

# The importance of intraoperative evaluation for parathyroid cancer

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## Abstract

**Aim:** There is no examination to determine the exact diagnosis of parathyroid cancer before surgery. The aim of this study was to discuss our surgical experience and the intraoperative findings suggestive of cancer, in parathyroid cancers operated with the diagnosis of primary hyperparathyroidism.

**Material and Methods:** Six patients with parathyroid cancer who were operated on between May 2012 and January 2017, in the Department of General Surgery, Cukurova University were included in the study. Age, sex, complaints of the patients, calcium and parathormone values, imaging methods for localization, intraoperative findings from surgical notes were evaluated retrospectively.

**Results:** Of the patients, 4 were females and 2 were males. The mean age was 61.6±7.28 (50-71). While the lesion was spotted incidentally in three patients, swelling in the neck, back and hip pain, pancreatitis were other reasons for admission. The mean calcium levels were 13.05±1.86 (10.5-15.7) mg/dL, mean parathormone values were 937.4±756.9 (370-1814) pg/ml. Ultrasonography (USG) and parathyroid scintigraphy were performed to all patients. Thyroid scintigraphy was additionally performed on one patient for hyperthyroidism and then FNAB-FNAS was performed. This patient was operated on with suspected thyroid cancer. In intraoperative evaluation, all of the lesions were firm, adherent to the thyroid capsule and surrounding tissues. One patient had inferior laryngeal nerve invasion. In frozen examination, four patients with suspected parathyroid cancer was specified. Three patients had a lobectomy and 2 patients had en bloc lesion resection with total thyroidectomy. Lesion excision was performed in one patient. After final pathology results, re-operation was suggested, however the patient did not accept.

**Conclusion:** The definitive diagnosis in parathyroid cancer is made by postoperative pathological examination. In cases of primary hyperparathyroidism, in case of intravesical invasion of the thyroid capsule and surrounding tissues during intraoperative examination, parathyroid cancer should be suspected. In case of suspicious findings in frozen examination and intraoperative findings, the surgical plan may be changed and the necessity of secondary surgery can be eliminated.

**Keywords:** Parathyroidcarcinoma; thyroidectomy, hypercalcemia.

## INTRODUCTION

Parathyroid cancer is less than 0.1% of all cancers. It is the cause of 1-2% of primary hyperparathyroidism cases (1-3). It was described by De Quervain in 1904. Approximately 1,000 cases worldwide have been reported (4,5). The etiology is not fully elucidated. While exposure to ionized radiation at a young age increased the risk of parathyroid disease, this risk has not been described for the development of parathyroid carcinoma. It is mostly seen as sporadic. Five% are associated with hereditary syndromes. Familial hyperparathyroidism, multiple endocrine neoplasia MEN 1 and 2A may accompany the disease (5). Parathyroid carcinoma is detected in

approximately 10-15% of cases of hyperparathyroidism-jaw tumor (HPT-JT) (6,7). Generally, the forms progressing with syndromes include genes affecting molecular pathways such as CDC73 or MEN1 (8). Secondary and tertiary hyperparathyroidism is believed to be a potential risk factor for the development of parathyroid cancer (9). Parathyroid cancer should be suspected in patients presenting with elevated plasma parathyroid hormone levels and rarely with a solid mass in the neck. This rare endocrine malignancy can usually be diagnosed preoperatively and during surgery without definite diagnosis. There is no definitive examination before the operation (10). WHO has recognized the diagnostic criteria for parathyroid carcinoma as a demonstration of

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metastatic disease or vascular, perineural or capsular tumor invasion (11). In previous studies, parathyroid cancers were defined as intra-operatively 3 cm above, irregular, grayish-white, firm, often adherent or infiltrating masses (12,13). In this study, we present our surgical experience in patients with parathyroid cancer and intraoperative findings suggesting parathyroid cancer in patients who were operated for primary hyperparathyroidism.

## MATERIAL and METHODS

Six patients who were operated on due to hyperparathyroidism between May 2012 and January 2017, in the Cukurova University, and received a parathyroid cancer diagnosis were included in this retrospective study. Age, sex, complaints of the patients, calcium and parathormone values, imaging methods for localization, intraoperative findings from surgical notes were evaluated retrospectively. IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) package program was used for statistical analysis of the data. Values are given as mean  $\pm$  standard deviation (SD) and minimum-maximum.

## RESULTS

Of the patients, 4 were females and 2 were males. The mean age was  $61.6 \pm 7.28$  (50-71). One patient presented with swelling in the neck, 1 patient with back and hip pain and 1 patient with pancreatitis (Table 1). There was no familial hyperparathyroidism in their histories. The mean calcium levels were  $13.05 \pm 1.86$  (10.5-15.7) mg/dL and the mean parathormone values were  $937.4 \pm 756.9$  (370-1814) pg/ml. Ultrasonography (USG) and parathyroid scintigraphy were performed to all patients for preoperative localization. Lesion localization was detected as the lower right in three patients in and the lower left in 3 patients (Table 2). The patient presenting with a swelling in the neck was diagnosed with toxic multinodular goiter. In thyroid scintigraphy, FNAB-FNAS was performed from the cold nodule in the lower left of the thyroid. FNAB-FNAS was reported as suspected malignancy and the patient was operated with suspected thyroid cancer. Intraoperatively all of the lesions were solid, adherent to the thyroid capsule and surrounding tissues. Inferior laryngeal nerve invasion was detected in the patient who was operated due to thyroid cancer suspicion. In frozen

**Table 1. Characteristics of the patients**

Case no.	Age-Sex	Complaint
1	50/M	None, calcium level elevation found during testing
2	62/M	None, calcium level elevation found during testing
3	67/F	Lower back and back pain
4	58/F	Pancreatitis
5	62/M	Swelling on neck
6	71/F	None, calcium level elevation found during testing

examination, four patients were suspected of parathyroid cancer. Two patients had right lobectomy, one patient had left lobectomy and two patients had en bloc lesion resection with total thyroidectomy. Only lesion excision was performed in one patient. After final pathology results, re-operation was suggested, however the patient did not accept (Table 3).

During follow up, one patient was lost due to renal failure in the third postoperative month. One patient alive with bone metastasis and four patients alive without disease. Local nux was not detected and Overall survival  $47.5 \pm 30.3$  (3-85).

## DISCUSSION

Parathyroid cancer, a rare cause of primary hyperparathyroidism, constitutes 0.005% of all cancers (14). It is most frequently seen between 45-59 years of age. Male and female sexes are equally affected (15). In our series, the number of male patients were higher and the mean age was 61 years. Hypercalcemic symptoms are more prominent in parathyroid cancers than benign parathyroid tumors. Renal and skeletal system may be affected together. Complications of skeletal system include bone pain, osteopenia and pathological fractures. Polyuria, renal colic, nephrocalcinosis and nephrolithiasis form the complications of the renal system. Complications of the digestive system include abdominal pain, peptic ulcer and pancreatitis. Fatigue and depression are among psychiatric symptoms (1,2). In our study, three patients had no complaints except for the elevated levels of calcium. One patient presented with previous pancreatitis, one patient with common muscular

**Table 2. Calcium and parathormone values for each patient, imaging methods used for localization and lesion localization**

Case no.	Calcium value	Parathormone value	Imaging Method	Lesion localization
1	12 mg/dL	12370 pg/ml	Thyroid USG (+) Parathyroid scintigraphy (+)	Lower right
2	1.5 mg/dL	401 pg/ml	Thyroid USG (+) Parathyroid scintigraphy (+)	Top right, intrathyroidal
3	15.7 mg/dL	1714 pg/ml	Thyroid USG (+) Parathyroid scintigraphy (+)	Lower left
4	14.6 mg/dL	1817 pg/ml	Thyroid USG (+) Parathyroid scintigraphy (+)	Lower right and lower left
5	10.5 mg/dL	Not present preoperatively	Thyroid USG (+) and Thyroid scintigraphy (+)	Lower left (Operated on due to suspicion of thyroid malignancy)
6	13 mg/dL	385 pg/ml	Thyroid USG (+) Parathyroid scintigraphy (+)	Lower right

**Table 3. Performed surgery and intraoperative findings of each patient**

Case no.	Performed surgery (In addition to parathyroidectomy)	Frozen	Findings detected intraoperatively
1	Right lobectomy + isthmectomy	Parathyroid cancer suspicion	Lesion is solid, invading the thyroid capsule and surrounding tissues
2	Right lobectomy + isthmectomy	Parathyroid cancer suspicion	Lesion is solid, invading the thyroid capsule and surrounding tissues
3	Left lobectomy + isthmectomy	Parathyroid cancer suspicion	Lesion is solid, invading the thyroid capsule and surrounding tissues
4	Total thyroidectomy + Right central neck dissection	Parathyroid cancer suspicion	Both lesions are solid, invading the thyroid capsule and surrounding tissues, lymph node at right central
5	Total thyroidectomy	Operated on due to suspicion of thyroid malignancy. Frozen was not studied.	Lesion is solid, invading the thyroid capsule and surrounding tissues, inferior laryngeal nerve invasion (+)
6	Bottom right adenoma excision	No suspicion of cancer (Diagnosed in paraffin)	Lesion is solid, invading the thyroid capsule and surrounding tissues

joint pain and one patient with swelling in the neck. In their series of 133 cases, Obara and Fujimoto reported that serum calcium levels were between 10-24 mg/dl and 65% of the patients had levels higher than 14 mg/dl. High alkaline phosphatase values, hypophosphatemia and hyperchloremic metabolic acidosis were also observed (16,17). Preoperative parathyroid cancer should be suspected in patients with serum calcium levels above 14 mg/dL, accompanied by parathyroid hormone levels 3-15 times higher than the normal range (10). However, cases of non-functioning parathyroid carcinoma with no active PTH release, leading to normal calcium levels, have been reported in the literature. Its frequency is estimated to be around 10% (18). In our series, the mean Ca value was 13.05 mg/dl and the parathormone level was over 1,000 pg/ml in 2 patients and over 300 pg/ml in 3 patients. The presence of a palpable mass on the neck, the presence of recurrent laryngeal nerve palsy and simultaneous hyperparathyroidism in patients diagnosed with hyperparathyroidism should increase the suspicion of parathyroid cancer (19).

The presence of a palpable mass in the neck, which is seen approximately 35% in parathyroid cancer, is the most important examination finding for the clinician (20). Parathyroid adenomas are usually not palpable.

In the case of combined use of imaging methods, the sensitivity and accuracy of detection of lesion localization increases. Technetium-99 sestamibi scintigraphy and neck ultrasound combination are most commonly used for localization study. Imaging modalities are not useful in determining the malignancy potential of the lesion. Hisato HARA et al. reported in their series of 77 patients that malignant lesions are ultrasonographically heterogeneous, lobulated and larger. Parathyroid adenomas are seen as homogeneous, smooth and smaller sized lesions (21). Kebebew et al reported the sensitivity of localization of parathyroid carcinoma using sestamibi, MRI/CT, ultrasound and selective venous sampling as 79%, 93%, 69% and 83%, respectively (22). In our study, all lesions were localized preoperatively and no patients were

operated on with a diagnosis of parathyroid cancer. Fine needle aspiration by biopsy is not recommended due to the risk of parathyromatosis in patients with preoperative parathyroid cancer suspicion (23).

The main problem in diagnosis is distinguishing carcinoma from adenoma. It is very important for appropriate surgical method and to eliminate the need for secondary surgery. Parathyroid cancer should be considered when during neck exploration, large sized solid, intraoperative thick, gray or white encapsulated, solid masses, invading surrounding tissues (trachea, esophagus, carotid and/or recurrent laryngeal nerve) are observed (17). In a 163-case parathyroid carcinoma series by Obara and Fujimoto, with 23%, thyroid was found to be the most common organ involvement (2). Intraoperative findings are not clear in 75% of the cases and parathyroid cancer diagnosis is made postoperatively (3,10,24). In our study, in the intraoperative evaluation, if there was a solid invasive lesion in the thyroid capsule and surrounding tissues, parathyroid cancer was suspected and the surgical procedure was shaped according to this idea. It is important that each surgeon is aware of this disease.

"Frozen" studies are often unreliable for benign-malignant determination during surgery. In our cases, parathyroid cancer was suspected in 4 out of 5 patients who were studied with frozen. 1 patient had no suspicion of cancer.

The best treatment is the en bloc resection of the same side thyroid lobe as the tumor, and the surrounding soft tissue, prethyroid muscle, trachea and esophagus, if an invasion is present (17,25,26). Leaving the tumor behind during resection increases the tendency for local recurrence. Considering the absence of effective adjuvant therapy for microscopic or macroscopic disease, resection of RLN should be the preferred method if the tumor cannot be completely dissected from the nerve. We preferred to perform en bloc resection with nerve in our patient with recurrent nerve involvement. All parathyroid glands should be evaluated one by one and removed if necessary (10,27).

En bloc resection has the advantage of survival when compared to basic parathyroidectomy. In the series in the literature, the average survival was reported to be 89% in 69-month follow-up in patients treated with en bloc resection and 53% in the mean 62-month follow-up period in patients treated with simple parathyroidectomy. Young and colleagues compared parathyroidectomy, en bloc resection and delayed thyroidectomy in 136 cases of parathyroid carcinoma. The overall 5-year overall survival rate was 85.7% in patients who underwent parathyroidectomy, 84.0% in patients with the en bloc resection, and 100% in patients undergoing parathyroidectomy and delayed thyroid resection. Young et al. did not determine a difference in overall survival between the three surgical groups ( $p = 0.26$ ) (28). In our series, one patient developed mortality in the 3<sup>rd</sup> postoperative month due to renal failure.

The difference between en bloc resection and parathyroidectomy is its association with lower recurrence rates. Wang et al. found a recurrence rate of 28% in patients who underwent radical resection, and 62% in 87 patients who underwent parathyroidectomy, in their series of 234 cases (29). In parathyroid cancer, incomplete tumor resection also has a high local recurrence rate (30).

In parathyroid cancer, lymph node metastasis is rare. Lymph node involvement was detected in 15% of 286 cases in the American National Cancer Database (16). When metastasis to the lateral neck lymph nodes is detected, dissection of cervical II-V lymph nodes should be performed, and when central site metastasis is detected, central dissection should be performed. We performed central lymph node dissection in one patient. Excision of regional lymph nodes should be performed only in case of invasion (29).

An effective systemic oncological treatment of parathyroid carcinoma is not yet available. While parathyroid carcinoma has no standard chemotherapy regimen, it is also usually not effective in its treatment. Various regimens such as dacarbazine, nitrogen mustard, cyclophosphamide, actinomycin D, adriamycin and 5-fluorouracil have been used in the literature. The use of adjuvant chemotherapy in parathyroid cancer treatment is determined individually (2,31,32,33). Some authors suggest that radiotherapy will decrease recurrence (33,34). Three of our patients received radiotherapy treatment.

Renal failure, cardiac arrhythmias, pancreatitis and uncontrolled hypercalcemia are the most common causes of death. In the treatment of symptomatic hypercalcemia, hydration, calcimimetics (Cinacalcet) and bisphosphonates are used (35).

## CONCLUSION

In conclusion, parathyroid carcinoma is a rare endocrine malignancy with variable clinical features. Successful surgical treatment requires preoperative suspicion of disease and intraoperative awareness of the malignant potential of the lesion. In order to prevent the need for secondary surgical intervention, the surgical plan can be

changed based on intraoperative findings in patients who will be operated due to primary hyperparathyroidism. The success rate of treatment can be increased by applying a comprehensive surgical approach with intraoperative evaluation.

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