ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(1):73-86 // doi 10.5505/amj.2023.09734

THYROID CANCER IN ADOLESCENTS AND YOUNG ADULTS

Nagihan Bestepe[1], Ahmet Dirikoç[2], Husniye Baser[2]
Mustafa Omer Yazicioglu[3], Aysegul Aksoy Altinboga[4], Didem Ozdemir[2]
Oya Topaloglu[2], Reyhan Ersoy[2], Bekir Cakir[2]

[1]Ankara City Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey
[2]Ankara Yildirim Beyazit University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey
[3]Ankara City Hospital, Department of General Surgery, Ankara, Turkey
[4]Ankara Yildirim Beyazit University Faculty of Medicine, Department of Pathology, Ankara, Turkey

Correspondence:
Nagihan Beştepe (e-mail: nagihanbestepe@gmail.com)

Submitted: 19.11.2022 // Accepted: 07.03.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: The incidence of thyroid cancer (TC) is increasing in adolescent and young adult (AYA) patients. Many types of cancer diagnosed in the AYA age group differ significantly in clinical and pathological features from cancers diagnosed in older age groups, but data on TC are limited. Our aim was to compare the clinicopathological features of TC in AYAs and adults ≥40 years old.

Materials and Methods: In total, 1013 patients with TC were retrospectively reviewed. Thyroid functions, ultrasonographic features of malignant nodules, cytological and histopathological findings, and recurrence and persistence rates were compared in AYAs and patients ≥40 years old.

Results: There were 229 (22.61%) AYA patients and 784 (77.39%) patients ≥40 age group. Of all cancer types, 93.12% in AYAs and 93.58% in the ≥40 age group were papillary thyroid cancer (PTC) (p=0.772). Multifocal thyroid tumors were detected in 62 (27.07%) of AYAs and 269 (34.31%) of the ≥40 age group (p=0.039). Incidental thyroid tumors were detected in 113 (37.05%) of AYAs and 583 (52.01%) of the ≥40 age group (p<0.01). The extrathyroidal extension (ETE) was detected in 9.61% of AYAs and 16.33% of patients ≥40 years old (p=0.012). Capsular and vascular invasion, lymph node metastasis, distant metastasis, persistence, and recurrence rates were similar.

Conclusion: There was no increase in the aggressive clinical and pathological features of TC in AYAs. ETE, multifocal tumors and incidental tumors were less common in AYAs than in patients ≥40 years old. PTC is the most common type in both groups, while the follicular variant PTC (FVPTC) subtype is increased in AYAs. Thyroid nodules should be carefully evaluated in AYAs, and diagnostic procedures should be recommended without delay. However, when TC is diagnosed in AYAs, the overtreatment potential of a disease with an excellent prognosis should also be considered.

Keywords: Adolescents and young adults; thyroid cancer, cytopathology, histopathology.

Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, and its overall incidence has increased significantly in the last 30 years.[1] Cancer in adolescents and young adults (AYAs) is defined by the National Cancer Institute (NCI) as diagnoses occurring among those aged 15 to 39 years.[2] TC is the most diagnosed cancer in AYA aged 20 to 29 years in both sexes, and most of the new cases are papillary thyroid cancers (PTC) that do not affect disease-specific mortality.[3] The incidence of TC in AYAs in the USA has increased exponentially in both women and men in the last two decades.[3] In addition, adolescents have an incidence of TC 10 times higher than young children, and it was shown that TC is five times more common in women than men during adolescence.[1] Although this increase in prevalence is often attributed to the increased use of imaging modalities and higher sensitivity of ultrasonography (US), there are also studies suggesting a true increase.[4] Still, data for AYAs are sparse. During the most recent ten years of available data, TC incidence rates rose rapidly in all AYA age groups, whereas mortality rates declined slightly by 0.5% annually. The 5-year relative survival rate for TC is generally high and exceeds 99% in AYA aged 20 to 39 years.[3]

Many types of cancer diagnosed in the AYA age group differ significantly from cancers diagnosed in other age groups in terms of risk factors, tumor biology, prognosis, and survival, but there are limited studies on TC in the literature. Previous studies have found that, although AYAs are more likely to be diagnosed with larger thyroid cancers or with locoregional lymph node involvement compared with older patients, they are less likely to be diagnosed with distant metastases and continue to have a better prognosis than their older counterparts.[5]

In this study, we aimed to compare clinical, ultrasonographical, cytological and histopathological features of TC in AYAs and patients ≥40 years old.

Materials and Methods

The medical records of patients who underwent thyroidectomy between December 2006 and September 2016 and were diagnosed with TC were retrospectively reviewed. The operation was performed based on the decision of a committee including endocrinology, general surgery, nuclear medicine, and pathology specialists. Patients with insufficient clinical data and histopathology reports, a second malignancy and unilateral resection, were excluded from the study. Local ethics committee approval was obtained in accordance with the ethical standards of the Helsinki Declaration.

Patients were subdivided into two age groups: 15-39 (AYAs) and ≥40 years old. Demographical and ultrasonographical features, cytological results and final histopathological diagnosis were obtained from medical records. Serum thyrotrophin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), antithyroid

peroxidase antibody (anti-TPOAb), and antithyroglobulin antibody (anti-TgAb) levels were measured by chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA and UniCel DXI 800, Beckman Coulter, Brea, CA). The normal ranges for TSH, fT3, fT4, antiTPOAb, and anti-TgAb were 0.4–4 μIU/mL, 1.57–4.71 pg/ mL, 0.85–1.78 ng/dl, 0–35 IU/mL, and 0–40 IU/mL, respectively. The thyroid antibody level over the upper range of normal was evaluated as positive. The patients were classified as euthyroidism (both TSH and fT4 within normal limits), hypothyroidism (elevated TSH with low fT4), and hyperthyroidism (suppressed TSH with elevated fT4) according to preoperative thyroid functions.

Thyroid US was performed using an Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) with a superficial probe (Model LA523 13–4, 5.5–12.5 MHz). The localization, diameters, ratio of anterior-posterior to transverse diameter (AP/T), volume, echogenicity, texture, marginal regularity, presence of microcalcification and macrocalcification and peripheral halo of nodules were evaluated.

Before the fine needle aspiration (FNA) procedure, all patients were informed about the risks and possible complications related to the procedure, and their approval was obtained. FNA was carried out with a 27-gauge needle and 20-mL syringe under US guidance (Logic Pro 200 GE and 7.5 MHz probe, Kyunggigo, Korea) by experienced endocrinologists. All nodules >1 cm and nodules ≤1 cm with at least one suspicious US feature such as hypoechoic, irregular margins, absence of halo and presence of microcalcification were evaluated by FNA. Cytological findings were classified as non-diagnostic (ND), benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy and malignant according to Bethesda System.[6]

The type, size, multifocality and incidentality of the tumor, capsular invasion, vascular invasion, lymph node metastasis (LNM) and extrathyroidal extension (ETE) were recorded from histopathology reports. Malignant lesions were classified as PTC, follicular thyroid cancer (FTC), Hurthle cell cancer (HCC), well-differentiated tumor of uncertain malignant potential (WDT-UMP), medullary thyroid cancer (MTC) and anaplastic thyroid cancer. Histological variants of PTC were further grouped as classical, follicular, oncocytic, tall cell, and others (encapsulated, solid/trabecular, diffuse sclerosing, columnar cell, warthin-like).

All statistical analyzes were performed with a software package program (SPSS, version 11.5 for Windows; SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was tested with Kolmogorov–Smirnov test. Descriptive statistics were presented as mean ± SD, with medians minimum–maximum) for continuous variables and percentages (%) for categorical variables. The differences in groups were compared by the student's t-test for parametric variables and the Mann–Whitney U test for

nonparametric variables. The chi-square test was used to investigate the difference between the groups regarding the categorical variables. A value of $p<0.05$ was considered to indicate statistical significance.

Results

The data of 1013 patients who were diagnosed with TC histopathologically were analyzed. 229 (22.61%) patients were in the AYA group (15-39), and 784 (77.39%) were in the ≥ 40 age group. There were 187 (81.66%) female and 42 (18.34%) male patients in the AYA group (Table 1). In the ≥40 age group, there were 602 (76.79%) females and 182 (23.21%) males. There was not any significant difference in sex distribution between groups (p=0.117). The mean age was 32.03±4.95 and 54.54±9.24 years in AYAs and ≥40 age groups, respectively (p< 0.001). Serum TSH, fT3, fT4 and anti-TPO and anti-Tg antibody positivity at the time of diagnosis were similar in both groups (p=0.094, p=0.253, p=0.857, p=0.626 and p=0.871, respectively). Family history of thyroid cancer and radiation history to the head and neck region were similar in both groups (p=0.969 and p=0.657, respectively). Preoperative ultrasonography features, operation indications and surgical approach were similar in AYAs and in the ≥40 age group (Table 1).

Cytological and histopathological features in AYAs and ≥40 age patients are compared in Table 2**.** There were a total of 1426 malignant foci, 305 (21.39%) were in AYAs, and 1121 (78.61%) were in the ≥40 age group. 62 (27.07%) of AYAs and 269 (34.31%) of ≥40 age group had multifocal TC (p=0.039). LNM, capsular invasion, vascular invasion, lymphatic invasion, and distant metastasis rates were similar in both groups (p=0.246, p=0.848, p=0.134, p=0.752 and p=0.889, respectively) (Table 2). ETE was detected in 22 (9.61%) of the tumors of the AYAs and in 128 (16.33%) of the tumors of patients ≥40 years old (p=0.012). Distant metastases were observed in a total of 5 patients in the study population. Lung metastases were observed in 1 patient in AYAs. In the ≥40 age group, two patients had lung metastases, 1 had vertebral bone metastases, and 1 had pelvic bone metastases with lung.

Histopathological features of malignant nodules are compared in Table 3. Tumor diameter was 10.14±11.54 mm in the AYAs, and 11.52±15.56 mm (p=0.184) in the ≥40 age group 198 (64.92%) and 719 (64.14%) tumor foci were microcarcinoma in AYAs and ≥40 age group, respectively (p=0.801). While 113 (37.05%) of tumors in AYAs were incidental, 583 (52.01%) tumors in the ≥40 age group were incidental (p<0.001).

The histopathological tumor type distribution was similar in both groups. 284 (93.12%) of tumors in AYAs and 1049 (93.58%) of tumors in patients ≥40 years old were PTC (p=0.772). Classical variant PTC was significantly higher in the ≥40 age group, while follicular variant PTC (FVPTC) was significantly higher in AYAs (p=0.005 and p=0.003, respectively). Oncocytic and tall cell variant PTC were similar in both groups (p=0.333 and p=0.653, respectively).

Table 1. Clinical and ultrasonographical features of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Age	32.03±4.95	54.54±9.24	**<0.001**
Sex Female Male	 187 (81.66) 42 (18.34)	 602 (76.79) 182 (23.21)	 0.117
Family history of thyroid cancer (n/%)	4 (1.75)	14 (1.79)	0.969
Radiation history to the head and neck region (n/%)	1 (0.44)	2 (0.26)	0.657
TSH (μIU/mL)	1.66 ±2.14	1.63± 1.65	0.094
fT4 (ng/dL)	1.17±0.36	1.16 ±0.31	0.857
fT3 ((pg/mL)	3.27±2.03	3.24±0.87	0.253
Anti-TPO positivity (n =202)	48 (26.66)	154 (23.91)	0.626
Anti-Tg positivity (n = 201)	46 (25.32)	155 (24.54)	0.871
Functional status Euthyroid Hypothyroid Hyperthyroid	 177 (77.29) 19 (8.30) 33 (14.41)	 566 (72.20) 64 (8.16) 154 (19.64)	 0.196
Nodule number in ultrasonography	3.08± 2.69	4.66± 3.41	**<0.001**
Ultrasonography features of malignant nodule			
Anteroposterior diameter (mm) Transverse diameter (mm) Longitudinal diameter (mm)	10.91 (4.53-43.12) 12.1 (5.33–68.28) 16.2 (4.24–92.32)	11.7 (4.24-41.1) 12.5 (3.46–92.32) 17.5 (3.9–94.21)	0.142 0.134 0.112
AP/T	0.87± 0.23	0.89 ± 0.25	0.512
Volume (cm3)	0.98 (0.04–118.61)	0.94 (0.03–223.43)	0.081
Localization Right Left Isthmus	 128 (55.90) 97 (42.36) 4 (1.74)	 430 (54.85) 339 (43.24) 15 (1.91)	 0.954
Texture Solid Cystic/mixed	 221 (96.51) 8 (3.49)	 756 (96.43) 28 (3.57)	 0.955
Echogenicity Isoechoic Hypoechoic Iso-hypoechoic	 86 (37.55) 53 (23.14) 90 (39.31)	 296 (37.76) 178 (22.70) 310 (39.54)	 0.990
Microcalcification	92 (40.17)	328 (41.84)	0.653
Macrocalcification	78 (34.06)	278 (35.46)	0.697
Hypoechoic halo	47 (20.52)	144 (18.37)	0.463
Irregular margins	137 (59.83)	454 (57.91)	0.605
Surgical approach BTT/NT Hemithyroidectomy	 226 (98.69) 3 (1.31)	 774 (98.72) 10 (1.28)	 0.967

Operation indications			
Giant nodule	37 (16.16)	142 (18.11)	
Hyperthyroidism	16 (6.99)	68 (8.67)	
Cytology			
Malignant	37 (16.16)	137 (17.47)	
Suspicious for malignancy	36 (15.72)	100 (12.76)	
FN/SFN	16 (6.99)	40 (5.10)	0.458
AUS/FLUS and suspicious ultrasonography features	40 (17.47)	156 (19.90)	
Non-diagnostic	23 (10.04)	73 (9.31)	
Parathyroid pathology	1 (0.43)	26 (3.32)	
Other	23 (10.04)	42 (5.36)	

(TSH: thyrotropin, fT3: free triiodothyronine, fT4: free thyroxine, anti-TPO: antithyroid peroxidase antibodies, anti-Tg: antithyroglobulin antibodies, US: ultrasonography, AP/T: ratio of anterior-posterior to transverse diameter, BTT/NT: bilateral total thyroidectomy/near-total thyroidectomy, FN/FNS: follicular neoplasm/suspicious for follicular neoplasm, AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance)
*Significant p values are indicated as bold in the table

The mean follow-up period was similar in the two groups (p=0.876) (Table 4). Radioactive iodine (RAI) ablation was performed in 183 (79.91%) of AYAs and 630 (80.36%) of the ≥40 age group (p=0.882). Seventy-three (39.89%) AYAs and 263 (41.75%) ≥40 age group were ablated with an RAI dose greater than 100 mCi. Persistence and recurrence rates were similar in the two groups (p=0.499 and p=0.407, respectively). The mean time of recurrence was 28.43±16.42 months in AYAs and 22.54±4.43 months in the ≥40 age group (p=0.438).

Table 2. Cytological and histopathological features of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Cytological diagnosis			
Non-diagnostic	23 (10.04)	73 (9.31)	0.739
Benign	77 (33.62)	278 (35.46)	0.608
AUS/FLUS	40 (17.47)	156 (19.90)	0.413
FN/SFN	16 (6.99)	40 (5.10)	0.272
Suspicious for malignancy	36 (15.72)	100 (12.76)	0.247
Malignant	37 (16.16)	137 (17.47)	0.642
Total tumor foci	305 (21.39)	1121 (78.61)	
Tumor number per patient	1.52±1.23	1.57±1.12	0.064
Multifocality	62 (27.07)	269 (34.31)	**0.039**
Lymph node metastasis	21 (9.17)	58 (7.40)	0.246
Capsular invasion	68 (29.69)	238 (30.36)	0.848
Vascular invasion	10 (4.37)	56 (7.14)	0.134
Extrathyroidal extension	22 (9.61)	128 (16.33)	**0.012**
Lymphatic invasion	5 (2.18)	20 (2.56)	0.752
Distant metastases	1 (0.44)	4 (0.51)	0.889

(AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, FN/SFN: follicular neoplasm/suspicious for follicular neoplasm, PTC: papillary thyroid cancer, WDT-UMP: well-differentiated tumor of uncertain malignant potential)
*Significant p values are indicated as bold in the table

Table 3. Histopathological features of malignant thyroid nodules in adolescent and young adult patients and ≥40 age patients

	AYA patients (15-39) n (%) 305 (21.39)	**≥40 age patients n (%) 1121 (78.61)**	**P***
Tumor diameter	10.14 ± 11.54	11.52 ± 15.56	0.184
Microcarcinoma	198 (64.92)	719 (64.14)	0.801
Incidentality	113 (37.05)	583 (52.01)	**<0.001**
Tumor type			
Papillary	284 (93.12)	1049 (93.58)	0.772
Follicular	8 (2.62)	23 (2.05)	0.544
Hurthle cell	4 (1.31)	17 (1.51)	0.792
Medullary	3 (0.98)	12 (1.07)	0.895
Anaplastic	1 (0.33)	4 (0.36)	0.940
WDT-UMP	5 (1.64)	16 (1.43)	0.785
PTC variants	n=273	n=1016	
Classical	206 (75.46)	842 (82.87)	**0.005**
Follicular	52 (19.05)	123 (12.11)	**0.003**
Oncocytic	8 (2.93)	20 (1.97)	0.333
Tall cell	4 (1.46)	19 (1.87)	0.653
Other	3 (1.10)	12 (1.18)	0.910

(PTC: papillary thyroid cancer, WDT-UMP: well-differentiated tumor of uncertain malignant potential)
*Significant p values are indicated as bold in the table

Table 4. Follow-up data of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Follow-up period (month)	40.42 ± 22.78	39.56 ± 14.12	0.876
RAI treatment	183 (79.91)	630 (80.36)	0.882
RAI dose (mCi)			
≤100	110 (60.11)	367 (58.25)	0.654
>100	73 (39.89)	263 (41.75)	
Persistence	5 (2.18)	12 (1.53)	0.499
Recurrence	1 (0.44)	7 (0.89)	0.407
Recurrence time (months)	28.43 ± 16.42	22.54 ± 4.43	0.438

(RAI: radioactive iodine)
Significant p values are indicated as bold in the table

Discussion

Many types of cancer diagnosed in the AYA age group differ significantly from cancers diagnosed in other age groups in terms of clinical and histopathological features, but information on TC is limited. In our study, we did not observe an increase in aggressive clinical and pathological features of TC in AYAs. There was no difference

in LNM, capsular and vascular invasion in AYAs, and ETE was less common. Multifocal tumors and incidental tumors were less common in AYAs than in patients ≥40 years old. While PTC was the most common type in both groups, the FVPTC subtype was increased in AYAs.

In recent years TC has become one of the most common cancers in the AYA population.[1] This increase in the incidence of TC can be attributed to various risk factors such as overdiagnosis. Excessive iodine intake, diagnostic radiation and environmental exposure are some other causes blamed for this increase. The major risk factor for the development of PTC is radiation exposure to the head and neck region, especially during childhood and adolescence.[7] Most cases of radiation-induced PTC are due to therapeutic radiation administered to treat a previous malignancy.[8] The onset period is usually between 10 and 20 years after exposure to radiation. Exposure to major environmental RAI from the Chernobyl nuclear accident in 1986 is another risk for the development of PTC, especially in children and adolescents.[9] In previous studies, the clinical behavior of radiation-induced TC does not appear to differ significantly from sporadic tumors.[10] In our series, the history of radiation to the head and neck region in AYA patients was similar to the ≥40 age group. We did not find any difference between the groups in terms of family history of thyroid cancer. In addition, the role of iodine in the pathogenesis of TC is controversial. Dietary iodine deficiency is associated with FTC, while excess iodine increases the risk of PTC.[11] In our study, while more than 90% of AYAs had PTC, a small number of FTC were detected, and no trend towards FTC was observed in AYAs. Accordingly, our country seems to have turned from iodine deficiency to excessive iodine intake.

The pathological classification and histological criteria of DTCs in AYAs are the same as in adults. While PTC accounts for more than 90% of cases in the AYA population,[3] FTC is rare. Low-risk subtypes (classic and follicular variants) of PTC remain the most common. Solid/trabecular and diffuse sclerosing subtypes of PTC are considered high-risk in adults[12,13] but are unclear in AYAs. In accordance with the literature, in our study, more than 90% of AYAs had PTC, and a small number of FTC were detected. MTC, poorly differentiated tumors, and anaplastic TC are rarer in younger patients. MTC accounts for approximately 5% of all thyroid malignancies, and the mean age at diagnosis is 50 years. Only about one-third of MTC cases occur in patients younger than 40 years old.[14] In our study, we did not find any difference in the rate of MTC and anaplastic thyroid carcinoma between AYAs and patients ≥40 years old.

Several clinicopathological features, such as age, gender, tumor size, ETE, LNM and distant metastasis, are well-known prognostic factors in PTC patients.[15] ETE is defined as the spread of the tumor beyond the thyroid capsule to adjacent soft tissue. It is generally accepted that advanced ETE adversely affects the results of PTC. Previous studies have shown that tumor size and older age are independent risk factors for ETE, and patients with ETE are more likely to have positive surgical margins.[16] That is, sustained tumor growth will increase the likelihood of the tumor extension beyond the thyroid capsule, especially in peripheral tumors. Aging restrains

adaptive immunity and makes the tumor microenvironment more immunosuppressive, which may facilitate the invasion process.[17] In our study, ETE was more common in patients ≥40 years old than in the AYAs.

The relationship between age and multifocality is not clear. In some studies, no significant relationship was found between increasing age and multifocality,[18] while in others, an increased risk of multifocality was reported in patients >45 years old.[19] In our study, multifocal TC was significantly higher in the ≥40 years old patients than in the AYAs. Previous studies showed a significant correlation between LNM, ETE and tumor size and multifocality, suggesting that multifocality is an indicator of disease progression. Multifocality has also been shown to be associated with an increased risk of disease recurrence.[20]

The increase in incidental TC (ITC) is one of the most important factors responsible for the increase in the incidence of total cancer. There are controversial findings with regard to ITC rates in different age populations. Although some previous studies have reported no change in rates of ITC according to age,[21] some have reported that it is more prevalent in older ages.[22] In our study, ITC was detected more frequently at older ages. A possible reason for this finding may be the increase in the frequency of admission to the hospital for different reasons as the age increases and the increase in the use of imaging studies that are responsible for the detection of incidental thyroid lesions. In addition, elderly patients with an incidental thyroid lesion may be subject to more aggressive diagnostic follow-up than younger individuals, which may lead to an increased incidence of ITC in these patients.

Although pediatric and AYA patients more commonly present with local extension, cervical node involvement, and pulmonary metastases, there is an excellent overall survival rate (>95%) 30 years after treatment.[23] This likely reflects the underlying tumor biological differences between pediatric/adolescent and adult patients. Some tumor subtypes, such as FVPTC and diffuse sclerosing variants of PTC, are more common in children and young adults than in older individuals.[24] FVPTC is the second most common PTC variant and is characterized by follicular growth pattern and cytological features of papillary carcinoma.[25] Similarly, in our study, FVPTC was significantly higher in the AYAs than in the ≥40 age group.

Most AYAs diagnosed with TC are treated according to the approaches used in adult patients. However, increasing evidence suggests that AYAs are molecularly different from other age groups and have a higher risk of long-term and late effects, including infertility, sexual dysfunction, cardiovascular disease, and future cancers, compared with older patients. Since children and adolescents with PTC are more likely to have cervical lymph node and pulmonary metastases, an aggressive treatment approach is often followed, which includes total thyroidectomy followed by radioiodine residual ablation.[26] Given the high overall survival rate, the complications and acute, subacute, and delayed toxicities of the chosen therapy should be carefully considered.

Despite an excellent overall prognosis for AYAs with DTC, there are many challenges that affect disease morbidity. First, AYAs are more likely to have no health insurance than older patients, and this age group is more likely to experience delays in cancer diagnosis due to the lack of cost-effective early detection methods. The risks of surgical complications are closely related to the age of the patient, the extent of the disease, and the experience of the surgeon. Although these relationships are well known, some of the young patients continue to have thyroid surgery in centers with insufficient thyroidectomy experience. In particular, the associated risks of thyroidectomy, including recurrent laryngeal nerve palsy, hypoparathyroidism, and the need for lifelong thyroid hormone replacement, are more devastating for the AYA population. In addition to surgical complications, there are several reports suggesting an increased risk of non-thyroid, secondary malignancies in patients receiving RAI compared to those not receiving RAI.[27] Therefore, although DTC is a disease with low disease-specific mortality, it can progress with short and long-term complications.

RAI therapy is used following thyroid surgery to prevent disease recurrence and to treat persistent or metastatic TC.[28] The increasing diagnosis of TC in recent years and the frequent occurrence of AYAs with metastatic disease may be a factor that increases the use of RAI in this population. The toxicities associated with RAI therapy are dose-related. RAI may cause temporary gonadal dysfunction, but subsequent infertility is rare except after high doses.[28] In addition, an increased risk of secondary malignancy has been reported after RAI treatment for TC.[29] Although serious adverse events are rare and possibly due to cumulative and higher doses of RAI treatment, they may be of particular concern for AYAs.

There are some limitations in our study. Firstly, it is a retrospective and single-center study. Secondly, central lymph node dissection is not routinely performed in patients who underwent thyroidectomy in our center, and this may have confused the nodal status of the patients. However, prophylactic central lymph node dissection is still controversial, and there is no definite recommendation in favor of this procedure.[30] In addition, the inability to perform molecular tests in our center during our study is another limitation. Lastly, the mean follow-up time in our study was relatively low, which might have caused low recurrence rates in our series.

In conclusion, we did not observe an increase in the aggressive clinical and pathological features of TC in AYAs. US and cytopathological features of malignant nodules in AYAs seem to be mostly identical with ≥40 years old patients. LNM, capsular and vascular invasion do not differ, and ETE is less common in AYAs. FVPTC subtype is increased in AYAs. Multifocal and incidental tumors are less common in AYAs. The incidence of TC is increasing rapidly in AYAs, and it is important for primary care physicians to refer patients to an endocrinology specialist for the diagnosis of thyroid nodules detected in AYAs and regular follow-up of patients with TC. Thyroid nodules in AYAs should be evaluated carefully, and diagnostic procedures should be offered without delay. On the other hand, the potential for overtreatment of a disease with an excellent prognosis, regardless of stage, should be considered when TC is diagnosed in AYAs.

ANKARA MEDICAL JOURNAL

Ethical Considerations: The present study was approved by the ethics committee of Ankara City Hospital (REC number: E1-21-2082, Date:20.10.2021).

Conflict of Interest: The authors declare no conflict of interest. No funding was received.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30 (doi:10.3322/caac.21590).
2. US Department of Health and Human Services. Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer. Report of the Adolescent and Young Adult Oncology Progress Review Group. NIH publication 06-6067. US Department of Health and Human Services; 2006.
3. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer Statistics for Adolescents and Young Adults, 2020. CA Cancer J Clin. 2020;70(6):443-459; (doi:10.3322/caac.21637).
4. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. JAMA. 2017;317(13):1338-1348 (doi:10.1001/jama.2017.2719).
5. Vriens MR, Moses W, Weng J, et al. Clinical and molecular features of papillary thyroid cancer in adolescents and young adults. Cancer. 2011;117(2):259-267 (doi:10.1002/cncr.25369).
6. Cibas ES, Ali SZ. NCI thyroid FNA state of the science conference. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009;132(5):658–665 (doi:10.1309/AJCPPHLWMI3JV4LA).
7. Mihailescu DV, Schneider AB. Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery. J Clin Endocrinol Metab. 2008;93(6):2188–93 (doi:10.1210/jc.2008-0055).
8. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141(3):259–77.
9. Demidchik YE, Saenko VA, Yamashita S. Childhood thyroid cancer in Belarus, Russia, and Ukraine after Chernobyl and at present. Arq Bras Endocrinol Metabol 2007;51(5):748–62 (doi:10.1590/s0004-27302007000500012).
10. Naing S, Collins BJ, Schneider AB. Clinical behavior of radiation-induced thyroid cancer: factors related to recurrence. Thyroid 2009;19(5):479–85 (doi:10.1089/thy.2008.0343).
11. Burgess JR, Dwyer T, McArdle K, Tucker P, Shugg D. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978–1998) during a transition from iodine sufficiency to iodine deficiency. J Clin Endocrinol Metab. 2000; 85(4):1513–1517 (doi:10.1210/jcem.85.4.6554).
12. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008.World J Surg. 2010;34(6):1192–1202 (doi:10.1007/s00268-009-0364-0).
13. Collini P, Massimino M, Mattavelli F, Barisella M, Podda M, Rosai J. Tall cell variant of papillary thyroid carcinoma in children: report of three cases with long-term follow-up from a single institution. Int J Surg Pathol. 2014;22(6):499–504 (doi:10.1177/1066896914545399).

14. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer. 2006;107(9): 2134-42 (doi:10.1002/cncr.22244).
15. Ito Y, Miyauchi A, Kihara M, Fukushima M, Higashiyama T, Miya A. Overall survival of papillary thyroid carcinoma patients: a single institution long-term follow-up of 5897 patients. World J Surg. 2018;42(3):615–22 (doi:10.1007/s00268-018-4479-z).
16. Wang LY, Ghossein R, Palmer FL, et al. Microscopic positive margins in differentiated thyroid cancer is not an independent predictor of local failure. Thyroid. 2015;25(9):993–8 (doi:10.1089/thy.2015.0141).
17. Wu Y, Wei J, Chen X, et al. Comprehensive transcriptome profiling in elderly cancer patients reveals aging-altered immune cells and immune checkpoints. Int J Cancer. 2019;144(7):1657–63 (doi:10.1002/ijc.31875).
18. Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurence/persistence of papillary thyroid carcinoma, World J. Surg. 2013;37(2):376–84 (doi:10.1007/s00268-012-1835-2).
19. Singhal S, Sippel RC, Chen H, Schneider DF. Distinguishing classical papillary thyroid microcancers from follicular variant microcancers, J. Surg. Res. 2014;190 (1):151–6 (doi:10.1016/j.jss.2014.03.032).
20. Joseph KR, Edirimanne S, Eslick GD. Multifocality as a prognostic factor in thyroid cancer: A meta-analysis. International Journal of Surgery. 2018; 50:121–5 (doi:10.1016/j.ijsu.2017.12.035).
21. Kaliszewski K, Diakowska D, Strutyńska-Karpińska M, Wojtczak B, Domosławski P, Balcerzak W. Clinical and histopathological characteristics of patients with incidental and nonincidental thyroid cancer. Arch Med Sci. 2017;13(2):390-5 (doi:10.5114/aoms.2016.59579).
22. Bahl M, Sosa JA, Nelson RC, Esclamado RM, Choudhury KR, Hoang JK. Trends in incidentally identified thyroid cancers over a decade: a retrospective analysis of 2,090 surgical patients. World J Surg. 2014;38(6):1312-7 (doi:10.1007/s00268-013-2407-9).
23. Francis GL, Waguespack SG, Bauer AJ, et al. Management Guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015;25(7):716–59 (doi:10.1089/thy.2014.0460).
24. Schlumberger M, Pacini F. Thyroid tumors. Paris: Nucleon; 2003
25. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: A clinicopathologic study of a problematic entity.Cancer 2006;107(6):1255–64 (doi:10.1002/cncr.22138).
26. Chow SM, Law SC, Mendenhall WM, et al. Differentiated thyroid carcinoma in childhood and adolescence clinical course and role of radioiodine. Pediatr Blood Cancer 2004;42(2):176 –83 (doi:10.1002/pbc.10410).
27. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg 2010;34(6):1192–1202 (doi:10.1007/s00268-009-0364-0).
28. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid

Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1-133 (doi:10.1089/thy.2015.0020).

29. Lang BH, Wong IO, Wong KP, Cowling BJ, Wan KY. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery 2012;151(6):844-50 (doi:10.1016/j.surg.2011.12.019).
30. Qu H, Sun GR, Liu Y, He QS. Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2015;83(1):124–32 (doi:10.1111/cen.12583).