endocrines

MDPI

Article

Clinicopathological and Molecular Predictors of Recurrence in Adolescents and Young Adults with Papillary Thyroid Carcinoma: A Central Asian Cohort Study

Madina Mussulmanova [1], Zhanna Mussazhanova [2,*], Laura Pak [3,*], Aidana Rakhmankulova [1], Saltanat Bolsynbekova [4], Altay Dyussupov [5] and Tolegen Kurmangaliyev [6]

1 Department of Clinical Oncology, Radiology, and Nuclear Medicine named after Professor D.R. Musinov, Semey Medical University, Semey 071400, Kazakhstan; 87madina87@mail.ru (M.M.); dana77792@mail.ru (A.R.)
2 Department of Fundamental Medicine, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan
3 Office of the Chairman of the Management Board, National Research Oncology Center, Astana 010000, Kazakhstan
4 Center of Cytopathomorphology, Immunohistochemistry, and Translational Oncology, National Research Oncology Center, Astana 010000, Kazakhstan; salta72.72@mail.ru
5 Office of the Rector, Semey Medical University, Semey 071400, Kazakhstan; altaydyus@gmail.com
6 Department of Mammology and Gynecology, Center of Nuclear Medicine and Oncology, Semey 071400, Kazakhstan; tolesha85@gmail.com
* Correspondence: ghannakz@mail.ru (Z.M.); laura_pak@mail.ru (L.P.); Tel.: +7-707-101-1393 (L.P.)

Abstract

Background/Objectives: Although papillary thyroid carcinoma generally has an excellent prognosis, recurrence remains an important clinical problem in adolescents and young adults (AYA), while the prognostic value of molecular markers in this population is still unclear. This study aimed to identify clinicopathological and molecular predictors of recurrence in young patients with papillary thyroid carcinoma from Kazakhstan. **Methods**: This retrospective multicenter study included 246 consecutive patients with histologically confirmed papillary thyroid carcinoma. Tumor specimens collected between 2016 and 2020 were obtained from three tertiary oncology centers in Kazakhstan. **Results**: In the AYA subgroup, none of the evaluated clinicopathological or molecular variables was significantly associated with recurrence after multivariable adjustment. TERT promoter-related alterations showed the largest estimated association with recurrence, with an odds ratio (OR) of 9.05 (95% confidence interval [CI], 1.00–59.86; $p = 0.333$), while lymph node metastasis demonstrated the strongest trend toward poorer progression-free survival in the overall cohort, with a hazard ratio (HR) of 9.61 (95% CI, 0.92–100.49; $p = 0.059$); no significant predictors of overall survival were identified. **Conclusions**: Recurrence risk among adolescents and young adults with papillary thyroid carcinoma is heterogeneous and may be more accurately assessed by combining conventional clinicopathological factors with molecular markers, particularly TERT promoter mutation status. These findings support a more personalized approach to postoperative surveillance and precision management of young patients in Central Asia.

Keywords: Kazakhstan; Central Asian; papillary thyroid carcinoma; adolescents and young adults; recurrence; TERT promoter mutation

Check for updates

Academic Editor: Marco Falasca

Received: 5 August 2026
Revised: 13 October 2026
Accepted: 14 October 2026
Published: 16 October 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Although papillary thyroid carcinoma (PTC) is associated with excellent long-term survival, disease recurrence remains a major clinical challenge in adolescents and young adults (AYA). Because AYA patients are predominantly in their reproductive, professionally active, and socially productive years, recurrent disease may have consequences that extend far beyond oncologic outcomes. Recurrence often necessitates repeated imaging studies, reoperations, prolonged surveillance, and lifelong follow-up, increasing psychological distress, healthcare burden, and potentially compromising quality of life despite excellent overall survival. Therefore, preventing recurrence or identifying patients at the highest risk of recurrence has become an important clinical goal.

AYA, defined by the National Cancer Institute as individuals aged 15–39 years, are recognized as a distinct patient population with unique biological and clinical characteristics [1]. Numerous studies have demonstrated that AYA patients more frequently present with larger primary tumors, cervical lymph node metastases, and higher recurrence rates than older adults, despite maintaining an excellent disease-specific survival [2,3]. However, AYA patients should not be considered a homogeneous group, as only a subset will eventually develop recurrent disease.

Current international guidelines primarily rely on conventional clinicopathological factors for postoperative risk stratification. However, these factors do not adequately identify which young patients are at greatest risk of recurrence. Molecular biomarkers, particularly BRAF V600E and TERT promoter (TERT-p) mutations, may improve risk assessment, yet their clinical value specifically within the AYA population remains insufficiently defined.

In Kazakhstan and the broader Central Asian region, the incidence of thyroid cancer has steadily increased during the past decade [4]. At the same time, population-specific evidence regarding recurrence risk among AYA patients remains unavailable. Because clinical practice and healthcare resources differ across regions, identification of risk factors derived from local populations is essential for developing individualized follow-up strategies and optimizing patient management.

To our knowledge, this is the first study to investigate clinicopathological and molecular predictors of recurrence among AYA patients with PTC in a Central Asian population. Rather than simply comparing AYA with older adults, our objective was to identify characteristics associated with recurrence within the AYA group in order to define clinically relevant risk criteria that may facilitate personalized surveillance and long-term management of these young patients.

2. Materials and Methods

2.1. Participants

A total of 246 consecutive patients with histologically confirmed PTC were included in this retrospective multicenter study. Tumor specimens were collected between 2016 and 2020 from three tertiary oncology centers in Kazakhstan: the Kazakh Institute of Oncology and Radiology (Almaty), the Center of Nuclear Medicine and Oncology (Semey), and the Multidisciplinary Center for Oncology and Surgery (Ust-Kamenogorsk).

None of the patients had a documented history of therapeutic or occupational radiation exposure. All tumors were independently reviewed and reclassified according to the 5th edition of the World Health Organization Classification of Endocrine and Neuroendocrine Tumours (2022) by two experienced pathologists: Masahiro Nakashima and Hirokazu Kurohama.

Patients were categorized into two age groups: adolescent and young adult (AYA) patients aged 15–39 years (n = 80), according to the National Cancer Institute definition, and older adult patients aged >39 years (n = 166).

2.2. Droplet Digital PCR Analysis of BRAF V600E and TERT Promoter Mutations

The BRAF V600E mutation and TERT-p mutations (C228T and C250T) were assessed using droplet digital polymerase chain reaction (ddPCR) with commercially available mutation-specific primer/probe assays (Bio-Rad Laboratories, Hercules, CA, USA). Fluorescent FAM-labeled probes were used to detect mutant alleles, whereas HEX-labeled probes identified the corresponding wild-type sequences. The analytical performance and validation of these assays have been reported previously [5–7].

Each ddPCR reaction was prepared in a final volume of 20 µL, containing ddPCR Supermix for Probes (No dUTP), mutation-specific primers and probes, and 5 µL of genomic DNA. Droplets were generated using the QX200 Droplet Generator (Bio-Rad Laboratories, Hercules, CA, USA), followed by PCR amplification and droplet fluorescence analysis according to the manufacturer's recommended protocol. Fluorescence data were processed using QuantaSoft software (Bio-Rad Laboratories, Hercules, CA, USA), and mutation calls were assigned based on previously validated assay criteria [5–7].

For the molecular analyses, BRAFV600E positivity and TERT-p positivity were evaluated independently, irrespective of the status of the other mutation. Tumors harboring both BRAFV600E and TERT-p mutations were additionally classified as double-positive to assess the combined molecular profile.

2.3. DNA Extraction

Genomic DNA was isolated from formalin-fixed paraffin-embedded (FFPE) thyroid tumor tissues using the Maxwell® RSC DNA FFPE Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. In patients with multifocal PTC, the largest tumor focus was selected for molecular analysis. Tumor-rich regions were identified on hematoxylin and eosin (H&E)-stained reference slides by an experienced pathologist before DNA extraction.

FFPE tissue blocks were sectioned at 8 µm, and 2–5 sections were collected depending on tumor size. After deparaffinization with xylene and ethanol washes, genomic DNA was purified using the automated Maxwell® RSC system (Promega Corporation, Madison, WI, USA). DNA concentration and purity were assessed using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA).

2.4. Follow-Up and Outcome Definitions

Follow-up data were obtained from institutional medical records and included information on disease status, recurrence, progression, and survival. Recurrence was defined as the appearance of structural and/or biochemical evidence of papillary thyroid carcinoma after a documented period of no evidence of disease following initial treatment. Persistent disease was defined as structural and/or biochemical evidence of disease that remained detectable after initial treatment without an intervening disease-free period. Only events occurring after a documented disease-free interval were classified as recurrence in recurrence-specific analyses.

Progression-free survival (PFS) was defined as the time from initial treatment to the first documented evidence of disease recurrence or progression. Disease progression included the appearance of new structural disease or documented worsening of previously identified disease during follow-up. Patients who had no documented recurrence or progression were censored at the date of their last available follow-up.

Overall survival (OS) was defined as the time from initial treatment to death from any cause. Patients who were alive at the last available follow-up were censored on that date. Because follow-up information was incomplete for a subset of patients, time-to-event

analyses were performed using available follow-up data, and the number of evaluable patients varied according to outcome data availability.

2.5. Statistical Analysis

Patients were classified into adolescent and young adult (AYA, 15–39 years) and older (>39 years) groups according to the National Cancer Institute definition. Continuous variables were summarized as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Proportions displayed in figures were presented with 95% Wilson confidence intervals. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared by the log-rank test. Multivariable analyses for OS and PFS were performed using penalized Cox proportional hazards regression. Independent predictors of recurrence within the AYA cohort were evaluated using multivariable logistic regression. When complete or quasi-complete separation resulted in unstable maximum likelihood estimates because of the limited number of recurrent events, penalized logistic regression with bootstrap-derived confidence intervals and bootstrap-derived p values was applied.

Clinicopathological, molecular, histopathological, and follow-up data were unavailable for a subset of patients. Therefore, all analyses were performed using an available-case (complete-case) approach, and sample sizes varied according to data availability for individual variables. Percentages were calculated using the number of available observations for each variable. Given the exploratory nature of recurrence analyses and the limited number of recurrent events, no formal correction for multiple testing was applied. Statistical significance was defined as a two-sided $p < 0.05$. All statistical analyses were performed using R software (version 4.5.1).

3. Results

3.1. Clinicopathological and Molecular Characteristics Between AYA and Older Patients

A total of 246 patients with PTC were included and classified into AYAs (AYA, 15–39 years) and older adults (>39 years). Compared with older patients, the AYA group demonstrated significantly more aggressive local disease despite their younger age. The median tumor size was significantly larger in AYA patients (19.5 mm [IQR, 14.0–30.0]) than in older adults (15.0 mm [IQR, 10.0–20.0]; $p = 0.024$). Likewise, tumors larger than 20 mm were significantly more common in the AYA group (38.8% vs. 22.4%, $p = 0.012$) (Table 1).

Table 1. Comparison of clinicopathological and molecular characteristics between adolescent and young adult and older patients with papillary thyroid carcinoma.

Variable	AYA	Older	*p* Value
Median size, mm (IQR)	19.5 [14.0–30.0]	15.0 [10.0–20.0]	0.024
Tumor size > 20 mm	31/80 (38.8%)	37/165 (22.4%)	0.012
LN	28/64 (43.8%)	29/124 (23.4%)	0.007
Recurrence	7/79 (8.9%)	3/150 (2.0%)	0.035
BRAF	41/78 (52.6%)	124/163 (76.1%)	0.001
TERT-p	4/75 (5.3%)	12/155 (7.7%)	0.591
BRAF/TERT-p	3/36 (8.3%)	9/43 (20.9%)	0.207

Note: Percentages were calculated using available cases for each variable; therefore, denominators differ because of missing clinicopathological or molecular data. AYA, adolescent and young adult (individuals aged 15–39 years); Older, individuals aged >39 years; IQR, interquartile range; mm, millimeters; LN, lymph node metastasis; BRAF, BRAF V600E irrespective of TERT-p mutation; TERT-p, TERT-p irrespective of BRAF V600E; BRAF/TERT-p, double BRAF V600E and TERT-p mutant.

Lymph node metastasis was observed almost twice as frequently among AYA patients (43.8% vs. 23.4%, $p = 0.007$), and recurrence occurred more than four times as often in AYA patients compared with older adults (8.9% vs. 2.0%, $p = 0.035$). The principal differences between the two age groups are illustrated in Figure 1.

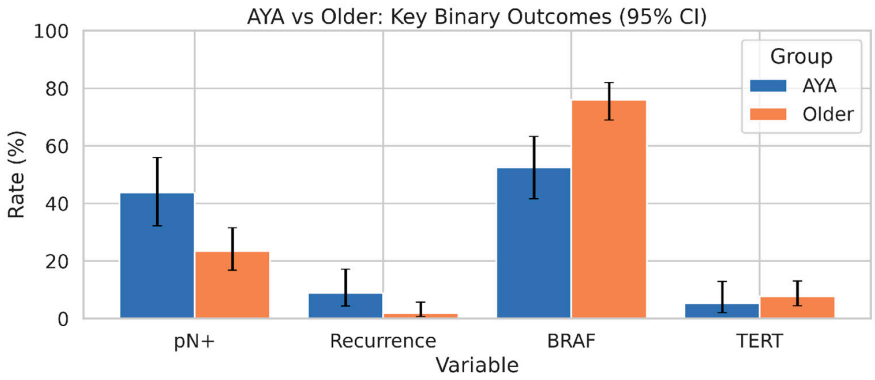


Figure 1. Comparison of major clinicopathological and molecular differences between AYA and older patients. Bars represent proportions with 95% Wilson confidence intervals. The figure summarizes the principal differences between age groups, including lymph node metastasis, recurrence, and frequencies of BRAF V600E and TERT-p mutations. Statistical comparisons are reported in Table 1. AYA, adolescent and young adult (individuals aged 15–39 years); Older, individuals aged >39 years.

Molecular analysis demonstrated a significantly lower prevalence of BRAF V600E mutations in AYA patients than in older adults (52.6% vs. 76.1%, $p < 0.001$). In contrast, the frequencies of TERT-p mutations and BRAF V600E/TERT-p double-positive tumors did not differ significantly between the two age groups. Kaplan–Meier analysis demonstrated generally favorable overall survival in both age groups. However, older patients exhibited significantly lower overall survival compared with AYA patients (log-rank $p = 0.0405$). A more pronounced decline in survival was observed in the older group during the first 100–120 months of follow-up, whereas survival in the AYA group remained relatively stable. Beyond this period, the estimated survival probability remained lower among older patients. Nevertheless, the later portions of the Kaplan–Meier curves should be interpreted cautiously because of uncertainty in long-term survival estimates (Figure 2).

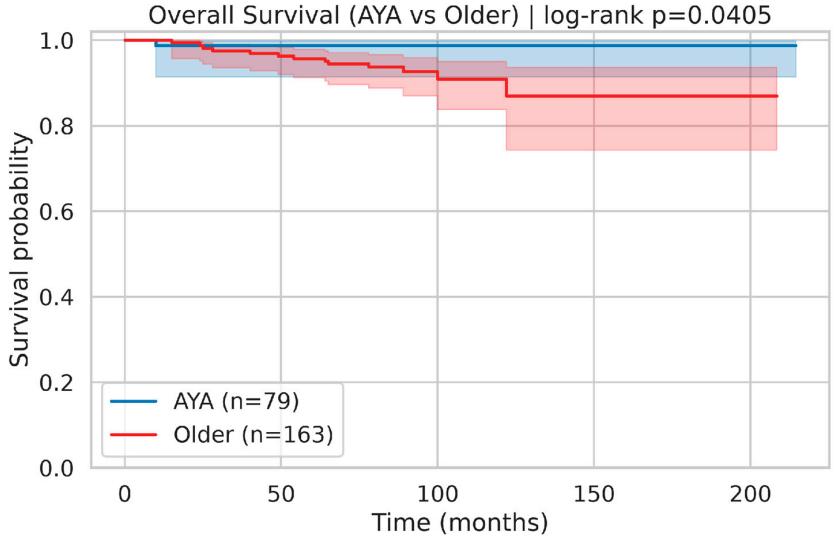


Figure 2. Kaplan–Meier curves comparing overall survival between adolescent and young adult (AYA) patients and older adults. Shaded regions represent 95% confidence intervals. Survival distributions were compared using the log-rank test. AYA, adolescent and young adult (individuals aged 15–39 years); Older, individuals aged >39 years.

3.2. Clinicopathological and Molecular Predictors of Recurrence in AYA Patients

To identify factors associated with recurrence specifically among young patients, clinicopathological and molecular characteristics were compared between recurrent and non-recurrent cases within the AYA cohort (Table 2).

Table 2. Clinicopathological and molecular characteristics associated with recurrence in adolescent and young adult patients.

Variable	AYA Recurrence	AYA Non-Recurrence	*p* Value
Male	3/7 (42.9%)	10/72 (13.9%)	0.083
Median size, mm (IQR)	22.0 [17.5–37.5]	17.5 [12.8–30.0]	0.161
Tumor size > 20 mm	4/7 (57.1%)	26/72 (36.1%)	0.417
LN	6/7 (85.7%)	21/56 (37.5%)	0.036
Pathologic T category	2.0 [2.0–3.0]	1.0 [1.0–2.0]	0.018
BRAF	4/7 (57.1%)	37/70 (52.9%)	1.000
TERT-p	3/7 (42.9%)	1/67 (1.5%)	0.002
BRAF/TERT-p	2/4 (50.0%)	1/31 (3.2%)	0.029
Ki-67, % (median, IQR)	3.0 [1.0–9.0]	4.0 [3.0–7.0]	0.525
AIT	1/6 (16.7%)	16/28 (57.1%)	0.175
Vascular invasion	0/6 (0.0%)	18/71 (25.4%)	0.326

Note: Analyses were performed using available cases; therefore, denominators vary among variables. AYA, adolescent and young adult; IQR, interquartile range; mm, millimeters; LN, lymph node; Pathologic T category, tumor category, TNM classification (WHO 5th edition); BRAF, BRAF V600E irrespective of TERT-p mutation; TERT-p, TERT-p irrespective of BRAF V600E; BRAF/TERT-p, double BRAF V600E and TERT-p mutant; Ki-67, Ki-67 labeling index; AIT, autoimmune thyroiditis.

Recurrent AYA patients demonstrated significantly more advanced local disease than non-recurrent patients. Lymph node metastasis was present in 85.7% of recurrent cases compared with 37.5% of non-recurrent patients ($p = 0.036$), while primary tumors exhibited significantly higher pathological T stage ($p = 0.018$).

Among molecular markers, TERT-p mutations showed the strongest association with recurrence, being detected in 42.9% of recurrent patients compared with only 1.5% of non-recurrent patients ($p = 0.002$). Likewise, BRAF V600E/TERT-p double-positive tumors were significantly enriched among recurrent AYA patients (50.0% vs. 3.2%, $p = 0.029$). In contrast, BRAF V600E mutation alone did not distinguish recurrent from non-recurrent AYA patients (57.1% vs. 52.9%, $p = 1.000$). Male sex and tumors larger than 20 mm tended to be more common among recurrent patients, although these differences did not reach statistical significance. Likewise, no significant associations were observed for Ki-67 index, autoimmune thyroiditis, or vascular invasion morphology.

3.3. Exploratory Recurrence Risk Model for AYA Patients

To explore whether a combination of clinicopathological and molecular characteristics could improve identification of high-risk AYA patients, an exploratory recurrence alert profile was constructed using four predefined risk factors (Table 3).

The recurrence alert profile is graphically illustrated in Figure S1, showing an approximately six-fold increase in recurrence frequency among patients harboring two to four predefined risk factors. Patients presenting with zero or one risk factor had a recurrence rate of only 3.6%, whereas those harboring two to four risk factors demonstrated a markedly higher recurrence rate of 21.7%, representing approximately a six-fold increase in recurrence frequency.

Table 3. Exploratory clinicopathological and molecular risk model for recurrence in adolescent and young adult patients.

Alert Group	N	Recurrence, *n* (%)	CI Low	CI High
0–1 factors	56	2 (3.6%)	0.985	12.119
2–4 factors	23	5 (21.7%)	9.664	41.904

Note: Patients were stratified according to the number of predefined recurrence-associated risk factors. Recurrence rates are presented together with Wilson 95% confidence intervals (CI). This exploratory model has not been externally validated and should be interpreted as hypothesis-generating. N, total number of cases.

3.4. Multivariable Analysis of Progression-Free Survival

Penalized multivariable Cox regression was performed to evaluate factors associated with progression-free survival. Lymph node metastasis demonstrated the strongest association with poorer progression-free survival, with a hazard ratio (HR) of 9.610, although the result narrowly missed statistical significance ($p = 0.059$) (Table S1). Forest plot visualization of the multivariable Cox model is provided in Figure S2. TERT-p-related molecular alterations also showed a strong trend toward shorter progression-free survival (HR 0.170, $p = 0.097$). No statistically significant associations were observed for age group, sex, tumor size, or BRAF V600E mutation. Progression-free survival did not differ significantly between AYA and older patients (log-rank $p = 0.820$; Figure S3). Given the limited number of recurrent events, these multivariable findings should be considered exploratory.

3.5. Multivariable Analysis of Overall Survival

Multivariable Cox regression demonstrated no significant associations between clinicopathological or molecular variables and overall survival. Neither age group, sex, tumor size, lymph node metastasis, BRAF V600E mutation, nor TERT-p-related alterations significantly influenced overall survival in this cohort (Table S2). Forest plot visualization of the multivariable OS model is presented in Figure S4. These findings are consistent with the excellent long-term prognosis generally observed in PTC, including among AYA patients.

Although the unadjusted Kaplan–Meier analysis demonstrated a statistically significant difference in overall survival between AYA and older patients (log-rank $p = 0.0405$), this association was not statistically significant after multivariable adjustment (HR = 1.58, 95% CI: 0.71–3.51; $p = 0.264$). Similarly, BRAF V600E mutation status was not significantly associated with overall survival in the adjusted model (HR = 1.29, 95% CI: 0.59–2.84; $p = 0.526$). These findings indicate that the observed unadjusted survival differences cannot be attributed specifically to BRAF V600E mutation status.

3.6. Multivariable Model of Recurrence in AYA Patients

An exploratory penalized multivariable logistic regression model was performed to evaluate independent predictors of recurrence within the AYA population.

Although none of the variables reached statistical significance after adjustment, TERT-p-related molecular alterations demonstrated the largest estimated effect, with an odds ratio of approximately 9 for recurrence (Table S3). Male sex and lymph node metastasis also showed positive associations with recurrence, whereas tumor size greater than 20 mm did not contribute independently after adjustment. The estimated effect sizes of individual predictors are presented in Figure S5.

4. Discussion

The present retrospective multicenter study investigated clinicopathological and molecular factors associated with recurrence among adolescents and young adults (AYA) with papillary thyroid carcinoma (PTC) in a Central Asian cohort. Our findings demon-

strated that AYA patients had larger primary tumors, more frequent lymph node metastases, and higher recurrence rates than older adults, despite generally favorable overall survival. Within the AYA group, lymph node involvement, higher pathological T category, and TERT promoter alterations were associated with recurrence in univariate analyses. However, none of the evaluated factors remained statistically significant after multivariable adjustment. These findings highlight the heterogeneity of recurrence risk among young patients with PTC and suggest that conventional clinicopathological characteristics and selected molecular alterations may provide complementary prognostic information. Nevertheless, given the limited number of recurrent events, these associations should be regarded as exploratory rather than as validated predictors suitable for immediate clinical application. Recent comparative studies have shown that AYA patients more frequently present with larger tumors, lymphatic invasion, and cervical lymph node metastases than older adults [8,9]. However, AYA patients should not be considered a homogeneous clinical entity, as their clinicopathological characteristics and molecular drivers may differ substantially even within this age group [10].

The observed association with TERT-p alterations is consistent with recent evidence linking these mutations to more aggressive biological behavior in PTC [11]. AYA patients presented with significantly larger tumors, more frequent cervical lymph node metastases, and more than a four-fold higher recurrence rate despite maintaining excellent overall survival. These findings are consistent with previous studies demonstrating that PTC in younger individuals often exhibits more aggressive local behavior while preserving an excellent long-term prognosis [12,13]. This apparent paradox has been attributed to differences in tumor biology, host immune response, and favorable responsiveness to treatment among younger patients [14]. Our Kaplan–Meier analysis further supports this concept, showing significantly better overall survival in AYA patients than in older adults despite the higher recurrence burden observed in the younger group. Importantly, overall survival was significantly better in AYA patients than in older patients despite the higher recurrence burden observed in the AYA group. In contrast, progression-free survival did not differ significantly between the age groups (log-rank $p = 0.820$; Figure S2). This apparent discrepancy emphasizes that recurrence or disease progression and overall survival represent distinct clinical outcomes in PTC. The superior overall survival of AYA patients is likely influenced by age-related factors beyond the tumor characteristics associated with progression, including the strong effect of age incorporated into the TNM staging system. Thus, the clinicopathological and molecular factors associated with recurrence in our cohort should not be interpreted as direct predictors of overall survival. Although BRAF V600E mutations were significantly more frequent among older patients, their higher prevalence did not translate into a statistically significant independent association with overall survival in our multivariable model. This finding suggests that differences in survival between age groups may reflect a combination of clinical, molecular, and age-related factors rather than BRAF V600E mutation status alone. Furthermore, the higher recurrence rate observed in AYA patients despite their more favorable overall survival highlights the distinction between recurrence risk and mortality. The potential prognostic contribution of coexisting BRAF V600E and TERT promoter mutations should also be considered; however, the relatively small number of molecularly defined events in our cohort limits definitive conclusions.

However, one of the most important observations of the present study is that AYA patients should not be regarded as a homogeneous population. Although recurrence occurred significantly more frequently in AYA patients overall, only a small subset eventually developed recurrent disease. From a clinical perspective, this distinction is particularly important because AYA patients are generally in their reproductive, professionally active, and socially productive years. Disease recurrence frequently results in repeated imaging

studies, reoperations, prolonged surveillance, and lifelong follow-up, all of which may substantially increase psychological distress and impair quality of life despite excellent survival. Therefore, identifying those young patients who truly require intensified surveillance represents a more rational strategy than applying uniform follow-up protocols to all AYA patients.

Among the molecular markers investigated, TERT promoter mutations showed the strongest association with recurrence in the univariate analysis of AYA patients. TERT promoter mutations were detected in 42.9% of recurrent cases compared with 1.5% of non-recurrent cases ($p = 0.002$). Similarly, tumors harboring both BRAF V600E and TERT promoter mutations were more frequent among patients with recurrence. In contrast, BRAF V600E mutation status was not significantly associated with recurrence within the AYA subgroup. However, these molecular associations were not confirmed as statistically significant independent predictors after multivariable adjustment.

Previous thyroid cancer studies have emphasized the prognostic significance of TERT promoter mutations and their coexistence with BRAF V600E. Bullock et al. reported an association between TERT promoter mutations and adverse clinical outcomes, including recurrence and disease-related mortality [15]. Similarly, the systematic review and meta-analysis by Yin et al. demonstrated associations between TERT promoter mutations and aggressive clinicopathological features, including disease persistence or recurrence and mortality [16].

Recent molecular studies have also highlighted age-related differences in the genetic landscape of PTC. Bulanova Pekova et al. investigated RET fusion genes in pediatric and adult thyroid carcinomas, highlighting the importance of considering gene rearrangements when evaluating molecular characteristics and clinical outcomes [17]. Hlozek et al. reviewed the clinical relevance of genetic alterations in thyroid cancer, emphasizing the importance of interpreting molecular findings alongside established clinical and pathological characteristics [18]. Studies of pediatric thyroid carcinoma have additionally highlighted the contribution of oncogenic gene fusions, including RET and NTRK rearrangements, suggesting that molecular analyses limited to BRAF V600E and TERT promoter mutations may not fully capture the genetic heterogeneity of thyroid tumors in younger patients [19].

Although our study did not include fusion gene analysis, the observed association between TERT promoter alterations and recurrence supports further investigation of their potential prognostic relevance in AYA patients. These findings should be considered preliminary and require confirmation in larger cohorts with broader molecular profiling.

The clinical relevance of TERT promoter mutations in our study lies primarily in their potential contribution to postoperative recurrence risk assessment rather than treatment selection. The 2025 American Thyroid Association (ATA) guidelines recognize that available molecular findings may complement conventional clinicopathological risk stratification, although routine postoperative molecular profiling is not recommended [20]. Similarly, the 2022 European Thyroid Association (ETA) pediatric guidelines emphasize risk-adapted management and follow-up [21]. In our cohort, TERT promoter alterations, particularly in combination with BRAF V600E, were associated with recurrence in univariate analyses but were not confirmed as independent predictors after multivariable adjustment [22]. Therefore, our findings support further investigation of TERT promoter mutations as potential complementary prognostic markers but do not justify changes to established treatment or surveillance strategies.

Another clinically relevant finding was the strong association between lymph node metastasis and recurrence. Nearly 86% of recurrent AYA patients presented with pathological lymph node involvement compared with only 38% of non-recurrent patients. Likewise, recurrent patients exhibited significantly higher pathological T stage, while male sex and

tumor size greater than 20 mm demonstrated consistent trends toward increased recurrence risk. Although these variables did not remain statistically significant after multivariable adjustment because of the limited number of recurrent events, both the penalized Cox and penalized logistic regression models showed effect estimates in the same direction, suggesting that these clinicopathological characteristics may contribute to recurrence risk in young patients. Similar observations have been reported in previous studies of young patients with PTC, in which lymph node involvement and other adverse clinicopathological features were associated with more aggressive disease behavior [8,9]. Interestingly, BRAF V600E mutations were significantly less frequent in AYA patients than in older adults, consistent with previous thyroid cancer studies reporting age-related differences in the molecular landscape of PTC [8,10]. In contrast, the overall prevalence of TERT-p mutations and BRAF V600E/TERT-p double-positive tumors did not differ significantly between age groups. Because of the relatively small number of TERT-p-mutated tumors, larger multicenter studies will be required to clarify age-related differences in TERT-p alterations.

One of the novel aspects of the present study is the development of an exploratory recurrence risk model integrating conventional clinicopathological variables with molecular findings. Although this exploratory model requires external validation, it illustrates the potential clinical value of combining conventional clinicopathological characteristics with molecular markers for individualized risk stratification in young patients. Patients harboring two or more predefined risk factors demonstrated an approximately six-fold higher recurrence rate than those with zero or one factor. Rather than relying on a single predictor, this approach reflects the principles of precision oncology, where individualized risk assessment is based on the combined contribution of multiple clinicopathological and molecular characteristics. Such integrated models may facilitate more personalized postoperative surveillance while avoiding unnecessary investigations in low-risk patients.

From a regional perspective, these findings have particular importance for Kazakhstan and other Central Asian countries. Thyroid cancer incidence has steadily increased throughout the region [4], whereas population-specific evidence regarding recurrence risk among young patients has remained unavailable. Differences in healthcare organization, access to molecular diagnostics, and postoperative follow-up strategies limit the direct applicability of data generated in Western or East Asian populations. To our knowledge, this study is the first to define recurrence-associated clinicopathological and molecular characteristics specifically among Central Asian AYA patients with PTC. These findings therefore provide an initial evidence base for developing individualized surveillance strategies adapted to regional clinical practice.

Several limitations should be acknowledged. First, this was a retrospective multicenter study, and not all clinicopathological and molecular variables were available for every patient because of incomplete archival material and follow-up information. Second, only seven recurrent events occurred within the AYA cohort. Consequently, the multivariable Cox and penalized logistic regression analyses should be interpreted cautiously, and the estimated effect sizes regarded as hypothesis-generating rather than definitive. In addition, molecular profiling was limited to the selected alterations investigated in this study and did not include gene fusion analysis, which represents an important direction for future investigation in AYA PTC. Finally, external validation in larger independent Central Asian and international cohorts will be necessary before these findings can be translated into routine clinical practice.

In conclusion, although adolescent and young adult patients with papillary thyroid carcinoma generally experience excellent long-term survival, recurrence remains an important clinical challenge because it affects individuals during their reproductive, professionally active, and socially productive years. Our findings indicate that recurrence risk within

the AYA population is heterogeneous and may be more accurately stratified by combining conventional clinicopathological factors with molecular markers, particularly TERT-p mutation status. This study provides the first population-specific evidence for Central Asia supporting a more personalized approach to postoperative surveillance and represents an important step toward implementing precision oncology for young patients with papillary thyroid carcinoma.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines7040062/s1, Table S1: Multivariable Cox regression analysis for progression-free survival; Table S2: Multivariable Cox regression analysis for overall survival; Table S3: Penalized multivariable logistic regression model for recurrence in adolescent and young adult patients; Figure S1: Recurrence rates according to the exploratory clinicopathological and molecular risk model; Figure S2: Forest plot of the multivariable Cox regression model for progression-free survival; Figure S3: Progression-free survival according to age group in patients with papillary thyroid carcinoma; Figure S4: Forest plot of the multivariable Cox regression model for overall survival; Figure S5: Forest plot of the penalized multivariable logistic regression model for recurrence in AYA patients.

Author Contributions: Conceptualization, M.M., Z.M. and L.P.; methodology, M.M. and Z.M.; validation, Z.M., L.P. and S.B.; formal analysis, M.M. and Z.M.; investigation, M.M., A.R. and S.B.; resources, M.M., A.R., S.B., A.D. and T.K.; data curation, M.M. and A.R.; writing—original draft preparation, M.M. and Z.M.; writing—review and editing, M.M., Z.M., L.P., A.R., S.B., A.D. and T.K.; visualization, M.M. and Z.M.; supervision, L.P. and A.D.; project administration, M.M., L.P. and A.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Atomic Bomb Disease Institute, Nagasaki University, and the Program of the Network-Type Joint Usage/Research Center for Radiation Disaster Medical Science.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Semey Medical University, Kazakhstan (protocol code 4b, approved on 10 March 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. For minors, informed consent was obtained from the parents or legal guardians of all participants prior to enrolment in the study.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions concerning participant information.

Acknowledgments: The authors gratefully acknowledge Masahiro Nakashima and Hirokazu Kurohama of Nagasaki University, Japan, for their expert pathological assessment and for independently reviewing and reclassifying all tumors according to the fifth edition of the World Health Organization Classification of Endocrine and Neuroendocrine Tumours (2022).

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AIT	Autoimmune thyroiditis
AYA	Adolescent and young adult
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CI	Confidence interval
ddPCR	Droplet digital polymerase chain reaction
DNA	Deoxyribonucleic acid
FAM	6-Carboxyfluorescein

FFPE	Formalin-fixed paraffin-embedded
H&E	Hematoxylin and eosin
HEX	Hexachlorofluorescein
HR	Hazard ratio
IQR	Interquartile range
LN	Lymph node
OR	Odds ratio
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PTC	Papillary thyroid carcinoma
TERT	Telomerase reverse transcriptase
TNM	Tumor–node–metastasis
WHO	World Health Organization

References

1. National Cancer Institute. Adolescents and Young Adults with Cancer. Available online: https://www.cancer.gov/types/aya (accessed on 5 August 2025).
2. Jia, M.-J.; Wang, S.; Li, Y.; Liu, X.-N.; Jiang, F.; Li, H.-L. Global burden of thyroid cancer among adolescents and young adults, 1990–2021, and projections to 2050: An analysis based on the GBD 2021. *Front. Endocrinol.* **2025**, *16*, 1503144. [CrossRef] [PubMed]
3. Ariello, K.; Hadi, A.-N.; Denburg, A.; Gupta, S. Survival outcomes for adolescent and young adults with cancer in low- and middle-income countries: A systematic review. *JCO Glob. Oncol.* **2025**, *11*, e2400326. [CrossRef] [PubMed]
4. Espenbetova, M.Z.; Bidakhmetova, A.M.; Krykpayeva, A.S.; Yespenbetova, B.A.; Toleutayeva, D.M.; Serikbayev, A.S.; Tukinova, A.R.; Uasheva, L.B. Epidemiology of thyroid cancer in Kazakhstan and in areas adjacent to the former Semipalatinsk Nuclear Test Site in 2013–2023. *Asian Pac. J. Cancer Prev.* **2025**, *26*, 691–699. [CrossRef] [PubMed]
5. Tanaka, A.; Matsuse, M.; Saenko, V.; Nakao, T.; Yamanouchi, K.; Sakimura, C.; Yano, H.; Nishihara, E.; Hirokawa, M.; Suzuki, K.; et al. TERT mRNA expression as a novel prognostic marker in papillary thyroid carcinomas. *Thyroid* **2019**, *29*, 1105–1114. [CrossRef] [PubMed]
6. Nakao, T.; Matsuse, M.; Saenko, V.; Rogounovitch, T.; Tanaka, A.; Suzuki, K.; Higuchi, M.; Sasai, H.; Sano, T.; Hirokawa, M.; et al. Preoperative detection of the TERT promoter mutations in papillary thyroid carcinomas. *Clin. Endocrinol.* **2021**, *95*, 790–799. [CrossRef] [PubMed]
7. Otsubo, C.; Mussazhanova, Z.; Kurohama, H.; Shalgimbayeva, G.; Ueki, N.; Matsuoka, Y.; Madiyeva, M.; Sato, S.; Yamashita, H.; Nakashima, M. A new indicator to differentiate thyroid follicular inclusions in cervical lymph nodes from patients with thyroid cancer. *Int. J. Mol. Sci.* **2023**, *24*, 490. [CrossRef] [PubMed]
8. Nguyen, V.P.T.; Kurohama, H.; Akazawa, Y.; Nguyen, T.N.A.; Matsuda, K.; Matsuoka, Y.; Mussazhanova, Z.; Yokota, K.; Satoh, S.; Yamashita, H.; et al. Clinicopathological and molecular characteristics of papillary thyroid carcinoma in adolescent and young adult patients. *Endocr. J.* **2025**, *72*, 221–227. [CrossRef] [PubMed]
9. Wang, L.; Zheng, Y.; Ye, Y.; Jiang, Z.; Lu, J.; Chen, G. Association between different regional lymph node metastases of papillary thyroid carcinoma in adolescents and young adults. *Oncol. Lett.* **2024**, *27*, 204. [CrossRef] [PubMed]
10. Li, H.; Han, R.; Meng, L.; Sun, Y.; Zhao, M.; Zhou, W.; Xie, J.; Yu, D.; Shen, L.; Zhou, Y.; et al. Nodal metastases associated with fusion oncogenes are age dependent in young adult patients with thyroid cancer. *J. Clin. Endocrinol. Metab.* **2023**, *109*, 143–150. Correction in *J. Clin. Endocrinol. Metab.* **2024**, *109*, e1421. https://doi.org/10.1210/clinem/dgae065. [CrossRef] [PubMed]
11. Sako, A.; Matsuse, M.; Saenko, V.; Tanaka, A.; Otsubo, R.; Morita, M.; Kuba, S.; Nishihara, E.; Suzuki, K.; Ogi, T.; et al. TERT promoter mutations increase tumor aggressiveness by altering TERT mRNA splicing in papillary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* **2024**, *109*, e1827–e1838. Correction in *J. Clin. Endocrinol. Metab.* **2024**, *109*, e1989. https://doi.org/10.1210/clinem/dgae442. [CrossRef] [PubMed]
12. Zhao, H.; Hu, J.; Cui, L.; Gong, Y.; Huang, T. Association between iodine nutrition and cervical lymph node metastasis of papillary thyroid microcarcinoma. *Front. Endocrinol.* **2023**, *14*, 1164069. [CrossRef] [PubMed]
13. Huang, J.; Ngai, C.H.; Deng, Y.; Tin, M.S.; Lok, V.; Zhang, L.; Yuan, J.; Xu, W.; Zheng, Z.-J.; Wong, M.C.S. Cancer incidence and mortality in Asian countries: A trend analysis. *Cancer Control* **2022**, *29*, 10732748221095955. [CrossRef] [PubMed]
14. Hatch-McChesney, A.; Lieberman, H.R. Iodine and iodine deficiency: A comprehensive review of a re-emerging issue. *Nutrients* **2022**, *14*, 3474. [CrossRef] [PubMed]
15. Bullock, M.; Ren, Y.; O'Neill, C.; Gill, A.; Aniss, A.; Sywak, M.; Sidhu, S.; Delbridge, L.; Learoyd, D.; de Vathaire, F.; et al. TERT promoter mutations are a major indicator of recurrence and death due to papillary thyroid carcinomas. *Clin. Endocrinol.* **2016**, *85*, 283–290. [CrossRef] [PubMed]

16. Yin, D.T.; Yu, K.; Lu, R.Q.; Li, X.; Xu, J.; Lei, M.; Li, H.; Wang, Y.; Liu, Z. Clinicopathological significance of TERT promoter mutation in papillary thyroid carcinomas: A systematic review and meta-analysis. *Clin. Endocrinol.* **2016**, *85*, 299–305. [CrossRef] [PubMed]
17. Bulanova Pekova, B.; Sykorova, V.; Mastnikova, K.; Vaclavikova, E.; Moravcova, J.; Vlcek, P.; Lancova, L.; Lastuvka, P.; Katra, R.; Bavor, P.; et al. RET fusion genes in pediatric and adult thyroid carcinomas: Cohort characteristics and prognosis. *Endocr. Relat. Cancer* **2023**, *30*, e230117. [CrossRef] [PubMed]
18. Hlozek, J.; Pekova, B.; Rotnágl, J.; Holý, R.; Astl, J. Genetic Changes in Thyroid Cancers and the Importance of Their Preoperative Detection in Relation to the General Treatment and Determination of the Extent of Surgical Intervention-A Review. *Biomedicines* **2022**, *10*, 1515. [CrossRef] [PubMed]
19. Colli, S.L.; Boycho, M.E.; Papendieck, P.; Mangone, F.M.; Chiesa, A.; García Lombardi, M.; Medín, M.; De Matteo, E.N.; Lorenzetti, M.A.; Preciado, M.V. Prevalent genetic alterations in pediatric thyroid carcinoma: Insights from an Argentinean study. *PLoS ONE* **2025**, *20*, e0323271. [CrossRef] [PubMed]
20. Ringel, M.D.; Sosa, J.A.; Baloch, Z.; Bischoff, L.; Bloom, G.; Brent, G.A.; Brock, P.L.; Chou, R.; Flavell, R.R.; Goldner, W.; et al. 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer. *Thyroid* **2025**, *35*, 841–985. [CrossRef] [PubMed]
21. Lebbink, C.A.; Links, T.P.; Czarniecka, A.; Dias, R.P.; Elisei, R.; Izatt, L.; Krude, H.; Lorenz, K.; Luster, M.; Newbold, K.; et al. 2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma. *Eur. Thyroid J.* **2022**, *11*, e220146. [CrossRef] [PubMed]
22. Yang, J.; Gong, Y.; Yan, S.; Chen, H.; Qin, S.; Gong, R. Association between TERT promoter mutations and clinical behaviors in differentiated thyroid carcinoma: A systematic review and meta-analysis. *Endocrine* **2020**, *67*, 44–57. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.