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Thyroid Cancer Incidence and Clinicopathological Differences in Patients with End-Stage Renal Failure

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Abstract

Aim: In the present study we aimed to determine the prevalence of thyroid cancer and the clinicopathological properties of papillary thyroid cancer (PTC) in a patient population undergoing dialysis for end-stage renal failure (ESRF).

Material and Methods: We retrospectively reviewed all thyroid ultrasonography (USG) examinations performed between January 2007 and December 2015 to determine the incidence of nodular thyroid disease in ESRF and normal patient populations. For both patient groups, differences between patient and tumor characteristics were evaluated in patients diagnosed to have PTC.

Results: Among 29.381 patients who underwent thyroid USG examination, 3.491 were included in the ESRF group and 25.890 in the control group. Tyroid cancer was detected in 77 (2.2%) of 3.491 patients in Group 1 and 338 (1.3%) of 25.890 patients in Group 2. Thyroid cancer was significantly more prevalent in patients with ESRF.

Discussion: When only patients with papillary thyroid cancer were considered, no significant difference existed between the two groups with respect to the prevalence of PTC, although PTC cases in the ESRF group had a significantly higher rate of aggressive characteristics such as capsule invasion, multifocality, and lymph node metastasis. Whereas thyroid cancer is more common in patients with ESRF compared to normal controls, papillary thyroid cancer was not significantly more prevalent in the ESRF group.

Conclusion: PTC in the ESRF group having more aggressive properties than those in the control group suggests that PTC should be diagnosed earlier in their course, treated more aggressively, and followed more closely in ESRF.

Keywords: End-Stage Renal Failure; Fine Needle Aspiration Biopsy; Papillary thyroid cancer; Metastasis

Introduction

Nodular disease of the thyroid gland is the most common thyroid pathology. Its incidence increases with aging and varies by the population studied. In autopsy studies, more than 50% of adults had non-palpable thyroid nodules, most of which were smaller than 1 cm. The reported prevalence of palpable nodules is below 20% [1].

Compared to a thyroid cancer prevalence of 1-2% in the general population, patients with end-stage renal failure (ESRF) have an increased prevalence of these condition, ranging between 3% and 13% [2,3]. Maisonneuve et al investigated cancer risk by multi-center studies in a large patient population undergoing dialysis; and they found that cancer incidence increased in 831.804 patients undergoing dialysis for ESRF compared to the general population of the United States of America, Europe, Australia, and New Zealand [3,4]. A metaanalysis comprising 10 studies found an average cancer risk of 7.6 while another metaanalysis of 5 studies reported an average risk of 0.98 [5,6].

Prior studies have reported that patients with ESRF have an increased risk of certain cancer types, of which kidney, urinary bladder, thyroid, and other endocrinological organ cancers are the most common [3,4].

In the present retrospective study it was aimed to determine the prevalence and the clinicopathological properties of thyroid cancer in a patient population undergoing dialysis for ESRF at our clinic.

Materials and Methods

This study retrospectively reviewed the medical data of 29.381 patients who were examined at the General Surgery, Endocrinology, and Nephrology outpatient clinics of Başkent University Hospital. All study subjects underwent thyroid ultrasonography at the Radiology Department of the same institution between January 2007 and December 2015. The subjects were divided into ESRF (Group 1) and non-ESRF (Group 2) groups. All patients were ESRF when they were diagnosed with thyroid cancer. The prevalence, ultrasonographic properties, and the Fine needle aspiration biopsy (FNAB) results of the thyroid nodules were recorded. Both groups were compared for their demographic properties and pathology results.

FNAB Technique and Pathological Examination

Fine needle aspiration biopsy was performed for nodules meeting USG criteria suspicious for malignancy (irregular borders, microcalcifications, increased vascularity, hypoechogenicity) and for those who lack USG criteria but were deemed to portend a clinical malignancy risk (family history for any thyroid cancer, history of radiotherapy to neck region).

FNAB results of thyroid nodules were categorized as benign (nodular hyperplasia, lymphocytic thyroiditis), malignant (papillary thyroid cancer, medullary thyroid cancer, anaplastic carcinoma), suspicious for malignancy (follicular neoplasia, suspicious for follicular neoplasia), and insufficient material (a sample containing less than 6 follicles).

Surgery

Surgery was recommended for patients having nodules with malignant or suspicious FNAB results, or for patients who had signs of compression or multiple benign nodules with complicated follow-up, biopsy sampling of which would be impractical. FNAB was repeated when the result was inconclusive. The decision whether to apply a conservative or an invasive therapy was based on clinical and radiological grounds. All patients who were diagnosed to have a malignancy in FNAB examination and/or intraoperative frozen examination underwent total thyroidectomy.

Pathology Examination

All preparations with a pathology result consistent with thyroid cancer were re-examined by a single academic member of our faculty after the operation. The histological types and pathological properties (tumor size, multifocality, bilaterality, capsule invasion, lymph node metastasis, and co-occurrence with chronic lymphocytic thyroiditis) of thyroid cancers determined by the re-examination of the thyroidectomy materials were specified in the pathology report.

Statistical Analysis

Statistical analyses were performed using SPSS Windows 15 software package. Descriptive statistics included mean ± standard deviation for normally distributed variables and number and percentage (%) for nominal variables. The means of normally distributed variables were compared with Student's t test. Nominal variables were compared using Pearson Chi-Square or Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

Among 29.381 patients who underwent a thyroid USG examination between January 2007 and December 2015, 3.491 were included in the ESRF group (Group 1) and 25.890 in the control group (Group 2). Of 29.381 patients who underwent thyroid USG examination, 11.319 (38.5%) had nodular thyroid disease. The prevalence of thyroid nodules was significantly higher in Group 2 compared to Group 1 (10.095 (38.9%) vs 1.224 (35.1%), respectively; p=0.001). The prevalence of single nodules was comparable in both groups (43.7% vs 4.543 (45%), respectively; p=0.39). The prevalence of multiple nodules was also similar in both groups (689 (56.3%) vs 5.552 (55%), respectively; p = 0.39) (Table 1).

	Group 1(3.491)	Group 2(25.890)	p
Patients with nodular thyroid disease	1.224 (35.1%)	10.095(39.0%)	0.001
Patients with single nodule	535 (43.7%)	4.543 (45.0%)	0.390
Patients with 2 or more thyroid nodules	689 (56.3%)	5.552 (55.0%)	0,390
Largest nodule size (cm)	2,3±2,1 (0.2-7)	2,1±2 (0.1-9.5)	0.758

p<0.05 denotes statistical significance

Table 1: The comparison of the rate of nodular thyroid disease and the ultrasonographic properties of the thyroid nodules between the two groups

A greater number of patients in Group 1 than Group 2 underwent FNAB (962 (78.6%) vs 4.936 (48.9%), respectively; p =0.001). The prevalence of malignant/suspicious FNAB samples were comparable in Group 1 and Group 2 (173 (18.0%) vs 996 (20.2%), respectively; p=0.118). Group 1 and Group 2 had similar prevalences of benign/insufficient FNAB samples (789 (82.0%) vs 3.940 (79.8%), respectively; p=0.118) (Table 2).

	Group 1 (n=1.224)	Group 2 (n=10.095)	p
Patients undergoing FNAB	962 (%78.6)	4.936 (%48.9)	0.001
Malignant/suspicious FNAB result	173 (%18.0)	996 (%20.2)	0.118
Benign/insufficient FNAB result	789 (%82.0)	3.940 (%79.8)	0,118

p<0.05 denotes statistical significance. (FNAB: fine needle aspiration biopsy)

Table 2: The comparison of the thyroid FNAB results of patients with thyroid nodules between the two groups

One hundred and sixteen (67.5%) of 173 patients with malignant/suspicious FNAB result in Group 1 and 724 (72.6%) of 996 patients with malignant/suspicious FNAB result in Group 2 were operated at our hospital. One hundred and sixty-one (20.4%) of 789 patients with benign/insufficient FNAB result in Group 1 and 607 (15.4%) of 3.940 patients with benign/insufficient FNAB result in Group 2 were operated. Among patients with malignant/suspicious FNAB result, the final pathology result was thyroid cancer in 71 (61.2%) of 116 patients in Group 1 and in 350 (48.3%) of 724 patients in Group 2 (p=0.408).

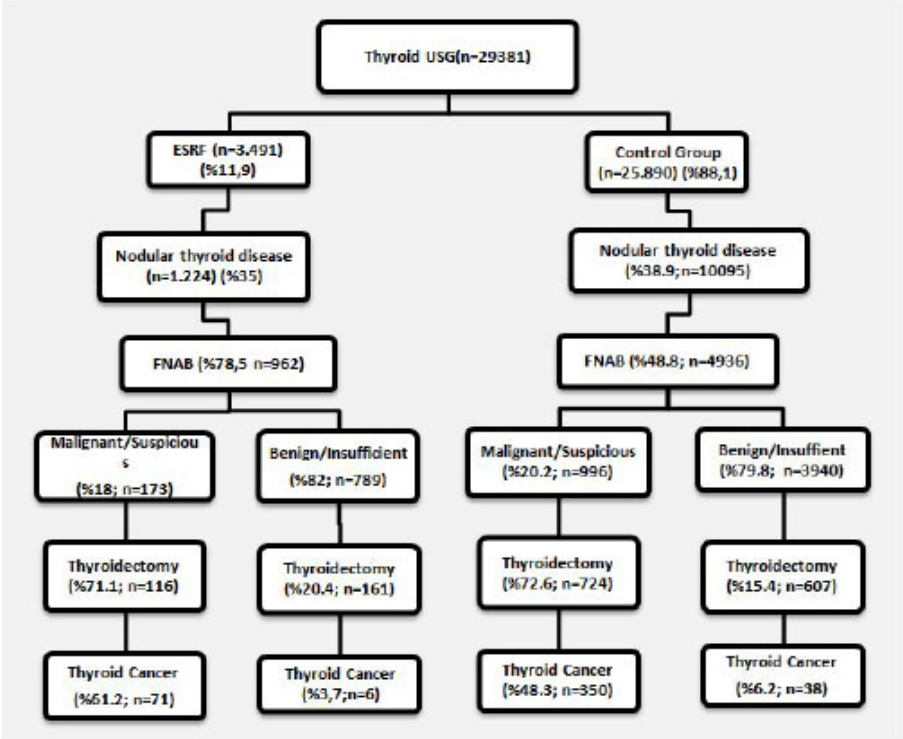
Among patients with benign/insufficient FNAB result, the final pathology result was thyroid cancer in 6 (3.7%) of 161 patients in Group 1 and 38 (6.3%) of 607 patients in Group 2 (p=0.753).

The final pathology result was still thyroid cancer in 278 (92.0%) of 302 patients with malignant FNAB result while only 22 (3.3%) of 662 patients with benign FNAB result had thyroid cancer in the final pathology examination. Accordingly, the sensitivity and specificity of FNAB examinations performed at our hospital were 92.05% and 96.39%, respectively (95% confidence interval) (Table 3, Figure 1).

	Pathology result malignant	Pathology result benign
FNAB result malignant	278 (%92.05)	24 (%3.61)
FNAB result benign	22 (%7.95)	640 (%96.39)

(FNAB: fine needle aspiration biopsy)

Table 3: Sensitivity and specificity of FNAB examination performed at our hospital



USG: Ultrasonography; ESRF: End-Stage Renal Failure; FNAB: Fine Needle Aspiration Biopsy

Figure 1: The number of patients diagnosed with thyroid disease based on ultrasonography examination and those diagnosed with thyroid cancer based on FNAB result

In Group 1, 16 (88.9%) of 18 patients were operated with central lymph node dissection and 2 (11.1%) modified radical neck dissection. In Group 2, 58 (86.6%) of 67 patients were operated with central lymph node dissection and 9 (13.4%) modified radical

neck dissection. Sixty-seven (59.3%) of 113 lymph nodes removed in Group 1, and 239 (55.8%) of 428 lymph nodes removed in Group 2 had metastatic involvement (p=0.510).

An analysis of the patients who were operated on the basis of clinical findings, sonographic properties, and FNAB results demonstrated that thyroid cancer existed in 77 (6.3%) of 1.224 patients in Group 1 and 388 (3.8%) of 10.095 patients in Group 2. ESRF patients had a significantly higher prevalence of thyroid cancer detected at surgery performed for similar indications (p=0.001).

A comparison based on the final pathology results of the patients with thyroid cancer in the two groups revealed that there were no significant differences between gender distribution, age, and thyroid functions. As for the histological types of thyroid cancer, 69 (89.67%) patients in Group 1 had papillary thyroid cancer, 4 (5.2%) had follicular thyroid cancer, and 4 (5.2%) had medullary thyroid cancer. Three hundred and thirty-two (85.6%) patients in Group 2 had papillary thyroid cancer, 37 (9.5%) had follicular thyroid cancer, 15 (3.9%) had medullary thyroid cancer, and 4 (1%) had anaplastic thyroid cancer. There was no significant difference between the two groups with regard to the prevalences of histological types (Table 4).

		Group 1(3.491)	Group 2(25.890)	p
Age		47.2±13,9 (18-78)	50,5±14,7(16-88)	0.074
Sex (male/female)		26/51	98/290	0.123
TSH (µUI/ml)		1.24±1.14 (0.01-20)	1.56±1.14 (0.04-28.6)	0.865
Cancer incidence in patients with thyroid nodule		77/1.224 (%6.3)	388/10.095 (%3.8)	0.001
Histological types of thyroid cancer	**Papillary thyroid cancer**	69 (%89.6)	332 (%85.6)	0.347
	Follicular thyroid cancer	4 (%5.2)	37 (%9.5)	0.275
	Medullary thyroid cancer	4 (%5.2)	15 (%3.9)	0.535
	Anaplastic carcinoma	0	4 (%1.0)	1

p<0.05 denotes statistical significance.(thyroid stimulating hormone)
Table 4: Demographic properties and thyroid cancer types of patients diagnosed with thyroid cancer in the ESRF and control groups

As PTC was the most common type of thyroid cancer, clinicopathological properties of PTC were compared in both groups. This comparison revealed that there was no significant difference with respect to age, sex, tumor size, and chronic lymphocytic thyroiditis in Group 1. On the other hand, Group 1 was characterized by a significantly higher prevalence of lymph node metastasis, capsule invasion, and multifocality than Group 2 (p=0.033, p=0.001, p=0.001).

A comparison of the subtypes of papillary thyroid cancer showed that the classical PTC was significantly more common in Group 1 and papillary microcarcinoma in Group 2. The aggressive subtypes (tall cell variant, columnar cell variant, and diffuse sclerosing variant) were more common in the ESRF group (p=0.040) (Table 5).

		Group 1(3.491)	Group 2(25.890)	p
Age		48.0±13,6 (16-78)	50,0±14,4 (18-88)	0.295
Sex (male/female)		24/45	82/250	0.084
Tumor size (cm)		1.3±0.56 (0.4-4)	0.97±0.55 (0.1-4)	0.112
Lymph node metastasis		15 (%21.7)	40 (%12.0)	0.033
Capsule invasion		32 (%46.3)	67 (%20.2)	0.000
Multifocality		40 (%58.0)	119 (%35.8)	0.001
Thyroiditis		24 (%34.8)	86 (%25.9)	0.133
Subtypes of papillary thyroid cancer	**Classical PTC**	36 (%52.2)	127 (%38.3)	0.032
	Papillary microcarcinoma	16 (%23.2)	151 (%45.5)	0.001
	Follicular variant	5 (%7.2)	15 (%4.5)	0.361
	Classical PTC	36 (%52.2)	127 (%38.3)	0.032
	Papillary microcarcinoma	16 (%23.2)	151 (%45.5)	0.001
Aggressive subtypes (Tall cell varyant, columnar cell variant, Diffuse sclerosing variant)		8 (%11.6)	15 (%4.5)	0.040
Other subtypes (Encapsulated, trabecular, oncocytic, cribriform, clear cell variant)		4 (%5.8)	24 (%7.2)	0.800

p<0.05 denotes statistical significance. (PTC: papillary thyroid cancer)
Table 5: Clinicopathological differences between patients diagnosed with papillary thyroid cancer in the ESRF and control groups

Discussion

The prevalence of thyroid nodules in ESRF patients has been variably reported in different series using different diagnostic methods. While prevalences ranging between 50% and 75% have been reported in autopsy series, USG studies have reported prevalences ranging between 13% and 40% [7,8]. Although there are usually no large-scale studies in the literature, it has been reported that the prevalence of nodular thyroid disease is somewhat greater in ESRF population compared to the general population [9]. In a study by Şahin I, *et al* (2004), it was reported that 53 (23.4%) of 226 patients with CRF had thyroid nodules. However, that study did not provide any information about the prevalence of thyroid nodules in the normal population, and made no comparative analysis [10]. In our study, on the other hand, thyroid nodules were present in 1.224 (35.1%) of 3.491 ESRF patients. Nevertheless, in contrast to literature data, we detected a higher prevalence of thyroid nodules in the normal population than the ESRF group (39% vs 35%). We believe that this difference likely resulted from the fact that thyroid USG was generally performed for clinical suspicion in patients in Group 2 whereas it was almost routinely performed due to various reasons, mainly secondary hyperparathyroidism in ESRF.

FNAB was performed for 962 (78.6%) patients in Group 1 and 4.936 (48.9%) patients in Group 2 found to have nodules in sonographic examination. It was noteworthy that FNAB was performed at a greater rate in the ESRF patients. A higher FNAB rate in this group was likely due to a higher risk of malignancy, both clinically and sonographically. Whereas the sensitivity of FNAB has been reported to range between 65% and 98% (mean 83%), its specifity ranges between 72% and 100% (mean 92%) [11,12]. In our study, FNAB labeled 278 (92.05%) patients with a final pathology result of malignancy as malignant and 22 (7.95%) as benign. Among patients with a benign FNAB result who were still operated with thyroidectomy due to clinicopathological indications (sonographic properties of nodules, presence of local symptoms, family history, history of radiation, and physical examination findings), 640 (96.39%) had no cancer in the pathology examination whereas 24 (3.61%) patients had a malignant FNAB result but no thyroid cancer in pathology specimens. Based on these results, FNABs performed by interventional radiologists and examined by experienced pathologists of our hospital have one of the highest sensitivity and specificity figures ever reported (sensitivity 92%, specificity 96%).

A recent study pointed to an increase in the prevalence of thyroid cancer in ESRF patients. In a study comprising 28.049 patients on dialysis, the risk of thyroid cancer was found to increase by 2.9 folds in women [13]. A multicenter study conducted in England and some European countries indicated that compared to normal population, the risk of developing thyroid cancer increased 4.8 folds in young female dialysis patients, and 2 folds in older dialysis patients [14]. Our study similarly demonstrated a greater prevalence of thyroid cancer in ESRF patients than the normal population when a comparison was done between patients who presented to our clinic and were found to have thyroid nodules (p=0.001). The potential mechanisms of malignant transformation of thyroid nodules in ESRF patients may include immune dysfunction, reduced antioxidant capacity, parathormone excess, vitamin D deficiency, chronic infections, medications, DNA repair errors, and the carcinogenic potential of dialysis. All of these potential mechanisms may lead to an increased risk of developing thyroid cancer in ESRF [7]. On the other hand, an increased prevalence of thyroid cancer incidentally detected by neck USG examinations periodically performed for secondary and tertiary hyperparathyroidism in ESRF patients may also have contributed to an excess risk of thyroid cancer risk in this patient group. A parallel increase in cancer risk with longer dialysis durations in these studies supports this hypothesis [13]. It cannot be overlooked that ESRF patients undergo frequent neck imaging studies as the duration of dialysis is prolonged [4]. However, our results revealed that although nodular thyroid disease was more common in the normal population, thyroid cancers detected after the operation had a higher prevalence in ESRF patients, suggesting a true increase in risk for this patient group. While there was no significant difference between the groups with thyroid cancer with respect to age, sex, and thyroid functions, both groups were characterized by a greater thyroid cancer risk in women than in men (66% in Group 1; 74% in Group 2). A comparison of histological types of thyroid cancer between the groups revealed that papillary thyroid cancer was the most common type in both groups (89.6% in Group 1, 85.6% in Group 2). In addition, when this patients with ESRF were diagnosed with thyroid cancer, the risk of anesthesia must be carefully cosidered, although the risk of surgery was not different from the normal population, but these patients must be preparedbefore surgery. We did not find any difference between the two groups when comparing thyroid cancer patients with ESRF and without ESRF in terms of surgical complications.

Papillary carcinomas are slowly growing tumors with a favourable prognosis. However, as they present with a very diverse disease spectrum, many scoring systems had to be developed to determine their prognosis. Many independent factors affect the prognosis of DTCs including advanced age (>40-45 years), tumor size (>4 cm), capsule invasion, extra-capsular spread, distant organ metastasis, male gender, lymph node metastasis, multicentricity, vascular invasion, and aggressiveness (more aggressive variants include tall cell variant, columnar cell variant, and diffuse sclerosing variant) [13]. Our study failed to show any significant difference between the two groups with respect to age although the mean ages of both groups were above 40 years (48 years in Group 1 and 50 years in Group 2). Furthermore, both groups were similar in terms of gender distribution although PTC was more common in women in both groups (65% in Group 1 and 75% in Group 2).

Tumor size is a prognostic parameter that has been shown by many studies to have a negative impact on survival, and therefore it was incorporated in almost all scoring systems. Carcangiu et al reported that papillary microcarcinomas had a lower mortality rate and a longer survival compared to tumors larger than 1 cm in size. Cady and Rossi identified tumor size as the main prognostic

factor and included it in the AMES scoring system [15,16]. In our study, the mean tumor size was 1.3 cm in ESRF patients with thyroid cancer and 0.97 in patients with thyroid cancer in Group 2. Despite being statistically non-significant, tumor size greater than 1 cm in ESRF patients indicates that PTC will behave more aggressively. On the other hand, comparable tumor size in both groups was explained by the fact that a more widespread use of thyroid USG and FNAB has allowed the detection and excision of thyroid cancers at an earlier stage, before reaching a larger size.

Papillary thyroid cancer is usually multifocal. Although the effect of multifocality on prognosis remains contraversial, Antonaci et al reported that multifocal PTCs showed a more aggressive biological and clinical course [17]. Multifocality was present in 40 (58.0%) ESRF patients with thyroid cancer and 119 (35.8%) patients in Group 2.

Many studies have identified capsule invasion as one of the most important prognostic factors for papillary thyroid carcinomas [16,17]. Capsule invasion was observed in 32 (46.3%) ESRF patients with papillary thyroid cancer and 67 (20.2%) patients in Group 2. This suggests that, despite the lack of any significant difference between both groups in terms of tumor size, papillary thyroid cancer behaves more aggressively when there exists capsule invasion in ESRF patients. Furthermore, Gülben et al found that, apart from multifocality, patients having solely capsule invasion had a significantly higher prevalence of lymph node metastasis [18].

Lymphocytic inflammatory reaction accompanies papillary thyroid cancer at varying rates (0.5-37.9%) [19]. Some researchers have reported that papillary thyroid cancers accompanied by chronic lymphocytic thyroiditis at initial diagnosis were at earlier stages and had lower rates of recurrence and a better prognosis [20]. In our study, 24 (34.8%) ESRF patients and 119 (35.8%) patients in Group 2 with papillary thyroid cancer had chronic lymphocytic thyroiditis. No significant difference was found between the two groups with respect to the rate of accompanying chronic lymphocytic thyroiditis. Papillary carcinoma variants exhibit some prognostic differences. The tall cell, columnar, and diffuse sclerosing cell variants have a poor prognosis while the encapsulated and follicular variants portend a favourable prognosis [21]. The tall cell variant is associated with a cumulative rate of 25% for vascular invasion, extrathyroidal soft tissue invasion, and distant organ metastasis. Furthermore, this variant is associated with a 2-3 times higher recurrence and mortality rates than the classical type [22]. Jalisi et al, in a metaanalysis published in 2010, demonstrated that the relative risk of recurrence increased by 4.61 folds and mortality by 16.47 folds in these patients [23]. The columnar cell variant is quite rare although it is associated with distant metastasis at a rate of approximately 90% [23]. Similarly, the majority of diffuse sclerosing type has lymph node metastasis and approximately 25% has lung metastasis. Thompson et al reported in 2005 that 18 (81%) of 22 patients with diffuse sclerosing PTC had lymph node metastasis [24].

We also investigated the subtypes of thyroid carcinoma. We found out that classical thyroid cancer was more common in Group 1 and microcarcinoma in Group 2. We attributed the increased prevalence of microcarcinoma in the normal population to a more widespread use of thyroid USG and FNAB in recent years, leading to an earlier diagnosis of thyroid cancers and excision of tumors before they reach a larger size. We also detected a significantly greater prevalence of subtypes showing aggressive behavior in the ESRF group (p=0.040). This finding explains why PTC in ESRF patients make more lymph node metastasis.

Conclusion

In conclusion, early detection and treatment of thyroid cancers has gained much importance in ESRF patients due to both their increased prevalence and poor prognostic factors. We suggest that when clinical suspicion for thyroid cancer is high, frequent and close follow-up as well as early use of FNAB will lead earlier detection of these cancers. Despite these parameters, however, the prognosis of thyroid cancer is not entirely known in this patient population, largely because ESRF's prognosis remains poor itself. Therefore, it is necessary to determine long-term outcomes of ESRF patients treated for thyroid cancer.

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