

Endocrine-related Abnormalities in Locally Advanced Head and Neck Cancer Surgery Patients after Chemoradiation: A Myth or Mystery

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ABSTRACT

Patients with head and neck malignancy with locally advanced disease often require chemoradiation, and those patients who undergo chemoradiation encounter more endocrine/metabolic-related complications after surgery.

Materials and methods: We evaluated 36 locally advanced head and neck cancer patients who had undergone chemoradiation, followed by surgery during the period from February 2021 to June 2022 for various endocrine-related abnormalities, such as hyponatremia, hypokalemia, hypothyroidism, hypocalcemia, and complications associated with surgery in relation to these endocrine abnormalities.

Results: Among these 36 patients, 20 patients developed hyponatremia, four patients developed hypokalemia, and nine patients developed hypocalcemia at some point of time after the surgery, and their preoperative (pre-OP) values were normal. A total of 13 patients had subclinical hypothyroidism even before the surgery. Wound morbidity was more among these patients.

Conclusion: If all patients with head and neck cancers who are all undergoing surgery after chemoradiation are evaluated for electrolyte abnormalities, such as hyponatremia, hypocalcemia, and hypothyroidism, it may reduce the perioperative and postoperative (post-OP) complications and it may shorten the hospital stay, help in early recovery, and may avoid life-threatening conditions.

Keywords: Chemoradiation, Endocrine abnormalities, Head and neck cancer, Hypocalcemia, Hyponatremia, Hypothyroidism, Neck surgery.

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INTRODUCTION

In 2030, according to World Health Organization estimation, there will be 4,39,000 head and neck cancers, especially in oral cavity and oropharynx worldwide.¹ In India, head and neck cancers account for almost one-fifth (21.3%) of all cancers and constitute nearly one-third (32.4%) of all cancers in males.² In terms of stage during diagnosis, 29% of cases are categorized as localized disease (early stage disease), 47% as regional disease (with nodal involvement), and 20% as distant metastasis disease.³ Head and neck cancers most often need multimodality management with surgery, definitive or adjuvant radiation therapy, and chemotherapy.⁴

Head and neck malignancy patients with advanced disease or disease location not amenable to primary resection will undergo radiation therapy before surgery. Surgical procedure for head and neck malignancy varies from simple wide excision to complex procedures, which may require free flap reconstruction to maintain the contour and cosmesis for the patient.

Usually, irradiated patients tend to develop more complications after head and neck surgery. Those patients may encounter wide range of complications, such as wound infection, wound dehiscence, flap morbidity, electrolyte abnormalities, and endocrine abnormalities, particularly related to thyroid and parathyroid gland. Pre-OP baseline evaluation may help in avoiding complications through early correction of metabolic and endocrine abnormalities.

MATERIALS AND METHODS

All patients with locally advanced head and neck malignancies who underwent radiation therapy before surgery are included in the study. Those patients are evaluated with blood investigation,

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such as hemoglobin, renal function test, liver function test, serum sodium, potassium, thyroid function test, and serum calcium at the time of admission (before surgery) and 3 days after surgery, sequentially, on 2nd and 6 weeks after surgery. These parameters and their abnormalities are observed, and they are compared to those values in the subsequent weeks and correlated with the clinical symptoms of hyponatremia, hypothyroidism, and hypocalcemia. The recovery status in terms of post-OP stay duration in hospital, early ambulatory, and early oral feeding are accounted for and compared with endocrine abnormalities.

Study Design

All patients with head and neck malignancies who underwent radiation and planned for surgery were included in the study from period of February 2021 to June 2022 in center for oncology and informed written consent was obtained from those patients.

Exclusion Criteria

- Patients with preexisting renal disorders.
- Patients with any known endocrine abnormality, such as thyroid adrenal disorder, even before the radiation therapy.
- Patients with history of any childhood or previous irradiation.

Data Collection

Among 36 patients, 20 patients developed hyponatremia, and four patients developed hypokalemia. A total of 13 patients developed subclinical hypothyroidism. About nine patients developed hypocalcemia. Only one patient developed all four abnormalities. Around three patients developed both hyponatremia and hypokalemia. A total of six patients developed both hypothyroidism and hypocalcemia. Six patients developed hyponatremia with hypothyroidism. Only 10 patients' post-OP periods went uneventful without these abnormalities.

RESULTS

Among those 36 patients, 55.5% developed hyponatremia (nine patients were diagnosed during immediate post-OP period, and 11 patients were diagnosed during 2-week evaluation). Nearly 11.1% developed hypokalemia, 36.1% had subclinical hypothyroidism, and 25% developed hypocalcemia. Only with six patients we found out that syndrome of inappropriate antidiuretic hormone (SIADH) is the cause of hyponatremia in our study by using urine osmolality and serum osmolality, and all were diagnosed during the 3rd post-OP day evaluation (Tables 1 to 5).

Among complications rate, nine patients had both flap dehiscence and chyle leak, and four patients underwent resuturing. Out of 11 patients with chyle leaks, only three patients had clinically significant chyle leaks, and others had subclinical chyle leaks

Table 1: Type of cancers

Tongue	14
Buccal mucosa	12
Alveolus	6
Floor of mouth	2
Larynx	2

Table 2: Age/sex

Age-group	28–74
Male	30
Female	6

Table 3: Node status

N1	11
N2	19
N3	6

N1, N2, N3 denotes nodal staging as per TNM

Table 4: Complications

Flap dehiscence	19
Chyle leak	11
Resuturing/surgery	9
Bleeding	3
Death	1

(elevation of drain tube triglycerides). Out of 19 patients with flap dehiscence, 11 patients had hyponatremia, and one patient had hypokalemia. Out of 14 patients with chyle leak, nine patients had hyponatremia, and one had hypokalemia. Among those nine patients with both flap dehiscence and chyle leak, eight patients had hyponatremia, and two patients had hypokalemia.

A total of 13 patients had subclinical hypothyroidism even before surgery after the radiation therapy, and none of the patients developed new onset of hypothyroidism after the surgery. These patients do not have any thyroid functional abnormality or symptoms before the radiation therapy.

Out of 12 patients, three patients had hypocalcemia during pre-OP evaluation. A total of nine patients developed hypocalcemia in the 2nd week. All these nine patients showed normal calcium levels during presurgery and during immediate post-OP (i.e.) day 3 evaluation.

- Average hospital stay is 19 days.
- Average stay in patients without any major complications is 12 days.
- Average stay in patients with major complications is 28 days.

DISCUSSION

Hyponatremia can be classified as acute or chronic. In head and neck cancer surgery patients, acute hyponatremia is more common than chronic one. Hyponatremia is defined as serum sodium levels <135 mEq/L.^{5,6} The short-term adverse effects include infection, cerebral edema, seizures, and even infarction. Moreover, chronic hyponatremia may even cause severe cognitive impairment.⁷ Mild hyponatremia is defined as serum sodium concentration <135 mEq/L (132–134); when serum sodium levels are <132 mEq/L, it is termed as moderate hyponatremia, serum sodium levels <130 mEq/L is defined as severe hyponatremia, and it is life-threatening when sodium levels are <125 mEq/L or patient with clinical signs of hyponatremia.⁸ For all of our patients with acute hyponatremia, we ruled out SIADH. In all of our cases with hyponatremia, values range from 127 to 134 mEq/L.

In Mesko et al. study, they found there was an increased incidence of hyponatremia in head and neck surgery patients who underwent nodal dissection as a consequence of SIADH.⁹ Almost 3% of patients who are all undergoing surgery for head and neck cancer are associated with SIADH.¹⁰ SIADH is most commonly associated with oral cavity cancers and less frequently associated with cancers of larynx, nasopharynx, hypopharynx, or other sites in head and neck.¹¹

Cerebral salt wasting syndrome (CSWS) is defined when patients present with two of the four following signs— (1) clinical symptoms related to hypovolemia, including persistent hypotension, dryness of mucous membranes, increased pulse rate, or postural hypotension; (2) central venous pressure level

Table 5: Results

Hyponatremia	Mild (<135 mEq/L)	10
	Moderate (<132 mEq/L)	7
	Severe (<130 mEq/L)	3
Hypokalemia		4
Hypothyroidism		13
Hypocalcemia		9

usually <6 cm of water (H₂O); (3) negative fluid balance, which is determined by daily intake/output chart or weight loss; and (4) laboratory evidence of dehydration, such as elevated hematocrit, high hemoglobin, serum albumin, or blood urea.¹²

The paramount importance to differentiate between SIADH and CSWS is in patients with SIADH, we need to restrict the fluid, while for those with CSWS, we need to supplement the sodium.

Platinum compounds are one of the most common chemotherapeutic agents used in chemoradiation protocols in head and neck cancer. These agents can directly damage renal tubules, which affects sodium absorption. This eventually leads to hyponatremia.¹³

In our institutional study, >50% of patients developed hyponatremia at some point of time after surgery. As a routine, we advise all of head and neck cancer surgery patients to have Ryles tube feeding from the day of surgery. It includes at least 3 L of liquid with 20 gm of table salt in 1 L of H₂O and remaining with milk, fresh juices, and tender coconut H₂O, along with protein powder supplementation with two raw eggs daily.

For those patients who developed hyponatremia, we supplemented 40 gm of salt instead of 20 gm in 1 L of H₂O. About 1 L of tender coconut H₂O instead of 500 mL. Values are repeated on the next day. None of our patients developed life-threatening conditions because of hyponatremia due to our timely intervention. Only one among the 36 patients developed persistent hyponatremia for 5 days and needed intravenous supplementation of 3% sodium chloride.

The incidence of hyponatremia increases with an increase in complication rate that could be due to prolonged Ryles tube and delay in starting of oral feeds.

Hypothyroidism can be classified into clinical and subclinical hypothyroidism. When the concentration of thyroid stimulating hormone (TSH) is higher than the normal range and free thyroxine (FT4) is lower than the normal range, the condition is coined with a terminology called clinical hypothyroidism. The term subclinical hypothyroidism is used when the patient has high TSH levels and normal FT4 levels.¹⁴

The common clinical symptoms of hypothyroidism include easy fatigability, lethargy, cold intolerance, excessive weight gain, constipation, aural changes, and dry scalp skin.¹⁵ Patients with slight deviation from normal range do not show any obvious symptoms, while severe cases can have an increased incidence of cardiovascular events, such as cardiac failure, cardiac fibrillation, especially atrial fibrillation, coronary heart disease, and even risk of cardiac arrest,¹⁶⁻¹⁸ which varies according to age, sex, duration of symptoms, the severity of disease, and other comorbidities.

The mechanism of radiation-induced hypothyroidism has been poorly understood; it may be associated with fibrosis of thyroid gland, vascular proliferation, and due to excessive immune response.¹⁹⁻²¹ Moreover, radiation therapy can directly damage the thyroid cells, either by interfering with the mitosis of a cell or by affecting the blood supply directly.²²

At the time of admission itself, we did thyroid function tests for all patients who had undergone radiation therapy. We found 12 patients with altered values of thyroid function tests. Almost all patients had normal triiodothyronine and T4 with increased TSH values. None of them were symptomatic. Subclinical hypothyroidism patients may end up with anesthetic complications, such as delayed recovery from general anesthesia, which is commonly used for surgery in head and neck cancer patients.

Table 6: Radiotolerance dose of organs in head and neck

<i>Organs/parts in the head and neck</i>	<i>Mean tolerance dose (GY)—fractionated</i>
Thyroid gland	30–40
Parotid gland	<25
Mandible	Up to 70
Larynx	<60
Pharyngeal constrictors	<44
Cochlea	<45
Mucosa	65–77

For all these patients, we supplemented T4 in the pre-OP period itself in order to avoid complications in perioperative and post-OP periods (Table 6).^{23,24}

Since the parathyroid glands are closely associated with the thyroid glands, radiation to neck may directly or indirectly affect those glands also, and patient may go for hypocalcemia. The hypocalcemia may be temporary or permanent one. The normal serum calcium level ranges from 8.5 to 10.5 mg/dL.²⁵ The most common manifestation of hypocalcemia is increased neural excitability. Patients are most commonly present with tingling sensations around the mouth and along the tip of the fingers.

The most common cardiovascular manifestations associated with hypocalcemia are electrical rhythm disturbances. There may be positive Chvostek and/or Trousseau signs and even psychiatric manifestations in these patients.²⁵ We diagnosed nine patients with hypocalcemia in the post-OP period during the 2nd week, and all of those patients showed a normal calcium level on the 3rd day of surgery. All patients recovered from hypocalcemia during the 6th week of evaluation. We supplemented all patients who have diagnosed hypocalcemia with calcium 500 mg thrice a day along with vitamin D. None of the patients were symptomatic at the time of diagnosis and during the hospital stay.

CONCLUSION

Endocrine and metabolic abnormalities tend to occur with high incidence in patients with locally advanced head and neck cancers after surgery. Most of these abnormalities can be easily treated if diagnosed early; if not intervened properly, it can be life-threatening. Hence we suggest to anticipate and treat these abnormalities, which may reduce the perioperative and post-OP complications, which can shorten the hospital stay and helps the patient in early recovery.

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