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ORIGINAL RESEARCH

Clinical behaviors of rare variants of papillary thyroid carcinoma are associated with survival: a population-level analysis

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Objective: This study was to evaluate the risk factors of survival in patients with columnar cell variant (CCV) and encapsulated variant (ECV).

Materials and methods: The Surveillance, Epidemiology, and End Results database (1988–2013) was used to compare the characteristics of CCV and ECV with those of classic papillary thyroid carcinoma (PTC). Survival was analyzed by the Kaplan–Meier method, the log-rank test, and Cox multivariate regression. Multivariate logistic regression was used to further analyze lymph node metastases and distant metastasis. There were 765 CCV, 529 ECV, and 39,035 PTC patients. ECV tumors were similar to PTC in terms of overall survival, disease-specific survival, age, sex, and distant metastasis.

Results: Compared with PTC, CCV tumors tended to be larger, with a higher incidence rate among males and in patients ≥65 years of age. CCV was associated with higher rates of extrathyroidal extension, multifocality, lymph node examinations, and lymph node and distant metastases ($p<0.0001$). Significant differences were found in 10-year overall survival (97.14% vs 89.15%, $p<0.0001$) and disease-specific survival (99.08% vs 93.07%, $p<0.0001$) between PTC and CCV. In CCV, distant metastasis (hazard ratio 5.125, $p<0.0001$) and lymph nodal metastasis (hazard ratio 2.152, $p=0.032$) predicted a poor prognosis. After adjustment, distant metastasis was independently associated with age ≥65 years, and lymph nodal metastasis was independently associated with female sex (odds ratio [OR] 0.341 [0.234–0.496]), extrathyroidal extension (OR 2.453 [1.368–4.397]), multifocality (OR 2.168 [1.318–3.569]), size >20 mm, ≤40 mm (OR 1.851 [1.170–2.928]), and size >40 mm (OR 1.847 [1.088–3.136]).

Conclusion: ECV appears to have a similar prognosis to PTC, while CCV has a worse prognosis than classic PTC. Treatment with external beam radiotherapy and radioactive implants should be conducted carefully in patients with CCV.

Keywords: columnar cell, encapsulated variant, disease-specific survival, external beam radiotherapy, distant metastasis, SEER

Introduction

The incidence of thyroid cancer increased by 211% between 1975 and 2013 in the USA, largely due to the increased incidence of papillary thyroid cancer (PTC), which currently accounts for 80% of all cases of thyroid cancers. The overall survival (OS) rate has remained between 90% and 95% in recent decades. PTC is a low-risk histologic type of cancer and is associated with high disease-specific survival (DSS).[1–4] This type of cancer has been characterized by factors, such as age, sex, tumor size, extrathyroidal extension (ETE), nodal metastasis, and distant metastasis.[5–7]

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Among all subtypes of thyroid cancer, columnar cell variant (CCV) and encapsulated variant (ECV) are rare subtypes that have not been exclusively studied. CCV was first described in 1986, and although its biological behavior is still unclear,[8,9] CCV has been characterized by a papillary morphology, the presence of pseudostratified columnar cells, and absence of sparse colloid and psammoma bodies.[10] CCV accounts for only 0.15%–0.4% of PTC cases but is much more aggressive than classic PTC.[11–18] ECV is characterized by the presence of a complete fibrous capsule with tumor cells showing nuclear features similar to those of PTC. Although these morphological characteristics have been long recognized, ECV was formally recognized in the 2017 World Health Organization (WHO) classification of endocrine tumors.

Although the clinical characteristics of classic PTC are clearly defined, the clinical signs of CCV and ECV are currently ambiguous and remain controversial. Studies on CCV and ECV largely consist of case reports, and neither large sample analyses nor multicenter cross-sectional studies have been undertaken.

This study performed an analysis of rare variants of PTC among a large population. We compare the clinical and pathologic characteristics of CCV and ECV with those of classic PTC and identify risk factors associated with survival, distant metastases, and nodal metastasis.

Materials and methods

Data source and study participants

The data source for this study was the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI), which provides population-based cancer registries covering ~28% of the US population. This article does not contain any studies with human participants or animals performed by any of the authors. The data of this article are from the SEER Program of the NCI, which is a public database that does not require ethical approval.

Cases of PTC, CCV, and ECV from 1988 to 2013 were selected from all 18 registries using ICD-O-3 codes 8260/3 (PTC), 8343/3 (ECV), and 8344/3 (CCV). The exclusion criteria were as follows: 1) the presence of secondary malignancies, 2) the presence of other primary thyroid malignancies, 3) age <18 years, and 4) a history of previous surgery for PTC.

The demographic variables of interest included sex, age at diagnosis, and race. The clinical variables of interest included surgical therapy (lobectomy or total thyroidectomy), radiation therapy (none, radioisotopes, external-beam radiation therapy [EBRT], radioactive implant, and other), and survival status (OS and DSS) as of December 31, 2013. OS and DSS were calculated as the time in years from diagnosis until death and disease-specific death, the last date of contact with the living patient, or December 31, 2013, whichever came first. The pathologic variables of interest included tumor size of the primary cancer taken as its largest dimension, multifocality, ETE, the number of lymph nodes examined, and nodal and distant metastases. ETE was defined as tumor invasion beyond the thyroid capsule.

Statistical analysis

Summary statistics were used to describe the baseline characteristics of the patients (Table 1). Analysis of variance and the chi-square test were used to analyze categorical and continuous variables, respectively. OS and DSS were analyzed using the Kaplan–Meier method, and the log-rank test was used to determine whether differences in survival were statistically significant (Figure 1). A Cox proportional hazards regression model was built to evaluate the effects of variables on cancer mortality in CCV patients, which was subsequently adjusted for a multivariate analysis of patient characteristics and tumor characteristics. The hazard ratios (HRs) for the relationships between each variable and DSS were calculated using a binary Cox regression model. Univariate and multivariate logistic regression models were used to evaluate independent predictors of lymph mode metastasis and distant metastasis in CCV. Variables with $p<0.05$ were considered statistically significant.

Our analyses were performed with SPSS v19 (SPSS, Inc., Chicago, IL, USA) and SAS software version 9.2 (SAS Institute, Cary, NC, USA). Because SEER data reflect public and de-identified information, this study was considered exempt from institutional review board approval at our institution.

Results

There were 529 cases of ECV, 765 of CCV, and 39,035 of classic PTC diagnosed during the study period. Patients with PTC were followed for up to 26 years, while ECV and CCV patients were followed for up to 13 years. No published systematic reviews or prospective analyses have been found with regard to the use of EBRT in CCV patients, and the Database of Abstracts of Reviews and Effects yielded no results. This lack of data and the conflicting reports on EBRT in CCV prompted this summary of existing evidence to better inform clinicians.

Characteristics

The clinical and pathological characteristics of the patients are summarized in Table 1. Compared with classic PTC, CCV more frequently affected patients aged ≥65 years old (23.53% vs 11.84%, $p<0.0001$) and males (25.88% vs 22.51%, $p=0.0272$). CCV tumors tended to have a larger mean size

Table 1 Clinical characteristics and pathologic characteristics of classic PTC compared with those of the CCV and ECV

Characteristics	Classic PTC, N=39,035	ECV, N= 529	X^2	*p*-value	CCV, N=765	X^2	*p*-value
Age (years)			2.1384	0.3433		102.74	<0.0001
Mean ± SD	46.55±14.31	46.65±13.85			51.77±15.69		
≥18–44	18,189 (46.60)	256 (48.39)			264 (34.51)		
≥45–64	16,226 (41.57)	204 (38.56)			321 (41.96)		
≥65	4620 (11.84)	69 (13.04)			180 (23.53)		
Size (mm)			20.5867	0.0001		222.96	<0.0001
Mean ± SD	17.82±16.77	21.56±27.76			26.40±20.00		
≤10	14,338 (36.73)	150 (28.36)			155 (20.26)		
>10–20	12,967 (33.22)	182 (34.40)			227 (29.67)		
>20–40	9072 (23.24)	146 (27.60)			243 (31.76)		
>40	2658 (6.81)	51 (9.64)			140 (18.30)		
Sex			0.0090	0.9243		4.88	0.0272
Female	30,248 (77.49)	409 (77.32)			567 (74.12)		
Male	8787 (22.51)	120 (22.68)			198 (25.88)		
Race			9.6812	0.0215		4.37	0.2241
Black	1721 (4.41)	31 (5.86)			35 (4.58)		
White	31,857 (81.61)	446 (84.31)			641 (83.79)		
Others	5012 (12.84)	49 (9.26)			79 (10.33)		
Unknown	445 (1.14)	3 (0.57)			10 (1.31)		
Surgery			8.7350	0.0031		7.34	0.0067
Lobectomy	2280 (5.84)	47 (8.88)			27 (3.53)		
Thyroidectomy	36,755 (94.16)	482 (91.12)			738 (96.47)		
Lymph nodes examination			71.5909	<0.0001		36.60	<0.0001
Examined	23,330 (59.77)	220 (41.59)			540 (70.59)		
Not examined	15,705 (40.23)	309 (58.41)			225 (29.41)		
Radiation			8.3272	0.0803		199.46	<0.0001
None	16,335 (41.85)	244 (46.12)			211 (27.58)		
Radioisotopes	21,069 (53.97)	274 (51.80)			482 (63.01)		
External-beam radiation therapy	357 (0.91)	2 (0.38)			41 (5.36)		
Radioactive implants	443 (1.13)	3 (0.57)			14 (1.83)		
Unknown	831 (2.13)	6 (1.13)			17 (2.22)		
Overall survival	96.98% (37,856/1179)	96.03% (508/21)	0.090	0.765	89.02% (681/84)	174.85	<0.0001
10-year	97.14% (37,920/1115)	96.22% (509/20)	0.111	0.739	89.15% (682/83)	180.28	<0.0001
Disease-specific survival	99.02% (38,654/381)	98.87% (523/6)	0.0079	0.9291	93.07% (712/53)	174.84	<0.0001
10-year	99.08% (3864/361)	98.87% (523/6)	0.005	0.944	93.07% (712/53)	281.81	<0.0001
Multifocality			29.1761	<0.0001		311.67	<0.0001
Unifocal	16,505 (42.28)	285 (53.88)			177 (23.14)		
Multifocal	10,992 (28.16)	125 (23.63)			136 (17.78)		
Unknown	11,538 (29.56)	119 (22.50)			452 (59.08)		
Extrathyroidal extension			45.8179	<0.0001		409.64	<0.0001
Extrathyroidal	8157 (20.90)	47 (8.88)			392 (51.24)		
Intrathyroidal	30,878 (79.10)	482 (91.12)			373 (48.76)		
Lymph nodal metastasis			79.6437	<0.0001		59.21	<0.0001
≥ Positive lymph nodes	14,019 (35.91)	91 (17.20)			378 (49.41)		
No positive lymph node	25,016 (64.09)	438 (82.80)			387 (50.59)		
Distant metastasis			1.0505	0.3054		46.68	<0.0001
Distant metastasis	300 (0.77)	2 (0.38)			23 (3.01)		
No distant metastasis	38,735 (99.23)	527 (99.62)			742 (96.99)		

Note: Percentages total 100% by column.
Abbreviation: CCV, columnar cell variant; ECV, encapsulated variant; PTC, papillary thyroid carcinoma.

than PTC tumors (26.40±20.00 mm vs 17.82±16.77 mm, $p<0.0001$), with significantly higher rates of ETE (51.24% vs 20.90%, $p<0.0001$) and nodal metastasis (49.41% vs 35.91%, $p\leq0.0001$). In addition, CCV patients had more regional lymph nodes than PTC patients (70.59% vs 59.77%, $p<0.0001$), and CCV patients were 4 times more likely to have distant metastasis than PTC patients (3.01% vs 0.77%, $p<0.0001$). CCV patients were more likely to undergo total

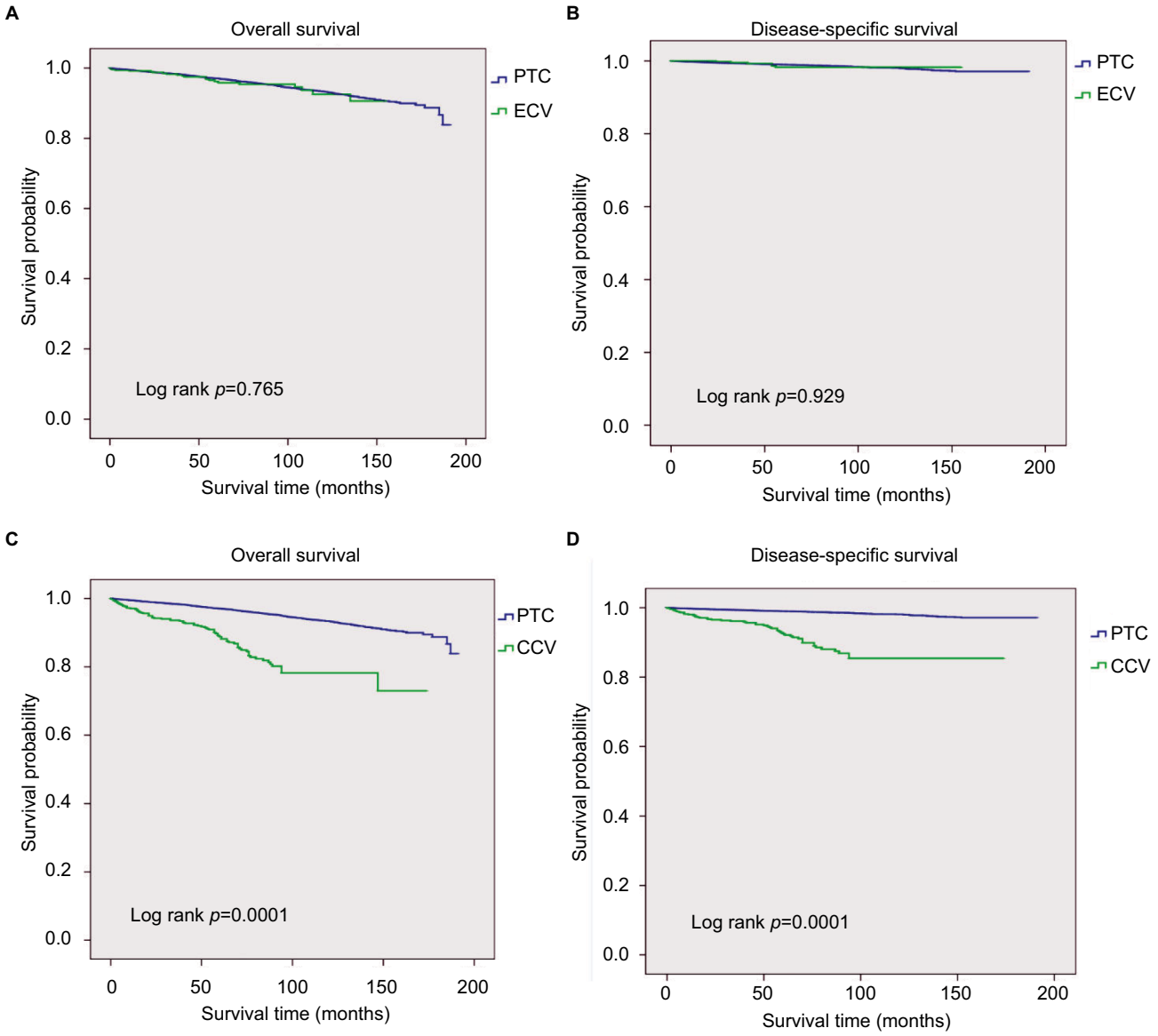

Figure 1 OS and DSS of patients of thyroid carcinoma.
Notes: (**A**) Kaplan–Meier analysis of OS between PTC and ECV; (**B**) Kaplan–Meier analysis of DSS between PTC and ECV; (**C**) Kaplan–Meier analysis of OS between PTC and CCV; (**D**) Kaplan–Meier analysis of DSS between PTC and CCV.
Abbreviations: CCV, columnar cell variant; DSS, disease-specific survival; ECV, encapsulated variant; OS, overall survival; PTC, papillary thyroid carcinoma.

thyroidectomy (96.47% vs 94.16%, p=0.0067) than PTC patients. However, significantly lower rates of multifocality were observed among CCV patients (17.78% vs 28.16%, p<0.0001).

The age and sex of ECV and PTC patients were similar. The mean tumor size among classic PTC cases was smaller than that among ECV cases (17.82±16.77 vs 21.56±27.76, p<0.0001). Among patients whose lymph nodes were examined (41.59% vs 59.77%, p<0.0001), nodal metastases were most common among PTC patients (17.20% vs 35.91%, p<0.0001). The rate of ETE in classic PTC patients was 2.35-fold higher than ECV patients (20.90% vs 8.88%, p<0.0001). No differences were found between ECV and PTC patients with respect to the rates of radiation (radioactive iodine [RAI] 51.80% vs 53.97%, p=0.0803) and distant metastasis (0.38% vs 0.77%, p=0.3054). However, PTC patients were more likely to undergo total thyroidectomy vs lobectomy than classic ECV patients (94.16% vs 91.12%, p=0.0031).

Survival

All-cause mortality occurred in 10.98% of CCV patients (n=84), 3.97% of ECV patients (n=21), and 3.02% of PTC patients (n=1179), while disease-specific mortality occurred in 6.93% of CCV patients (n=53), 1.13% of ECV patients

(n=6), and 0.98% of classic PTC patients (n=381). The 10-year DSS rates for CCV, ECV, and classic PTC patients were 93.07%, 98.87%, and 99.08%, respectively, and the univariate analysis of survival revealed no association between ECV and PTC in terms of OS and DSS. However, patients with CCV tended to have lower rates of OS and DSS than patients with PTC (10-year OS: 89.15% vs 97.14%, $p<0.0001$, 10-year DSS: 93.07% vs 99.08%, $p<0.0001$). In comparing these 2 subgroups, CCV patients exhibited significantly worse OS and DSS rates ($p<0.0001$; Figure 1).

Multivariate survival analyses for risk factors of 10-year DSS

Cox proportional hazards models were applied to quantify the prognostic significance of demographic features, tumor factors, and treatment, including adjustments for competing risk factors (Table 2). ECV and CCV differed in terms of 10-year DSS. The univariate and multivariate analyses of survival revealed no association between OS and DSS in ECV. An age >45 years remained a risk factor and age >65 years remained the strongest risk factor for 10-year DSS in CCV (HR=5.93 and 10.70; $p=0.018$, $p=0.002$). CCV patients with EBRT and radioactive implants, nodal metastasis, and distant metastasis had higher risks associated with 10-year DSS (HR=3.77, 2.15, 5.13, $p<0.05$, respectively).

Table 2 Cox multivariate regression analyses of factors associated with 10-year DSS among 765 patients with CCV, SEER (1988–2013)

Risk factor	HR	95% CI	*p*-value
Age ≥45 years	5.927	1.350–26.030	0.018
Age ≥65 years	10.704	2.425–47.254	0.002
EBRT	3.772	1.235–11.521	0.020
Radioactive implants	4.918	1.249–19.362	0.023
Lymph nodal metastases	2.152	1.067–4.341	0.032
Distant metastases	5.125	2.381–11.032	<0.0001

Notes: References: age ≤45 years; no radiation; localized disease with no lymph node metastasis; no distant metastases.
Abbreviations: CCV, columnar cell variant; DSS, disease specific survival; EBRT, external-beam radiation therapy; SEER, Surveillance Epidemiology and End Results.

Predictors of local nodal metastasis and distant metastasis

In patients with CCV, distant metastasis was independently associated with age ≥65 years (odds ratio [OR] 5.6 [1.57–20.07]). Local nodal metastasis was independently associated with female sex (OR 0.341 [0.234–0.496]), ETE (OR 2.453 [1.368–4.397]), multifocality (OR 2.168 [1.318–3.569]), size >20 mm and ≤40 mm (OR 1.851 [1.170–2.928]), and size >40 mm (OR 1.847 [1.088–3.136]) (Table 3).

Discussion

To our knowledge, this study is the first large population-level analysis of encapsulated and columnar cell variants of PTC. Although CCV is known to be more aggressive and ECV to be indolent compared with classic PTC, controversy remains with regard to their prognoses.[11,12,15,18–22] ECV was defined recently in the WHO classification of endocrine tumors.[20] Most cases of CCV show a poor prognosis and high mortality.[19] However, some cases of CCV, characterized as typically small, circumscribed or encapsulated tumors similar to ECV, have shown a more optimistic prognosis.[10,23] Because previous studies regarding these rare variants largely consist of case reports and single-institution cohorts, we collected hundreds of cases from the SEER to define the relationships between clinicopathological characteristics and the DSS rates of these variants.

Table 3 Logistic multivariate regression analyses of factors associated with nodal metastases and distant metastases among 765 patients with CCV, SEER (1988–2013)

CCV	*p*-value (lymph nodal metastasis)	OR (CI)	*p*-value (distant metastasis)	OR (CI)
≥65 (years)			0.0080	5.609 (1.568–20.066)
White	0.0100	3.139 (1.315–7.494)		
Others	0.1505	2.051 (0.770–5.458)		
Unknown	0.1435	3.247 (0.670–15.734)		
Female	<0.0001	0.341 (0.235–0.496)		
Extrathyroidal	0.0026	2.453 (1.368–4.397)		
Multifocal	0.0023	2.168 (1.318–3.569)		
Unknown	0.1042	1.707 (0.896–3.255)		
>10–20 (mm)	0.0996	1.467 (0.930–2.314)	0.7851	0.679 (0.042–11.000)
>20–40 (mm)	0.0086	1.851 (1.170–2.928)	0.0935	5.868 (0.742–46.419)
>40 (mm)	0.0230	1.847 (1.088–3.136)	0.0553	7.717 (0.954–62.392)

Notes: References: age 18–44 years; Black; male sex; intrathyroidal; unifocal; tumor size ≤10 mm.
Abbreviations: CCV, columnar cell variant; SEER, Surveillance Epidemiology and End Results.

We found that some patients with CCV exhibited more aggressive features than patients with classic PTC, including ETE, lymph node examination, and nodal and distant metastases. Compared with classic PTC, ECV is characterized by lower rates of ETE, lymph nodal examination, and nodal metastasis. In our study, ECV had a similar rate of survival, whereas CCV had a lower rate of survival than classic PTC. Although no association was found between ECV and OS or DSS, our study was underpowered to detect such differences. However, in CCV patients, we found that age ≥45–64 years, age >65 years, EBRT, radioactive implants, and lymph nodal and distant metastases were associated with 10-year DSS.

Surprisingly, our survival analysis of CCV revealed that ETE, tumor size, and multifocality were not risk factors of 10-year DSS, which completely contradicts previous studies on PTC. Nevertheless, because CCV exhibits more aggressive behavior than classic PTC, we postulate that patients with CCV may experience higher rates of tumor recurrence and mortality. These results may have important clinical implications at the operative level. The management of CCV is controversial, and the current guidelines of the American Thyroid Association recommend total thyroidectomy or near-total thyroidectomy and lobectomy, central lymphadenectomy, and postoperative RAI as indicated.[13] Total thyroidectomy or near-total thyroidectomy and lobectomy did not result in a significant difference in survival in our study. However, the rates of definitive hypoparathyroidism and recurrent laryngeal nerve injury following total thyroidectomy and total thyroidectomy associated with routine central lymph node dissection were higher than that after lobectomy and total thyroidectomy.[24,25] Patients have been treated by these 2 types of surgeries in our studies. In addition, a subgroup analysis indicated that operative treatment may be related to decreased effects of ETE, multifocality, and tumor size. We assumed that columnar-cell histology inherently represents a more aggressive variant of PTC,[26] and therefore, nodal and distant metastases were risk factors for survival in our study. Univariate analysis after multivariate adjustment revealed that male sex, ETE, multifocality, and tumors size >4 cm were associated with higher risks of nodal metastasis, whereas age >45 years was the only risk factor for distant metastasis. Therefore, due to the successful use of appropriate surgical modalities, tumor size and multifocality would not have a significant effect on survival.

EBRT is typically reserved as a last resort after surgery and RAI have been attempted.[21] Some studies revealed that EBRT has been traditionally used to treat incompletely resected tumors, unresectable diseases, and aggressive variants, and to reduce the risk of locoregional recurrence.[27,28] Other retrospective reviews failed to show any differences in loco-regional control and survival between patients who had received EBRT and those who had not.[29] Interestingly, EBRT and radioactive implants were risk factors for 10-year DSS in CCV patients according to our analysis. Patients treated with EBRT had visibly more aggressive tumor characteristics compared with patients who had not undergone EBRT. Sometimes, the risk of recurrence depends on ETE, patient age, and tumors with a reduced iodine uptake.[30–34] In our study, patients who underwent EBRT showed significantly higher rates of aggressive characteristics, such as age ≥65 years, lymph node metastasis, and distant metastasis. Therefore, we suspect that EBRT is limited in its ability to improve survival time and is also a risk factor for 10-year DSS. Future research on CCV is needed to further elucidate this issue.

Preoperative diagnosis of CCV is difficult,[35] and such diagnosis should be more clearly established. CCV tumors have unique pathologic characteristics and are composed of pseudostratified columnar cells, some of which may include neoplastic cells with elongated nuclei, hyperchromasia, and supranuclear and/or subnuclear cytoplasmic vacuolization.[36] Some studies demonstrated that certain molecular and immunophenotypic features were associated with the diagnosis and prognosis of CCV, such as the Ki67/Mib1 labeling index, $BRAF^{V600E}$, CEA, nuclear cyclin D1, CK7, CK20, CDX2, and bcl-2.[9,10,19,37] More work needs to be conducted to define the characteristics of CCV that provide the most valuable diagnostic, therapeutic, and prognostic information.

Limitations

Limitations of this study include those inherent to the SEER database, such as coding errors and limited data on CCV and ECV. CCV was first reported in the SEER database in 2001, and the mean follow-up of 10 years limits the survival analysis. Because CCV and ECV are rare tumors, our study may be underpowered to discover more subtle differences among CCV, ECV, and PTC. Despite these limitations, this is the largest study to date on this topic. Furthermore, the SEER database does not provide data regarding recurrence.

Overall, ECV and CCV are rare tumors that share various characteristics. ECV tends to be more indolent than classic PTC, whereas the CCV of papillary carcinoma shows a poor prognosis compared with conventional PTC. Early detection of CCV and aggressive intervention in patients with these tumors, especially those aged <45 years old, could lead to more favorable outcomes. Furthermore, CCV patients should be carefully treated with EBRT.

Conclusion

ECV appears to have a prognosis similar to that of classic PTC, while CCV has a worse prognosis than classic PTC. Treatment with EBRT and radioactive implants should be conducted carefully in patients with CCV.

Acknowledgments

This study used the SEER database. The interpretation and reporting of these data are the sole responsibilities of the authors. The authors acknowledge the efforts of the applied Research Program, NCI; the Office of Research, Development and Information, and the Surveillance, Epidemiology and End Results (SEER) Program tumor registries in the creation of this database.

Author contributions

SW conceived and designed the study, CJ performed data collection and analysis, TC helped with construction and manuscript writing, JL contributed to the discussion, XZ supervised this data, SH contributed to the discussion, SL interpreted the data, and JW participated in the design of the study. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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