

Parathyroid Carcinoma and Recurrent Hyperparathyroidism: Challenges and Management Options

Original
Article

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ABSTRACT

Introduction: Parathyroid carcinoma is very rare, but it is resembling important cause of recurrent hyperparathyroidism. Till now no clear guidelines for treatment of parathyroid carcinoma and its associated conditions including hyperparathyroidism. The aim of the study to evaluate the incidence and management modalities of such challenging cases.

Material and Methods: Retrospective study for 129 patients diagnosed as primary hyperparathyroidism From march 2012 to June 2020,. Recurrent hyperparathyroidism developed in 7 cases 6 patients of them due to parathyroid carcinoma .medical records and patients characteristics and pathological evaluation and treatment modalities were reviewed.

Results: Parathyroid carcinoma diagnosed in 6 patients (4.6%);, 4 males and 2 females with a mean age of years (61.5) range 54–72 years. The mean serum calcium at the initial diagnosis of parathyroid carcinoma cases was 12.73 mg/dL (10.8.–14.2 mg/dL). Elevated serum parathormone were noted in all patients preoperatively, with a mean of 1691.5 pg/mL (630 –3366 pg/ mL). parathyroidectomy done in 5 patients and en block resection in one case in the initial operation, all cases developed recurrence of manifestation from (7 month-26 months) , reoperation needed for all cases and one case needed radiotherapy.

Conclusion: Parathyroid carcinoma is very challenging disease with high rate of recurrence, multidisciplinary approach including surgery, medical treatment for hypercalcemia is needed to improve patients outcome .

Key Words: En block resection, parathyroid carcinoma, recurrent hyperparathyroidism, sestamibi scan.

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INTRODUCTION

Primary hyperparathyroidism (1HP) is a hypercalcemia disorder resulting from an over increase in parathyroid hormone (PTH) production by one or more parathyroid glands. The landmark of this disease is the presence of hypercalcemia and abnormal high level of PTH. 1HPT is common in females than in males and more common in old ages^[1]. Surgical treatment still the main line of treatment^[2]. Aim of surgery is removal of hypersecreting parathyroid gland(s), with preservation of the normal parathyroid gland to reach normal postoperative calcemic state^[3], implementation of intraoperative PTH technique (IOPH), improves the outcome of surgery and decrease the incidence of persistent or recurrent HPT, as half- life of parathyroid hormone is relatively short (less than 10 minutes), rapid decrease in the circulating PTH hormone occurred after excision of the abnormal gland(s)^[4]. Allowing the surgeon to finish the surgery without the need to do further exploration of the neck.

The definition of recurrent HPT is a reappearance of finding related to hypercalcemia after 6 months of successful operation in patient in whom normal calcium level achieved^[5-6], there are only few data on the epidemiology of recurrent 1HPT. Studies considered the incidence between 2.5 and 9.8%^[7]. Also, recurrence of HPT may occur up to few years after initial treatment, so long term follow up after treatment of 1HPT is indicated^[7].

The etiology of persistent and recurrent HPT either due to factors either related to the initial surgery, or the biological or anatomical variation of the pathology. Surgical experience and optimal operative approach play important role in treatment success. Treatment failures may occur due to parathyroid anatomical variation occurred due to embryological variations in glandular numbers which leading to supernumerary or ectopic glands. Biological causes leading HPT to be more difficult to treated like familial parathyroid hyperplasia , parathyroid carcinoma(PC)^[8].

Parathyroid carcinoma is very uncommon, responsible for 0.2% to 3% of 1HPT patients^[9]. More than half of these cases showing recurrence of the HPT. Recurrence usually occurs near the original location or in cervical lymph nodes^[10].

En-bloc resection of the pc decreases the incidence of recurrence, inadequate removal of the tumor, an infiltration of the surrounding, and metastatic lesion are indicator of poor prognosis^[10]. reoperation still the main palliative treatment strategy^[9], our study aiming to evaluate patients with recurrent 1HPT due to parathyroid carcinoma retrospectively to evaluate the different management modalities for the treatment of this rare type of primary hyperparathyroidism.

MATERIAL AND METHODS

Retrospective descriptive study for patients diagnosed as recurrent 1ry HPT From march 2012 to June 2020, 129 patients operated for 1ry HP in Maxillofacial, Head and Neck surgery unit, Surgery department , Sohag university during this period. Recurrent hyperparathyroidism due to parathyroid carcinoma noticed in 6 cases. The diagnosis of PC was by postoperative histopathological examination, We addressed all cases' data:

1. The clinical picture of the patients;
2. Laboratory investigations of the patients, serum calcium, phosphorus, serum parathormone on admission;
3. Preoperative localization studies in form of neck ultrasonography, Neck CT or MRI, sestamibi scan;
4. Operative techniques of all patients addressed from patients operative notes. In all cases recurrence diagnosed by increases serum calcium or serum parathormone or both of them.

RESULTS

Recurrent HPT developed to 7 cases of 129 cases operated for 1 HPT (5.4 %), one case due to parathyroid hyperplasia, parathyroid carcinoma diagnosed in 6 patients (4.6%);, 4 males and 2 females with a mean age of years (61.5) range 54–72 years.

The patient's demographic and characteristic data of 6 patients with parathyroid carcinoma were summarized (Table 1). All cases diagnosed postoperatively by postoperative pathological examination. Their clinical presentations are reported in (Table 2). The difference between cases of parathyroid carcinoma and other cases of 1ry HPT regarding preoperative serum calcium, and parathormone were shown in (Table 3). The mean serum calcium at the initial diagnosis of parathyroid carcinoma cases was 12.73 mg/dL (10.8–14.2 mg/dL). Elevated serum PTH was noted in all patients preoperatively, with a mean of 1691.5 pg/mL (630–3366 pg/ mL). All cases in our study underwent neck ultrasonography (US) examination which was positive in diagnosis of parathyroid tumors in 5 of 6 (83 %) the only case which was not diagnosed by US was retrosternal in the anterior mediastinum.

Sestamibi scan was true-positive in all cases of parathyroid carcinoma (sensitivity 100%). CT scans of the neck and mediastinum were able to localize the parathyroid carcinoma in 4 patients in whom the scans were done. The tumor detected in the right inferior gland in 3 patients, in the left inferior gland in 2 patients, and in anterior mediastinum in one case. The mean tumor size in the initial surgery was 3.6 cm (range 1.5–4.9 cm)., recurrence of manifestation was observed in all cases of parathyroid carcinoma. the mean time of recurrence of HPT was 14.6 months (7-26 months). all recurrent cases underwent reoperation to control regional recurrence, only one case needed radiotherapy.

Table 1: Patients presentations and clinical characteristics of cases of recurrent HPT due to PC

No	Age	Sex	Clinical picture	Serum calcium	Serum PTH	Treatment outcome
1	62	male	Bone pain and pathological fracture, ultrasonography showed solid mass lesion related to lower pole of right thyroid. sestamibi scan showed lesion suggesting parathyroid tumor	14.2	883	Excision of the parathyroid mass revealed PC, postoperative pTH was normal with normal serum calcium for more than 1 .5 year then the patient developed recurrent hypercalcemia and HPT, U/s and CT revealed suspicious neck nodes, the patient underwent neck dissection of the metastatic lymph nodes and after that the patient followed up for 1 year than he developed recurrent hypercalcemia and HPT . PET CT revealed few bone metastases
2	54	male	Bone pain and nephrolithiasis neck U/S revealed hypoechoic solid mass lesion related to lower pole of the thyroid with positive sestamibi scan	13.5	2234	Excision of the parathyroid lesion which revealed to be PC, postoperatively serum calcium and PTH became normal, then manifestation recurred after 8 months with hypercalcemia and recurrent 1ry HPT, localization studies revealed neck recurrence followed by excision of the recurrent PC with sound postoperative period for 2 years (Figure 1).
3	61	male	Bone pain, numbness, nephrolithiasis localization studies revealed left inferior parathyroid mass	12	2076	Excision of the mass which was PC, normalization of serum calcium and PTH but recurrence of hypercalcemia and HPT recurred after 7 months, localization studies was negative, the decision was conservative treatment and follow up with medical treatment in form of cinacalcet, but serum calcium was still high, PET CT is done 6 months later revealed bone metastases in scapula and skull and the patient treated with bisphosphonate with poor response
4	64	female	Nephrolithiasis and bone pain, numbness N/S revealed solid mass lesion suggesting left inferior parathyroid lesion and positive sestamibi scan	10.8	630	Left inferior parathyroidectomy with subsequent normalization of serum ca and PTH, 26 months later the patient developed recurrent hypercalcemia and HPT, and renal impairment, localization studies revealed lung metastases and treated medically with bisphosphonate and cinacalcet.
5	56	female	Neurological manifestations and bone pain, brown jaw tumor	12,4	960	Localization studies revealed right lower neck parathyroid mass, excision of the mass revealed PC complete excision of the mass with sound postoperative period for 18 months and complete ossification of the brown jaw tumour then the pt. developed recurrent hypercalcemia and recurrent HPT localization studies revealed, lung metastases treatment continued with endocrinologist by good hydration and bisphosphonate
6	72	male	Bone pain, numbness, impairment of renal function, ultrasonography revealed neck mass with retrosternal extension, CT showed mediastinal mass	13.5	3366	Neck exploration with block excision of the mass and sternotomy to resect the mediastinal mass which revealed PC with sternomaistoid infiltration followed by radiotherapy, postoperative period with normal CA and PTH , recurrence of manifestations with hypercalcemia and HPT occurred 11 month later , localization studies and PET CT revealed bone metastases treated by hydration, diuretics, cinaclct and bisphosphone to regulate serum calcium (Figure 2)

abbreviations: US ultrasonography , CT , computed tomography; PET , positron emission tomography PC, parathyroid carcinoma; PTH, parathyroid hormone Ca, calcium

Table 2: Clinical pictures of patient with 1ry HPT due to PC

Clinical feature	Number of cases
Bone pain	6/6
Neck mass	0/6
Nephrolithiasis	2/6
Neurologic symptoms	4/6
Brown jaw tumor	1/6

Table 3: laboratory investigation and sensitivity of sestamibi scan in patients with 1HPT due to PC versus those with adenomas

parameters	Parathyroid carcinoma	Adenoma and hyperplasia
Serum calcium	Mean 12.7(10.8-14.2)	11.9(8.7-13.2)
PTH	Mean 1691 (630-3366)	467 (102–2040)
Sensitivity of sestamibi	100%	86%

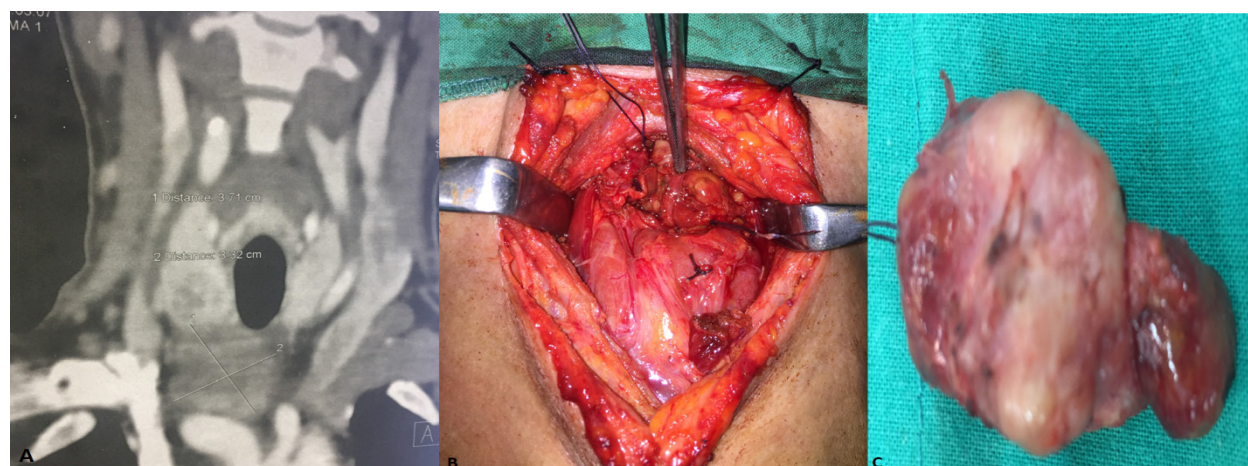


Fig. 1: A, preoperative CT showing lower neck mass B, showing parathyroid mass C, excision of the parathyroid mass

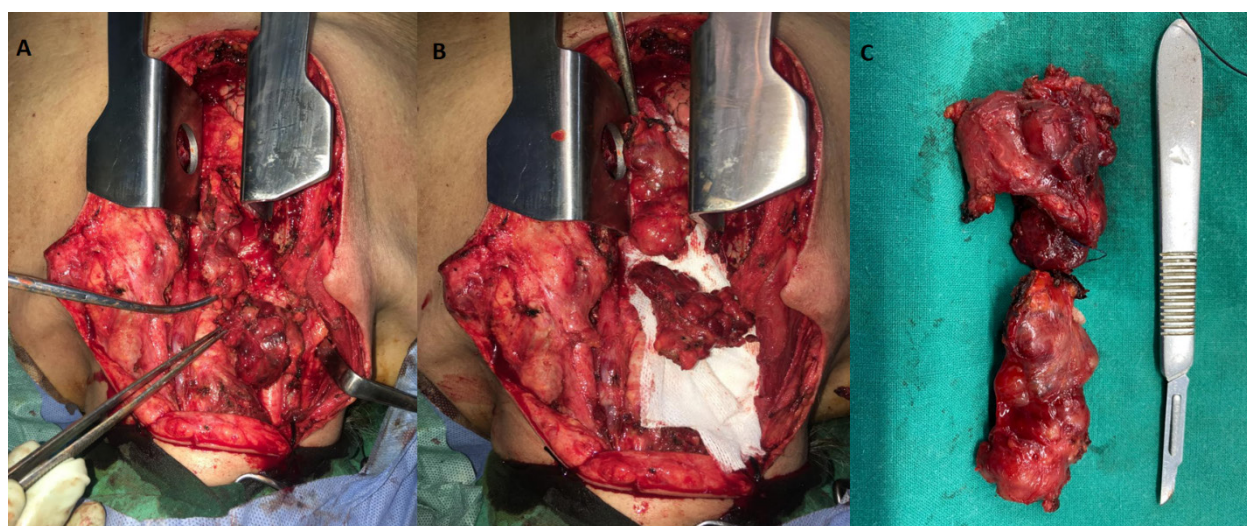


Fig. 2: A- B, parathyroid mass with mediastinal extension and infiltration of sternomastric muscle. C, after excision of the mass after sternotomy

DISCUSSION

Parathyroid adenoma is the main cause of 1HPT and parathyroid carcinoma (PC) is very rare to be encountered in the day-to-day practice of hyperparathyroidism with incidence from 0.2%-4%^[11]. Parathyroid malignancy resembling important factor for the occurrence of recurrent and persistent hyperparathyroidism^[12].

In our study recurrent HPT occurred in 7 cases (5.4 %) of 129 cases presented to our department most of cases due to PC 6 cases which matches with Electron K *et al*, as they founded that most of cases of recurrent or persistent 1HPT was due to parathyroid carcinoma^[13].

In our study parathyroid carcinoma patients the mean age was 61.5 range (54-72 year) while Gennaro F *et al* mean age was 60 year (30 -78 year)^[14].

In our study parathyroid carcinoma patients presented in 4 men and 2 women, also Electron K.13 Male / female was 13/5, while in 1HPT due to adenoma or hyperplasia more common in females also in our cases of 1HPT due to adenomas and hyperplasia it was more common in females.

When serum calcium levels higher than 13 mg/dL and PTH levels 5 to 15 times the high limit of normal this alarming the possibility of parathyroid carcinoma to be the cause of hyperparathyroidism^[15]. In our study 3 patients were suspicious of parathyroid carcinoma because of their high serum calcium and PTH levels.

3 cases were not chemically indicative of malignancy, as their serum calcium levels is below 13 mg/dL, while their PTH levels were extremely high. These findings explain the large overlap between benign and malignant tumors regarding the laboratory findings.

Imaging studies were crucial before surgical intervention. In our series neck US was fundamental in preoperative localization. Five of six patients with PC were diagnosed by neck US, which matches with other series^[13,15,16]. All cases of recurrent HPT due to PC did sestamibi scan which were positive in all cases suggesting parathyroid tumor. Some reports concluded that sestamibi scan more sensitive in diagnosis of PC more than other causes of 1 HPT as adenomas and hyperplasia which matches with result of our study in which the sensitivity

of sestamibi scan in diagnosis of PC was 100% while in adenomas and hyperplasia was 86%^[11,13].

We depended in all our cases in intraoperative serum PTH to evaluate the complete removal of the tumors and the success of the procedure as that decrease the incidence of surgical failure and occurrence of persistent HPT 4 .

Fine needle aspiration cytology (FNAC) not done in our cases of parathyroid tumors as the sensitivity of FNAC in diagnosis of PC is very low and with possibility of seedling of cells with subsequent parathyromatosis and recurrence. Most of reports not recommended FNAC^[13,15,16].

We did not use intraoperative frozen section technique as it is not available in our center also because no guidelines for management of HPT recommending frozen section examination^[17].

While Diani K *et al* used frozen section in all neck procedures. And Intraoperative frozen section diagnosed two cases of six cases of PC^[16].

In our study, only one case did en bloc resection because the tumor was founded adherent to the surrounding tissue like thyroid gland and sternomastoid muscle, in most of our patients we did only parathyroidectomy as the were no local malignant features in the initial diagnosis and the primary operation.

The histopathological examination of the postoperative specimen revealed PC and the diagnosis depended on capsular and vascular invasion, abnormal growth pattern. (Figure 3).

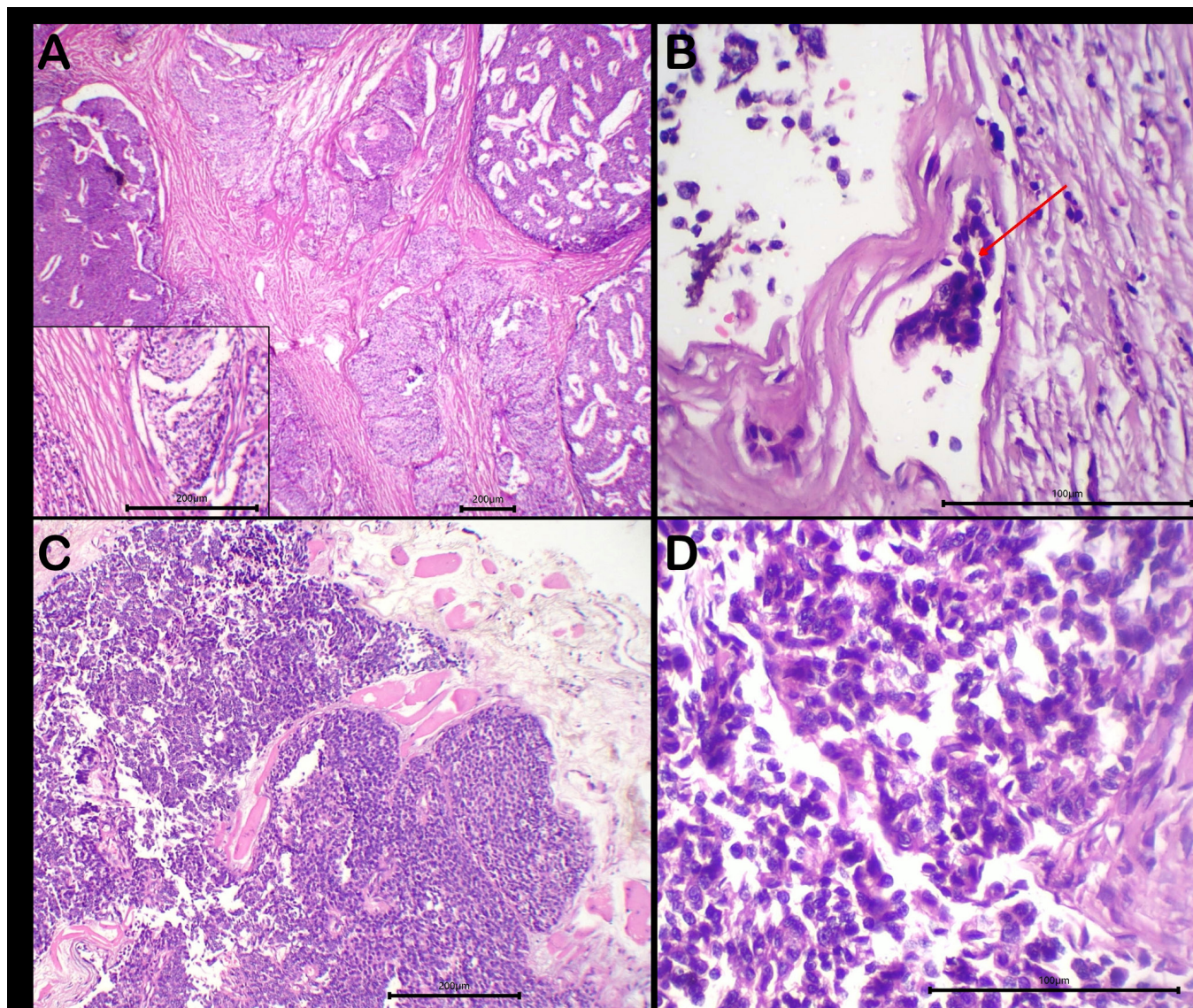


Fig. 3: Histopathological characters of parathyroid carcinoma: The tumors showed nodular microscopic growth pattern with frequent fibrous septation (A), capsular break (Inset), vascular invasion (B, red arrow) and infiltration of adjacent skeletal muscles (C). The tumor cells are usually uniform in size and shape with mild to moderate nuclear atypia (D). H&E stained sections; magnification is x40 for A, x100 for inset and C and x400 for B and D.

Diani K *et al* concluded that recurrences developed 3 years after the primary surgery, and the recurrence mainly occurred in the neck regional operative field, and the main presentation of recurrent case is recurrent hypercalcemia and recurrent HPT^[16]. While in our study the recurrence of manifestation occurred from 7 months to 26 months from the initial surgery, in most of cases (5 cases) the reoperation weren't curative as after the 2nd surgery the patients developed manifestation of hypercalcemia and HPT mostly due to distant metastases, most of studies^[18,19] concluded no statistical significant difference between radical en bloc resection and local excision of parathyroid tumor especially that there is no evidence confirmed malignancy before the initial surgery, while other reports suggested radical resection from the start when there is any suspicion of malignancy as severe hypercalcemia or 10 time above the normal serum parathormone to obtain adequate control and decrease the incidence of recurrence^[20-21] Radiotherapy is indicated only in one case of our study as the tumor was very aggressive with gross infiltration of sternomastoid muscle and surrounding thyroid tissue and vessels but chemotherapy was not indicted in this study because PC is considered chemoresistant. But some few reports showed decreased recurrence rate with postoperative radiotherapy^[22,23]. And other report used chemotherapy, but the evidence of the success of postoperative chemotherapy are not confirmed till now^[24].

Long-term follow up is mandatory and during which we used calcimimetic to decrease the blood calcium level, The incidence of recurrence of hypercalcemia or hyperparathyroidism in our study was high as all patients developed recurrence of manifestation mostly due to recurrence of lesion as in neck nodes or distant metastases while electron K *et al* showed recurrence in 84% of cases and other reports showed recurrence rate 50%-60%^[11,13,14].

In our case series management of recurrence of manifestation due to distant metastases was by using calcimimetic and bisphosphonate to control hypercalcemia and associated complication which is the documented regimen for palliative management of hypercalcemia due to distant metastases^[25].

Till now there is no consensus on guidelines for management of parathyroid carcinoma as the disease is very rare. And most of studies usually consisting of few case series, more studies with high number of cases are needed to a create guideline for management of parathyroid carcinoma.

CONCLUSION

Recurrent hyperparathyroidism is challenging to head and neck surgeons, parathyroid carcinoma on of the important cause of recurrent HPT. In parathyroid

carcinoma, recurrence is common. Diagnosis of PC depend on postoperative pathological examination by the abnormal mitotic figures, capsular invasion and vascular invasion. En bloc radical resection is the treatment of choice when locoregional recurrence occurred to control the hypercalcemia and associated conditions, as neither chemotherapy nor radiotherapy is effective. more studies with large number of cases is needed to achieve guidelines for optimum treatment of parathyroid carcinoma.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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