia impairs renal concentrating ability, leading to polyuria and volume depletion, which further exacerbates hypercalcemia in a vicious cycle [5,6]. Severe or prolonged hypercalcemia can cause structural kidney damage, including nephrocalcinosis and AKI [3,5]. Conversely, pre-existing CKD alters the pharmacokinetics and safety profiles of antiresorptive agents such as bisphosphonates, complicating management decisions [4,7].

For this narrative review, a comprehensive literature search was performed in PubMed, MEDLINE, Embase, and Google Scholar databases from inception through April 2026. Key search terms included “hypercalcemia of malignancy,” “malignancy-associated hypercalcemia,” “PTHrP,” “onco-nephrology,” “cancer-associated hypercalcemia,” “bisphosphonates,” “denosumab,” and “malignancy-associated kidney injury.” Priority was given to high-impact original articles, recent systematic reviews, clinical practice guidelines (particularly the 2023 Endocrine Society Guideline), and publications from the last 10 years. Relevant references from selected articles were also screened manually.

This comprehensive narrative review synthesizes current knowledge on the pathophysiology, diagnosis, treatment, and renal complications of HCM, highlighting practical implications for patient care and the essential collaboration between oncology and nephrology teams. While this review focuses on adults in accordance with the 2023 Endocrine Society Clinical Practice Guideline, it is worth noting that HCM in pediatric patients presents distinct etiological considerations, including a higher proportion of calcitriol-mediated hypercalcemia, granulomatous conditions, and rare genetic syndromes such as William's syndrome, alongside different pharmacological safety profiles for antiresorptive agents in growing bone. Clinicians managing pediatric malignancy-associated hypercalcemia should consult dedicated pediatric endocrinology and oncology resources.

Pathophysiology of Hypercalcemia of Malignancy

Calcium homeostasis is tightly regulated by parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and fibroblast growth factor 23, acting on bone, kidney, and intestine [6]. In HCM, tumor-related mechanisms disrupt this balance, leading to net calcium release that overwhelms renal compensatory capacity [3,4]. Four main mechanisms are recognized [1].

Table 1. Mechanisms of Hypercalcemia of Malignancy

Mechanism	Frequency	Key Mediator	Typical Associated Cancers	Laboratory Findings	Primary Treatment Implications
Humoral (HHM)	~80%	PTHrP	Squamous cell (lung, head/neck, esophagus), breast, renal cell, bladder	Suppressed PTH, elevated PTHrP, low/normal 1,25-D, low phosphate	Antiresorptive agents (bisphosphonates or denosumab)
Local Osteolytic	20–30%	Cytokines (IL-1β, IL-6, TNF-α, RANKL)	Breast, multiple myeloma, prostate (extensive bone mets)	Suppressed PTH, variable PTHrP	Antiresorptive agents + tumor-directed therapy
Calcitriol-Mediated	1–5%	Ectopic 1-α-hydroxylase	Hodgkin and non-Hodgkin lymphomas	Suppressed PTH, elevated 1,25-D, normal/high phosphate	Glucocorticoids ± antiresorptive agents
Ectopic PTH Secretion	<1%	PTH	Ovarian, lung, and parathyroid carcinoma	Elevated PTH	Antiresorptive ± calcimimetics (for parathyroid carcinoma)

Additional contributors include immobilization and, rarely, medication effects [1]. These pathways converge on increased bone resorption and altered renal handling of calcium, overwhelming the kidney's ability to excrete the calcium load [6].

Malignancy-Associated Kidney Damage: Mechanisms Beyond Hypercalcemia

Malignancy can damage the kidneys through several distinct mechanisms, some of which may coexist with HCM and complicate its management [5].

Direct Tumor Infiltration

Malignant cells can directly infiltrate the renal parenchyma, interstitium, or collecting system. This is most commonly seen in lymphomas and leukemias, but also occurs in metastatic solid tumors, causing renal enlargement, AKI, tubular dysfunction, or obstructive uropathy [3,5].

Tumor Lysis Syndrome (TLS)

TLS is an oncologic emergency characterized by rapid cell breakdown, typically after chemotherapy. It leads to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. AKI results primarily from uric acid and calcium-phosphate crystal deposition [3,5]. TLS and HCM are distinct (opposing effects on calcium), but both can cause AKI; differentiation is critical. Clinicians should explicitly distinguish TLS from HCM at presentation, as their calcium profiles are diametrically opposed — hypercalcemia in HCM versus hypocalcemia in TLS — yet both carry a high risk of AKI and may rarely coexist in patients receiving cytotoxic therapy for calcium-elevating malignancies such as lymphoma.

Paraneoplastic Glomerulopathies

These include minimal change disease (hematologic malignancies), membranous nephropathy (solid tumors), and amyloidosis (multiple myeloma), typically presenting with proteinuria or nephrotic syndrome rather than acute hypercalcemic crises [3,5].

Renal Consequences of Hypercalcemia of Malignancy

Kidney involvement is common in HCM (up to 60% in severe cases) and creates a self-perpetuating cycle [5]. Figure 1 summarizes the vicious cycle of hypercalcemia-associated malignancy and kidney involvement.

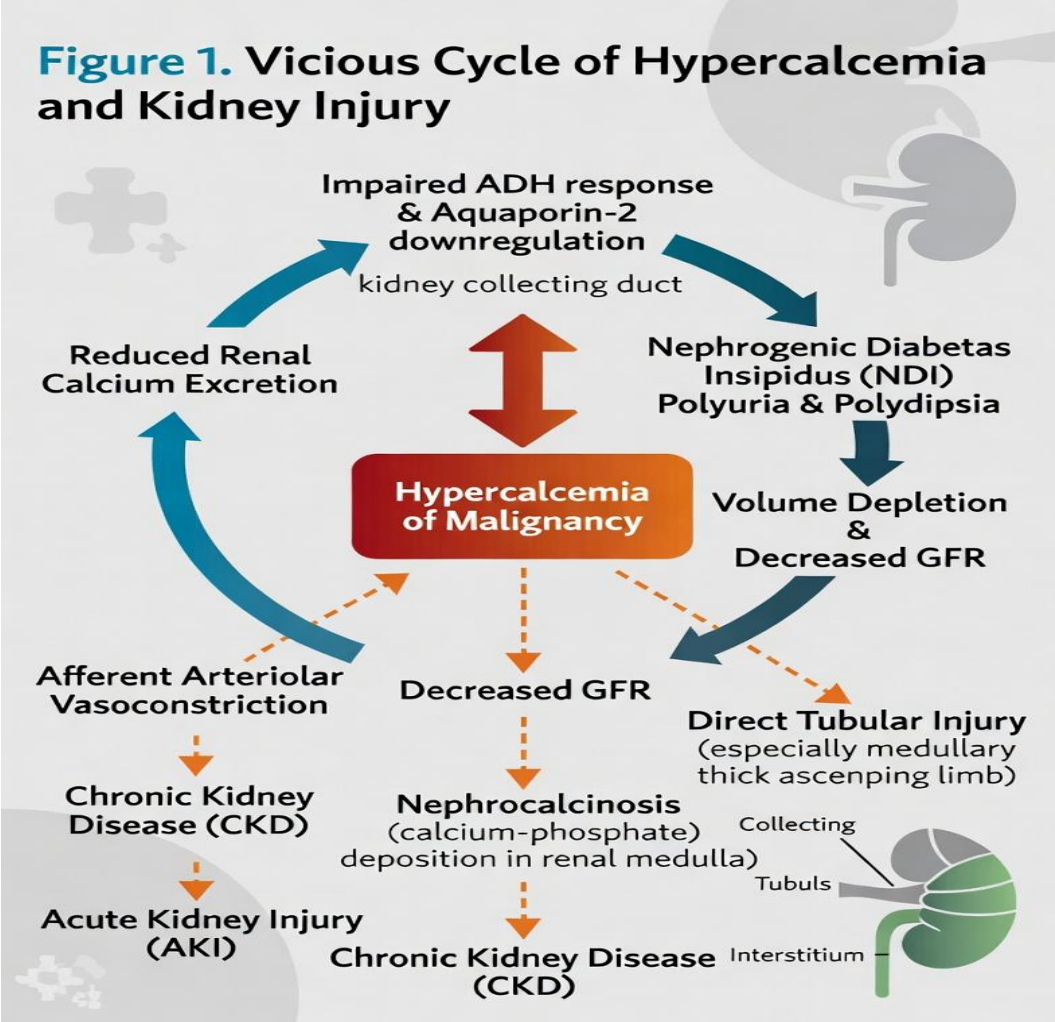

Figure 1. Vicious Cycle of Hypercalcemia and Kidney Injury

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Hypercalcemia impairs the kidney's concentration ability, leading to nephrogenic diabetes insipidus and polyuria. This results in volume depletion and a reduced glomerular filtration rate, which in turn decreases calcium excretion and worsens hypercalcemia. Direct renal effects also include afferent arteriolar vasoconstriction, tubular injury, nephrocalcinosis, and progression to acute kidney injury [5,6].

Impaired Urinary Concentrating Ability and Nephrogenic Diabetes Insipidus
Hypercalcemia downregulates aquaporin-2 water channels and disrupts the medullary concentration gradient, causing polyuria, polydipsia, and nephrogenic diabetes insipidus (NDI) [6]. This leads to free water loss, volume depletion, hypernatremia, and further impairment of calcium excretion [5,6].

Acute Kidney Injury (AKI)
The pathogenesis of AKI in HCM is multifactorial [5]. Prerenal injury is the most common initial mechanism, driven by volume depletion resulting from polyuria, vomiting, and reduced oral intake. Intrinsic renal injury supervenes through afferent arteriolar vasoconstriction and direct tubular injury, particularly affecting the medullary thick ascending limb, which is highly sensitive to calcium-mediated vasoconstriction and ischemia. Postrenal obstruction may also contribute when nephrolithiasis results in ureteric obstruction, particularly in the context of chronic or recurrent hypercalciuria. The severity of AKI correlates with both the degree and duration of hypercalcemia [3].

Nephrocalcinosis
Chronic or recurrent hypercalcemia leads to calcium-phosphate deposition in the renal medulla, potentially progressing to tubular dysfunction and CKD [6,10]. In malignancy, this is often compounded by light-chain injury, chemotherapy nephrotoxicity, or TLS [5].

Clinical Presentation and Diagnosis

Clinical Features

Symptoms are usually nonspecific and depend on severity and rate of rise [1,3]. Mild hypercalcemia (10.5–12 mg/dL [2.62–3.00 mmol/L]): fatigue, constipation, polyuria. Moderate levels (12–14 mg/dL [3.00–3.50 mmol/L]): dehydration, nausea, muscle weakness, confusion. Severe hypercalcemia (>14 mg/dL [>3.50 mmol/L]: somnolence, seizures, coma, arrhythmias, and AKI [3,4].

Laboratory Evaluation

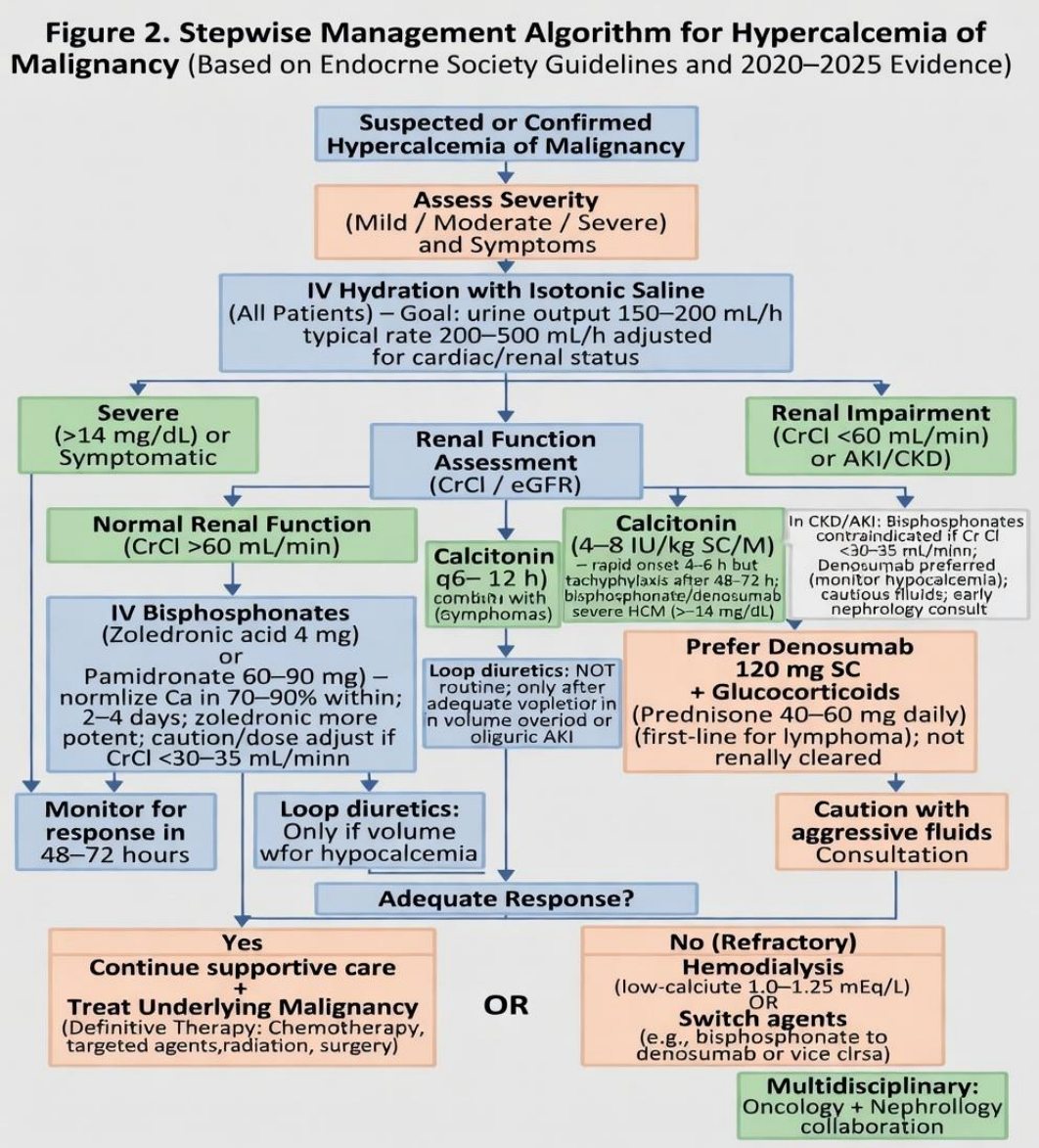
Measure corrected or ionized calcium. Key tests include intact PTH (suppressed in most HCM), PTHrP, 1,25-dihydroxyvitamin D, phosphate, renal function, serum protein electrophoresis, and 25-hydroxyvitamin D [3,5,8]. Clinicians should be aware that PTHrP assays are subject to significant inter-laboratory variability and lack universal standardization, with differences in antibody specificity, the molecular fragment measured (N-terminal, mid-molecule, or C-terminal), and reference ranges across platforms. A detectable but low PTHrP result should therefore be interpreted cautiously and in conjunction with the overall clinical picture and repeat testing at a reference laboratory may be warranted when clinical suspicion remains high despite an initially negative or borderline result [9,10].

Differential Diagnosis

Includes primary hyperparathyroidism (elevated or inappropriately normal PTH, milder and chronic elevation), granulomatous disease, vitamin D toxicity, and others [3,6]. Serum calcium >13 mg/dL at presentation strongly suggests malignancy [3].

Management of Hypercalcemia of Malignancy

Treatment goals are to lower serum calcium rapidly, relieve symptoms, protect organ function (particularly kidneys), and address the underlying malignancy for durable control [5,7]. Figure 2 represents a stepwise management flowchart for hypercalcemia of Malignancy (based on Endocrine Society guidelines and 2020-2025 evidence).



Legend: *Figure 2. This flowchart presents a practical, evidence-based stepwise approach to the management of hypercalcemia of malignancy (HCM). The algorithm begins with an initial assessment of severity and symptoms, followed by universal intravenous isotonic saline hydration. Subsequent branches are guided by renal function assessment and clinical severity. Key interventions include calcitonin as bridge therapy, intravenous bisphosphonates (zoledronic acid or pamidronate) for patients with normal renal function, and denosumab plus glucocorticoids (preferred in renal impairment or calcitriol-mediated HCM such as lymphomas). Loop diuretics are restricted to specific situations after volume repletion. The pathway emphasizes monitoring for response (48–72 hours), treatment of refractory cases with hemodialysis or agent switching, and the essential role of definitive antineoplastic therapy. Special considerations for patients with chronic kidney disease (CKD) or acute kidney injury (AKI) are integrated, including preference for denosumab, cautious fluid administration, and early nephrology involvement. Multidisciplinary collaboration (oncology + nephrology) is recommended for complex or refractory cases. All dosages, indications, and cautions are derived directly from the referenced guidelines and recent comparative studies (2020–2025).*
Abbreviations: HCM = Hypercalcemia of Malignancy, CrCl = Creatinine Clearance, AKI = Acute Kidney Injury, CKD = Chronic Kidney Disease, SC = Subcutaneous, IM = Intramuscular, IU = International Units, mEq/L = milliequivalents per liter, IV = Intravenous, Ca = Calcium.

Intravenous Hydration

Intravenous isotonic saline is the cornerstone of initial management for all patients with symptomatic or severe HCM [5,7]. Normal saline corrects volume depletion and promotes calciuresis. The typical initial fluid rate is 200–500 mL/hour, adjusted for cardiac and renal status [3,7].

Loop Diuretics
Loop diuretics were historically used, but current guidelines recommend against their routine use because they do not lower calcium more effectively than saline alone and may worsen volume depletion [3,7]. They should only be considered after adequate volume repletion in patients with volume overload or oliguric AKI [7].

Calcitonin
Calcitonin acts rapidly (within 4–6 hours) but is limited by tachyphylaxis after 48–72 hours [3,7]. The typical dose is 4–8 IU/kg subcutaneously or intramuscularly every 6–12 hours. It is useful as a bridge therapy in severe hypercalcemia while awaiting the onset of antiresorptive agents [2]. The Endocrine Society suggests combination with an IV bisphosphonate or denosumab for adults with severe HCM (serum calcium >14 mg/dL) [7].

Antiresorptive Therapy: Bisphosphonates
Intravenous bisphosphonates (zoledronic acid 4 mg or pamidronate 60–90 mg) are highly effective, normalizing calcium in 70–90% of patients within 2–4 days [3,4]. Zoledronic acid is generally more potent. Renal considerations: generally contraindicated or require dose adjustment and slower infusion if CrCl <30–35 mL/min; caution in moderate CKD [1,2].

Denosumab
Denosumab (120 mg subcutaneously) is a RANKL inhibitor that is at least as effective as bisphosphonates and preferred in renal impairment because it is not cleared by the kidneys [4,7]. A 2025 comparative study showed comparable or slightly superior calcium reduction with denosumab and lower rates of hypocalcemia in some analyses [11].

Glucocorticoids
Glucocorticoids are first-line for calcitriol-mediated HCM from lymphomas [7,8].

Calcimimetics
Primarily used in parathyroid carcinoma [3,7].

Emerging and Investigational Agents
Beyond currently approved antiresorptive therapies, several agents targeting bone resorption pathways are under active investigation. Romosozumab, an anti-sclerostin monoclonal antibody, modulates the Wnt signaling pathway and is approved for osteoporosis but has not yet been evaluated in HCM. Selective cathepsin K inhibitors, such as odanacatib, demonstrated potent antiresorptive activity in bone-metastatic disease in early trials, though their role in HCM management remains undefined [12]. As targeted oncologic therapies increasingly suppress tumor-driven PTHrP or cytokine release, their indirect calcium-lowering effects may reduce future reliance on dedicated antiresorptive treatment. These developments warrant monitoring in upcoming clinical trials.

Hemodialysis: Indicated in refractory or life-threatening cases (especially with severe AKI or calcium >18–20 mg/dL) using low-calcium dialysate [2,7].

Definitive Therapy: Effective antineoplastic treatment is essential for sustained control of HCM [1,7].

Special Considerations: Management in the Setting of Renal Impairment
Managing HCM in patients with pre-existing CKD or AKI is challenging [6,9]. As noted in Sections 6.4 and 6.5, bisphosphonates are generally contraindicated when CrCl <30–35 mL/min, whereas denosumab is preferred in renal impairment without dose adjustment, though monitoring for hypocalcemia is especially important in CKD patients [2,7]. Fluid management (**Section 6.1**) must be cautious in patients with heart failure or advanced CKD, and early nephrology consultation is recommended [5]. Hemodialysis is highly effective for rapid calcium reduction and volume control in severe cases, using low-calcium dialysate (1.0–1.25 mEq/L) [5,7].

Monitoring and Complications of Therapy
Regular monitoring of serum calcium, renal function, and electrolytes is mandatory [7]. Hypocalcemia is a particular concern with denosumab and, to a lesser extent, bisphosphonates [11]. Prevention and management of treatment-induced hypocalcemia is an integral part of therapy. All patients initiating antiresorptive

therapy should receive calcium supplementation (typically 500–1000 mg elemental calcium daily in divided doses) and vitamin D (cholecalciferol 800–2000 IU daily), with dose adjustments guided by serum calcium, phosphate, and 25-hydroxyvitamin D levels. In patients with CKD, active vitamin D analogues such as calcitriol (0.25–0.5 mcg daily) may be required due to impaired renal 1-α-hydroxylation. Serum calcium should be monitored at 1, 2, and 4 weeks after initiation of denosumab and periodically thereafter, with more frequent monitoring in patients with advanced CKD, hypomagnesaemia, or concurrent loop diuretic use [7]. Other complications include osteonecrosis of the jaw with long-term use and renal toxicity from bisphosphonates [7].

Prognosis and Clinical Relevance

HCM portends advanced disease and reduced survival, yet rapid normalization of calcium can improve symptoms, preserve organ function, and allow delivery of cancer-directed therapies [1,2]. Renal complications amplify urgency and limit therapeutic options [5]. Multidisciplinary collaboration improves short-term outcomes [2,7].

Conclusions

Hypercalcemia of malignancy remains a common and serious complication of advanced cancer. The bidirectional relationship between HCM and kidney damage is a critical consideration in patient management. A stepwise approach—aggressive hydration, mechanism-specific antiresorptive therapy (preferring denosumab in renal impairment), calcitonin for severe cases, and definitive treatment of the underlying malignancy—optimizes outcomes. Early involvement of both oncology and nephrology teams is essential.

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