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Trial to Predict Malignancy of Affected Parathyroid Glands in Primary Hyperparathyroidism

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Abstract. Parathyroid cancer is rare but relatively frequent in Japan compared to Western countries. Surgical parathyroidectomy is the primary choice for radical treatment of primary hyperparathyroidism (pHPT), hence it is important to distinguish malignant from benign tumor in the determination of surgical indication as well as method of operation. However, it is not easy to diagnose parathyroid cancer prior to operation. In the present study, we analyzed the background data, biochemical data and bone mineral density (BMD) of 131 patients with pHPT (111 benign and 20 malignant). BMD of the lumbar spine and mid-radius was measured by dual-energy X-ray absorptiometry. Serum levels of calcium, alkaline phosphatase (ALP), and parathyroid hormone (PTH) were significantly higher in malignant group compared to benign one. The extent of elevation of mid PTH seemed to be higher than that of intact PTH in malignant group. Age-, gender-, and race-adjusted BMD of distal one-third of radius was significantly decreased in malignant group compared to benign one, although that of lumbar spine was not significantly different between the two groups, indicating that osteopenia was marked in the region which was rich in cortical bone in malignant group. On the other hand, serum levels of calcium, ALP, and mid PTH as well as age were selected as predictors of malignancy in univariate logistic regression analysis, while serum level of intact PTH was not selected. In conclusion, radial BMD was lower in malignant group compared to benign one in pHPT. Serum levels of calcium, ALP and mid PTH were useful to predict malignancy of affected parathyroid glands in pHPT patients.

Key Words: Parathyroid gland, Primary hyperparathyroidism, Parathyroid hormone, Bone mineral density
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PRIMARY hyperparathyroidism (pHPT), a relatively common endocrine disorder, is now recognized as a disorder with few overt manifestations, presenting most often as asymptomatic hypercalcemia [1]. Since pHPT frequently occurs in postmenopausal women [2], it is also important as a casual factor in secondary osteoporosis. PHPT is histologically classified into three groups: adenoma, hyperplasia, and cancer. Since most parathyroid carcinoma present a clinical and biochemical profile similar to benign parathyroid disorders, it poses a difficult diagnostic problem. In most reports in United States and Europe, parathyroid cancer accounts for only 1% of patients with pHPT [3, 4]. However, parathyroid cancer may be somewhat more common in Japan than in Western countries, accounting for 5% of patients with pHPT [5]. Since surgical parathyroidectomy (PTX) is the primary choice for the radical treatment of pHPT, it is important to distinguish malignant from benign tumor in the determination of surgical indication as well as method of operation.

Some of the clinical features of parathyroid cancer

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compared to pHPT caused by benign parathyroid tumor have been previously reported. Serum levels of parathyroid hormone (PTH), alkaline phosphatase (ALP), and calcium are higher in parathyroid cancer than in benign tumors [3, 4, 6]. A cervical mass is frequently palpable in parathyroid cancer, and the proportion of patients with renal or bone disease is relatively higher in parathyroid cancer than in benign parathyroid tumor [6, 7]. However, it is not easy to diagnose parathyroid cancer prior to operation.

In the present study, we compared the preoperative background data, biochemical data and bone mineral density (BMD) between patients with benign and malignant parathyroid tumors in our institution. Moreover, we analyzed the predicting factors for malignancy of affected parathyroid glands in preoperative pHPT.

Subjects and Methods

Subjects

One hundred and ninety-one patients who were diagnosed as pHPT have been hospitalized in Kobe University Hospital from 1987 to 2001. PTX was recommended to all pHPT patients whose abnormal parathyroid glands were successfully identified by imaging techniques and who had no serious complications, regardless of whether patients met the surgical indications of the NIH [8]. Several patients refused operation. Of those receiving operations, we retrospectively and consecutively evaluated 131 patients who did not have complicated diseases that might cause changes in bone metabolism such as hepatic or renal dysfunction, hyperthyroidism, rheumatoid arthritis and cerebral infarction. No patients were taking drugs or hormones that might influence bone metabolism, such as supplemental calcium, vitamin D, estrogen or bisphosphonate. The 131 patients (age, 57 ± 1 yr; mean ± SEM) included 38 men and 93 women. All data were compatible with the existence of pHPT. All subjects were successfully operated, with removal of their abnormal parathyroid glands. Surgical pathology showed adenoma in 101, hyperplasia in 10 and carcinoma in 20 patients. The diagnosis of parathyroid carcinoma was made on the basis of pathologic and clinical criteria [9]. The parathyroid carcinoma had characteristic histopathology and bone metabolism, with at least one of the following features: (1) evidence of local invasion of adjacent organs (thyroid, trachea, esophagus, nerves); (2) evidence of metastasis in the cervical lymph node(s) or a distant site; (3) histologic features, including mitoses, trabecular growth pattern, dense fibrous bands and capsular or vascular invasion. The clinical and biochemical data were obtained by reviewing the chart records at admission. This study was approved by the ethical review board of Kobe University Hospital. The subjects gave their informed consent to participate in the study.

Biochemical measurements

Serum concentrations of calcium, phosphorus, and ALP were measured by automated techniques at the central laboratory of Kobe University Hospital (normal range: Ca, 8.5–9.9 mg/dL; P, 2.4–4.5 mg/dL; ALP, 100–303 IU/L). Intact PTH and mid-region PTH were measured by immunoradiometric assay (Allegro Intact PTH RIA kit, Nichols Institute Diagnostics, San Juan Capistrano, CA; normal range, 10–65 pg/mL) [10, 11] and RIA (Yamasa hypersensitive PTH-RIA kit, Yamasa Shoyu Co. Ltd., Tokyo, Japan; normal range, 160–520 pg/mL) [12] respectively. The intact PTH RIA kit only reacts with human (h) PTH-(1–84), whereas hPTH-(1–34), hPTH-(39–84), and hPTH-(39–68) are nonreactive [13]. The Yamasa PTH-RIA kit consists of chicken PTH antiserum raised by Hruska *et al.*, ^{125}I-labeled [Tyr^{43}] hPTH-(44–68) as a radioligand, and synthetic hPTH-(1–84) as a standard [14]. This assay recognizes the fragments containing at least the amino acid sequence of 44–68 in the PTH molecule and intact PTH as well.

BMD measurements

BMD measurements were performed before PTX. BMD values were measured by dual-energy X-ray absorptiometry (DXA) using QDR-2000 (Hologic Inc., Waltham, MA) at lumbar spine and distal one-third of radius [15]. BMD was automatically calculated from the bone area (cm^2) and bone mineral content (BMC) (g) and expressed absolutely in g/cm^2. The z-score is the number of SDs a given measurement differs from the mean for a sex-, age-, and race-matched reference population. The t-score is the number of SDs that a given measurement differs from the mean for a normal young adult reference population. The coefficients of variation (precision) of measure-

ments of the lumbar spine and radius were 0.9 and 1.9%, respectively.

Statistical analysis

All data are expressed as the mean ± SEM for each index. A regression analysis was performed using the statistical computer program Abacus Concepts StatView (Abacus Concepts, Inc., Berkeley, CA). Univariate logistic regression analyses were performed to evaluate association between preoperative parameter and histology. Comparisons between two groups were made with unpaired t-test. P-values less than 0.05 were considered significant.

Results

Clinical characteristics of parathyroid carcinoma

We first compared various indices between benign and malignant parathyroid tumors. As shown in Table 1, the average age of the patients in malignant group was approximately 8 yr younger than that of patients in benign one. The ratio of affected women to men was almost 1 : 1 in malignant group, while there was a female predominance in benign one. Height, body weight, and body mass index as well as the proportion of patients with vertebral fracture or renal stone were not significantly different between two groups.

Comparison of biochemical markers and BMD between benign and malignant parathyroid tumors

We compared biochemical markers between benign and malignant groups. As shown in Table 2, serum levels of calcium and ALP were significantly higher in malignant group, compared to benign one. There were no significant differences between the two groups in the data such as serum levels of phosphorus, creatinine, creatinine clearance, urinary level of calcium, renal tubular reabsorption of phosphate (%TRP and $TmPO_4$/GFR). Serum levels of intact PTH of benign group and malignant group were 228 ± 27 and 397 ± 138 pg/ml (mean ± SEM) ($p = 0.027$), respectively (Fig. 1). On the other hand, serum levels of mid PTH of benign group and malignant group were 2595 ± 307 and 5277 ± 1503 pg/ml (mean ± SEM)

Table 1. Comparison of various indices between benign and malignant parathyroid tumors

	Benign	Malignant	p
number	111	20	
Age (years)	58 ± 1	50 ± 3	0.010
height (cm)	155.0 ± 0.8	157.0 ± 2.2	0.276
body weight (kg)	54.7 ± 0.9	53.0 ± 2.6	0.289
BMI (m/kg^2)	22.9 ± 0.4	21.6 ± 0.7	0.171
ratio of male to female	29 : 82	9 : 11	0.098
presence of vertebral fracture (%)	4.1%	6.3%	0.702
presence of renal stone (%)	31%	40%	0.462

BMI: body mass index All data were expressed as mean ± SEM.

Table 2. Comparison of biochemical markers between benign and malignant parathyroid tumors

	Normal Range	Benign	Malignant	p
Ca (mg/dl)	8.4–9.9	11.6 ± 0.1	12.7 ± 0.4	0.0009
P (mg/dl)	2.4–4.5	2.5 ± 0.0	2.3 ± 0.1	0.059
ALP (IU/L)	100–303	423 ± 33	845 ± 243	0.012
Creatinine (mg/dl)	0.5–1.3	0.9 ± 0.0	0.9 ± 0.1	0.967
C_{Cr} (ml/min)		81.3 ± 4.1	80.2 ± 7.5	0.996
C_{Ca}/C_{Cr}		0.026 ± 0.001	0.027 ± 0.003	0.774
U_{Ca}/U_{Cr}		0.38 ± 0.02	0.42 ± 0.05	0.359
% TRP (%)		74.8 ± 1.5	71.5 ± 3.9	0.339
$TmPo_4$/GFR (mg/dl)		2.6 ± 0.5	1.4 ± 0.1	0.368

All data were expressed as mean ± SEM.

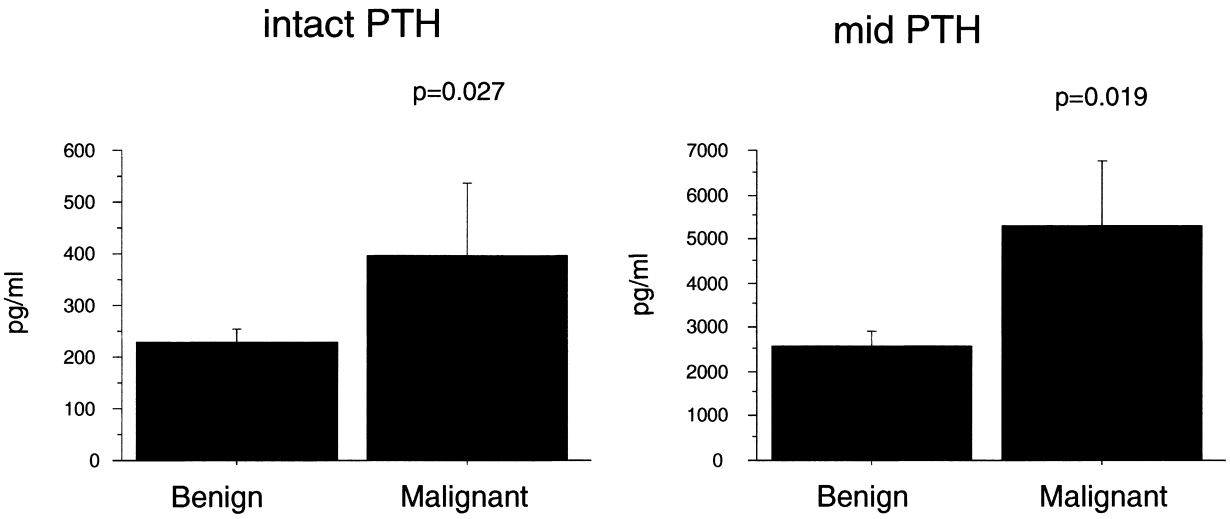

Fig. 1. Comparison of serum PTH levels between benign and malignant parathyroid tumors. All data are expressed as mean ± SEM.

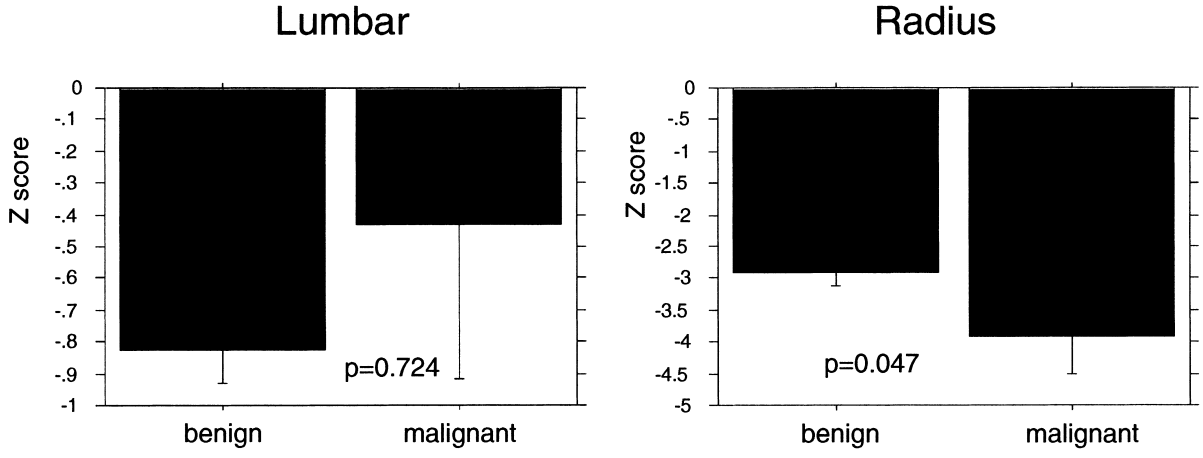

Fig. 2. Comparison of BMD between benign and malignant parathyroid tumors. All data are expressed as mean ± SEM.

(p = 0.019), respectively. The extent of elevation of mid PTH tended to be higher than that of intact PTH. These findings indicated that both intact and mid PTH levels were higher in malignant group compared to benign one (Fig. 1). Next, we compared BMD of radius and lumbar spine between benign and malignant groups. As shown in Fig. 2, age-, gender-, and race-adjusted BMD (z-score) of radius was significantly decreased in malignant group (–2.93 ± 0.20) compared to benign one (–3.91 ± 0.60) (p = 0.047), although that of lumbar spine was not significantly different between the two groups (p = 0.724).

Prediction of parathyroid cancer before operation

In order to analyze the predicting factors for malignancy of affected parathyroid gland in pHPT, we employed a univariate logistic regression analysis. When a univariate logistic regression analysis was performed with the presence of parathyroid cancer as a dependent variable, serum levels of calcium, ALP and mid PTH as well as age were selected, while serum level of intact PTH was not selected (Table 3). Moreover, when a multiple logistic regression analysis for prediction of parathyroid cancer was performed with serum calcium and mid PTH as the independent variables, mid PTH was found to be associated with malignant tumors (odds ratio: 1.67, 95% confidential interval: 1.01–2.75 per SD increase, p = 0.047).

Table 3. Univariate logistic regression analyses in the prediction of malignancy of affected parathyroid glands in primary hyperparathyroidism

	unit	Δincrease (SD)	odds ratio	95%Cl	p
Ca	mg/dl	1.4	1.98	1.27–3.09	0.003
ALP	IU/I	489	1.76	1.12–2.76	0.014
mid PTH	pg/ml	3230	1.73	1.07–2.81	0.027
age	years	14.8	0.59	0.37–0.94	0.027
intact PTH	pg/ml	301	1.45	0.95–2.19	0.082

Discussion

Researchers have noted that in parathyroid carcinoma the ratio of affected women to men was approximately 1 : 1 in most series, while there was marked female predominance (ratio of 3–4 : 1) in benign parathyroid tumor [3, 16, 17], and that the average age of the patients with parathyroid carcinoma was in the fifth decade, approximately ten years younger than that of patients with adenoma, who most often presented in their fifties or sixties [3, 16, 17]. In the present study, the ratio of female to male was approximately equal in malignant group, and the average age was significantly younger than that in benign group, which was compatible with the previous findings. Considerations of gender and age, however, may be of little help in clinically evaluating the individual patient. The kidney and skeleton are classical target organs of PTH and previous reviews indicate that they are affected with greater frequency and severity in parathyroid carcinoma [3, 16, 17]. In the present study, the frequencies of vertebral fracture and renal stone were somewhat higher in malignant group, compared to those in benign group in pHPT but not significantly so, probably due to the small population of subjects treated in the present study. In regard to the biochemical data, the serum levels of calcium, ALP and PTH in malignant group were significantly higher than those in benign group. These findings were in agreement with the reports by other investigators that the severity of hypercalcemia and the elevation of PTH were greater in patients with parathyroid carcinoma [3, 4, 6].

PTH is reported to be correlated with the activation frequency and cortical porosity in bone [18]. In patients with pHPT, persistently high levels of PTH induce high turnover state in bone, owing to the acceleration of both bone resorption and bone formation. Since the increase in bone resorption is more potent than that in bone formation, the excess entering the blood causes hypercalcemia and bone disease. Patients with pHPT have reduced BMD at cortical sites [19, 20], and parathyroidectomy for pHPT has been associated with increased BMD [21–23]. Cortical bone is predominant in the distal one third of the radius, whereas cancellous bone is rich in the lumbar spine. In the present study, age-, gender-, and race-adjusted BMD of radius was significantly decreased in malignant group compared to benign one, although that of lumbar spine was not significantly different between the two groups, and that of malignant group tended to be higher than that of benign group. The present data are compatible with previous findings that pHPT patients usually had reduced cortical BMD and relatively well preserved trabecular BMD [24]. Moreover, the present findings indicate that osteopenia is marked in the region which is rich in cortical bone, and that BMD is relatively well maintained in the region which is rich in cancellous bone in malignant tumor in spite of higher levels of PTH, compared to benign tumor. In large proportion of patients with pHPT, decrease in BMD of lumbar spine was milder than that of radius [20, 25–27]. Duan *et al*. [28] reported that cancellous bone was increased by both PTH deficiency and excess. In that study, cortical bone loss was shown by PTH deficiency and accelerated by PTH excess. Therefore, PTH excess would be anabolic and catabolic at cancellous and cortical bones, respectively. In the present study, the serum PTH level of patients in malignant group was significantly elevated than that in benign tumor group, indicating that the influence of PTH on cortical bone in patients with malignant tumor was severer than that in patients with benign tumor. The anabolic action of PTH on cancellous bone might in part explain the relatively well preserved vertebral BMD in malignant tumor.

In the present study, the extent of elevation of mid PTH seemed to be higher than that of intact PTH in malignant tumor. Moreover, serum levels of calcium, ALP and mid PTH as well as age were selected as predictors of malignancy in univariate logistic regression analysis, although serum level of intact PTH was not selected. These data suggest that not only serum calcium level but also serum levels of mid PTH and ALP are important factors for the prediction of malignancy of affected parathyroid glands in pHPT. Intact PTH is metabolized in peripheral serum, and secreted in parathyroid not only as traces of intact PTH but also as various kinds of PTH molecules. Namely, large amounts of mid-region/carboxyl (C)-terminal fragment as well as traces of intact PTH exist in peripheral serum. It has been generally accepted that PTH exerts its biological activity via the amino-terminal region of its molecule. However, there are several lines of evidence that indicate that PTH(1–84), intact PTH, possesses certain biological effects other than those of PTH (1–34) [29–33]. It has previously been reported that a change in serum calcium alters the ratio of intact hormone to C-terminal fragments in circulation by modulating PTH secretion or peripheral metabolism, and that the ratio of C-terminal to amino-terminal PTH increases during hypercalcemia [34–36]. In the present study, the extent of elevation of mid PTH tended to be higher than that of intact PTH in malignant group compared to that in benign group. Moreover, when a multiple logistic regression analysis for the prediction of malignancy was performed with serum calcium and mid PTH as the independent variables, mid PTH was found to be significantly associated with malignancy, indicating that mid PTH is related to malignancy independently of serum calcium. These findings suggested that the fragments of mid- or C-terminal portion of PTH are predominantly being produced from malignant tumors. Alternatively, the peripheral metabolism of PTH might be enhanced in malignant tumors. Previous studies revealed that the binding sites for the C-terminal region of PTH were distinct from those for its amino-terminal region [37, 38]. Moreover, there are several lines of evidence on the biological actions of mid-region or C-terminal fragments of PTH [39–41]. Mid-region of PTH stimulated the proliferation of chicken chondrocytes [42]. As for bone, Murray *et al*. [41] demonstrated that human PTH-(53–84) stimulated dexamathasone-induced ALP activity in osteoblastic ROS 17/2.8 cells. Moreover, our previous study revealed that C-terminal fragments of PTH stimulated the expression of type-1 collagen and insulin-like growth factor-binding protein-5 in osteoblastic UMR-106 cells [43]. On the other hand, we demonstrated that C-terminal fragments of PTH stimulated osteoclast differentiation and osteoclastic bone resorption in mouse bone cell cultures [44]. These findings suggested that an excess of mid- or C-terminal PTH fragments in malignant group cause bone loss in cortical bone and result in a higher bone turnover rate.

We previously reported that serum ALP level and the severity of cortical bone mass reduction were the best predictors of the changes in lumbar BMD after PTX [45]. In the present study, we demonstrated that serum level of ALP in malignant group was significantly higher compared to that in benign group, when serum ALP level was selected as a predictor of malignancy in univariate logistic analysis. These findings indicated that parathyroid malignant tumors should be suspected in patients with relatively higher levels of serum ALP in pHPT.

It is difficult to predict parathyroid carcinoma prior to operation. In cases suspected of parathyroid cancer, an aggressive initial surgical approach is often considered. In a study involving 197 pHPT patients including 11 cases of malignancy, Shortel *et al*. [46] reported that patients with pHPT characterized by markedly high serum calcium and PTH levels, palpable mass, and severe clinical presentation should be suspected of parathyroid carcinoma. While the present study included a much larger number of malignant cases, our data supported their previous reports. Moreover, the present study is the first to demonstrate that mid PTH is more useful than intact PTH to predict malignancy of affected parathyroid glands in pHPT.

Parathyroid carcinoma is believed to account for 0.5% to 4% of all cases of pHPT [3, 5]. In contrast, the frequency of the disease is more common in Japan than in Western countries, accounting for approximately 5% of patients with pHPT [5]. Moreover, 5.2% of patients operated for pHPT were found to have parathyroid carcinoma in an Italian study [47]. In the present study, the higher frequency of parathyroid carcinoma compared to that in previous reports [3–5] might be attributed to racial differences. Alternatively, the percentages of pHPT patients who are asymptomatic in Japan are not as high as in the United States [48]. Moreover, it is possible that the subjects admit-

ted to Kobe University Hospital, a tertiary care center, might represent a population with a relatively severer pathological state of pHPT, hence might not be entirely representative of Japanese pHPT patients.

In conclusion, the distal one-third of radius BMD was lower in malignant tumor compared to that in benign tumor in pHPT. Serum levels of calcium, ALP and mid PTH were useful to predict malignancy of affected parathyroid glands in pHPT patients.

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