NONFUNCTIONAL PARATHYROID CARCINOMA

Goetz A. Giessler, MD, and Derrick J. Beech, MD
Memphis, Tennessee

Parathyroid carcinoma is a rare entity accounting for 0.5% to 5% of parathyroid neoplasia. Most of these malignancies present as functional hormone-producing masses with elevated serum levels of parathormone and calcium. These tumors may also be nonfunctional. Clinical detection of nonfunctioning parathyroid malignancies preoperatively is primarily based on symptoms of an expanding neck mass. This ominous complaint is typically accompanied with an advanced stage of the disease at initial diagnosis. Because there is a paucity of data in the literature regarding nonfunctioning parathyroid carcinoma, prognosis can not be readily assessed. In both functional and nonfunctional parathyroid carcinoma, early surgery has proven to be the only curative treatment approach whereas both chemotherapy and radiation therapy fail to produce systemic or regional benefit when used alone. Hence, parathyroid cancer should be considered in every patient evaluated for a neck mass regardless of the blood calcium and blood parathormone level. (*J Natl Med Assoc.* 2001;93:251–255.)

Key words: parathyroid ♦ carcinoma ♦ nonfunctioning

Parathyroid carcinoma accounts for only 0.5% to 5% of all parathyroid tumors. The majority of these malignancies produce elevated levels of functional parathyroid hormone.[1,2] Patients that present with hyperparathyroidism are more likely to have their disease clinically detected early due to signs of profound hypercalcemia. A palpable neck mass, gastrointestinal, renal, musculoskeletal and psychological symptoms are the more commonly found symptoms of patients presenting with this disease. These generalized complaints are also evident with hypercalcemia from benign causes; thus making final diagnosis of malignancy dependent on intraoperative findings or on final pathologic evaluation of the resected parathyroid gland.

In the small percentage of patients with nonfunctioning parathyroid carcinoma, the presence of a neck mass is often the only clinical finding making preoperative detection more difficult. This review details the management of parathyroid cancer, particularly the nonfunctional variant.

INCIDENCE AND PATIENT DEMOGRAPHICS

Parathyroid carcinoma is a rare entity accounting for only 0.5% to 5% of cases of primary hyperparathyroidism.[3,4] There is no significant gender preponderance[5] and the initial diagnosis is made in 84% of patients in their third through sixth decade.[3] In general, patients with parathyroid carcinoma are approximately ten years younger than those with benign parathyroid tumors.[5,6] An association with familial patterns or previous neck irradiation has not been shown. Of these malignancies, only 25% are nonfunctioning.[1,7] These percentages should be interpreted with caution because of the

 From the Technische Universitaet Munich, Germany and University of Tennessee-Memphis, Department of Surgery, Memphis, Tennessee. Requests for reprints should be addressed to Derrick J. Beech, MD, Chief, Surgical Oncology, The University of Tennessee-Memphis, Department of Surgery, 956 Court - G215, Memphis, TN 38163.

Table 1. Initial Presenting Symptoms of Malignant Parathyroid Neoplasias

Clinical Symptoms	
Functional parathyroid carcinoma	Nonfunctional parathyroid carcinoma
nausea and vomiting	palpable neck mass
polyuria and thirst	hoarseness
constipation	dyspnea
peptic ulcer disease	dysphagia
pancreatitis	decreased range of motion in the neck (pain)
nephrolithiasis	
demineralizing bone diseases	
psychological symptoms	
(palpable neck mass)	

relatively small number of cases. Less than 30 cases are reported in the world literature of nonfunctioning parathyroid cancer.

SIGNS AND SYMPTOMS

Most patients with parathyroid cancer present with symptoms of hypercalcemia such as nausea, vomiting, depression, polyuria, or polydipsia with gastrointestinal complaints such as constipation, pancreatitis, or peptic ulcer disease. Skeletal manifestations may also be present, including bone pain, osteitis fibrosa cystica (brown tumors), diffuse subperiosteal bone resorption and spontaneous fractures, or deterioration of renal function due to massive interstitial calcification or renal calculi. Patients with functioning parathyroid carcinomas may frequently have several of these symptoms. Typically, serum calcium levels are higher in malignant parathyroid tumors, which is an important clinical finding to differentiate carcinoma from adenoma of the parathyroid gland. Serum calcium level is greater than 14 mg/dL in 39% to 75% of patients, and the parathyroid hormone (PTH) level is elevated up to 40 times the maximal value in patients with functional parathyroid carcinoma. The usual pattern of PTH production in adenomas typically does not exceed three times the normal upper limit.[8,9]

In contrast to adenomas,[10] malignant tumors of the parathyroid gland are often palpable at diagnosis (32 to 75% of cases).[6,11] Pain is not a typical feature in parathyroid carcinomas of functional and nonfunctional types.[2,12,13] Myalgia, diffuse spinal osteopenia, and generalized skeletal pain can all account for a decreased range of motion, whereas these symptoms are almost exclusively due to the elevated calcium levels in secreting parathyroid carcinoma.[4,14,15] In the nonsecreting parathyroid tumor, decreased range of motion is primarily due to local invasion of adjacent tissues and tumor expansion, which may cause dysphagia and hoarseness due to involvement of laryngeal structures. The latter seems to be a common presenting symptom in the nonfunctional carcinoma, because it is detected usually later in a more advanced stage due to the lack of hypercalcemia-associated symptoms.[2,9] Several investigations of patients with functional carcinoma do not report hoarseness or dysphagia as an initial symptom[3–5] or found it very rarely[16,17] (Table 1). Skulchan and associates[18] reported a 53-year-old patient with craniofacial and femoral osteolytic lesions, exophthalmos and a large painful neck mass that caused dyspnea.

HISTOLOGIC PATTERN

The classical histologic criteria to differentiate an adenoma from a carcinoma of the parathyroid gland were initially described 1973 by Schantz and Castleman.[3] These features include fibrous trabeculae, mitotic figures, capsular invasion, and vascular invasion and are useful criteria for determining malignancy (Table 2). Scarring from previous hemorrhage or surgery and the accidental location of mitotic figures in endothelial cells can lead to misinterpretation. Tumor cell entrapment in the fibrous capsule can pretend invasiveness and is not a sign of malignancy if true penetration of the capsule is not found histologically.[19] Cellular atypia and variation are not found to be helpful in the diagnosis.[3] A uniform cell pattern seemed to be more common in parathyroid malignancies.[4] The triad macronucleoli, more than five mitoses per 50 high power fields and necrosis is associated with aggressive and recurrent disease.[20] Immunoperoxidase staining to exclude thyroid origin is obligatory.[2,8]

Table 2. Histological and Surgical Criteria for Evaluating Malignancy in a Parathyroid Mass

Gross and microscopic findings for parathyroid carcinoma	
Microscopic criteria for parathyroid carcinoma	Macroscopic criteria for parathyroid carcinoma
trabecular pattern	gray-white color
invasiveness (true capsular penetration)	firm, lobular nodules
vascular invasion	adherent to adjacent structures
uniform cell pattern	intensive surround scarring
mitotic figures in stroma cells	metastases

Elevated serum levels of beta human chorionic gonadotropin (βHCG) was found to be helpful as another hint for malignancy in some studies,[6,8] whereas others could not repeat this finding.[21] Recent studies using immunohistochemical staining demonstrates a link between functional parathyroid carcinoma and the MiB-1 tumor gene, whereas elevated levels of mutated p53 and bcl-2 were not useful in evaluating malignancy.[10,22] The role of these findings in nonfunctional carcinomas have yet to be established.

Classical light microscopic criteria used to differentiate a functioning from a nonfunctioning carcinoma do not exist.[23] Immunoperoxidase staining of parathormone can help in the differential diagnosis.[24,25] Electron microscopic studies of nonfunctional parathyroid carcinomas showed accumulation of glycogen nodules but were contradictory about the relation between the number of intracellular secretory granules and the functional status of the tumor.[9,23]

Due to the difficulties in the histologic diagnosis, several authors suggest a possible adenoma-carcinoma sequence in the pathogenesis of the parathyroid carcinoma.[1,21] Other investigators report that such a sequence does not exist but is rather a failure in correct interpretation of the clinical, surgical, and histopathological features.[3] In general, the clinical, intraoperative, and pathologic picture should guide the final diagnosis.[14] The surgeon is an integral member of the team with early involvement being essential because suspicious lesions of the parathyroid glands should not undergo a transcutaneous needle biopsy since the decision regarding malignancy is made intraoperatively.

DIAGNOSTIC RADIOLOGY

In addition to CT scan and MRI imaging, the radionuclide subtraction scans with technetium-99m/thallium-201 resulted in good preoperative localization of functioning and nonfunctioning parathyroid carcinomas.[2,6,10] Unfortunately, these latter imaging studies are of limited value preoperatively for localization due to their low resolution.

TREATMENT

Surgery

Operative resection is the only effective treatment modality for these malignancies.[26,27] In functional carcinomas, surgical resection results in temporary control of elevated calcium levels by debulking operations.[19,28] Because the microscopic evaluation of frozen and permanent sections can be inconclusive, the decision for extensive surgery has often been based on the macroscopic appearance in situ. Parathyroid carcinomas are typically hard, grayish-white nodules surrounded by a dense fibrous capsule.[29] Intensive scarring and adherence to adjacent structures is common and highly suspicious for malignancy.[3,8,10,12] Parathyroid carcinomas can be well vascularized[2] and spontaneous hemorrhage can occur. Depending on the extent of the disease an en bloc resection of the tumor, ipsilateral thyroid lobe and isthmus together with a neck dissection only in case of lymph node involvement is recommended as the standard procedure.[10] It is of utmost importance that the capsular integrity of the tumor is preserved to prevent spillage of tumor cells.[30] Therefore, the surgeon should refrain from intraoperative biopsies, which will usually not reveal an unequivocal intraoperative diagnosis.[8] The recurrent laryngeal nerve should be resected if adherent or involved.[11] Nonfunctional tumors often demand more extensive surgical approaches, as described above, because of the higher incidence of local invasion or metastasis at diagnosis. The usual pattern of dissemination involves spread to regional lymph nodes, lung, or liver.[3,26,31] Distant lymphatic or hematogenous metastases should be resected if possi-

ble as this can lead to improved survival.[11,26] There is no evidence, however, that nonfunctional parathyroid carcinomas are more aggressive than the secreting type. The prognosis in both forms is highly dependent on the meticulous resection of all tumor suspicious tissue.

Chemotherapy/Radiation Therapy

The treatment of malignant parathyroid neoplasms with chemotherapy has not yet proven to be universally effective in large series.[8,21] Successful results are anecdotal and have yet to be proven beneficial, particularly in nonfunctioning parathyroid carcinomas.[9,32] Adjuvant radiotherapy in functioning tumors resulted also only a in few long term remissions.[16,23] The effectiveness in treatment of nonfunctional parathyroid carcinomas is still controversial.[2,9,33]

OUTCOME

The overall prognosis of the nonfunctioning parathyroid carcinoma is not favorable.[2] Late-staged presentation, often with metastases, and ineffective adjuvant therapies result in dismal outcomes. Operative resection is the only effective treatment modality. The lack of an adequate parameters for follow up make curative therapy very difficult. Death in patients with nonfunctional parathyroid tumors is primarily due to the volume of regional disease and metastases.[1] Few patients survive longer than 2 years.[34,35]

SUMMARY

In summary, nonfunctional parathyroid carcinoma is a rare malignant disease, which often is detected late due to a paucity of symptoms, of which a palpable neck mass is the most common. Histologic criteria are not always sufficient to establish the diagnosis and often the diagnosis is made intraoperatively. Because complete removal of all malignant tissue remains the most effective method of controlling this disease, the surgeon must be attune to the possibility of a parathyroid malignancy and include this differential diagnosis. An en bloc resection of all suspicious tissue should be performed if the diagnosis is in doubt. The overall surgical, clinical and pathologic picture is required to adequately diagnose and treat this malignancy. The prognosis of nonfunctional parathyroid carcinoma is usually poor because of detection at advanced stages, the relative ineffectiveness of adjuvant treatment modalities and the lack of adequate parameters for clinical follow-up.

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REFERENCES

1. Aldinger KA, Hickey RC, Ibanez ML, et al. Parathyroid carcinoma: a clinical study of seven cases of functioning and two cases of nonfunctioning parathyroid cancer. *Cancer.* 1982;49: 388–397.

2. Klink BK, Karulf RE, Maimon WN, et al. Nonfunctioning parathyroid carcinoma. *Am Surg.* 1991;57:463–467.

3. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. *Cancer.* 1973;31:600–6005.

4. Wynne AG, van Heerden J, Carney JA, et al. Parathyroid carcinoma: clinical and pathological features in 43 patients. *Medicine.* 1992;71:197–205.

5. Wang CA, Gaz RD. Natural history of parathyroid carcinoma. Diagnosis, treatment and results. *Am J Surg.* 1985;149:522–527.

6. Fujimoto Y, Obara T. How to recognize and treat parathyroid carcinoma. *Surg Clin N Am.* 1987;67:343–357.

7. Holmes EC, Morgon DL, Ketcham AS. Parathyroid carcinoma: a collective review. *Ann Surg.* 1969;169:631–635.

8. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, et al. Parathyroid carcinoma: features and difficulties in diagnosis and management. *Surgery.* 1983;94:906–915.

9. Bondeson L, Sandelin K, Grimelius L. Histopathological variables and DNA cytometry in parathyroid carcinoma. *Am J Surg Pathol.* 1993;17:820–829.

10. Murphy MN, Glennon PG, Diocee MS, et al. Nonsecretory parathyroid carcinoma of the mediastinum. Light microscopic, immunocytochemical and ultrastructural features of a case, and review of the literature. *Cancer.* 1986;58:2468–2476.

11. Park ST, Condemi G, Shakir KM, et al. Parathyroid carcinoma: report of three cases and review of the literature. *Milit Med.* 1998;163:246–249.

12. Shane E. Parathyroid carcinoma. *Curr Ther Endocrinol Metab.* 1997;6:565–568.

13. Fyfe ST, Hoover LA, Zuckerbraun L, et al. Parathyroid carcinoma: clinical presentation and treatment. *Am J Otolaryngol.* 1990;11:268–273.

14. Stavraka-Kakavaki A, Fronistas O, Toumbouros M, et al. Parathyroid carcinoma: report of three cases. *Clin Nucl Med.* 1992;17:1–3.

15. McCance DR, Kenny BD, Sloan JM, Russell CF, Hadden DR. Parathyroid carcinoma: a review. *J Royal Soc Med.* 1987;80: 505–509.

16. van Heerden JA, Weiland LH, ReMine WH, et al. Cancer of the parathyroid glands. *Arch Surg.* 1979;114:475–480.

17. Chow E, Tsang RW, Brierley JD, Filice S. Parathyroid carcinoma—the Princess Margaret Hospital experience. *Int J Rad Oncol Biol Phys.* 1998;41:569–572.

18. Mashburn MA, Chonkich GD, Chase DR, et al. Parathy-

roid carcinoma: two new cases—diagnosis, therapy and treatment. *Laryngoscope.* 1987;97:215–218.

19. Skulchan V, Tepmongkol P, Dharamadach A, et al. Malignant tumor of the parathyroid gland: report of case. *J Med Assoc Thailand.* 1983;66:812–817.

20. McKeown PP, McGarity WC, Sewell CW. Carcinoma of the parathyroid gland: is it overdiagnosed? A report of three cases. *Am J Surg.* 1984;147:292–298.

21. Bondeson L, Sandelin K, Grimelius L. Histo pathological variables and DNA cytometry in parathyroid carcinoma. *Am J Surg Pathol.* 1993;17:820–829.

22. Vetto JT, Brennan MF, Woodruf J, et al. Parathyroid carcinoma: diagnosis and clinical history. *Surgery.* 199;114:882–892.

23. Vargas MP, Vargas HI, Kleiner DE, et al. The role of prognostic markers in parathyroid tumors. *Modern Pathol.* 1997; 10:12–17.

24. Yamashita H, Noguchi S, Nakayama I, et al. Light and electron microscopic study of nonfunctioning parathyroid carcinoma. Report of a case with a review of the literature. *Acta Pathologica Japonica.* 1984;34:123–132.

25. Ordonez NG, Ibanez ML, Samaan NA. Immunoperoxidase study of uncommon parathyroid tumors. *Am J Surg Pathol.* 1983;7:535–542.

26. Wahl RA, Konig M, Schmidt-Gayk H, et al. Hormone active versus hormone inactive parathyroid gland cancer. *Wiener Medizinische Wochenschrift.* 1988;138:461–464.

27. Vainas IG, Tsilikas C, Grecu A, et al. Metastatic parathyroid carcinoma (mPCa): natural history and treatment of a case. *J Exp Clin Cancer Res.* 1997;16:429–432.

28. Vasquez-Quintana E. Parathyroid carcinoma: diagnosis and management. *Am Surg.* 1997;63:954–957.

29. Shortell C.K., Andrus C.H., Phillips C.E. Jr, et al. Carcinoma of the parathyroid gland: a 30-year experience. *Surgery.* 1991;110:704–708.

30. Trigonis C, Cedermark B, Willems J, et al. Parathyroid carcinoma—problems in diagnosis and treatment. *Clin Oncol.* 1984;10:11–19.

31. Cordeiro AC, Montenegro FL, Kulcsar MA, et al. Parathyroid carcinoma. *Am J Surg.* 1998;175:52–55.

32. Shapiro DH, Jurado R. Recurrent parathyroid carcinoma: value of aggressive surgical approach. *J Florida Med Assoc.* 1984;71:937–938.

33. Bukowski RM, Sheeler L, Cunningham J, Esselstyn C. Successful combination chemotherapy for metastatic parathyroid carcinoma. *Arch Intern Med.* 1984;144:399–400.

34. Merlano M, Conte P, Scarsi P, et al. Non-functioning parathyroid carcinoma: a case report. *Tumori.* 1985;71:193–196.

35. Collins FD, Warren MC, Palmer FJ, et al. Nonfunctioning parathyroid carcinoma: a case history. *J Surg Oncol.* 1986;31: 60–61.