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Research article

Long-term survival outcomes of systemic therapy in patients with isolated and mixed medullary thyroid cancer

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ABSTRACT

Background: Medullary thyroid carcinoma (MTC) is an uncommon thyroid cancer with limited treatment options for advanced disease. A small subset exhibits mixed MTC histology with both medullary and well-differentiated components. We investigated survival outcomes with systemic therapy in isolated versus mixed MTC using a large population-based cohort.
Methods: Patients diagnosed with MTC from 2000 to 2019 were identified in the National Cancer Institute's Surveillance, Epidemiology, and End Results database. The overall and thyroid cancer-specific survivals were compared between isolated (n = 1814) and mixed (n = 113) MTC cohorts. The impact of postoperative systemic therapy on survival was analyzed.
Results: No significant difference in 10-year overall survival was observed between isolated (77.4 %) and mixed (75.2 %) MTC in a cohort of 1927 patients. Median overall survival was similar between isolated (136.9 months) and mixed MTC (129.0 months), $p = 0.81$. While systemic therapy improved 10-year survival in isolated MTC (83.2 % vs. 76.9 %, $p < 0.001$), no benefit was seen in mixed MTC (76.4 % vs. 74.2 %, $p = 0.82$). Multivariate analysis confirmed survival gains with systemic therapy for isolated (HR = 0.763, 95%CI = 0.590–0.987, $p = 0.040$) but not mixed MTC (HR = 0.909, 95%CI = 0.268–3.079, $p = 0.88$).
Conclusions: In this large population-based study, no significant survival difference was observed between isolated and mixed MTC. Systemic therapy was associated with improved survival in isolated MTC, but not in the mixed subtype. These findings suggest a differential treatment response that warrants further investigation in prospective studies and may inform histology-tailored management strategies for mixed MTC.

1. Introduction

Thyroid cancer represents the most prevalent malignancy of the endocrine system, accounting for nearly 3 % of all new cancer cases in the United States [1]. Medullary thyroid carcinoma (MTC) is an uncommon histological variant that arises from the parafollicular C cells of the thyroid and accounts for 3–5% of all thyroid malignancies [2]. MTC can occur in either sporadic (75 %) or hereditary (25 %) forms [3]. Hereditary MTC is associated with germline mutations in the RET proto-oncogene and is a part of multiple endocrine

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neoplasia type 2 (MEN2) syndrome [4].

MTC has a unique clinical behavior compared to other well-differentiated thyroid cancers. It does not accumulate radioactive iodine and lacks expression of thyroid transcription factors; TTF-1 and paired box gene 8 (PAX8) [5]. MTC also secretes calcitonin and carcinoembryonic antigen (CEA), sensitive tumor markers for diagnosis and post-treatment monitoring [6]. However, MTC often presents at an advanced stage with loco-regional or distant metastasis. Moreover, metastatic MTC portends a poor prognosis with 10-year survival rates of 40 % compared to over 90 % for papillary and follicular thyroid carcinomas [7].

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy arising from the parafollicular C cells of the thyroid gland. Unlike differentiated thyroid cancers, MTC does not concentrate radioiodine and is, therefore, not responsive to radioactive iodine therapy [8]. The primary treatment for MTC is surgical resection, but recurrent or metastatic disease is common, necessitating systemic therapies [9]. Conventional cytotoxic chemotherapy has shown limited efficacy in MTC [10]. In recent years, molecular targeted therapies, particularly tyrosine kinase inhibitors like vandetanib and cabozantinib, have emerged as promising systemic treatment options for advanced MTC [11]. However, the survival impact of these newer agents in large real-world MTC populations, especially those with mixed histology, remains unclear [12].

A small subset of MTC tumors can exhibit mixed histopathological features with both medullary and well-differentiated (papillary/follicular) components. These mixed MTC variants constitute around 2–6% of all MTC [13]. The clinical behavior and prognosis of mixed MTC are not well characterized compared to classical MTC. Moreover, it is unknown if the response to systemic therapies differs between isolated and mixed MTC histological subtypes. In this sense, this study utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to investigate survival outcomes with systemic therapy in a large population-based cohort of MTC patients. The investigators compared the long-term overall survival of patients with isolated MTC versus mixed MTC subtypes. Additionally, the impact of postoperative systemic therapy on survival outcomes in isolated and mixed MTC cohorts was analyzed.

2. Methods

2.1. Ethical statement

In compliance with ethical research practices, the necessary permissions were secured to access the SEER database through a duly signed research data agreement form by a co-author (blinded). The research protocol has been reviewed and approved by the Institutional Review Board (# 2023–449), exempting the requirement for informed consent due to the retrospective nature of the study and the utilization of anonymized, publicly available data.

2.2. Study design and data source

This retrospective cohort study utilized data from the Surveillance, Epidemiology, and End Results (SEER) program (https://seer.cancer.gov/). SEER is an authoritative population-based cancer registry that collects information on cancer incidence, treatment, and survival outcomes across several geographic regions, covering approximately 34.6 % of the population [14]. Data from 2000 to 2019

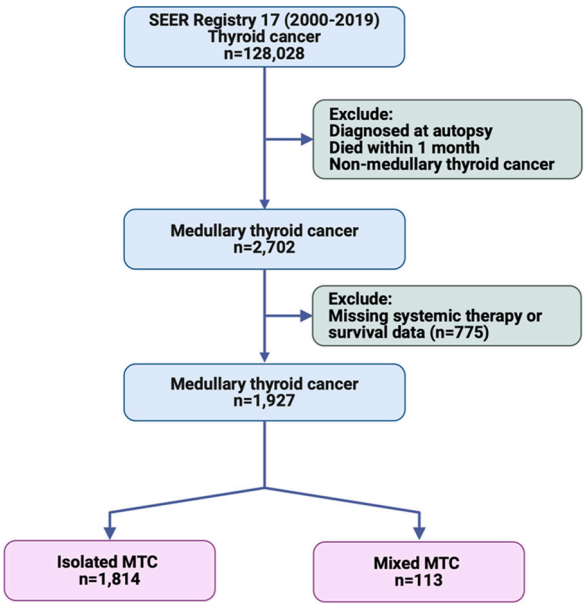

Fig. 1. Workflow for cohort recruitment from SEER database.

were extracted from SEER 17 registries for this analysis.

2.3. Study population with inclusion and exclusion criteria

Patients diagnosed with primary malignant medullary thyroid cancer between 2000 and 2019 were identified in SEER using the International Classification of Diseases for Oncology, third edition histology codes (ICD-*O*-3): 8345/3 (medullary carcinoma with amyloid stroma); 8346/3 (mixed medullary-follicular carcinoma); 8347/3 (mixed medullary-papillary carcinoma); 8510/3 (medullary carcinoma NOS). Patients were included if they had histologically confirmed MTC and complete information on demographics, tumor characteristics, treatment details, and survival. Patients were excluded if MTC diagnosis was made only on autopsy or death certificate, had prior or synchronous tumors, died within one month of diagnosis, or had incomplete/unknown data on systemic treatment or survival (Fig. 1).

2.4. Study variables

Patient demographic variables included age, sex, race, ethnicity, marital status, and residence location. Tumor variables comprised the year of diagnosis, histology, American Joint Committee on Cancer stage at diagnosis (tumor size, nodal involvement, and metastases), and SEER historical stage (localized, regional, distant). Treatment details included type of primary surgery (none, lobectomy, total thyroidectomy), use of radioactive iodine, external beam radiation therapy, and systemic therapy. The primary outcomes assessed were overall survival and thyroid cancer-specific survival. Overall survival was calculated from the date of MTC diagnosis to death from any cause, while cancer-specific survival was computed from diagnosis until death specifically attributed to thyroid cancer.

2.5. Statistical analysis

Descriptive statistics were used to summarize demographic, clinicopathologic, and treatment characteristics. Chi-square tests compared categorical variables between isolated and mixed MTC cohorts. Time to treatment was defined as the interval from date of diagnosis to first documented treatment with surgery, radiation, or systemic therapy. Systemic therapy encompassed chemotherapy, molecular targeted therapy, and other non-localized treatments. Overall and thyroid cancer-specific survival was estimated using the Kaplan-Meier method, and differences were assessed by log-rank test. Multivariable Cox proportional hazards regression models were constructed to determine the association between mixed MTC histology and mortality risk, adjusting for potential confounders. Two-sided $p < 0.05$ was considered statistically significant. All analyses were conducted using SPSS version 28 (*IBM Corp, Armonk, NY*).

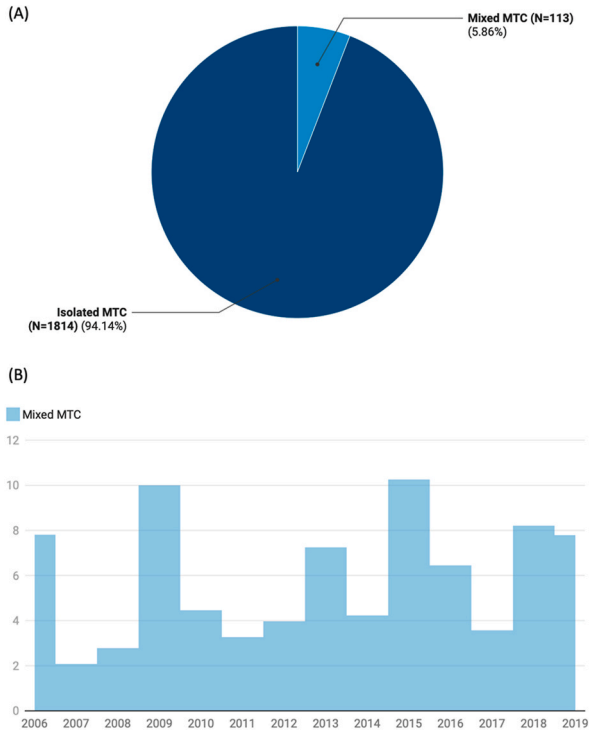

Fig. 2. Description of the study population. (**A**) Distribution of isolated and mixed MTC cases over the study period. (**B**) Temporal trends in incidence of mixed MTC histological variant. Data source: SEER registry 17 (https://seer.cancer.gov/).

3. Results

3.1. Characteristics of the study population

A total of 1927 MTC patients were included, comprising 1814 (94.14 %) with isolated MTC and 113 (5.86 %) with mixed MTC (Fig. 2A). Among the histological codes, medullary carcinoma NOS (8510/3) was the most common at 78.7 %. Medullary carcinoma with amyloid stroma (8345/3) accounted for 15.4 %, while the mixed subtypes mixed medullary-follicular carcinoma and mixed medullary-papillary carcinoma comprised 1.9 % (N = 37) and 3.9 % (N = 76), respectively. The proportion of mixed MTC remained relatively steady over the study period from 2006 to 2019, ranging from 2.08 % to 10.26 % annually. No clear temporal trends were observed (Fig. 2B).

The baseline characteristics were balanced between the isolated and mixed MTC groups, except patients with mixed MTC were younger (40.7 % vs. 52 % aged <55 years, $p = 0.025$) (Table 1).

Regarding pathological features, patients with mixed MTC had less advanced N staging (N0: 65.5 % vs. 53.5 %, $p = 0.047$). There was no difference in T and M stages between the groups (Table 2).

3.2. Management and disease outcomes

The treatment modalities differed between isolated and mixed MTC. Patients with mixed MTC were more likely to undergo total thyroidectomy (87.3 % vs. 92.8 %, $p = 0.041$) and receive radioactive iodine (22.1 % vs. 2 %, $p < 0.001$) and external beam radiation therapy (28.3 % vs 10.5 %, $p < 0.001$). The use of systemic therapy was also higher in the mixed MTC cohort, though it has borderline significance (62.8 % vs. 53.3 %, $p = 0.052$) (Table 3). There were no recurrence events reported. The rates of second primary malignancy were low overall and not significantly different between isolated (13.2 %) and mixed MTC (10.6 %), $p = 0.56$. Survival status was similar between isolated and mixed MTC ($p = 0.89$), with 83.6 % alive at the end of follow-up. While thyroid cancer-specific mortality was lower in mixed (6.2 %) versus isolated MTC (10.6 %), death from other causes was higher in the mixed cohort (10.6 % vs. 5.7 %, $p = 0.013$) (Table 3).

Table 1
Demographic and socioeconomic characteristics of the study population.

Characteristics	Levels	Total patients (N = 1927)	Isolated MTC (N = 1814)	Mixed MTC (N = 113)	*p*-value
Age (years)	<55 years	989 (51.3)	943 (52)	46 (40.7)	**0.025**
	≥55 years	938 (48.7)	871 (48)	67 (59.3)	
Sex	Female	1157 (60)	1087 (59.9)	70 (61.9)	0.69
	Male	770 (40)	727 (40.1)	43 (38.1)	
Race	White	1590 (83.7)	1499 (83.8)	91 (82)	0.47
	Black	153 (8.1)	145 (8.1)	8 (7.2)	
	API	144 (7.6)	132 (7.4)	12 (10.8)	
	AI/AN	12 (0.6)	12 (0.7)	0 (0)	
Ethnicity	Not Hispanic/Latino	1558 (80.9)	1464 (80.7)	94 (83.2)	0.62
	Hispanic/Latino	369 (19.1)	350 (19.3)	19 (16.8)	
Metropolitan	Metropolitan >1 M pop	1096 (57)	1033 (57)	63 (55.8)	0.84
	Metropolitan >250 K-1M	470 (24.4)	439 (24.2)	31 (27.4)	
	Metropolitan of <250 K	141 (7.3)	132 (7.3)	9 (8)	
	Non-metropolitan adj to a Metropolitan	127 (6.6)	122 (6.7)	5 (4.4)	
	Non-Metropolitan not adj to Metropolitan	90 (4.7)	85 (4.7)	5 (4.4)	
Residency	Urban	1707 (88.6)	1604 (88.4)	103 (91.2)	0.64
	Rural	217 (11.3)	207 (11.4)	10 (8.8)	
Household annual income	$75,000+	555 (28.8)	524 (28.9)	31 (27.4)	0.74
	$70,000 - $74,999	176 (9.1)	165 (9.1)	11 (9.7)	
	$65,000 - $69,999	310 (16.1)	285 (15.7)	25 (22.1)	
	$60,000 - $64,999	313 (16.2)	299 (16.5)	14 (12.4)	
	$55,000 - $59,999	115 (6)	108 (6)	7 (6.2)	
	$50,000 - $54,999	196 (10.2)	186 (10.3)	10 (8.8)	
	$45,000 - $49,999	117 (6.1)	109 (6)	8 (7.1)	
	$40,000 - $44,999	64 (3.3)	60 (3.3)	4 (3.5)	
	$35,000 - $39,999	55 (2.9)	52 (2.9)	3 (2.7)	
	< $35,000	26 (1.3)	26 (1.4)	0 (0)	
Household annual income	<$75,000	1372 (71.2)	1290 (71.1)	82 (72.6)	0.83
	≥$75,000	555 (28.8)	524 (28.9)	31 (27.4)	

Data are presented as numbers and percentages or median and interquartile range (IQR). Two-sided Chi-Square or Mann-Whitney U tests were used. Bold value indicates statistical significance at *p*-value <0.05. API: Asian or Pacific Islander, AI/AN: Am. Indian/Alaska Native, M: million.

Table 2
Clinical and pathological presentation of the study population.

Characteristics	Levels	Total patients (N = 1927)	Isolated MTC (N = 1814)	Mixed MTC (N = 113)	*p*-value
T staging	Tx	10 (0.5)	10 (0.6)	0 (0)	0.20
	T1	829 (43)	774 (42.7)	55 (48.7)	
	T2	463 (24)	433 (23.9)	30 (26.5)	
	T3	306 (15.9)	287 (15.8)	19 (16.8)	
	T4	147 (7.6)	143 (7.9)	4 (3.5)	
	NA	172 (8.9)	167 (9.2)	5 (4.4)	
N staging	N0	1045 (54.2)	971 (53.5)	74 (65.5)	**0.047**
	N1	812 (42.1)	776 (42.8)	36 (31.9)	
	NA	70 (3.6)	67 (3.7)	3 (2.7)	
M staging	M0	1743 (90.5)	1634 (90.1)	109 (96.5)	0.08
	M1	176 (9.1)	172 (9.5)	4 (3.5)	
	NA	8 (0.4)	8 (0.4)	0 (0)	
Site of metastasis	Liver	65 (3.4)	63 (3.5)	2 (1.8)	0.51
	Lung	44 (2.3)	44 (2.4)	0 (0)	0.19
	Bone	66 (3.4)	63 (3.5)	3 (2.7)	0.76
	Brain	8 (0.4)	8 (0.4)	0 (0)	0.68
	Distal LN	15 (0.8)	14 (0.8)	1 (0.9)	0.75
	Other sites	7 (0.4)	7 (0.4)	0 (0)	0.57
Extension	Localized	973 (51.5)	909 (51.2)	64 (57.1)	0.16
	Regional	653 (34.6)	614 (34.6)	39 (34.8)	
	Distant	262 (13.9)	253 (14.2)	9 (8)	

Data are presented as numbers and percentages. NA: not available. A two-sided Chi-Square test was used. Bold values indicate statistical significance at *p*-value <0.05.

Table 3
Treatment modalities and disease outcomes in thyroid cancer patients.

Characteristics	Levels	Total patients (N = 1927)	Isolated MTC (N = 1814)	Mixed MTC (N = 113)	*p*-value
Management					
Cancer-directed surgery	Not performed	160 (8.3)	157 (8.7)	3 (2.7)	**0.021**
	Performed	1767 (91.7)	1657 (91.3)	110 (97.3)	
Extension of surgery	Lobectomy	132 (7.6)	118 (7.2)	14 (12.7)	**0.041**
	Total thyroidectomy	1609 (92.4)	1513 (92.8)	96 (87.3)	
Radioactive iodine	Not received	1866 (96.8)	1778 (98)	88 (77.9)	**<0.001**
	Received	61 (3.2)	36 (2)	25 (22.1)	
Radiation therapy	Not received	1704 (88.4)	1623 (89.5)	81 (71.7)	**<0.001**
	Received	223 (11.6)	191 (10.5)	32 (28.3)	
Systemic therapy	Not received	890 (46.2)	848 (46.7)	42 (37.2)	0.052
	Received	1037 (53.8)	966 (53.3)	71 (62.8)	
Time to treatment	<1 month	938 (51.1)	880 (51.1)	58 (52.3)	0.75
	1–3 months	813 (44.3)	763 (44.3)	50 (45)	
	4–6 months	68 (3.7)	66 (3.8)	2 (1.8)	
	≥6 months	15 (0.8)	14 (0.8)	1 (0.9)	
Clinical outcomes					
Second primary malignancy	Positive	251 (13)	239 (13.2)	12 (10.6)	0.56
Survival status	Alive	1611 (83.6)	1517 (83.6)	94 (83.2)	0.89
	Died	316 (16.4)	297 (16.4)	19 (16.8)	
Cause of death	Thyroid cancer	200 (10.4)	193 (10.6)	7 (6.2)	**0.013**
	Other causes	116 (6)	104 (5.7)	12 (10.6)	

Data are presented as numbers and percentages or median and interquartile range (IQR). Two-sided Chi-Square and Mann-Whitney U tests were used. Bold values indicate statistical significance at *p*-value <0.05. Systemic therapy encompasses chemotherapy, targeted therapy, and other non-localized treatments. Time to treatment is the time from diagnosis to initiation of the first treatment (surgery, radiation, or systemic therapy).

3.3. Survival analysis

In survival analysis, there was no significant difference in overall survival between isolated and mixed MTC (median 136.9 vs. 129.0 months, $p = 0.81$) (Fig. 3A–B). The 10-year overall survival rates were 77.4 % for isolated MTC and 75.2 % for mixed MTC. On multivariate Cox regression analysis adjusting for demographic and clinicopathological variables, mixed MTC histology was not an independent prognostic factor for overall mortality ($p = 0.054$). Other factors like older age (HR = 3.457, 95 % CI = 2.643–4.521, $p < 0.001$) and advanced stage (regional = HR 2.154, distant HR = 5.982, both $p < 0.001$) were associated with significantly higher mortality (Fig. 3C).

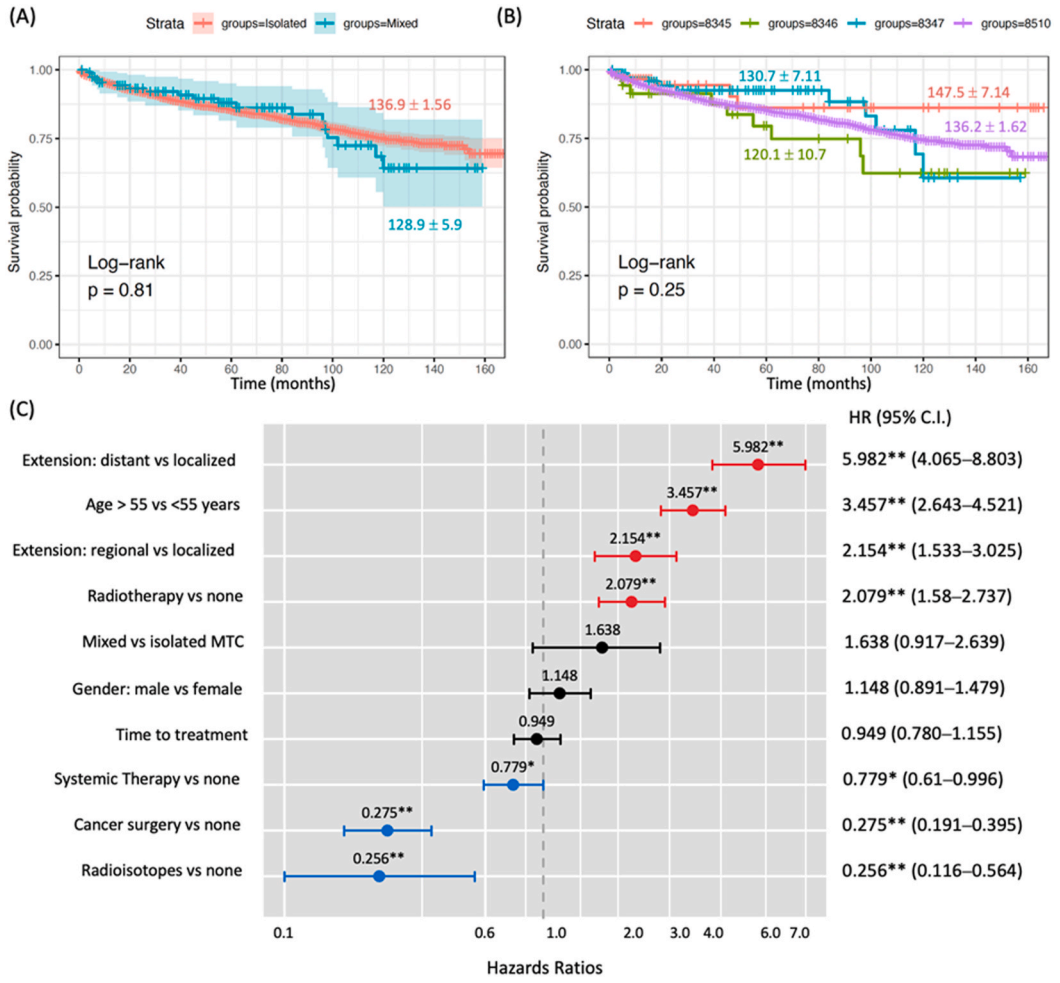

Fig. 3. Comparison of overall survival among different histological subtypes of medullary thyroid carcinoma. (**A**) Kaplan Meier curve depicting survival times in patients with isolated versus mixed MTC. Overall survival times for the MTC patients were 136.9 months (95%CI: 133.8–139.7). The survival estimates for isolated MTC and mixed MTC are 136.90 months (95 % CI: 133.84–139.95) and 128.99 months (95 % CI: 117.42–140.56) respectively. The difference in survival between the two groups was assessed using a log-rank test. (**B**) Kaplan Meier curve comparing survival times among different histological subtypes of MTC based on the ICD-0-3 codes: 8345/3: Medullary carcinoma with amyloid stroma, with a survival estimate of 147.52 months (95 % CI: 133.52–161.52). 8346/3: Mixed medullary-follicular carcinoma, with a survival estimate of 120.08 months (95 % CI: 99.05–141.10). 8347/3: Mixed medullary-papillary carcinoma, with a survival estimate of 130.76 months (95 % CI: 116.83–144.69). 8510/3: Medullary carcinoma, NOS (not otherwise specified), with a survival estimate of 136.21 months (95 % CI: 133.03–139.39). (**C**) Plot of the multivariate Cox regression analysis for the overall cohort, showing the predictor risk factors for mortality. Each predictor is represented with its corresponding hazard ratio (HR) and 95 % confidence interval (95%CI). All p-values are two-tailed, and significance was set at $p < 0.05$.

3.4. Impact of systemic therapy on survival

Regarding the impact of systemic therapy, its use was not associated with increased risk of subsequent malignancies (Table 4tbl4) but was associated with improved overall survival in the entire cohort (median survival times 141.8 vs 130.6 months, $p < 0.001$) as well as the isolated MTC subgroup (median 142.4 vs. 130.5 months), but not in the mixed MTC subgroup (median 113.1 vs. 126.9 months) (Fig. 4A–C).

Specifically, systemic therapy was associated with improved 10-year overall survival in isolated MTC (83.2 % vs. 76.9 %, log-rank $p < 0.001$) but not in mixed MTC (76.4 % vs. 74.2 %, log-rank $p = 0.82$). The survival benefit with systemic therapy persisted for isolated MTC (HR = 0.763, 95%CI = 0.590–0.987, $p = 0.040$) but not mixed MTC (HR = 0.909, 95%CI = 0.268–3.079, $p = 0.87$) after adjusting for confounders in multivariate analysis (Table 5 and Table 6).

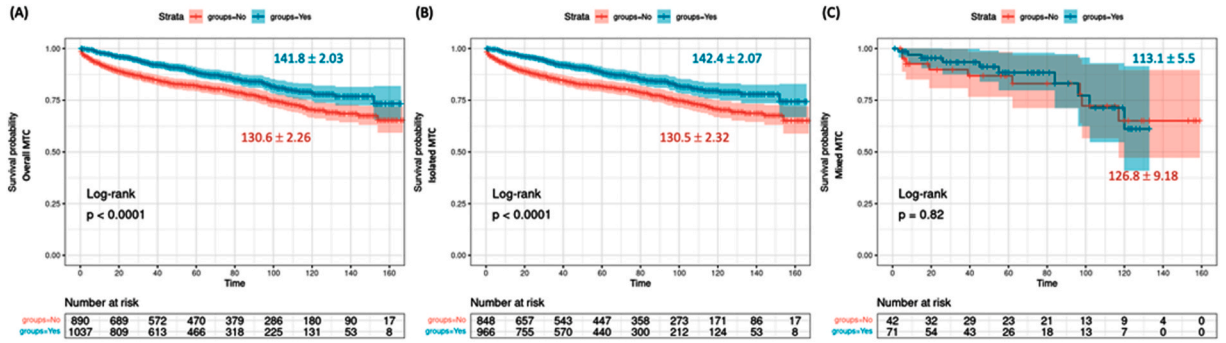

Fig. 4. Comparison of overall survival in patients undergoing postoperative systemic therapy versus those who underwent surgery. (**A**) Overall MTC. (**B**) Isolated MTC. (**C**) Mixed MTC. NB. Time in months.

4. Discussion

In this large population-based study, we did not identify significant differences in long-term overall or disease-specific survival between patients diagnosed with isolated versus mixed MTC histological variants. The 10-year overall survival rates were nearly identical at 77.4 % for isolated MTC and 75.2 % for the mixed subtype. Our findings in a cohort of 1927 patients, the largest analyzed to date, indicate both subtypes have similar biological behavior and clinical prognosis, contrary to some prior smaller studies suggesting more favorable outcomes with mixed MTC.

The treatment modalities did vary between isolated and mixed MTC, with the latter more likely to receive total thyroidectomy, radioactive iodine, and radiation therapy. The use of systemic therapy was also numerically higher in mixed MTC, though the difference only approached statistical significance. This likely relates to the mixed subtype exhibiting more well-differentiated features like increased radioiodine avidity, leading to the selection of therapies targeting both medullary and differentiated thyroid cancer pathways [15].

There were no recurrence events reported in this cohort. This may be related to the short follow-up duration, as recurrences in MTC often manifest several years later. The rates of second primary malignancies were low overall and did not significantly differ between isolated and mixed MTC. This suggests systemic therapy does not increase subsequent cancer risk, which has been a concern given the potential genotoxic effects of these agents [16].

The survival status was also similar between isolated and mixed MTC, with ~83 % alive at the end of follow-up, further supporting the lack of difference in overall survival. An interesting finding was that while thyroid cancer-specific mortality was lower in mixed MTC, death from other causes was higher compared to isolated tumors. The reduced cancer-specific deaths could be attributed to factors like earlier stage at diagnosis in mixed MTC, as evidenced by lower N staging in this study [17]. The higher non-cancer mortality may relate to mixed MTC patients being older with more comorbid conditions [17].

Systemic therapy with tyrosine kinase inhibitors or cytotoxic chemotherapy is increasingly used for advanced MTC [18–20]. Our study found a survival benefit with postoperative systemic therapy in the isolated MTC cohort, with 10-year survival improving from 76.9 % to 83.2 %. However, the mixed MTC subtype did not exhibit similar gains, with 10-year survival remaining at 74–76 % with systemic treatment.

The lack of survival improvement persisted for mixed MTC in multivariate analysis after controlling for demographic variables, tumor features, and treatment approaches. The sample size of mixed MTC was small, making estimates imprecise, but the hazard ratio close to unity suggests the absence of any clinically meaningful survival advantage with systemic therapy.

The lack of significant survival benefits with systemic therapy in mixed MTC is an intriguing finding that warrants further exploration. One potential explanation is that the differentiated component of mixed tumors may be less responsive to the kinase inhibitors and cytotoxic agents commonly used for advanced MTC [21]. The heterogeneous composition of mixed MTC may also confer distinct molecular dependencies and resistance mechanisms that attenuate the efficacy of conventional systemic therapies [22]. Further translational research is needed to delineate the genomic landscape and druggable vulnerabilities of mixed MTC, which may inform the development of rationally targeted treatment approaches for this rare subgroup [23]. Additionally, prospective clinical trials enriched for patients with mixed histology are crucial to rigorously evaluate the efficacy of existing and novel systemic therapies in this population [24].

The reasons for the differential response deserve further study. The mixed subtype shows more well-differentiated features like increased radioiodine uptake [25]. This could render medullary-specific systemic agents less effective if the well-differentiated component predominates. The variable histopathological composition of mixed MTC may result in heterogeneous treatment sensitivities [22].

Future research should evaluate whether therapies concurrently targeting medullary and well-differentiated pathways, like combination kinase inhibitors, could improve clinical outcomes in mixed MTC. The advent of novel agents for thyroid cancer has expanded the armamentarium of systemic treatments, providing opportunities for histology-guided therapy selection to improve patient outcomes [26].

Table 4
Comparison between cohorts who received systemic therapy and those who did not.

Characteristics	Levels	No systemic therapy (N = 890)	Systemic therapy (N = 1037)	*p*-value
Demographics				
Age (years)	<55 years	427 (48)	562 (54.2)	**0.007**
	≥55 years	463 (52)	475 (45.8)	
Gender	Female	535 (60.1)	622 (60)	0.96
	Male	355 (39.9)	415 (40)	
Race	White	726 (82.8)	864 (84.5)	**0.031**
	Black	87 (9.9)	66 (6.5)	
	API	59 (6.7)	85 (8.3)	
	AI/AN	5 (0.6)	7 (0.7)	
Ethnicity	Not Hispanic/Latino	701 (78.8)	857 (82.6)	**0.032**
	Hispanic/Latino	189 (21.2)	180 (17.4)	
Marital status	Married	471 (57.4)	611 (60.9)	0.48
	Domestic partner	3 (0.4)	8 (0.8)	
	Separated	9 (1.1)	10 (1)	
	Divorced	67 (8.2)	76 (7.6)	
	Widowed	57 (7)	56 (5.6)	
	Single	213 (26)	242 (24.1)	
Residency	Urban	782 (87.9)	925 (89.2)	0.56
	Rural	107 (12)	110 (10.6)	
Household annual income	<$75,000	674 (75.7)	698 (67.3)	**<0.001**
	≥$75,000	216 (24.3)	339 (32.7)	
Pathological data				
Histopathology	Isolated MTC	848 (95.3)	966 (93.2)	0.052
	Mixed MTC	42 (4.7)	71 (6.8)	
T staging	Tx	6 (0.7)	4 (0.4)	**0.012**
	T1	369 (41.5)	460 (44.4)	
	T2	218 (24.5)	245 (23.6)	
	T3	135 (15.2)	171 (16.5)	
	T4	61 (6.9)	86 (8.3)	
	NA	101 (11.3)	71 (6.8)	
N staging	N0	513 (57.6)	532 (51.3)	**<0.001**
	N1	319 (35.8)	493 (47.5)	
	NA	58 (6.5)	12 (1.2)	
M staging	M0	789 (88.7)	954 (92)	**0.041**
	M1	96 (10.8)	80 (7.7)	
	NA	5 (0.6)	3 (0.3)	
Extension	Localized	474 (55.3)	499 (48.4)	**<0.001**
	Regional	247 (28.8)	406 (39.4)	
	Distant	136 (15.9)	126 (12.2)	
Management				
Cancer-directed surgery	Positive	749 (84.2)	1018 (98.2)	**<0.001**
Extension of surgery	Lobectomy	89 (12.2)	43 (4.3)	**<0.001**
	Total thyroidectomy	641 (87.8)	968 (95.7)	
Radioactive iodine	Received	26 (2.9)	35 (3.4)	0.60
Radiation therapy	Received	265 (13.8)	125 (14)	0.74
Time to treatment	<1 month	437 (54.6)	501 (48.5)	**0.028**
	1–3 months	326 (40.7)	487 (47.1)	
	4–6 months	29 (3.6)	39 (3.8)	
	≥6 months	9 (1.1)	6 (0.6)	
Disease outcomes				
Second primary malignancy	Positive	112 (12.6)	139 (13.4)	0.64
Survival status	Alive	696 (78.2)	915 (88.2)	**<0.001**
	Died	194 (21.8)	122 (11.8)	
Cause of death	Thyroid cancer	117 (13.1)	83 (8)	0.17
	Other causes	77 (8.7)	39 (3.8)	

Data are presented as numbers and percentages or median and interquartile range (IQR). Two-sided Chi-Square or Mann-Whitney U tests were used. Bold values indicate statistical significance at *p*-value <0.05. API: Asian or Pacific Islander, AI/AN: Am. Indian/Alaska Native, M: million.

There are some limitations to our analysis that warrant consideration. The retrospective design is susceptible to selection biases and unmeasured confounding variables, such as patient comorbidities and treatment access, which could influence survival outcomes. The SEER database does not provide detailed information on the systemic therapy regimens, dosing schedules, compliance rates, or adverse events, limiting a deeper analysis of treatment efficacy and tolerability. Information on postoperative calcitonin and CEA levels was also unavailable. Additionally, the small sample size of patients with mixed MTC may affect the precision of our survival estimates.

Despite these limitations, our study benefits from a robust population-based design, capturing a broad spectrum of real-world outcomes in a large cohort of MTC patients. The extended duration of follow-up enables a thorough evaluation of long-term survival across different histological subtypes. Notably, the substantial sample size includes a sufficient number of rare mixed MTC cases,

Table 5
Impact of systemic therapy on overall and stratified survival.

Model	Cohorts	Overall survival		Cancer-specific survival	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Univariate	Overall MTC	0.61 (0.48–0.76)	**<0.001**	0.64 (0.48–0.85)	**0.002**
	Isolated MTC	0.59 (0.47–0.75)	**<0.001**	0.63 (0.47–0.84)	**0.002**
	Mixed MTC	0.9 (0.36–2.23)	0.82	0.81 (0.18–3.63)	0.78
Multivariate	Overall MTC	0.78 (0.61–1.0)	**0.047**	1.28 (0.91–1.81)	0.15
	Isolated MTC	0.76 (0.59–0.99)	**0.040**	1.28 (0.91–1.83)	0.16
	Mixed MTC	0.91 (0.27–3.08)	0.87	1.15 (0.87–1.52)	0.32

The regression model was adjusted by age, sex, disease extension, surgery, radioactive iodine, systemic therapy, and time to treatment. The Cox regression model was employed for overall mortality. Bold values indicate statistical significance at p-value <0.05.

Table 6
Predictor risk factors for mortality stratified by the type of MTC.

Risk factor	Isolated MTC		Mixed MTC	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age (years)	1.05 (1.04–1.06)	**<0.001**	1.11 (1.06–1.16)	**<0.001**
Gender: male vs. female	1.06 (0.81–1.38)	0.676	1.74 (0.47–6.48)	0.409
Extension: regional vs. localized	2.86 (2.02–4.05)	**<0.001**	1.54 (0.46–5.15)	0.481
Extension: distant vs. localized	10.21(6.92–15.1)	**<0.001**	16.9 (3.26–88.6)	**<0.001**
Time to treatment	0.89 (0.73–1.09)	0.248	0.96 (0.32–2.90)	0.935
Cancer-directed surgery vs. none	0.34 (0.24–0.50)	**<0.001**	0.65 (0.06–6.79)	0.717
Radioisotopes vs. none	0.25 (0.08–0.79)	**0.018**	1.82 (0.45–7.42)	0.401
Systemic Therapy vs. none	0.76 (0.59–0.99)	**0.040**	0.91 (0.27–3.08)	0.878

The Cox regression model was employed. Hazards ratio and 95 % confidence intervals are reported. Bold values indicate statistical significance at p-value <0.05.

providing a unique comparative insight into their prognosis relative to isolated tumors.

To overcome the limitations observed, we recommend prospective studies with detailed treatment data and advanced analytical methods, such as propensity score matching, to enhance the understanding of therapeutic impacts and support the validation of our findings. Further research in well-characterized cohorts will be crucial for confirming the role of systemic therapies in MTC management and may lead to more targeted, effective treatment protocols.

5. Conclusions

In summary, this large real-world investigation did not demonstrate significant survival differences between isolated and mixed MTC variants. While systemic therapy provided gains in isolated MTC, similar benefits were not observed in the uncommon mixed subtype. These findings can help optimize systemic treatment decisions based on MTC histological subtype, guiding more individualized and histology-directed management.

Given the paucity of data on mixed MTC, further research is warranted to better characterize its clinical behavior, prognostic factors, and outcomes with emerging systemic therapies. Collaborative multi-institutional studies can help assemble larger cohorts of this rare subtype to analyze survival. Detailed analyses of systemic therapy response based on the relative proportion of medullary versus well-differentiated components may also help refine treatment strategies.

As the therapeutic options for advanced thyroid cancer continue to expand, it is increasingly vital to personalize management based on tumor characteristics. The ongoing molecular elucidation of MTC and its variants may uncover new therapeutic targets and approaches to improve outcomes for this orphan disease. Our findings highlight the need to consider histological heterogeneity within MTC when selecting and sequencing systemic treatments to optimize patient survival.

Availability of data and materials

“The SEER data analyzed in this study is available at https://seer.Cancer.gov/."

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Ethics approval and consent to participate

The data of this study were obtained from the SEER database. The patients' data are public and anonymous, so this study does not require ethical approval and informed consent.

Consent for publication

None.

CRediT authorship contribution statement

Manal S. Fawzy: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Aziza Ali Alenezi:** Writing – review & editing, Resources, Data curation. **Baraah T. Abu AlSel:** Writing – review & editing, Validation, Resources, Data curation. **Eman A. Toraih:** Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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