**INTRODUCTION AND OBJECTIVES**

Parathyroid carcinoma (PC) is a very rare endocrine cancer, and a rare cause of primary hyperparathyroidism (PHPT). Data on PC is still scarce. The diagnosis of PC is challenging and the incidence seems to increase. Our aims were:

1) to investigate whether the incidence of PC has increased in Finland
2) to better characterize PC by comparing it to atypical parathyroid adenoma (AA) and parathyroid adenoma (A)
3) to identify potential early markers for a) malignancy b) recurrent PC, by assessing clinical, histological, immunohistological, surgical and other treatment characteristics as well as prognosis of PC, AA and A.

**PATIENTS AND METHODS**

**Study group** We re-examined all parathyroid carcinomas (PC; n=32) diagnosed in Finland during years 2000-2011. This group was compared to 28 patients with atypical parathyroid adenoma (AA) and 72 age- and gender-matched patients with parathyroid adenoma (A) from Helsinki University Hospital.

**Histological re-evaluation** The diagnosis of PC was re-examined in all primary tumors according to the WHO 2004 criteria (J.A. and E.R.). Of the original 39 PC cases, three were re-classified as thyroid carcinoma and excluded. Four other cases lacked tumor invasion and were re-classified as AA.

**Data collection** Clinical data, laboratory measurements as well as data on surgical and other treatments, and recurrences were collected retrospectively from medical records and revised by E.R. Survival data and causes of death of the study group, as well as population data were obtained from Statistics Finland. Mean age of the 32 PC patients (44% men) was 61 (17-83) yrs. The mean follow-up time was 6.7 (range 2.0-13.9) yrs.

**Immunohistochornical staining** for Ki-67, paraffinom and PTH were performed using TMA (Tissue Micro Array) analysis. For TMA, 3-6 cores were sampled from representative areas of primary tumor blocks and inserted into a recipient paraffin block. TMA blocks were cut into 4 μm slices and processed for Ki-67, paraffinom and PTH stainings. Ki-67 was assessed by Immunoratio (Tuominen et al.). PTH- and paraffinom stainings were assessed by two independent investigators (H.L. and E.R.).

**Ethics** The study protocol was approved by the institutional review board of Helsinki University Hospital, by the ethics committees of the four other Finnish University Hospitals, by National Supervisory Authority for Welfare and Health in Finland, and by the National Institute for Health and Welfare in Finland.

**RESULTS**

PC patients had higher serum ionized calcium (Ca-ion) and PTH levels compared to AA and A groups: 1.76 (1.61-1.97) mmol/l vs. 1.56 (1.50-1.70) vs. 1.44 (1.38-1.51), (median and IQR, reference range 1.15-1.30), and 989 (461-1518) vs. 355 (149-959) vs 160 (123-251) ng/l, reference range 15-65 ng/l, P < 0.001 for both. PC and AA demonstrated increased tumor size compared to A (P < 0.001).

PC patients had more often both bone and renal manifestations than AA and A patients (28% vs 7% vs 6%, respectively, P = 0.004) and were more often hospitalized for severe hypercalcemia (44% vs 22 vs 3%, P < 0.001). Twelve (37.5%) PC patients also had a benign parathyroid tumor in their medical history or during follow-up.

Histopathological characteristics of PC were chief cells (P = 0.004), diffuse growth pattern (P < 0.001), increased mitotic activity (P < 0.001), nuclear atypia (P = 0.003), higher Ki-67 (P < 0.001), and weaker/negative paraffinom stain (P < 0.001).

In the PC group, 9.4% had residual disease, and 21% of those cured had a recurrence. Five had metastatic disease. Although 12.5% of patients died of PC during follow-up, overall mortality did not differ between the subgroups (P = 0.94).

Nearly half (47%) of PC patients had two or more operations. External neck radiation and chemotherapy was given to 22% and 13% of PC patients, respectively. At diagnosis, lymph node status (P = 0.65), tumor necrosis (P = 0.006), mitotic activity (P = 0.045), and paraffinom stain (P = 0.01) differed between recurrent and non-recurrent PC. All recurrent tumors presented with vascular invasion (P = 0.29).

**CONCLUSIONS**

We present a nationwide cohort of PC from 2000-2011 (n=32), and demonstrate a five-fold increase in the incidence of PC in Finland in line with studies from USA and Australia (Lee et al, Brown et al).

PC associates with clinically more severe PHPT compared to AA or A, and has distinct histopathological features. Nearly 40% of PC patients have additional benign parathyroid tumors, and 47% of PC patients undergo 2 or more neck surgeries, increasing the risk for surgical complications.

PC should be suspected in all PHPT patients having S-Ca-ion > 1.70 mmol/l, as none of the benign cases reached this threshold. However, PC may also be characterized by milder hypercalceemia.

Histopathological features of aggressive, recurrent PC include lymph node metastasis, vascular invasion, necrosis, negative paraffinom staining and Ki-67 > 5%.

In PC, recurrence rate (21% in 6.7 yrs follow-up) is lower than that previously reported (Harari et al, Talat et al), and overall survival was not different from that of patients with adenomas.

**REFERENCES**


