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Original Article

Oncology Section

Management and Outcomes in Head and Neck Cancer Patients with Malignancy Related Hypercalcaemia, an Oncological Emergency: A Cohort Study from a Tertiary Care Hospital in Tamil Nadu

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ABSTRACT

Introduction: Malignancy-Related Hypercalcaemia (MRH) is a paraneoplastic syndrome often associated with various malignancies but has limited evidence available Head and Neck Cancers (HNC). Head and neck squamous cell carcinomas with MRH is rare but it has a unique propensity to induce hypercalcaemia, even in the absence of bone metastases. Despite its clinical significance, hypercalcaemia in this patient population is frequently missed, as its symptoms are often attributed to the underlying malignancy or its treatment.

Aim: The present study aimed to analyse data on patterns of care, define the clinical profile of hypercalcaemia in HNC patients, evaluate treatment strategies employed during hospitalisation, and assess survival outcomes.

Materials and Methods: The present cohort study was done and analysis was conducted on HNC patients hospitalised at Department of Radiation Oncology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India between January 2014 to July 2024 with symptomatic hypercalcaemia (serum total calcium >10.5 mg/dL) based on inpatient medical records. Data were extracted for the clinical profile, patterns of management and survival follow-up was from electronic medical records and telephonic follow-ups. Based on the serum total calcium levels, hypercalcaemia was categorised as mild, moderate and severe for the ranges, 10.5-11.9 mg/dL, 12-13.9 mg/dL; and more than 14 mg/dL, respectively. Descriptive statistics were used for categorical and continuous variables. Survival was analysed using Kaplan-Meier estimates using stata version 16.1 and python version 3.9.21.

Results: Total of 19 patients was included in the study. The cohort was predominantly men 17 (89.47%), with median age of 51 years. 17 (89.47%) of patients had oral cavity cancers as the primary site of malignancy, with 9 (52.94%) originating from the tongue and 8 (47.05%) buccal mucosa. Most common presenting symptom was bone pain 13 (68.42%). Hypercalcaemia management included 14 (73.68%) of patients receiving a combination of hydration and bisphosphonates like zoledronic acid, 5 (26.31%) received hydration alone and 2 (10.52%) hydration and bisphosphonates patients were administered calcitonin also. Of the 19 patients, four were lost to follow-up, Overall mortality rate in the followed up patients (n=15) was 100%, with 8 (53.3%) of deaths occurring during the hospitalisation within seven days. Median survival was seven days and 11 (73.3%) of patients succumbed within 30 days of hypercalcaemia diagnosis.

Conclusion: MRH remains a significant marker of poor prognosis. HNC patients who present with symptoms such as fatigue, lethargy, bone pain, or altered mental status should be evaluated for hypercalcaemia. Despite aggressive management, survival remains limited, emphasising the need for improved preventive and therapeutic strategies in future and necessity of early integration of palliative care team and psychological support in these patients.

Keywords: Bone resorption, Metastasis, Squamous cell carcinomas

INTRODUCTION

The MRH is a well-recognised metabolic emergency in oncology, yet its occurrence in HNCs is often overlooked or underreported in clinical practice [1]. Head and neck squamous cell carcinomas, although not very commonly compared to other squamous cell carcinomas but have a unique propensity to induce hypercalcaemia, frequently through the secretion of Parathyroid Hormone-related Peptide (PTHrP), even in the absence of bone metastases [2]. Despite its clinical significance, hypercalcaemia in this patient population is frequently missed, as its symptoms are often attributed to the underlying malignancy or its treatment [3].

Hypercalcaemia in malignancy is primarily driven by excessive bone resorption mediated by tumour-derived factors. It is primarily mediated by PTHrP secretion, local osteolytic metastases, increased calcitriol production and in rare cases, by ectopic Parathyroid Hormone (PTH) secretion. PTHrP is the most commonly implicated mediator, mimicking PTH and leading to increased osteoclast activity and calcium mobilisation from bone stores [4,5]. Other contributing factors include direct osteolytic metastases and tumour production of calcitriol, which enhances intestinal calcium absorption [6]. These mechanisms lead to increased calcium release from bones, decreased renal calcium excretion, and enhanced gastrointestinal calcium absorption, all contributing to elevated serum calcium levels [3].

The clinical manifestations of hypercalcaemia often range from nonspecific symptoms such as anorexia, nausea, constipation, polyuria, and general muscle weakness to more severe neurocognitive symptoms which includes confusion, stupor, and

coma, as well as cardiac arrhythmias and renal dysfunction [3]. These symptoms often overlap with those of advanced malignancy which further complicates timely diagnosis [7].

Symptomatology of hypercalcaemia is interrelated to the absolute elevation of serum calcium levels and the swiftness of rise. Mild hypercalcaemia (serum calcium 10.5-11.9 mg/dL, 2.6-3 mmol/L) may not cause symptoms. Moderate hypercalcaemia (serum calcium 12-14 mg/dL, 3-3.5 mmol/L) persisting over several months may be well tolerated and only vaguely symptomatic, while similar levels developing over a few weeks can result in florid symptoms. Severe hypercalcaemia (serum calcium >14 mg/dL, >3.5 mmol/L) is typically symptomatic owing to the absolute serum calcium level and is most often associated with malignancy, especially when the elevation occurs gradually over a few weeks [3].

With primary hyperparathyroidism and malignancy comprising nearly 90% of hypercalcaemia cases, diagnostic approaches that distinguish between these two entities are most advantageous. The epidemiology and natural history of both processes can assist in ascertaining the diagnosis before acquiring laboratory data. Among patients presenting to the hospital, hypercalcaemia of malignancy is 2-3 times more common than primary hyperparathyroidism, with the source of cancer often evident by history and physical examination. Cancer-associated hypercalcaemia is more likely to provoke symptomatic disease, whereas primary hyperparathyroidism will have mild elevations in serum calcium in patients without risk factors for cancer [8].

Despite the clinical importance of this metabolic disturbance, there is limited literature on the incidence, clinical profile, and outcomes of hypercalcaemia in HNC patients. Given the poor prognosis associated with hypercalcaemia in malignancy-where approximately 50 percent of such patients die within 30 days-timely recognition and intervention are crucial [9,10]. The lack of awareness and standardised protocols for screening and managing hypercalcaemia in HNC patients contributes to missed opportunities for improving patient outcomes. The present study aimed to present the institutional experience with MRH in HNC, highlighting its clinical spectrum, management, and outcomes.

The primary objectives of the study were to analyse a cohort of HNC patients who had malignant hypercalcaemia: a) to determine the incidence; b) to document the investigations and treatment plan given for inpatients diagnosed; and c) to evaluate the outcomes of these patients.

MATERIALS AND METHODS

The present retrospective cohort study was conducted in April 2025 in the Department of Radiation Oncology at Christian Medical College, Vellore, Tamil Nadu, India, and included patients between January 2014 and July 2024 and was followed up till death with highest being 400 days. Institutional approval was obtained prior to study initiation (IRB Min. No. 2504134, dated 23.04.2025).

Inclusion and exclusion criteria: The study included patients aged 18 years or older, diagnosed with HNC, who developed symptomatic hypercalcaemia defined as serum total calcium >10.5 mg/dL- and were hospitalised under the Department of Radiation Oncology during the study period. Patients younger than 18 years of age were excluded.

Study Procedure

Data collection was performed retrospectively using electronic medical records, discharge summaries, and follow-up phone calls to check the survival status of the patients, where necessary. Hypercalcaemia was categorised by severity based on total serum calcium levels as follows: mild (10.5-11.9 mg/dL), moderate (12.0-13.9 mg/dL), and severe (≥14.0 mg/dL), in accordance with established clinical guidelines [10].

The data variables collected included demographic details (age, gender, co-morbidities), clinical features (primary tumour site, Tumor Node Metastasis (TNM) (AJCC 8th edition) stage, presenting symptoms), and treatment-related parameters. Management details such as intravenous hydration, bisphosphonates, calcitonin, diuretics, and dialysis were noted. In addition, survival outcomes were assessed by recording the date of hypercalcaemia diagnosis, mortality status, and median survival following the diagnosis.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarise the categorical and continuous variables. Survival analysis was performed using the Kaplan-Meier method to estimate post-hypercalcaemia survival using stata version 16.1 and python version 3.9.21.

RESULTS

The study included 19 patients and [Table/Fig-1] provides the general characteristics. Majority 17 (89.47%) were male, with a median age of 51 {Interquartile Range (IQR) 45-65} years. The majority 17 (89.47%) were diagnosed with oral cavity cancer, with 9 (52.94%) originating from the tongue and 8 (47.05%) from the buccal mucosa being the most common subsites. The most common presenting symptom was bone pain 13 (68.42%) followed by generalised weakness and lethargy 5 (26.31%) and low intake 4 (21.05%). Out of all the study participants 8 (42.10%) of patients were diagnosed with stage IVA, 5 (26.31%) had stage IVB and 2 (10.52%) had stage IVC, stage III and stage I each.

Characteristics		n (%)
Gender	Male	17 (89.47)
	Female	2 (10.53)
Age	Median (IQR)	51 (45.65)
Primary subsite of disease HNC	Buccal mucosa	7 (36.85)
	Tongue	8 (42.11)
	Buccal mucosa and tongue	1 (5.26)
	Pyriform sinus	1 (5.26)
	Retromolar trigone	1 (5.26)
	Supraglottic	1 (5.26)
T stage at diagnosis	T1	2 (10.53)
	T2	2 (10.53)
	T3	7 (36.84)
	T4	5 (26.31)
	T4a	2 (10.53)
	T4b	1 (5.26)
N stage at diagnosis	N0	3 (15.79)
	N1	2 (10.53)
	N2	1 (5.26)
	N2c	2 (10.53)
	N2b	6 (31.58)
	N3b	5 (26.31)
M stage at diagnosis	M0	17 (89.47)
	M1	2 (10.53)
AJCC Staging 8th edition	I	2 (10.53)
	III	2 (10.53)
	IVA	8 (42.11)
	IVB	5(26.30)
	IVC	2 (10.53)
Co-morbidities	Hypothyroidism	2 (10.53)
	Tuberculosis	1 (5.26)
	Hypertension	1 (5.26)
	Diabetes mellitus	1 (5.26)
	No co-morbidities	14 (73.69)

Metastases at hypercalcaemia presentation	Yes	16 (84.21)
	No	3 (15.79)
Presenting symptoms at hypercalcaemia admission	Abdominal pain	1 (5.26)
	Altered sensorium	1 (5.26)
	Bone pain	13 (68.42)
	Breathing difficulty	2 (10.53)
	Constipation	3 (15.79)
	Cough	3 (15.79)
	Difficulty in walking	1 (5.26)
	Fever	1 (5.26)
	Oral cavity bleeding	1 (5.26)
	Hemoptysis	1 (5.26)
	Neck swelling	1 (5.26)
	Poor intake	4 (21.05)
	Swelling	1 (5.26)
	Trismus	1 (5.26)
	Voice change	1 (5.26)
	Vomiting	1 (5.26)
	Weakness	5 (26.31)

[Table/Fig-1]: Patient characteristics (N=19).

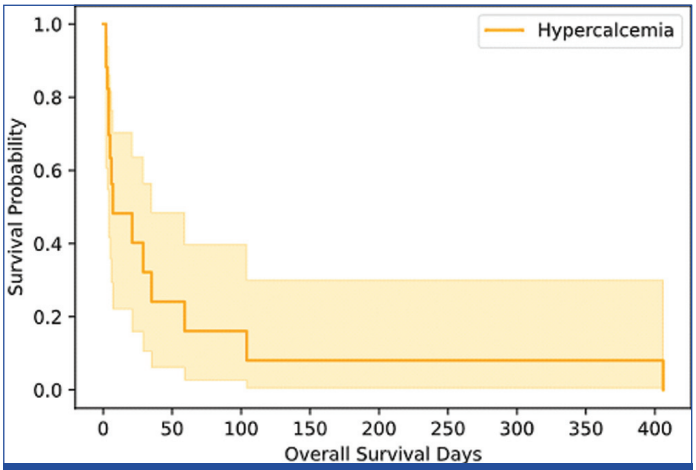
The Patients who presented with hypercalcaemia, the management strategies involved, and the outcomes are described in [Table/Fig-2] Most patients 15 (78.94%) presented during follow-up and was seen in majority 13 (68.42%) who had metastasis. Of these, majority 13 (68.41%) had severe hypercalcaemia while moderate and mild hypercalcaemia were equally observed in 3 (15.78%) patients, respectively.

Parameters		n (%)
Hypercalcaemia presentation at diagnosis (n=4)	Without metastases or local recurrence	1 (25)
	With metastases or local recurrence	3 (75)
Hypercalcaemia presentation at follow-up (n=15)	Local recurrence	2 (13.3)
	Metastases	10 (66.7)
	Local recurrence and metastases	3 (20)
Hypercalcaemia level grading during admission (serum levels)	Mild (10.5-11.9)	3 (15.79)
	Moderate (12-13.9)	3 (15.79)
	Severe (≥14)	13 (68.42)
Maximum hypercalcaemia level during admission	Median (IQR)	15.65 (13.7-16.2)
	Mean (SD)	15.29 (1.94)
	Range	11.6-20.09
Treatment given for hypercalcaemia	Hydration	19 (100)
	Bisphosphonates	11 (57.89)
	Diuretics	5 (26.31)
	Calcitonin	2 (10.52)
	Haemodialysis	2 (10.52)
Survival	Alive	-
	Died	15 (78.95)
	Lost to follow-up	4 (21.05)

[Table/Fig-2]: Hypercalcaemia management and outcomes in this cohort.

Hypercalcaemia treatment for the all the patient was with hydration, while majority 14 (73.68%) included a combination of hydration and bisphosphonates like zoledronic acid, which is a standard approach for MRH; out of which 2 (10.52%) also received calcitonin, 2 (10.52%) also underwent haemodialysis, 5 (26.32%) patients had hydration alone. In all the 19 patients who received hydration 5 (26.32%) received diuretics.

Out of the 19 patients, 15 were followed up, and four were lost to follow-up. The survival analysis shown in [Table/Fig-3] showed a median survival of seven days following the diagnosis of symptomatic hypercalcaemia. The in-hospital 7-day mortality rate in the 15 patients who were followed up was 8 (53.3%), and the 30-day mortality rate reached 11 (73.3%). All but one (14/15) patient died within 100 days from the date of diagnosis of hypercalcaemia and one survived close to 400 days.



[Table/Fig-3]: Kaplan Meier curves showing the overall survival curve of Hypercalcaemia patients.

DISCUSSION

The MRH is a life-threatening but often under recognised complication in HNCs. Despite its potential to occur even without bone metastases, it is frequently missed due to overlapping symptoms with advanced cancer. Early diagnosis is crucial, as MRH carries a high short-term mortality. This study explored the clinical features, management, and outcomes of MRH in HNC patients.

The present study evaluated metastasis-related hypercalcaemia in HNC patients and found that it is associated with extremely poor outcomes, with a median survival of only seven days and majority 8 (57.14%) died within 30 days. This highlights the urgent need for early recognition and intervention.

The study findings align with previous reports that MRH is associated with severe clinical illness and poor survival whose cause of death is multifactorial, with up to 50% of patients dying within 30 days of diagnosis [11]. Other studies have also demonstrated the aggressive nature of hypercalcaemia of malignancy and the limited survival benefit, underscoring the importance of timely diagnosis and management [8,9]. Use of bisphosphonates as the primary treatment has been well established, but recent studies highlight the superiority of denosumab in refractory cases [12]. Some suggest that prompt chemotherapy initiation in hypercalcaemia cancer patients may improve overall survival by reducing tumour burden [13].

The diagnostic approach to hypercalcaemia begins with confirmation of elevated serum calcium, ideally corrected for albumin levels, as 40% of serum calcium is albumin-bound [14]. Both total and ionised calcium should be measured for accuracy, especially in patients with abnormal albumin [15]. Serum phosphorus should also be measured because hypercalcaemia can be associated with both hyper and hypophosphatemia.

Once hypercalcaemia is established, measurement of PTH assists in distinguishing between PTH-mediated and non-PTH-mediated causes. It should be noted that since both PTH and PTHrP are similar molecules, both will not be concurrently elevated unless there are multiple aetiologies [16]. In malignancy-related cases, PTH is typically suppressed, and further evaluation may include measurement of PTHrP, vitamin D metabolites, and imaging to assess for bone metastases. Hence, the workup should include serum phosphate,

PTH and PTHrP, 25(OH)D and 1,25$(OH)_2$D (vitamin D metabolites), renal function tests (serum creatinine, glomerular filtration rate and 24-hour urine calcium and creatinine. This should be followed by a thorough clinical history and examination to identify risk factors, underlying malignancy, and potential contributing medications or co-morbidities [14].

The acute management strategy for MRH may include the following. Hydration with oral and intravenous normal saline is the key initial therapy, primarily for expanding intravascular volume and promoting calciuresis. Parenteral fluid administration will be effective at lowering serum calcium in acute kidney injury as well as in those with preserved glomerular filtration rates [17]. Fluid resuscitation acts via multiple mechanisms. It corrects the decline in glomerular filtration rate mediated by the direct renal vasoconstriction and natriuresis-induced volume contraction of hypercalcaemia [18].

Calcitonin provides a rapid but short-lived reduction in serum calcium (onset 4-6 hours, duration up to 48 hours). Calcitonin lowers blood calcium levels by inhibiting bone-resorbing osteoclasts and to a lesser extent by enhancing calcium excretion into the urine [19]. It begins to exert its effect within 4-6 hours and likely related to calcitonin receptors downregulation on osteoclasts. No dosing adjustments are necessary for renal failure. Side effects may include nausea and hypersensitivity reactions [18,20,21].

Bisphosphonates (zoledronic acid) are first-line agents for sustained calcium lowering (within onset 24-72 hours, duration 2-4 weeks). It should be within 48 hours as it takes approximately two to four days for them to take effect and inhibit osteoclast-mediated bone resorption [15,22].

Denosumab is effective in cases refractory to bisphosphonates or when renal insufficiency precludes bisphosphonate use. It is the only drug safe in renal failure and acts by inhibiting RANKL and thus osteoclast function. Denosumab dose could be 120 mg subcutaneously on days 1, 8, 15, and 29 and every four weeks thereafter and has been reported lower serum calcium within 10 days [23].

Glucocorticoids are particularly useful in calcitriol-mediated hypercalcaemia or lymphomas [24]. Cinacalcet could be reserved for parathyroid carcinoma or refractory cases due to its effect on PTH secretion [25]. Haemodialysis may be considered in severe, life-threatening hypercalcaemia unresponsive to medical therapy, especially when volume overload or renal failure is present [26].

A combination of calcitonin and an intravenous bisphosphonate or denosumab is recommended in severe hypercalcaemia [27]. In patients who already received an intravenous bisphosphonate but have refractory/recurrent MRH, the use of denosumab is suggested as initial treatment compared with only intravenous bisphosphonate or denosumab [28].

Our experience shows that metastasis-related hypercalcaemia in HNC patients signals advanced disease with extremely poor outcomes. In this cohort, majority died 14 (73%) which highlights the aggressive nature of this clinical syndrome and the challenges in managing these patients. Early identification, comprehensive workup-including targeted laboratory and imaging assessments-and prompt initiation of both supportive and disease-directed therapies although critical may not necessarily improve outcomes drastically in this high-risk group. Given the poor prognosis, early involvement of a multidisciplinary palliative care team is highly recommended.

Limitation(s)

This study is a retrospective study limited by a small sample size. However, it highlights an underreported cohort and includes detailed assessments of the inpatient records and follow-up data for 10 years and presents evidence in an Indian setting where report of hypercalcaemia is further limited.

CONCLUSION(S)

Malignancy related hypercalcaemia remains a significant marker of poor prognosis in HNC patients. It should be suspected in patients presenting with fatigue, altered mental status, or bone pain. Despite aggressive management, survival remains limited, emphasising the need for improved preventive and therapeutic strategies in future and early integration of palliative care and psychological support in these patients.

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