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PATIENTS WITH NECK ENDOCRINE TUMORS HAVE AN INCREASED INCIDENCE OF MALIGNANT DISEASES

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Summary

Introduction: Cancer patients are at higher risk of developing second primary cancer compared to the general population. Primary hyperparathyroidism is associated with a higher incidence of malignant disease.

This research aims to investigate the incidence of malignant diseases in patients treated for parathyroid adenoma and papillary thyroid carcinoma in the University Hospital for Tumors cohort.

Patients and Methods: Data about malignant diseases in patients treated for parathyroid adenoma and papillary thyroid cancer were collected from the Head and Neck Surgery Department (University Hospital for Tumors) database. Differences were tested using χ^2-test and the Mann-Whitney test.

Results: Among 75 patients surgically treated for parathyroid adenoma, fourteen (18.6%) had a malignant disease. Among 90 patients surgically treated for papillary thyroid cancer, thirteen (14.4%) were treated for another malignant disease. The difference between groups was not statistically significant (p=0.465). Breast cancer was the most common malignant disease in both groups.

Conclusion: Awareness of increased risk for malignancy in patients treated for neck endocrine tumors could lead to earlier detection of malignant diseases.

KEYWORDS: *parathyroid adenoma, papillary thyroid cancer, malignant disease*

INTRODUCTION

Awareness of the higher risk of second primary cancer in cancer patients is rising. According to current knowledge, for most primary sites, it is less than 10%(1,2). In one of the largest published populational studies 8.1% of patients (aged ≥18 years), who were diagnosed with a primary malignancy from the 10 most common cancer sites (prostate, breast, lung, colon, rectum, bladder, uterus, kidney, melanoma, and non-Hodgkin lymphoma) developed a second primary malignancy(1). More than half of patients who developed second primary cancer died of their second primary malignancy(1). Subsequent malignancies in cancer survivors constitute up to 20% of all cancer diagnoses(3).

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In papillary thyroid cancer survivors, there is an increased risk of developing a second primary malignancy in up to 15% of patients(4). The second primary malignancy sites are most frequently breast, bowel, and skin(4). Predisposing factors for the development of the second primary are family history of malignancy and younger age at papillary thyroid cancer diagnosis(4). Endocrine neoplasms are recognized as high-risk primary sites for developing secondary malignancy within multiple endocrine neoplasia (MEN) and other hereditary syndromes. There is a higher incidence of secondary papillary thyroid cancer in patients with breast cancer(5).

Although MEN syndrome, and primary hyperparathyroidism (PHPT) within MEN, are recognized as a risk factor for the development of malignant disease, sporadic PHPT is not widely recognized as a risk factor. PHPT is associated with a higher incidence of malignant disease. According to Charoenngam et al. the prevalence of malignant neoplasm in PHPT was 19%, with papillary thyroid cancer and breast cancer being the most prevalent types(6).

Parathyroid adenoma is the cause of PTHP in 80-85% of cases(7). PTHP is a disease characterised by an elevated level of parathyroid hormone and subsequent hypercalcemia. Hypercalcemia has many non-specific clinical manifestations and with time affects multiple organ systems. Diagnosis of PTHP is challenging due to asymptomatic persistence for years before diagnosis and treatment in many cases(8). There are differences in the presentation of the condition in the world's various regions(9). The incidence of PHPT in the population strongly depends on the frequency of biochemical screening for serum calcium(10).

Patients with cancer are routinely screened for calcium levels. Patients with malignancy and hypercalcemia can be divided into 2 major groups: those with and those without an elevated PTH level(11). In many of those patients, PTHP is diagnosed after a malignant disease.

This research aims to investigate the incidence of malignant diseases in patients treated for parathyroid adenoma and papillary thyroid carcinoma in the University Hospital for Tumors cohort.

PATIENTS AND METHODS

All patients treated for parathyroid adenoma between 2012 and 2020 in the Head and Neck Surgery Department (University Hospital for Tumors) were selected. Data about the occurrence of malignant disease was noted as well as age, gender, preoperative PTH, preoperative calcium level, and tumor size. In order to collect approximately a similar number of patients, data regarding thyroid cancer patients treated in the period 2012-2013 including age, gender, and malignant occurrence were extracted from the database.

Descriptive statistical methods were used. Differences in the prevalence of individual conditions were compared using the χ^2-test. Differences between groups of independent continuous variables were analysed using the Mann-Whitney U test. All statistical analyses were performed using SPSS (version 21).

RESULTS

There were 75 patients surgically treated for parathyroid adenoma. Fourteen, 14/75 (18.6%) patients had malignant disease. The mean age in the group of patients with malignant disease was 63.4± 9.7 years while the patients without malignant disease were on average 57.3 ± 12.5 years old. Although the patients with malignant disease were older than those without malignant disease the difference was not statistically significant (Mann-Whitney U test, p=0.096). There were 3 men (21.4%) and 11 women (78.6%) with malignancies corresponding to a 1:3 male to female ratio. In the group without malignancy, male to female ratio was 1:10 with 6/61 (9.8%) men and 55/61 (90.2%) women. The occurrence of malignancy between genders differs since there were 3/9 (33.3%) men and 11/66 (16.7%) women however there was no statistically significant difference in the occurrence of malignancy between genders (χ^2=1.449, df=1, p=0.229).

There were 90 patients surgically treated for papillary thyroid cancer. Thirteen (14.4%) patients were treated for another malignant disease. The mean age in the group of patients with malignant disease was 60.8 ± 10.2 years while the patients without malignant disease were on average 50.7 ± 15.4 years old. Patients with malignant disease

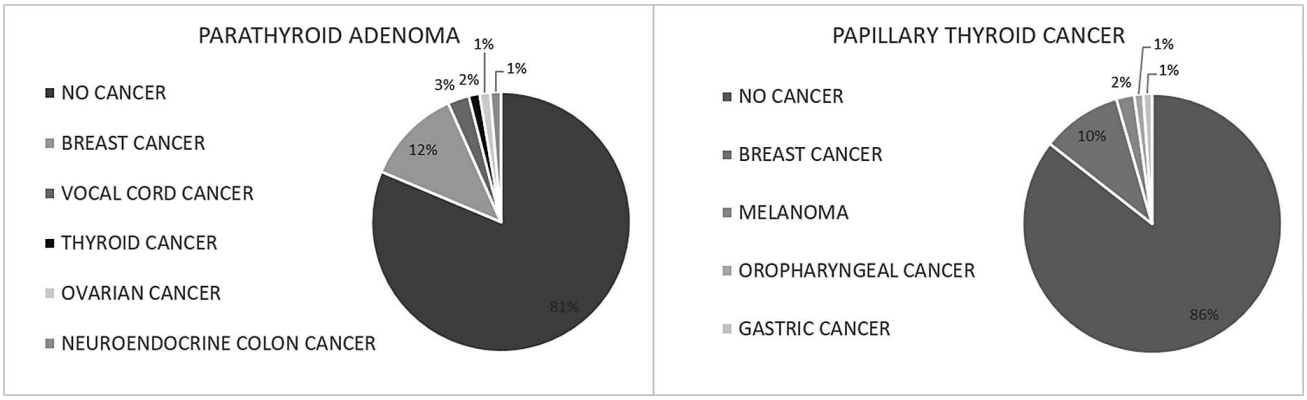

Figure 1. Incidence of second primary cancers in patients with parathyroid adenoma and papillary thyroid cancer.

were significantly older than those without malignancies (Mann-Whitney U test, p=0.025). Male to female ratio was 1:5 in both groups with 13/77 (16.9%) men without and 2/13 (15.4%) men with malignancies. The occurrence of malignancy between genders did not differ and there were 2/15 (13.3%) men and 11/75 (14.7%) women with malignant disease. There was no significant difference in the incidence of malignancy between genders (χ^2= 0.018, df=1, p=0.893).

In both groups, there were 9 patients with breast cancer (Figure 1).

In the group of patients with parathyroid adenoma one patient had papillary thyroid cancer, 2 had vocal cord cancer, one had neuroendocrine colon cancer, and one had ovarian cancer.

No statistically significant differences between groups of patients without or with secondary cancer in preoperative PTH values (pg/mL; median=101.00, minimum=32.94, maximum=511.00 vs. median=99.85, minimum=61.57, maximum=245.10, Mann-Whitney U test, p=0.577); serum calcium values (mmol/L; median=2.74, minimum=2.21, maximum=3.11 vs. median=2.69, minimum=2.54, maximum=2.99, Mann-Whitney U test, p=0.546) or size of parathyroid adenoma (mm; median=13, minimum=3, maximum=48 vs. median=17, minimum=9, maximum=28, Mann-Whitney U test, p=0.411) were found.

In the group of patients with papillary thyroid cancer, two patients were diagnosed with melanoma, one with gastric adenocarcinoma, and one with oropharyngeal cancer.

There were 13/90 (14.4%) patients with malignant disease in the papillary thyroid cancer group and 14/75 (18.6%) in the parathyroid adenoma group. Although the incidence was higher in the parathyroid adenoma group, it was not statistically significant (χ^2=0.533, df=1, p=0.465).

DISCUSSION

Results in our data series are comparable with previously published(4,6,12). Although repeatedly observed, the increased risk of malignant disease in patients with neck endocrine tumors did not change patient counselling, follow-up recommendations, or screening policies. The data source for this research was the University Hospital for Tumors database, a hospital specialized for treating malignant diseases, which presents a potential bias in patient selection. The other limitation is the lack of data on the exact time of diagnoses and laboratory parameters at the time of cancer diagnosis.

Advances in treatment options have led to improved cancer survival rates, making long-term follow-up strategies more important. The aetiology of second cancers is multifactorial, possible factors are primary cancer treatments, genetic susceptibility, lifestyle factors, and environmental exposures(3).

Multigene testing for hereditary forms of cancer is available for patients at increased risk of inherited susceptibility to cancer(13). Personal or family history of papillary thyroid cancer can contribute to patient selection for genetic testing(14). Similar recommendations for sporadic parathyroid adenoma are not available.

High diversity of other malignancy primary sites is found in the group of patients with neck endocrine tumors. This presents a problem, due to the lack of a universal, cheap, and widely available screening tool. Well-established screening programs for breast cancer worldwide enable early diagnosis. In many patients, it is the first diagnosis, and papillary thyroid cancer, and parathyroid adenoma are diagnosed in the follow-up period.

Patients treated for neck endocrine tumors should have their family history re-examined and risk of inherited susceptibility to cancer rechecked, counselled to strictly follow available national screening programs, avoid risk behaviours and report symptoms as soon as they develop.

Further investigations are needed to clear the connection between observed diseases, possibly leading to better solutions.

CONCLUSION

Many screening programs are based on recognising groups of patients at increased risk for malignancy. Awareness of increased risk in patients treated in head and neck or endocrine surgery departments could improve patient counselling and consequently lead to earlier detection of malignant disease. Further research is needed to define evidence-based recommendations for this group of patients.

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Sažetak

BOLESNICI S ENDOKRINIM TUMORIMA VRATA ČEŠĆE IMAJU MALIGNU BOLEST

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Uvod: Bolesnici liječeni zbog maligne bolesti imaju veći rizik razvoja druge primarne maligne bolesti u usporedbi s općom populacijom. Primarni hiperparatireoidizam povezan je s većom učestalošću malignih bolesti.

Cilj ovog istraživanja je ispitati učestalost malignih bolesti u bolesnika liječenih od adenoma paratireoidne žlijezde i papilarnog karcinoma štitnjače u kohorti bolesnika Klinike za tumore.

Bolesnici i metode: Podaci o zloćudnim bolestima u bolesnika liječenih od paratireoidnog adenoma i papilarnog karcinoma štitnjače prikupljeni su iz baze podataka Odjela za kirurgiju glave i vrata (Klinika za tumore). Razlike su testirane $\chi 2$-testom i Mann-Whitneyevim testom.

Rezultati: Od 75 bolesnika kirurški liječenih zbog paratireoidnog adenoma četrnaest (18,6%) je imalo malignu bolest druge lokalizacije. Od 90 bolesnika kirurški liječenih zbog papilarnog karcinoma štitnjače trinaest (14,4%) je liječeno i zbog druge maligne bolesti. Razlika između skupina nije bila statistički značajna (p=0,465). Rak dojke bio je najčešća maligna bolest u obje skupine.

Zaključak: Svijest o povećanom riziku od malignih bolesti kod bolesnika liječenih od endokrinih tumora vrata mogla bi dovesti do ranijeg otkrivanja malignih bolesti.

KLJUČNE RIJEČI: *adenom paratireoidne žlijezde, papilarni karcinom štitnjače, maligna bolest*