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Association of adjuvant radioactive iodine therapy with cancer-specific survival in columnar cell papillary thyroid carcinoma: A population-based analysis

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Abstract

Introduction: Columnar cell papillary thyroid carcinoma (CCPTC) is a rare histological phenotype with controversial prognostic implications. Whether adjuvant radioactive iodine (RAI) confers a cancer-specific survival (CSS) benefit in this population remains uncertain.

Objective: This study utilized a population-based registry to evaluate the impact of postoperative RAI on CSS in patients with CCPTC following thyroidectomy.

Methods: Individuals with CCPTC undergoing total thyroidectomy (2004–2015) were identified from Surveillance, Epidemiology, and End Results. After exclusions, 754 eligible patients (535 RAI, 219 no RAI) were included. Propensity score matching (1:1, caliper 0.1) balanced baseline characteristics. Cox regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for CSS. A nomogram integrating independent prognostic factors was constructed to predict 5-, 8-, and 10-year CSS.

Results: After matching, 187 balanced pairs were generated. Multivariable Cox analysis revealed no significant CSS difference between RAI-treated and untreated groups in the overall cohort (HR: 0.75; 95% CI: 0.35–1.61; $p = 0.46$) or the propensity-matched cohort (HR: 0.58; 95% CI: 0.16–2.04; $p = 0.39$). Subgroup analyses stratified by age, sex, tumor size, extrathyroidal extension, nodal status, and disease stage consistently found no CSS benefit from RAI (all $p > 0.05$). The nomogram demonstrated satisfactory predictive accuracy for 5-, 8-, and 10-year CSS.

Conclusion: In this real-world CCPTC cohort, adjuvant RAI was not associated with improved CSS, even among high-risk patients. Routine RAI administration may be unwarranted. These findings require validation through prospective, multicenter studies with extended follow-up and comprehensive treatment data.

Keywords: Columnar cell; Papillary thyroid carcinoma; Radioactive iodine; Therapy; Survival

1. Introduction

Papillary thyroid carcinoma (PTC) represents the most common endocrine malignancy, with a marked increase in incidence observed over recent decades.[1-4] Several histologic subtypes of PTC, such as the tall cell, columnar cell, and hobnail variants, are of particular clinical concern due to their more aggressive clinicopathological characteristics compared to conventional PTC.[5-9] Over the past two decades, progress in molecular pathology has enhanced the classification of thyroid neoplasms. The 2022 World Health Organization (WHO) classification of thyroid tumors highlights the combination of histologic structure, cytologic details, and molecular changes, officially acknowledging several aggressive PTC variants as distinct entities with implications for prognosis and treatment.[7] However, the clinical application of these subclassifications varies, and management approaches for rare variants like columnar cell papillary thyroid carcinoma (CCPTC) are still primarily based on data from conventional PTC or more common variants.[8,9] According to the 2015 American Thyroid Association (ATA) guidelines, these pathological subtypes are considered to carry an intermediate risk of disease recurrence.[10] These variants are linked to higher rates of metastasis and, in certain instances, reduced effectiveness of radioactive iodine (RAI) therapy, which may lead to poorer survival outcomes.[11,12]

The aggressive behavior of non-conventional PTC variants is not uniform; substantial heterogeneity exists even within the same histologic subtype. For instance, tall cell variant PTC has been consistently associated with *BRAF* V600E mutations and increased expression of genes involved in extracellular matrix remodeling, whereas hobnail variant PTC often exhibits *TP53* mutations and a high proliferative index.[5,7] CCPTC, by contrast, lacks a defining molecular signature to date, and its genomic landscape remains poorly characterized. This molecular ambiguity complicates both diagnosis and therapeutic decision-making, particularly in cases where histologic features are equivocal or overlap with those of tall cell variant or conventional PTC.[11] Consequently, clinicians are frequently compelled to rely on traditional clinicopathological risk factors—such as extrathyroidal extension (ETE), lymph node metastasis, and distant spread—to guide adjuvant therapy recommendations in CCPTC patients, despite limited evidence that such factors carry the same prognostic weight as in classic PTC.[12]

Columnar cell papillary thyroid carcinoma was first described by Evans in 1986.[13] Representing an exceptionally rare subtype, it comprises approximately 0.15–0.2% of all papillary thyroid carcinomas and has occasionally been classified alongside the tall cell variant in some literature.[14] Morphologically, CCPTC is defined by the presence of tall columnar epithelial cells featuring elongated, hyperchromatic, and pseudostratified nuclei. This nuclear morphology serves as a key diagnostic criterion that differentiates it from the tall cell variant, which possesses distinct nuclear features. For a tumor to be classified as CCPTC, comprehensive sampling must demonstrate that at least 30% of the neoplasm is composed of these characteristic columnar cells.[15] Epidemiologically, this variant shows a predilection for male patients, with peak incidence occurring in the fifth decade of life [16,17]. The aggressive clinical behavior associated with CCPTC is primarily linked to its infiltrative, non-encapsulated growth pattern. This biological characteristic correlates with rapid tumor progression, increased rates of local recurrence, and a higher propensity for distant metastasis.[11]

Whether CCPTC histology independently influences prognosis continues to be debated. While several retrospective analyses have reported inferior overall and disease-free survival compared with classic PTC, others have contended that this association is confounded by the higher prevalence of advanced age, larger tumor size, and nodal metastases among CCPTC patients.[15,18] Indeed, after adjusting for these covariates in multivariable models, some studies failed to demonstrate an independent effect of columnar cell morphology on survival.[18,19] This discrepancy may reflect differences in study populations, diagnostic thresholds, or the proportion of encapsulated versus infiltrative tumors included across cohorts. The encapsulated form of CCPTC, while uncommon, is linked to a more indolent disease progression similar to classic PTC, thereby questioning the assumption that columnar cell features consistently indicate an unfavorable outcome.[14,20] In separate analyses of the Surveillance, Epidemiology, and End Results (SEER) database, Wang *et al.*[21] and Jiang *et al.*[22] both reported that CCPTC shows higher rates of ETE, lymph node, and distant metastases, along with reduced overall survival when compared to classic PTC. Consequently, patients with CCPTC—particularly those with additional high-risk features—have traditionally been considered candidates for adjuvant RAI therapy following total thyroidectomy (TT).[20,23] Nonetheless, some investigators have challenged the notion that histologic subtype independently predicts outcome, contending that the supporting evidence is limited.[15,18,20] Moreover, several studies have suggested that CCPTC may exhibit intrinsic resistance to RAI therapy.[5,20]

The management of aggressive variants of PTC with RAI remains an area of ongoing debate and clinical uncertainty. In conventional PTC, adjuvant RAI therapy has demonstrated efficacy in lowering the risk of disease

recurrence among patients presenting with lymph node metastases, ETE, or specific high-risk molecular characteristics. However, its influence on cancer-specific survival (CSS) is generally more modest and typically necessitates extended follow-up periods, often spanning several decades, to become statistically evident.[24,25] For rare variants such as CCPTC, the available evidence is derived almost exclusively from small case series and single-institution reports, which are inherently susceptible to selection bias and insufficient statistical power.[5,11] Moreover, the ATA's intermediate-risk classification for CCPTC does not distinguish between patients who may derive substantial benefit from RAI and those in whom the potential harms—including salivary gland dysfunction, lacrimal duct obstruction, and secondary malignancies—may outweigh any modest therapeutic advantage.[10] This therapeutic equipoise is further compounded by the lack of prospective data on RAI responsiveness in CCPTC, as well as the absence of validated biomarkers predictive of iodine avidity in this population. To date, the majority of research on CCPTC has consisted of case reports and literature reviews, with a primary focus on pathological characterization. Given the paucity of documented cases, drawing definitive conclusions regarding this aggressive variant remains difficult. In particular, whether RAI therapy confers a prognostic advantage in CCPTC patients remains uncertain.

To tackle this unresolved question, we utilized a large population-based cohort from the SEER database to systematically evaluate the effect of RAI therapy on CSS in CCPTC. This study introduces several methodological advancements compared to earlier analyses of this patient group. First, we applied propensity score matching (PSM) to reduce observable selection bias in observational studies of RAI effectiveness, thus simulating a randomized trial setting. Second, we performed comprehensive sensitivity analyses with different matching criteria and subgroup stratifications to test the stability of our results. Third, we created and internally validated a new nomogram that incorporates independent prognostic factors for CSS in CCPTC, offering a quantitative instrument for personalized risk assessment that has been absent for this uncommon condition.

2. Methods

2.1. Study population

Patients diagnosed with CCPTC who underwent TT from 2004 to 2015 were identified from the SEER database. Case selection was based on the International Classification of Diseases for Oncology, Third Edition codes: site code C73.9 (thyroid gland) and histology code 8344/3 (papillary carcinoma, columnar cell variant). Surgical intervention was confirmed using procedure codes 40 or 50. Exclusion criteria comprised individuals younger than 18 years, those with multiple primary tumors, follow-up periods shorter than one month, or incomplete clinical or pathological records. Furthermore, patients who underwent external beam radiotherapy were excluded to restrict the analysis to those treated with curative intent (Figure 1).

This retrospective analysis employed de-identified, publicly available data extracted from the SEER database (SEER*Stat version 8.4.2). In compliance with the National Cancer Institute's data use agreement, SEER datasets are fully anonymized and publicly accessible, containing no personally identifiable information. According to 45 CFR §46.104(d)(4) of the United States Department of Health and Human Services Policy for the Protection of Human Research Subjects, research involving the secondary analysis of existing, publicly available, de-identified data does not meet the definition of human subjects research and is therefore exempt from institutional review board (IRB) oversight. Additionally, our institution's IRB formally determined that this study qualified for exemption under Category 4 of the Revised Common Rule. Written informed consent was not required, as individual patients cannot be identified directly or through linked identifiers. The study was performed in adherence to the ethical principles outlined in the Declaration of Helsinki (revised 2013), and its reporting follows the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology statement.

The dataset for each patient encompassed demographic variables such as sex, age at diagnosis, race, and year of diagnosis, along with clinical and pathological characteristics including tumor size, SEER historic stage, American Joint Committee on Cancer (AJCC) 6th edition Tumor–Node–Metastasis (TNM) stage, ETE status (categorized as none, minimal, or gross), number of positive lymph nodes (PLNs), RAI treatment, survival duration in months, follow-up outcomes, and cause of death. For analytical purposes, PLN count was grouped into three categories: ≤5, >5, or unknown. Tumor size was stratified into three ranges: ≤20 mm, 21–40 mm, and >40 mm. The year of diagnosis was divided into two time periods: 2004–2009 and 2010–2015. The primary outcome measure was CSS, defined as the time from the initial diagnosis to death due to thyroid cancer or the date of the last follow-up, whichever came first.

2.2. Statistical analysis

The clinicopathological features were analyzed by comparing patients who underwent RAI therapy with

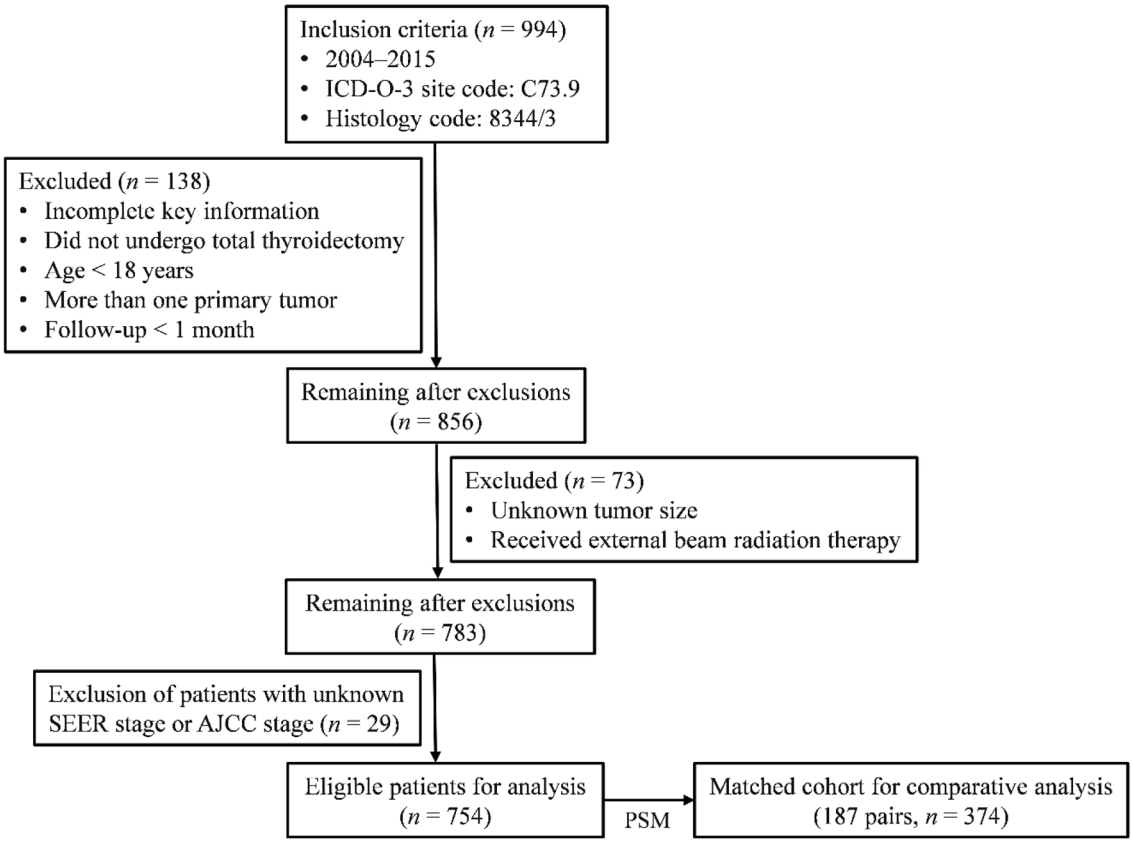

Figure 1. Study profile flowchart. This diagram illustrates the stepwise selection of patients with columnar cell papillary thyroid carcinoma from the SEER database.

those who did not, employing Student's *t*-test, chi-square test, or Wilcoxon rank-sum test based on data distribution and variable type. To mitigate potential selection bias associated with RAI administration and significant baseline disparities between groups, a PSM cohort was established to adjust for confounding variables.

Propensity scores were estimated using multivariable logistic regression incorporating 12 prespecified covariates selected based on clinical relevance and established associations with RAI treatment allocation in thyroid cancer: sex, age (continuous), race, year of diagnosis (2004–2009 vs. 2010–2015), tumor size (≤20 mm, 21–40 mm, >40 mm), SEER historic stage, AJCC 6th edition stage, T category, N category, M category, ETE status (none, minimal, gross), and PLN count (≤5, >5, unknown). The logistic regression model demonstrated acceptable discrimination with a *C*-statistic of 0.71 (95% confidence interval [CI]: 0.68–0.74). We performed 1:1 nearest-neighbor matching without replacement, utilizing a caliper width set at 0.1 standard deviations of the logit-transformed propensity score. This caliper width was predetermined, as it corresponds to 20% of the standard deviation of the propensity score logit, effectively balancing the trade-off between minimizing bias and retaining an adequate sample size. Standardized mean differences (SMD) were computed for all covariates both before and after matching; an absolute SMD below 0.1 was regarded as reflecting negligible imbalance. To evaluate the stability of the matching approach, sensitivity analyses were conducted using different caliper widths (0.05 and 0.2) and matching ratios (1:2 and 1:3). These alternative analyses produced consistent findings, which are summarized in the Results section.

To identify independent predictors of CSS, a multivariable Cox proportional hazards regression analysis was conducted. The strength of association between each variable and CSS was quantified using hazard ratios (HRs) along with their corresponding 95% CIs, and the results were visualized through forest plots. Based on the independent risk factors identified, a new nomogram was constructed to predict the probabilities of 5-, 8-, and 10-year CSS in both the overall cohort and the PSM cohort. Kaplan–Meier survival curves were generated, and log-rank tests were applied to compare CSS across

different groups. Statistical significance was defined as a two-sided p-value less than 0.05. All statistical analyses were performed using R software (version 4.3.2; https://www.r-project.org/).

3. Results

3.1. Baseline characteristics

A total of 994 patients diagnosed with CCPTC between 2004 and 2015 were initially identified. Following the exclusion of 240 individuals who did not meet the inclusion criteria, 754 patients with complete datasets were included in the final analysis. Among these, 535 patients (71.0%) underwent postoperative RAI therapy. Baseline demographic and clinical characteristics are summarized in Table 1. Compared to patients who did not receive RAI, those who underwent RAI treatment demonstrated a significantly higher proportion of males (26.7% vs. 17.8%, $p = 0.012$), larger primary tumor size (>40 mm: 16.4% vs. 8.2%, $p < 0.001$), more advanced disease stages according to SEER staging, AJCC staging, T category, and N category (all $p < 0.001$), a higher frequency of ETE ($p < 0.001$), and a greater proportion of patients with more than five PLN (22.2% vs. 9.6%, $p < 0.001$).

Prior to PSM, substantial intergroup differences were observed for multiple covariates, with absolute SMD exceeding 0.1 (range: 0.21–0.45) for sex, tumor size, ETE, N category, and PLN count, confirming the presence of considerable treatment selection bias. Following 1:1 nearest-neighbor matching, 187 well-balanced pairs were obtained. All 12 covariates demonstrated absolute SMD below 0.1 (range: 0.01–0.08), and no statistically significant differences were found between the groups for any baseline variable (Table 1). Sensitivity analyses using caliper widths of 0.05 and 0.2 produced matched cohorts with similarly balanced covariates (all SMD < 0.1) and yielded HRs for RAI therapy that were not materially different from the primary analysis (HR range: 0.55–0.63, all $p > 0.05$). Likewise, 1:2 and 1:3 matching confirmed the absence of a significant CSS benefit associated with RAI.

3.2. Impact of radioactive iodine therapy on cancer-specific survival

The median follow-up duration for the entire cohort was 100 months, with a range of 2 to 203 months and an interquartile range of 73 to 133 months. Throughout the observation period, 48 disease-specific deaths were recorded, accounting for 6.4% of the cohort. The cumulative 5-year and 10-year CSS rates for the entire cohort were 96.4% and 92.1%, respectively. Survival analysis demonstrated no statistically significant difference in CSS between the RAI-treated group and the non-RAI group, both in the overall cohort and in the PSM cohort (log-rank $p > 0.05$ for both comparisons) (Figure 2).

Multivariable Cox regression analysis identified older age, advanced AJCC stage, presence of distant metastasis, larger tumor size, and a PLN count exceeding five as independent predictors of disease-specific mortality in the overall patient population (all $p < 0.05$). Following PSM, only AJCC stage and a PLN count >5 retained their

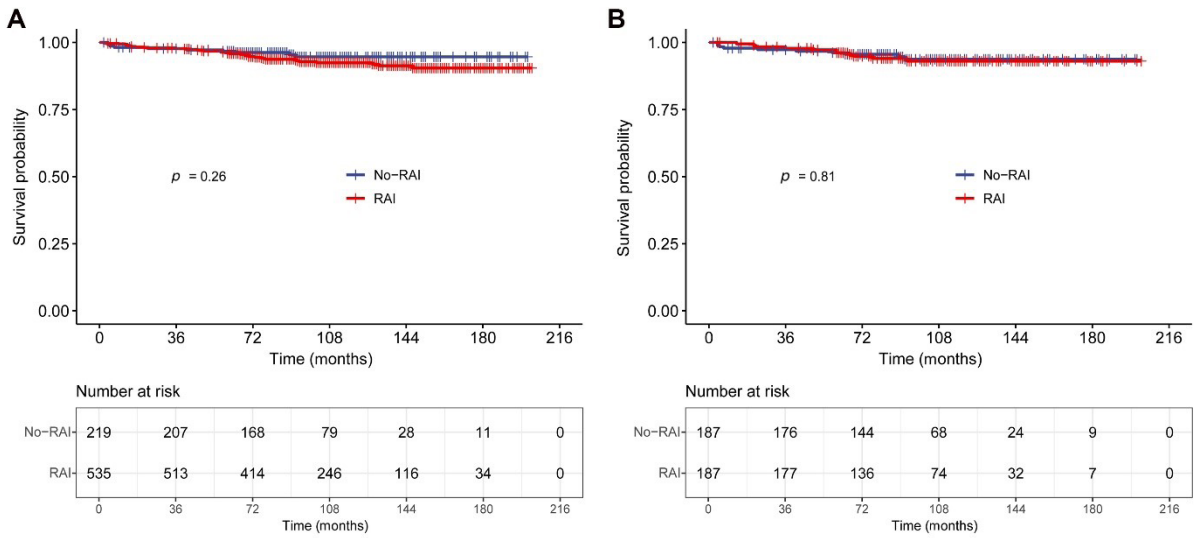

Figure 2. Kaplan–Meier survival curves comparing cancer-specific survival between columnar cell papillary thyroid carcinoma patients who received radioactive iodine (RAI) therapy and those who did not, in the overall cohort and after propensity score matching (PSM). (A) Overall cohort. (B) PSM cohort.

Table 1. Baseline demographic and clinicopathological characteristics of patients with CCPTC, stratified by RAI therapy status, in the overall cohort and the PSM cohort

Characteristic	Overall cohort (*n* = 754)			PSM cohort (*n* = 374)		
	No RAI, *n* (%)	RAI, *n* (%)	*p*-value	No RAI, *n* (%)	RAI, *n* (%)	*p*-value
n	219 (29.0)	535 (71.0)		187 (50.0)	187 (50.0)	
Age at diagnosis, years	48.4 ± 15.2	48.7 ± 14.3	0.81	47.9 ± 15.7	49.3 ± 13.5	0.369
Sex			0.012			0.521
Female	180 (82.2)	392 (73.3)		152 (81.3)	146 (78.1)	
Male	39 (17.8)	143 (26.7)		35 (18.7)	41 (21.9)	
Race			0.181			0.22
White	182 (83.1)	448 (83.7)		154 (82.4)	161 (86.1)	
Black	6 (2.7)	28 (5.2)		6 (3.2)	9 (4.8)	
Other/unknown	31 (14.2)	59 (11.0)		27 (14.4)	17 (9.1)	
Year of diagnosis			0.007			0.811
2004–2009	52 (23.7)	182 (34.0)		48 (25.7)	45 (24.1)	
2010–2015	167 (76.3)	353 (66.0)		139 (74.3)	142 (75.9)	
Tumor size, mm			<0.001			0.753
≤20	154 (70.3)	244 (45.6)		123 (65.8)	116 (62.0)	
21–40	47 (21.5)	203 (37.9)		46 (24.6)	51 (27.3)	
>40	18 (8.2)	88 (16.4)		18 (9.6)	20 (10.7)	
ETE			<0.001			0.858
No	61 (27.9)	96 (17.9)		48 (25.7)	52 (27.8)	
Minimal ETE	59 (26.9)	79 (14.8)		44 (23.5)	45 (24.1)	
Gross ETE	99 (45.2)	360 (67.3)		95 (50.8)	90 (48.1)	
Number of PLN			<0.001			0.721
≤5	132 (60.3)	290 (54.2)		111 (59.4)	104 (55.6)	
>5	21 (9.6)	119 (22.2)		21 (11.2)	25 (13.4)	
Unknown	66 (30.1)	126 (23.6)		55 (29.4)	58 (31.0)	
SEER stage			<0.001			0.364
Localized	119 (54.3)	140 (26.2)		87 (46.5)	89 (47.6)	
Regional	92 (42.0)	349 (65.2)		92 (49.2)	84 (44.9)	
Distant	8 (3.7)	46 (8.6)		8 (4.3)	14 (7.5)	
AJCC stage			<0.001			0.661
I/II	159 (72.6)	280 (52.3)		127 (67.9)	122 (65.2)	
III/IV	60 (27.4)	255 (47.7)		60 (32.1)	65 (34.8)	
T			<0.001			1.000
T1/T2	141 (64.4)	195 (36.4)		109 (58.3)	109 (58.3)	
T3/T4	78 (35.6)	340 (63.6)		78 (41.7)	78 (41.7)	
N			<0.001			0.749
N0	151 (68.9)	246 (46.0)		119 (63.6)	115 (61.5)	
N1	68 (31.1)	289 (54.0)		68 (36.4)	72 (38.5)	
M			0.702			0.749
M0	215 (98.2)	521 (97.4)		183 (97.9)	181 (96.8)	
M1	4 (1.8)	14 (2.6)		4 (2.1)	6 (3.2)	

Abbreviations: AJCC: American Joint Committee on Cancer; CCPTC: Columnar cell papillary thyroid carcinoma; ETE: Extrathyroidal extension; PLN: Positive lymph node; PSM: Propensity score matching; RAI: Radioactive iodine; SEER: Surveillance, Epidemiology, and End Results; TNM: Tumor–Node–Metastasis.

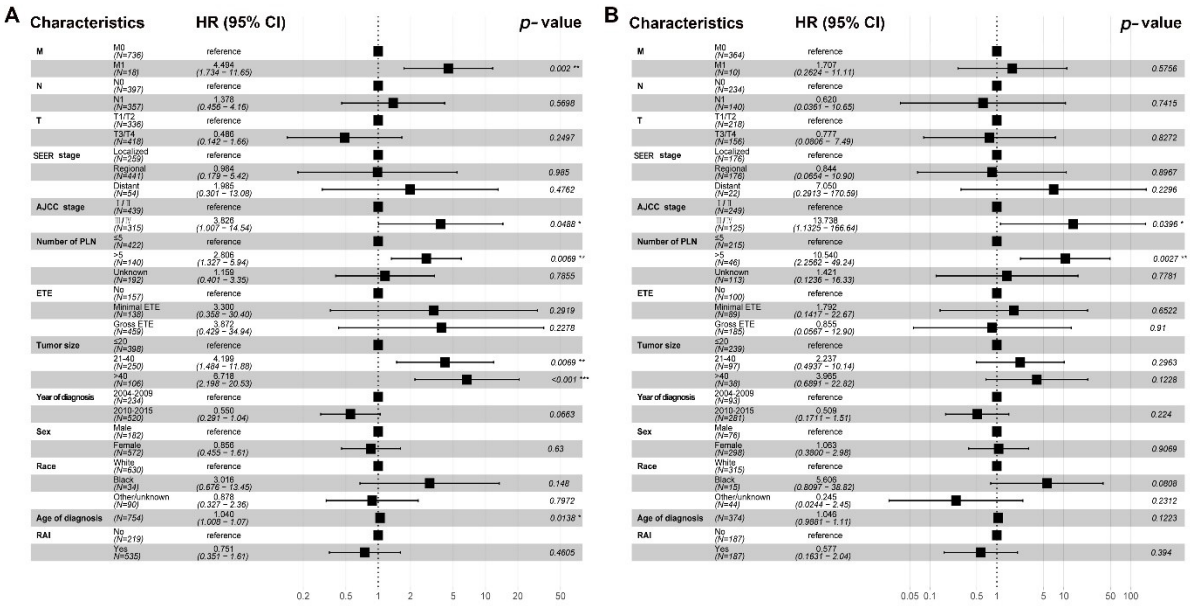

Figure 3. Multivariable Cox regression analysis of CSS in patients with CCPTC. Adjusted HRs with 95% CIs for factors associated with cancer-specific death are visualized in forest plots for (A) the overall cohort (n = 754) and (B) the PSM cohort (n = 374). The multivariable Cox model incorporated the following covariates: age at diagnosis (continuous, per 1-year increase), sex (female vs. male), race (White, Black, other/unknown), year of diagnosis (2004–2009 vs. 2010–2015), tumor size (≤20 mm, 21–40 mm, >40 mm), ETE (none, minimal, gross), AJCC 6th edition stage (I/II vs. III/IV), T category (T1/T2 vs. T3/T4), N category (N0 vs. N1), M category (M0 vs. M1), PLN count (≤5, >5, unknown), and RAI therapy (no vs. yes). HRs are plotted on a logarithmic scale, with the vertical dashed line indicating the null value (HR = 1.0). An HR < 1.0 indicates a lower hazard for the category listed first relative to the reference category, while an HR > 1.0 indicates a higher hazard. Error bars denote 95% CIs, and statistical significance was set at $p < 0.05$ (two-sided). The proportional hazards assumption was verified using Schoenfeld residual tests, yielding global $p > 0.05$ for both cohorts.
Abbreviations: AJCC: American Joint Committee on Cancer; CCPTC: Columnar cell papillary thyroid carcinoma; CI: Confidence interval; CSS: Cancer-specific survival; ETE: Extrathyroidal extension; HR: Hazard ratio; PLN: Positive lymph node; PSM: Propensity score matching; RAI: Radioactive iodine; SEER: Surveillance, Epidemiology, and End Results; TNM: Tumor–Node–Metastasis.

significance as unfavorable prognostic indicators (both $p < 0.05$). Notably, RAI therapy did not demonstrate a significant association with CSS in either the unadjusted cohort (HR: 0.75, 95% CI: 0.35–1.61; $p = 0.46$) or the PSM cohort (HR: 0.58, 95% CI: 0.16–2.04; $p = 0.39$) (Figure 3).

Based on the findings from the multivariable Cox regression analysis, a prognostic nomogram was developed to estimate the probabilities of 5-, 8-, and 10-year CSS. This model integrates several significant clinical variables, such as patient age, tumor dimensions, AJCC staging, M stage classification, and the number of PLN. The nomogram was applied to both the complete study cohort and the PSM cohort, as illustrated in Figure 4. Within this predictive tool, each clinicopathological parameter is allocated a distinct point score. The cumulative score, obtained by summing the individual points for all included factors, is then used to project the likelihood of survival at the designated time intervals.

To assess the impact of RAI treatment on CSS among different patient groups, subgroup analyses were conducted within the PSM cohort. These analyses were stratified by factors including age, sex, race, tumor size, year of diagnosis, SEER stage, AJCC stage, T category, N category, M category, extent of ETE, and number of PLN. The results indicated no statistically significant relationship between RAI administration and CSS across any of the clinicopathological subgroups examined. This lack of association persisted even in subgroups with high-risk characteristics, such as tumors larger than 40 mm (HR: 1.08, 95% CI: 0.33–3.54; $p = 0.90$), advanced AJCC stage (III/IV) disease (HR: 1.22, 95% CI: 0.50–2.95; $p = 0.66$), presence of distant metastasis (HR: 0.31, 95% CI: 0.06–1.62; $p = 0.17$), gross ETE (HR: 0.85, 95% CI: 0.34–2.16; $p = 0.74$), and more than five PLN (HR: 0.84, 95% CI: 0.27–2.61; $p = 0.77$), as detailed in Table 2.

4. Discussion

PTC comprises a diverse group of histologically distinct variants. Among them, CCPTC is histopathologically characterized by pseudostratified columnar cells.[17] Due to its low prevalence and the diagnostic challenges in differentiating it from other variants, the available literature is limited primarily to case reports and small institutional

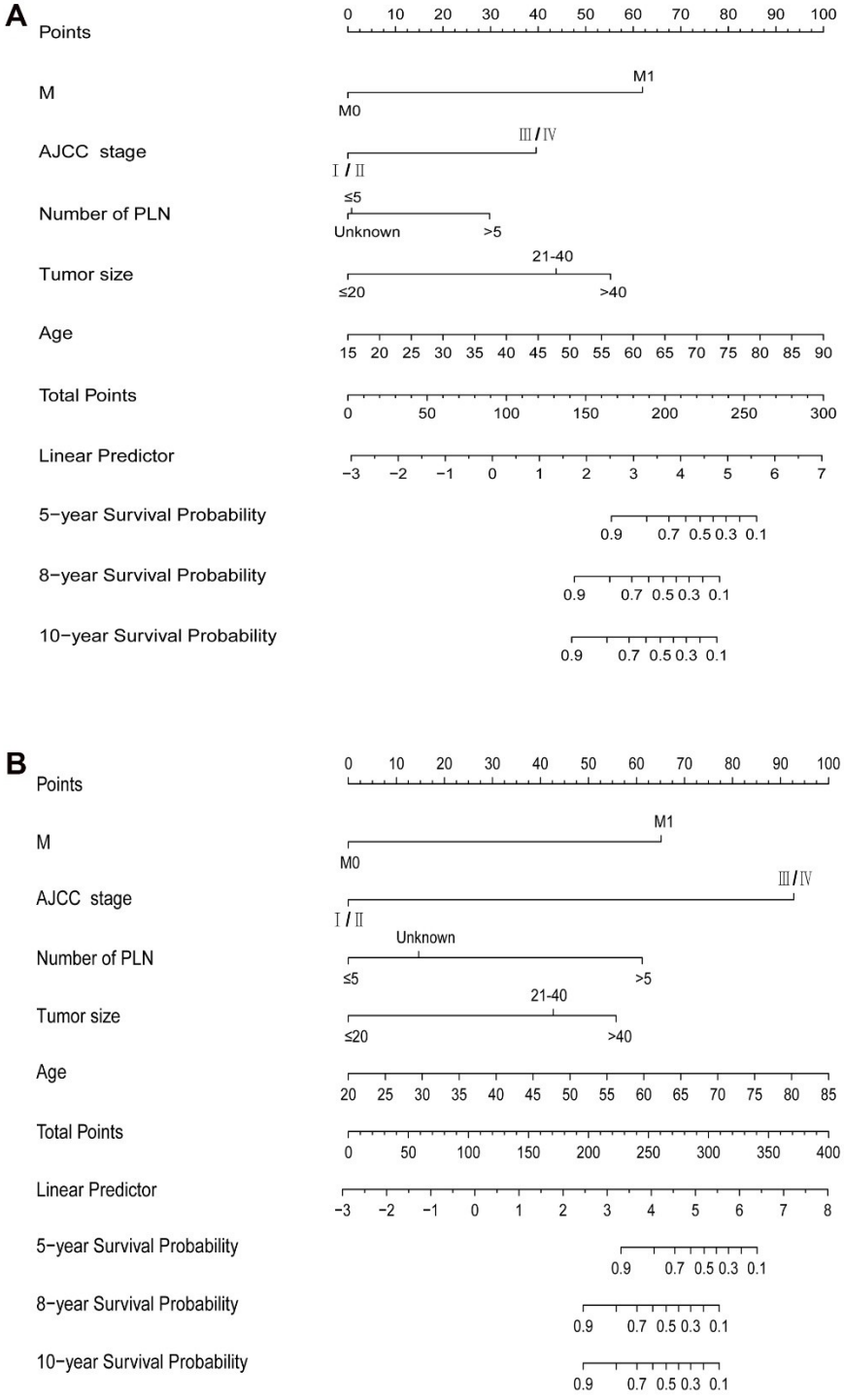

Figure 4. Nomogram for estimating 5-, 8-, and 10-year CSS among patients with CCPTC after TT. (A) Overall cohort (n = 754). (B) PSM cohort (n = 374). The nomogram was developed using independent prognostic factors derived from multivariable Cox regression analysis. For each predictor, a corresponding score is assigned based on the 0–100 scale shown at the top of the figure. The sum of these scores is located on the "Total Points" axis, from which a vertical line can be drawn downward to obtain the predicted probabilities of 5-, 8-, and 10-year CSS. Predictors in the nomogram include: M stage (M0 vs. M1); AJCC 6th edition stage (I/II vs. III/IV); number of PLN (≤5, unknown, >5); tumor size (≤20 mm, 21–40 mm, >40 mm); and age at diagnosis (continuous, ranging from 15 to 90 years).

Abbreviations: AJCC: American Joint Committee on Cancer; CCPTC: Columnar cell papillary thyroid carcinoma; CSS: Cancer-specific survival; PLN: Positive lymph node; M: Metastasis; TT: Total thyroidectomy.

Table 2. Evaluation of the effect of RAI on CSS across different patient subgroups in the PSM cohort

Stratified variables	HR for RAI therapy (95% CI)	*p*-value
Age, year		
<55	0.668 (0.112–4.005)	0.659
≥55	1.353 (0.502–3.642)	0.550
Sex		
Female	0.605 (0.177–2.066)	0.422
Male	1.946 (0.503–7.529)	0.335
Race		
White	0.982 (0.390–2.475)	0.970
Black	–	–
Other/unknown	–	–
Year of diagnosis		
2004–2009	0.718 (0.203–2.543)	0.607
2010–2015	1.716 (0.502–5.864)	0.389
Tumor size, mm		
≤20	–	–
21–40	2.478 (0.480–12.780)	0.278
>40	1.076 (0.327–3.536)	0.904
ETE		
No	–	–
Minimal ETE	–	–
Gross ETE	0.852 (0.336–2.158)	0.735
Number of PLN		
≤5	0.712 (0.119–4.260)	0.710
>5	0.842 (0.271–2.613)	0.766
Unknown	2.900 (0.301–27.910)	0.357
SEER stage		
Localized	0.948 (0.059–15.150)	0.970
Regional	0.907 (0.243–3.379)	0.884
Distant	0.658 (0.184–2.346)	0.518
AJCC stage		
I/II	–	–
III/IV	1.218 (0.504–2.945)	0.661
T		
T1/T2	0.995 (0.062–15.910)	0.997
T3/T4	1.133 (0.460–2.788)	0.787
N		
N0	1.563 (0.261–9.353)	0.625
N1	0.965 (0.362–2.571)	0.943
M		
M0	1.184 (0.429–3.266)	0.744
M1	0.311 (0.060–1.617)	0.165

Note: "–" represents Not estimable because of insufficient events within the subgroup.
Abbreviations: AJCC: American Joint Committee on Cancer; CSS: Cancer-specific survival; CI: Confidence interval; ETE: Extrathyroidal extension; HR: Hazard ratio; PLN: Positive lymph node; PSM: Propensity score matching; RAI: Radioactive iodine; SEER: Surveillance, Epidemiology, and End Results; TNM: Tumor–Node–Metastasis.

series. This scarcity of data has hindered a comprehensive understanding of CCPTC, and substantial debate remains regarding its clinical behavior, diagnostic criteria, optimal management, and prognosis. Some studies have indicated that CCPTC is associated with more aggressive features—including accelerated tumor growth, increased local invasion, and higher rates of lymph node metastasis—resulting in elevated risks of recurrence and mortality compared to classic PTC.[10,11,21,22] In contrast, other authors have reported that after adjusting for clinical and pathological factors, the columnar cell morphology itself does not independently predict worse outcomes.[11,15,19,20]

These contradictory findings complicate efforts to establish standardized treatment guidelines for CCPTC.

Radioactive iodine therapy has the potential to improve outcomes in selected PTC patients; however, its impact on the prognosis of CCPTC remains contentious. According to the 2015 ATA guidelines, CCPTC is classified as an intermediate-risk category for recurrent or persistent disease.[10] Given that CCPTC patients frequently present with higher rates of ETE, multifocality, and lymph node or distant metastases, TT followed by adjuvant RAI has been considered a reasonable therapeutic approach.[6,11,26] Nevertheless, CCPTC has been suggested to exhibit poor responsiveness to radiotherapy in some reports.[5] The 10-year overall survival rate for CCPTC is lower than that of classic PTC (approximately 89% vs. 97%).[22] In a study by Wang *et al.*, the mean survival time for CCPTC patients was 44.1 ± 33.0 months, compared with 48.9 ± 33.4 months for classic PTC patients.[21] Notably, the encapsulated or minimally invasive capsular variant of CCPTC has been associated with a more favorable prognosis, similar to that of classic PTC, whereas the extensively infiltrating form carries a poorer outcome.[14] Currently, the limited number of reported cases precludes definitive conclusions regarding CCPTC. In particular, whether RAI therapy confers a survival benefit in CCPTC patients remains unclear. Additionally, no predictive models have been established to estimate individual patient survival based on independent risk factors.

In the present analysis, we focused on evaluating whether RAI therapy influences CSS among CCPTC patients undergoing TT. To reduce confounding by indication and strengthen the validity of our findings, PSM was applied to balance baseline characteristics between treatment groups. While notable differences existed before matching, post-matching comparisons confirmed adequate comparability across all clinicopathological variables. Multivariable Cox regression revealed no significant association between adjuvant RAI and CSS in either the full cohort or the matched sample. Similarly, subgroup analyses across clinical strata—including patients with advanced age, large tumor size, advanced AJCC stage or T category, gross ETE, >5 PLN, or distant metastasis—consistently showed no CSS benefit from RAI. It should be noted, however, that the number of patients with distant metastases was limited, potentially reducing statistical power to detect a difference in this subset. In cases where metastatic lesions demonstrate iodine avidity, RAI may still offer value in achieving disease control and extending survival.

These findings should be interpreted with caution. According to current clinical guidelines, adjuvant RAI is typically recommended for patients at intermediate or high risk of recurrence following thyroid surgery, as well as for those with advanced disease—particularly in the presence of distant metastases.[27,28] In the adjuvant setting, recurrence-free survival is considered a more clinically relevant endpoint, as improvements in this outcome may eventually translate into long-term survival benefits. Given that most patients in this cohort presented with nonmetastatic disease—consistent with the typical biological behavior of CCPTC—it is reasonable to hypothesize that RAI may not be necessary for those with localized or locoregional involvement, especially in the absence of observed CSS differences. However, the lack of data on recurrence and the optimal timing of RAI administration limits the strength of this inference. Although subgroup analyses did not reveal a survival benefit from RAI, even among patients with advanced features, the small sample sizes in these subgroups may have reduced the statistical power to detect meaningful differences. It should also be noted that individuals receiving external beam radiotherapy were excluded from this study, as they were often considered to have incurable disease. These patients may have undergone multimodal treatment—including palliative surgery, RAI, external radiation, or targeted therapy—making it difficult to isolate the independent effect of RAI alone. Therefore, further investigation is needed to clarify whether RAI confers any advantage in this high-risk population.[29] Importantly, the present findings should not be generalized to patients with incurable disease.

As a visual tool that translates complex regression models into an accessible format, nomograms are commonly employed in clinical practice to support patient counseling and individualized therapeutic decision-making.[30,31] To date, no nomogram has been developed specifically to predict survival outcomes in patients with CCPTC following TT. To address this gap, we constructed a comprehensive prognostic model based on data from both the overall cohort and the PSM cohort, aiming to enhance risk stratification for this rare tumor type. By analyzing clinicopathological characteristics of CCPTC patients who underwent TT with or without adjuvant RAI in the SEER database, we performed multivariable regression to identify independent predictors for inclusion in the nomogram. Compared with the conventional AJCC staging system, our five-factor model—incorporating age, tumor size, AJCC stage, M stage, and PLN count—demonstrated improved predictive accuracy for CCPTC outcomes across both cohorts. This tool enables more precise estimation of individual prognosis and supports the design of tailored follow-up strategies.[32-34]

A fundamental limitation of this study—and one that warrants particular emphasis—is the use of CSS as

the primary endpoint. In differentiated thyroid cancer, including aggressive variants such as CCSPTC, CSS is a relatively insensitive metric for evaluating treatment efficacy due to the characteristically indolent disease course and high survival rates, even among higherrisk subgroups.[35] The 5 and 10year CSS rates in our cohort were 96.4% and 92.1%, respectively, with only 48 diseasespecific deaths (6.4%) observed over a median followup of 100 months. This low event rate substantially limits statistical power to detect modest, yet clinically meaningful, differences in survival attributable to RAI therapy. More importantly, CSS fails to capture the most clinically relevant outcome in this population: disease recurrence. For patients with intermediaterisk differentiated thyroid cancer, the primary therapeutic objective of adjuvant RAI is not necessarily prolongation of survival—which may remain uncompromised for decades—but rather reduction in the risk of locoregional recurrence, prevention of distant metastatic spread, and avoidance of repeat surgeries and additional radioiodine treatments, all of which carry cumulative morbidity and qualityoflife implications.[36,37] The 2015 ATA guidelines explicitly emphasize recurrence risk stratification as the cornerstone of adjuvant RAI decision-making.[10] Consequently, our inability to assess recurrencefree survival, structural disease persistence, or response to therapy (excellent, indeterminate, biochemical incomplete, structural incomplete) represents a critical evidence gap. This limitation is inherent to the SEER database, which does not capture longitudinal treatment response assessments, stimulated thyroglobulin levels, diagnostic or posttherapy wholebody scan findings, or structural imaging results.[38] Without these data, we cannot determine whether RAI therapy reduces the probability of clinically significant disease recurrence in CCPTC patients, nor can we identify subsets of patients who might achieve biochemical or structural complete responses to RAI. Furthermore, the lack of information regarding RAI preparation method (thyroid hormone withdrawal versus recombinant human TSH), administered activity, and number of treatment cycles precludes doseresponse analyses that might reveal efficacy in specific subgroups.[39]

Despite constraints inherent to retrospective analyses, this investigation yields several clinically relevant observations that may inform the management of patients with CCPTC. First, to the best of our knowledge, this represents the most comprehensive and methodologically robust evaluation to date, and it suggests that no clear CSS benefit even among individuals with conventionally high-risk features, including gross ETE, extensive nodal involvement, or large tumor dimensions. These observations call into question the routine administration of RAI to CCPTC patients based primarily on histologic subtype and intermediate-risk classification. Considering the considerable economic costs, potential acute and chronic toxicities—such as salivary and lacrimal gland dysfunction, myelosuppression, and secondary malignancies[40]—along with the psychological burden of radiation isolation, avoiding unnecessary RAI in carefully selected individuals presents a valuable opportunity to minimize overtreatment while maintaining favorable oncologic outcomes.

Second, our results reinforce the principle that adjuvant RAI decision-making should be guided by comprehensive risk stratification—incorporating age, tumor size, nodal burden, and extent of invasion—rather than histologic subtype alone. In the absence of a CSS benefit, the justification for RAI in CCPTC must rest on its potential to reduce recurrence, a question that remains unanswered and warrants dedicated prospective investigation. Third, the nomogram developed in this study provides a practical, individualized tool for estimating long-term CSS probabilities. By translating complex regression models into an accessible visual format, this nomogram can facilitate shared decision-making between clinicians and patients, particularly in scenarios where the utility of RAI is uncertain. For patients with predicted excellent CSS who are considering RAI omission, this tool offers empirical reassurance and may help avoid unnecessary treatment.

It is important to emphasize that these clinical implications are not synonymous with therapeutic nihilism. Rather, they call for a more nuanced, risk-adapted approach to RAI use in CCPTC—one that balances the absence of a survival benefit against the unresolved question of recurrence prevention. Until recurrence-focused evidence becomes available, the decision to administer or withhold RAI should remain individualized, grounded in multidisciplinary discussion and patient preference.

It is therefore essential to emphasize that our findings do not demonstrate that RAI is ineffective in CCSPTC; rather, they demonstrate that among patients who underwent TT, adjuvant RAI was not associated with improved CSS. These two statements are fundamentally different. For the majority of CCPTC patients who present with locoregional disease, RAI may still confer benefits in terms of recurrence prevention and biochemical remission—outcomes that cannot be evaluated using SEER data. Indeed, several large cohort studies of conventional PTC have demonstrated that RAI reduces recurrence risk without improving overall or CSS, particularly in intermediaterisk patients.[24,25] The same may be true for CCSPTC, and our results should not be misconstrued as evidence against RAI use in appropriate clinical scenarios.

Future investigations should prioritize the collection of recurrence and longitudinal response assessment data. Prospective registries specifically designed for rare thyroid cancer variants, or pooled analyses of institutional cohorts with granular clinical detail, are urgently needed to determine whether the recurrence risk reduction observed with RAI in conventional PTC extends to CCSPTC. Until such evidence becomes available, clinical decision-making regarding RAI in CCPTC should remain individualized, incorporating not only histologic subtype but also comprehensive risk stratification, including postoperative thyroglobulin levels, neck ultrasonography findings, and patient preference.

5. Conclusion

Based on real-world data from a population-based cohort, adjuvant RAI therapy did not demonstrate a significant survival advantage in patients with CCPTC who underwent TT, even among those presenting with high-risk clinicopathological features. However, given the high observed survival rates, the limited number of events, and—most critically—the complete absence of recurrence and response assessment data, these findings should not be interpreted as evidence that RAI lacks therapeutic value in this population. The question of whether RAI reduces recurrence risk or improves diseasefree survival in CCPTC remains unanswered and requires dedicated investigation. These results may inform shared decision-making discussions with patients, particularly those with localized disease who are considering RAI omission, but should not supplant comprehensive riskbenefit assessment by multidisciplinary teams. Prospective studies with longterm followup, serial response assessments, and detailed dosimetry data are essential to definitively establish the role of RAI in this rare histologic entity.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Ethical review and approval and participant consent were waived for this study due to the use of publicly available, de-identified data from the Surveillance, Epidemiology, and End Results (SEER) database, which does not involve any interaction with human subjects or access to identifiable private information.

Consent for publication

Not applicable.

Availability of data

Publicly available datasets were analyzed in this study. The original data that support the findings of this study are openly available in the software package SEER*Stat 8.4.2 (https://seer.cancer.gov/seerstat/).

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