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Personalized treatment of 95 poorly differentiated thyroid cancer/anaplastic thyroid cancer in 2019–2023

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Abstract

Background: Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) are both rare and aggressive thyroid cancers. Advances in targeted therapy and immunotherapy have changed treatment strategies and improved prognosis in these patients.

Methods: This single-center cohort study included patients diagnosed with locally advanced or metastatic PDTC/ATC at Fudan University Shanghai Cancer Center (FUSCC) between 2019 and 2023. Patients were either enrolled in clinical trials or received treatment based on clinical guidelines and expert consensus. Gene testing was conducted using next-generation sequencing of clinical samples.

Results: 95 patients were analyzed (PDTC = 34, ATC = 61). Median overall survival (OS) was 19.7 months for PDTC and 9.5 months for ATC ($P = 0.478$). Among 82 patients who underwent gene testing, the most frequent gene alterations in PDTC were *BRAF* (50.0%), *TERT* promoter (39.3%), and *TP53* (25.0%) mutations; in ATC, they were *TERT* promoter (55.6%), *BRAF* (42.6%), and *TP53* (25.9%) mutations. Compared with ATC patients, PDTC patients were more likely to receive best supportive care and less likely to be enrolled in clinical trials or treated with PD-1 inhibitors. The 1-year OS rates for PDTC/ATC patients receiving neoadjuvant therapy + surgery, systemic treatment, and supportive care only were 83.3, 51.2, and 5.7%, respectively ($P < 0.001$). After adjusting for covariates, neoadjuvant therapy + surgery (hazard ratio = 0.216, 95% confidence interval: 0.647–0.718, $P = 0.012$) was an independent predictor of superior OS.

Conclusion: Despite the generally poor prognosis, aggressive treatment, particularly neoadjuvant therapy, has been shown to improve survival. Personalized treatment is crucial for optimizing treatment strategies for PDTC/ATC.

Keywords: anaplastic thyroid cancer; poorly differentiated thyroid cancer; survival; personalized treatment; neoadjuvant therapy

Introduction

Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) both originate from follicular cells of the thyroid but differ in their degree of dedifferentiation. PDTC/ATC accounts for only 1–15% of all thyroid cancer cases yet is responsible for over 50% of thyroid cancer-related mortality (1, 2). The median overall survival (OS) of ATC reported in the literature is only 3–6.9 months (3, 4, 5, 6).

Traditionally, the management of PDTC/ATC required a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. However, advances in targeted therapy and immunotherapy have enabled personalized treatment based on gene alterations, greatly improving survival in PDTC/ATC. Dabrafenib (a BRAF inhibitor) and Trametinib (a MEK inhibitor) combination therapy has been confirmed to be highly effective in *BRAF* V600E-mutated ATC, with an objective response rate (ORR) of 69% (7). In addition, the RET inhibitor Selpercatinib has demonstrated an ORR of 79% in *RET* fusion-positive thyroid cancers, including PDTC/ATC (8). Moreover, adding Pembrolizumab (a PD-1 inhibitor) to multi-target kinase inhibitors (mTKIs) has shown promising results in PDTC/ATC regardless of gene alterations, particularly for tumors with high tumor mutational burden (TMB) and PD-L1 expression levels (9).

As a leading thyroid cancer center in China, we recently recruited a cohort of PDTC/ATC patients with locally advanced or metastatic disease and adopted a personalized approach to their treatment. However, the optimal treatment strategy and clinical outcomes for these patients remain matters of debate. This study aims to summarize the clinical features, treatments, and survival outcomes of locally advanced or metastatic PDTC/ATC in the context of personalized medicine.

Methods

Patients

This was a single-center retrospective cohort study. Patients diagnosed with locally advanced or metastatic PDTC/ATC at Fudan University Shanghai Cancer Center (FUSCC) between October 2019 and February 2023 were included. A thyroid cancer multidisciplinary treatment (MDT) panel, comprising experts in head and neck surgery, medical oncology, radiotherapy, radiology, pathology, and nuclear medicine, evaluated the patients. Eligible patients were screened for clinical trials or received treatment according to clinical guidelines and expert consensus. Diagnosis of PDTC/ATC was confirmed through core needle biopsy (CNB) of persistent or recurrent disease, pathology consultation of surgical excision from formalin-fixed paraffin-embedded (FFPE) specimens, or fine needle

aspiration (FNA) when CNB was not feasible. The primary endpoint of the study was OS. Progressive disease was defined as biopsy-confirmed recurrence or radiological evidence of disease progression. Radiological images were assessed by radiologists from the thyroid cancer MDT panel based on RECIST criteria. The current study was approved by the FUSCC Institutional Review Board. Written consent was obtained from each patient after full explanation of the purpose and nature of all procedures used.

Gene testing

Gene testing was performed using next-generation sequencing of CNB, FFPE, FNA, or surgical biopsy samples based on availability. The choice of gene test panel depended on the physician's recommendation, patient preference, and sample availability. The specific genes tested are listed in Supplementary Table 1 (see section on [Supplementary materials](#) given at the end of the article) and include those associated with thyroid cancer tumorigenesis and potential treatment targets.

Statistics

Baseline characteristics between groups were compared using the Chi-square test for categorical variables and the *t*-test for continuous variables. Progression-free survival (PFS) and OS were estimated and plotted using the Kaplan–Meier method, with comparisons made using the Log-rank test and Breslow test. Hazard ratios (HRs) were calculated using Cox proportional hazards models with 95% confidence intervals (CIs). A two-sided *P*-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 25 (IBM, USA) and STATA version 15.1 (StataCorp, USA).

Results

Baseline features

A total of 95 patients diagnosed with PDTC/ATC were included. The mean age was 62.9 ± 10.9 years, and 56.8% were female. Twelve patients had combined pathology types: five with ATC/papillary thyroid cancer (PTC), and seven with PDTC/PTC. Based on the primary pathology or the pathology of recurrent/metastatic disease, patients were categorized into two cohorts: PDTC ($n = 34$) and ATC ($n = 61$). In the PDTC cohort, 50.0% had a history of differentiated thyroid cancer (DTC) or concurrent DTC, compared to 16.4% in the ATC group ($P < 0.001$).

According to the 8th AJCC TNM system, 27 (28.4%) patients were staged T4a, and 41 (43.2%) were T4b. Eighty (84.2%) patients were N1, and 47 (49.5%) were M1. The most common site of distant metastasis was

Table 1 Comparison of the baseline features of PDTC and ATC. Bold values indicate statistical significance at $P < 0.05$.

Pathology*	Total, $n = 95$	PDTC, $n = 34$	ATC, $n = 61$	P -value†
Age, mean $\pm$ SD	62.9 $\pm$ 10.9	61.3 $\pm$ 13.4	63.8 $\pm$ 9.3	0.643
Female, n (%)	54 (56.8)	23 (67.6)	31 (50.8)	0.112
History of/concurrent DTC	27 (28.4)	17 (50.0)	10 (16.4)	<0.001
T stage, n (%)				0.248
T1-3	5 (5.3)	2 (5.9)	3 (4.9)	
T4a	27 (28.4)	12 (35.3)	15 (24.6)	
T4b	41 (43.2)	10 (29.4)	31 (50.8)	
Tx	22 (23.2)	10 (29.4)	12 (19.7)	
M stage, n (%)				0.226
M0	47 (49.5)	14 (41.2)	33 (54.1)	
M1	47 (49.5)	19 (55.9)	28 (45.9)	
Mx	1 (1.0)	1 (2.9)	0 (0.0)	
TNM stage, n (%)				<0.001
I-III	11 (11.6)	11 (32.3)	0 (0.0)	
IV	75 (78.9)	19 (55.9)	56 (91.8)	
x	9 (9.5)	4 (11.8)	5 (8.2)	
Site of distant metastasis				
Lung, n (%)	14 (14.7)	13 (38.2)	20 (32.8)	0.593
Bone, n (%)	8 (8.4)	4 (11.8)	4 (6.6)	0.381
Distant lymph node, n (%)	20 (21.1)	11 (32.4)	9 (14.8)	0.044
Liver, n (%)	4 (4.2)	2 (5.9)	2 (3.3)	0.545
Prior treatment				
None, n (%)	39 (41.1)	11 (32.4)	28 (45.9)	0.198
Surgery, n (%)	52 (54.7)	21 (61.8)	31 (50.8)	0.304
Systemic‡, n (%)	15 (15.8)	7 (20.6)	8 (13.1)	0.338

*Patients with two pathology types were categorized by the primary pathology type. † P -values were calculated by ANOVA test for age and Chi-square test for other variables. ‡Systemic treatment included targeted therapy, chemotherapy, immunotherapy, and radioactive iodine therapy.

PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; SD, standard deviation.

distant lymph nodes (21.1%), followed by lung (14.7%), bone (8.4%), and liver (4.2%). PDTC patients were more likely to metastasize to distant lymph nodes compared to ATC patients ($P = 0.044$). Since PDTC was staged based on DTC criteria instead of ATC criteria, the TNM stage distribution of PDTC differed significantly from that of ATC ($P < 0.001$, Table 1).

Up to 56 (58.9%) patients in the cohort had received prior treatment before arriving at our clinic, while 39 (41.1%) were treatment-naïve. Among those with prior treatment, 52 had undergone at least one thyroid surgery (range: 1–6). Thirty (31.6%) patients had total thyroidectomy, and 11 (11.6%) had subsequent radioactive iodine (RAI) therapy. In addition, three patients had prior radiotherapy, five had prior chemotherapy, and ten had prior targeted therapy, all of which were multi-target kinase inhibitors, including sorafenib, lenvatinib, anlotinib, and apatinib. The two groups were comparable in age, sex, T stage, M stage, and prior treatment (Table 1).

Survival of PDTC/ATC patients

In our cohort, 14 (14.7%) patients were lost to follow-up. The median follow-up time was 12.0 months (range: 0–45.5 months). Seventy progressions were observed during this period. The median PFS for PDTC and ATC

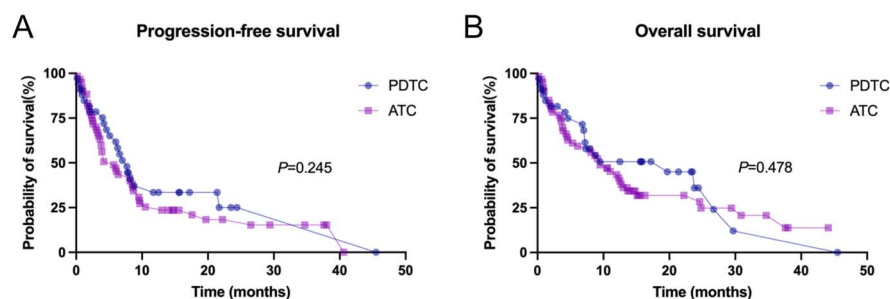
groups were 7.7 and 5.7 months, respectively. The 1-year PFS rates were 33.4% for PDTC and 25.4% for ATC, while the 3-year PFS rates were 25.1 and 15.3%, respectively ($P = 0.245$, Fig. 1A).

Sixty-three deaths occurred, 58 of which were due to thyroid cancer. The median OS was 19.7 months for PDTC and 9.5 months for ATC. The 1-year OS rates were 50.7% for PDTC and 43.5% for ATC, and the 3-year OS rates were 12.0 and 20.7%, respectively ($P = 0.478$, Fig. 1B).

Based on the AJCC TNM 8th system, 11, 4, 44, and 26 patients were staged as I-III, IVA, IVB, and IVC, respectively; nine patients could not be staged. The median OS for stage I-IVA, IVB, and IVC were 19.7, 12, and 6.1 months, respectively, with no significant differences detected ($P = 0.372$, Supplementary Fig. 1A).

Gene alterations in PDTC/ATC

Eighty-six (90.5%) patients underwent gene testing on cancer tissue, among whom 82 were tested at our institute with complete reports. Of these, 58 (70.7%) tests used CNB tissue, 18 (22.0%) used FFPE samples, 4 (4.9%) used FNA biopsies, and 2 (2.4%) used surgical biopsies. The gene mutation landscape of PDTC/ATC is shown in Fig. 2A.

**Figure 1**

Patients in the PDTC and ATC cohorts had similar survival. (A) The median PFS for PDTC and ATC groups were 7.7 and 5.7 months, respectively ($P = 0.245$). (B) The median OS for PDTC and ATC were 19.7 and 9.5 months, respectively ($P = 0.478$). PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer; PFS, progression-free survival; OS, overall survival.

BRAF V600E mutation was the most common gene alteration in PDTC (50.0%), followed by *TERT* promoter mutation (39.3%), *TP53* mutation (25.0%), *PIK3CA* mutation (25.0%), *MED12* mutation (7.1%), and *NRAS* mutation (7.1%) (Fig. 2B). Similarly, ATC cases were characterized by *TERT* promoter mutation (55.6%), *BRAF V600E* mutation (42.6%), *TP53* mutation (25.9%), *NRAS* mutation (24.1%), *MED12* mutation (9.3%), and *PTEN* mutation (7.4%) (Fig. 2C).

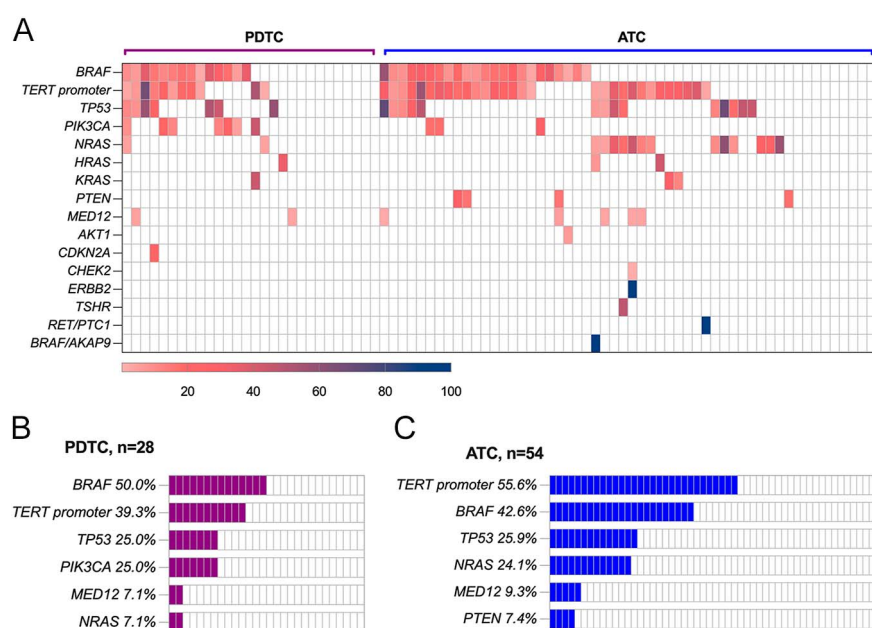
Based on the driver gene, 37 (45.1%) PDTC/ATC were driven by *BRAF V600E* mutation; 4 had *BRAF* mutations alone, and 33 had additional gene alterations, including 26 with *TERT* promoter mutations and 11 with *TP53* mutations. In total, 19 (23.2%) PDTC/ATC cases were driven by *RAS* mutations (16 *NRAS* and 3 *KRAS* mutations); 4 had *RAS* mutations alone, and others had concurrent *TERT* promoter (12 cases) or *TP53* (7 cases) mutations. Eight patients were driven by other single gene alterations, including one *RET-PTC3* fusion, three *TP53* mutations, two *TERT* promoter mutations, one *PTEN* mutation and one *MED12* mutation. No gene alterations were detected in 18 (22.0%) cases using the current panels. There was no significant difference

in OS among cancers driven by *BRAF* mutations, *RAS* mutations, or other mutations ($P = 0.513$, Supplementary Fig. 1B).

Treatment strategies

Overall, 41.1% patients were enrolled in clinical trials, 37.9% received standard care based on MDT discussion, and 21.1% received best supportive care (palliative care without active anti-cancer treatment). Notably, up to 32.4% of patients diagnosed with PDTC were treated with best supportive care, and only 17.7% were enrolled in clinical trials ($P = 0.002$), indicating they were undertreated compared with ATC patients.

Among the 72 patients receiving systemic treatment, 3 received chemotherapy, 27 received targeted therapy alone, and 42 received targeted therapy + PD-1 inhibitor. For 32 *BRAF*-mutated ATC/PDTC, 15 received a combination of *BRAF* inhibitor + MEK inhibitor ± PD-1 inhibitor (Dabrafenib + Trametinib, DT, 46.8%), while the remaining 17 received mTKIs ± PD-1 inhibitor (including lenvatinib, sorafenib, anlotinib, apatinib, and sulfatinib).

**Figure 2**

The gene mutation landscape of PDTC/ATC. (A) Gene alterations detected using the clinical panel in FUSCC; (B) The top altered genes in PDTC; (C) The top altered genes in ATC. PDTC: poorly differentiated thyroid cancer; ATC: anaplastic thyroid cancer; FUSCC: Fudan University Shanghai Cancer Center.

Table 2 Treatment summary in locally advanced and metastatic PDTC/ATC thyroid cancer. Bold values indicate statistical significance at $P < 0.05$.

Treatment	Total, $n = 95$	PDTC, $n = 34$	ATC*, $n = 61$	P-value
Treatment options				
Clinical trial, n (%)	39 (41.1)	6 (17.7)	33 (54.1)	0.002
Standard care, n (%)	36 (37.9)	17 (50.0)	19 (31.2)	
Best supportive care, n (%)	20 (21.1)	11 (32.4)	9 (14.8)	
Targeted therapy, $n = 69$				
BRAF inhibitor, n (%)	15 (21.7)	4 (18.2)	11 (23.4)	0.624
mTKI, n (%)	54 (78.3)	18 (81.8)	36 (76.6)	
PD-1 inhibitor, n (%)	42 (44.2)	9 (26.5)	33 (54.1)	0.009
Chemotherapy, n (%)	3 (3.2)	0 (0.0)	3 (4.9)	0.189
Local-regional treatment				
Direct surgery	2 (2.1)	1 (2.9)	1 (1.6)	0.672
Radiotherapy, n (%)	1 (1.1)	0 (0.0)	1 (1.6)	0.453
Neoadjuvant + surgery, n (%)	12 (12.6)	3 (8.8)	9 (14.8)	0.404

*Patients with two pathology types were categorized by the primary pathology type.

PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer; mTKI, multi-target kinase inhibitor.

In *BRAF*-mutated cancers, mTKI-based regimens showed non-inferior PFS compared to DT (median PFS 7.7 vs 6.3 months, $P = 0.256$, Supplementary Fig. 1C). In the ATC group, 54.1% received PD-1 inhibitors compared to 26.5% in the PDTC group ($P = 0.009$).

Locoregional treatment was offered to 15 patients: 2 underwent direct surgery, 1 received radiotherapy only, and 12 (12.6%) had surgical resection after neoadjuvant treatment (Table 2). Among those who had surgery post-neoadjuvant treatment, three were PDTC and nine were ATC. Neoadjuvant regimens included mTKIs + PD-1 inhibitors ($n = 7$), mTKIs alone ($n = 2$), and DT + PD-1 inhibitor ($n = 3$). Except for one patient with rapid progression, all patients underwent radiotherapy and resumed systemic therapy shortly after surgery.

Neoadjuvant treatment and surgery improve survival in PDTC/ATC

Univariate Cox regression identified liver metastasis ($P = 0.009$) and supportive care only ($P < 0.001$) as factors associated with inferior OS, while neoadjuvant therapy + surgery ($P = 0.006$) was a predictor of superior OS. Age, sex, pathology (PDTC vs ATC), T4b disease, and gene alterations were not significant prognostic predictors for OS (Supplementary Table 2). After adjusting for pathology type, age, and sex, liver metastasis (HR = 18.458, 95% CI: 3.245–105.009, $P = 0.001$), *TERT* promoter mutation (HR = 1.859, 95% CI: 1.012–3.417, $P = 0.046$), and supportive care only (HR = 14.557, 95% CI: 5.592–37.897, $P < 0.001$) were independent predictors of inferior OS, while neoadjuvant therapy + surgery (HR = 0.216, 95% CI: 0.047–0.718, $P = 0.012$) was an independent predictor of superior OS (Fig. 3A). In the subgroup of 35 *BRAF*-mutated ATC/PDTC patients who received targeted therapy, after adjusting for pathology type and sex, mTKI versus DT

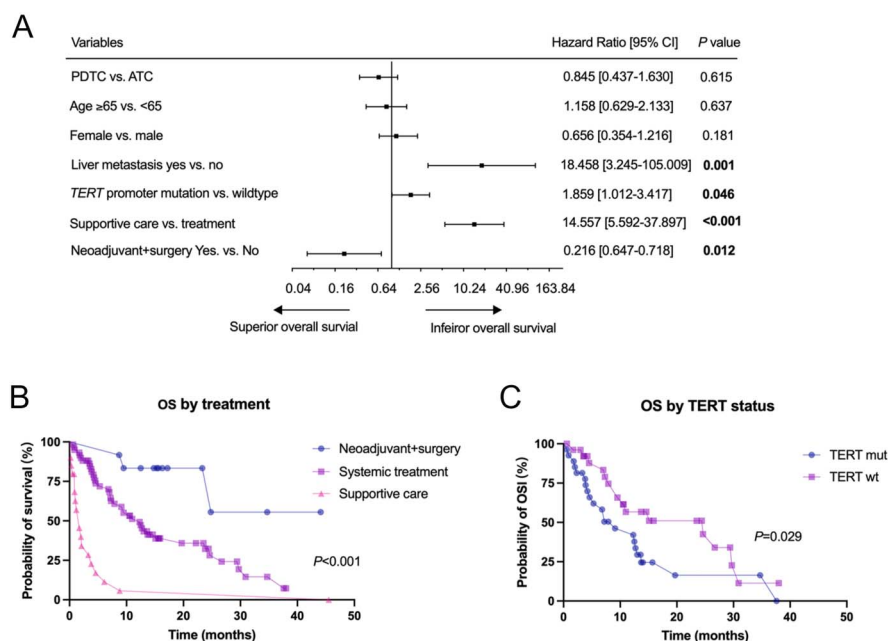
(HR = 2.28, 95% CI: 0.87–5.98, $P = 0.154$), and neoadjuvant therapy (HR = 0.27, 95% CI: 0.06–1.24, $P = 0.095$) were not significant prognostic predictors for OS due to limited sample size (Supplementary Table 3).

These results were consistent with the survival analysis, which showed distinct OS rates among patients treated with neoadjuvant therapy + surgery, systemic treatment only, and supportive care only ($P < 0.001$, Fig. 3B). The 1-year OS rates for these groups were 83.3, 51.2, and 5.7%, respectively. The median OS in the systemic treatment only and supportive care only groups was 12.3 and 1.7 months, respectively; the median OS in the neoadjuvant therapy + surgery group had not been reached at the time of analysis. Among patients treated with systemic therapy, those with *TERT* promoter mutations also displayed inferior OS compared with wild type in the short term, although the difference was not significant in the long term (median OS 9.1 vs 24.6 months, Breslow $P = 0.029$, log-rank $P = 0.061$ Fig. 3C).

Discussion

This study provides a real-life overview of locally advanced or metastatic PDTC/ATC patients from a single Chinese center, highlighting the considerable heterogeneity in clinical presentation, gene mutation profiles, and survival outcomes. Despite 78.9% of patients receiving active treatment (including clinical trials, neoadjuvant therapy, and targeted therapy), OS remained unfavorable, with a median OS of 19.7 months for PDTC and 9.5 months for ATC.

PDTC and ATC both originate from follicular cells of the thyroid and contribute to the majority of thyroid cancer-related deaths. In our cohort, 50.0% of PDTC patients had a previous history of DTC/concurrent DTC compared to only 16.4% in the ATC group. This observation was consistent with a previous study showing that DTC was

**Figure 3**

Neoadjuvant therapy and surgery improved OS in PDTC/ATC. (A) Forest plot showed that in the multivariate Cox regression model, liver metastasis, *TERT* promoter mutation, and supportive care only were independent predictors for inferior OS, while neoadjuvant therapy + surgery was an independent predictor for superior OS. (B) Patients treated with neoadjuvant therapy + surgery, systemic treatment, and supportive care only had distinct OS ($P < 0.001$). (C) Patients with *TERT* promoter mutations had inferior OS compared with wild type (median OS 24.6 vs 9.1 month, Breslow $P = 0.029$, log-rank $P = 0.061$).

present in more than 69% PDTC and 20% ATC (6). Nevertheless, although PDTC had a longer median OS than ATC in our cohort, the difference was not statistically significant. One possible explanation was that the PDTC and ATC cohorts had similar proportions of locally advanced disease (60%) and distant metastases (50%). The difference in group sizes might also have contributed to the lack of statistical significance. Furthermore, our study also showed that PDTC patients were less likely to be enrolled in clinical trials (several trials only enrolled ATC patients) and more likely to receive only supportive care, indicating that the PDTC cohort was undertreated compared to the ATC cohort. This undertreatment might reduce the survival difference between the groups. These results also suggested that the clinical behavior of PDTC was fundamentally different from that of DTC and should be treated as aggressively as ATC to achieve optimal survival. With advances in targeted therapy and immunotherapy, ATC patients in our cohort showed a trend toward improved survival of 9.5 months compared to historical data of 3 months (6). Liver metastasis was present in four PDTC/ATC patients and was an independent prognostic factor for inferior OS. All four patients had metastases to other sites concurrently (lung: $n = 2$, bone: $n = 1$, distant lymph nodes: $n = 3$), indicating high tumor burden and explaining the poor prognosis.

Although DT demonstrated robust clinical activity in *BRAF*-mutated ATC (7), it has not been approved by the Chinese National Medical Product Administration (NMPA) to treat ATC/PDTC and was unaffordable for most families. While *BRAF* mutation testing was mandatory for initiating DT, mTKI treatment could commence without awaiting gene test results. Patients

could decide whether to switch to DT after receiving their gene testing results or assessing mTKI efficacy. Consequently, only 46.8% of *BRAF*-mutated ATC/PDTC patients received DT +/- PD-1 inhibitor, with the remainder receiving mTKI +/- PD-1 inhibitor. The median PFS of DT in *BRAF*-mutated ATC/PDTC was 6.3 months, consistent with a recent meta-analysis of 6.7 months (95% CI: 4.7–34.2) (10). Interestingly, our data showed that mTKI +/- PD-1 inhibitor was also effective for *BRAF*-mutated ATC/PDTC, displaying a non-inferior median PFS of 7.7 months. This result was also consistent with a recent meta-analysis reporting a median PFS of 5.5 months (95% CI: 2.17–12.03), regardless of *BRAF* status (3). Several other studies showed that mTKI + PD-1 inhibitor as first-line treatment for ATC yielded a median PFS of 4.7 months and median OS of 6.3 months (4). These findings indicated that mTKI +/- PD-1 inhibitor could be a viable option for *BRAF*-mutated ATC/PDTC patients when DT is not feasible. Further investigation is warranted to directly compare the efficacy of these two treatment approaches in *BRAF*-mutated PDTC/ATC.

Combining PD-1 inhibitors with DT or mTKI in ATC/PDTC has been widely adopted, showing improved clinical outcomes. In a retrospective study of 71 *BRAF*-mutated ATC, adding pembrolizumab upfront or at progression to DT significantly prolonged PFS and OS compared to DT alone (11). Although no head-to-head trial compares mTKI + PD-1 inhibitor to mTKI alone, historical data suggest superior clinical outcomes. Two previous phase II trials evaluating lenvatinib monotherapy in ATC reported ORRs of less than 15% (12, 13). Meanwhile, Dierks *et al.* reported a median OS of 18.5 months in a retrospective study of six ATC/PDTC patients treated with lenvatinib and

Pembrolizumab. Long-term (>2 years) or complete responses were observed in patients with either high TMB or PD-L1 tumor proportion score >50% (9). The mechanism underlying sensitivity to immunotherapy might involve enrichment of CXCL13⁺ T lymphocytes in ATC samples, potentially promoting the development of early tertiary lymphoid structures (14). In our cohort, a marginal benefit of PD-1 inhibitor was observed with an HR of 0.68 (95% CI: 0.40–1.14, *P* = 0.140), indicating that a subgroup of patients might benefit from immunotherapy.

Another point of interest in our cohort was the illustration of the gene mutation landscape of PDTC/ATC in a Chinese population. *TERT* promoter, *BRAF*, and *TP53* mutations were the top three mutations in PDTC/ATC, similar to the findings in the Japanese population (15). *TERT* promoter mutation was not only the most prevalent gene alteration in ATC, but also an independent predictor of inferior short-time OS. This finding aligned with previous studies showing that *TERT* promoter mutation was a risk factor for recurrence in DTC and was associated with the more aggressive phenotype of thyroid cancer (15, 16, 17). *BRAF* mutation was present in less than half of patients and served as the major druggable target for PDTC/ATC. The lack of other druggable targets might contribute to the poor survival of PDTC/ATC. Our results also showed that up to 78% patients had at least one pathogenic gene mutation, and 40% had multi-gene mutations. The occurrence of multigene mutations has been associated with poorer survival in thyroid cancer (18), which explains the high prevalence of multi-gene mutations in PDTC/ATC.

As reported previously, local disease control was essential in PDTC/ATC; patients could still benefit from R0/1 resections despite distant metastasis (19). Wang *et al.* first reported a series of *BRAF*-mutated ATC patients who had complete surgical resection after neoadjuvant DT +/- PD-1 inhibitor treatment (20). The neoadjuvant strategy has since been evaluated by several studies, showing improved locoregional control and survival in PDTC/ATC (21). A recent study demonstrated that in the exploratory neoadjuvant group of 23 patients treated with DT followed by surgery, the median OS was the longest (63.0 months (CI: 15.5–110.5)) (11). These results were consistent with our cohort, in which PDTC/ATC patients treated with neoadjuvant therapy and surgery had superior survival. However, given the small sample size and heterogeneity within this subgroup, it is premature to draw definitive conclusions. In addition, neoadjuvant treatment helps identify patients responsive to systemic therapy and informs subsequent treatment strategies. Our data suggested that adjuvant radiotherapy and the maintenance of systemic therapy were important to achieve optimal results after neoadjuvant therapy + surgery; nevertheless, the optimal strategy remains to be determined.

This study has several limitations. First, 21.1% of PDTC/ATC patients received best supportive care only due to various socio-economic factors. The undertreatment of these

patients, particularly in the PDTC group, may underestimate the potential median survival achievable with active treatment. Next, the follow-up time was limited, and patients in the neoadjuvant group had not reached median OS. Furthermore, the gene test panels used were insufficient to detect all potential alterations in PDTC/ATC. Consequently, we failed to demonstrate the relationship between specific gene alterations and treatment sensitivity. Finally, TMB and PD-L1 expression were not routinely tested in PDTC/ATC samples in this cohort, and therefore we were unable to explore the efficacy of anti-PD-1 treatment with these markers.

Conclusion

In conclusion, the study presents a cohort of locally advanced or metastatic PDTC/ATC patients in China. Although the prognosis remains poor, aggressive treatment, particularly neoadjuvant therapy, has improved survival compared with historical data. Personalized treatment based on gene testing is essential for optimizing the management of PDTC/ATC.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/ETJ-24-0371>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

N-SH, W-JW, and YW were responsible for conception and design. YW, Q-HJ, and Jun Xiang provided administrative support. All authors were responsible for provision of study materials or patients. N-SH, J-YC, W-JW, J-QH, Y-JW, and W-LL were responsible for collection and assembly of data. N-SH, J-YC, and W-JW were responsible for data analysis and interpretation. All authors helped with manuscript writing. All authors approved the final manuscript.

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