Original Article

Survival advantage of radiotherapy and nomogram for patients with pulmonary neuroendocrine neoplasms: a propensity score-matched Surveillance, Epidemiology, and End Results database study

Jingtao Tong[1]^, Kaitai Liu[1]^, Guodong Xu[2]^, Wei Shen[3]^, Robert A. Ramirez[4], Qinning Wang[2], Hang Chen[2], Lu Zheng[1], Quan Xu[1], Hui Zhang[1]

[1]Department of Radiation Oncology and Chemotherapy, The Affiliated Lihuili Hospital of Ningbo University, Ningbo, China; [2]Department of Thoracic Surgery, The Affiliated Lihuili Hospital of Ningbo University, Ningbo, China; [3]Department of Pulmonary and Critical Care Medicine, The Third People's Hospital of Cixi, Ningbo, China; [4]Department of Internal Medicine, Division of Hematology and Oncology, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA

Contributions: (I) Conception and design: J Tong, K Liu; (II) Administrative support: K Liu, G Xu; (III) Provision of study materials or patients: Q Wang, H Chen, Q Xu; (IV) Collection and assembly of data: W Shen, L Zheng; (V) Data analysis and interpretation: J Tong, H Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kaitai Liu, PhD. Department of Radiation Oncology and Chemotherapy, The Affiliated Lihuili Hospital of Ningbo University, 57 Xingning Road, Yinzhou District, Ningbo 315040, China. Email: lkt1982@126.com.

Background: The standard treatment for pulmonary neuroendocrine neoplasms (pNENs) is surgery in the early stage and is generally determined according to the histologic type and stage. Radiotherapy (RT) is a treatment option for locally advanced or unresectable lung cancers. The aim of this study was to determine the prognostic value of RT in patients with pNENs using data from the Surveillance, Epidemiology, and End Results database.

Methods: We used propensity score matching analysis to balance differences in variables between the RT and no-RT groups. Univariate and multivariate Cox proportional hazards regression analyses were used to evaluate the factors related to overall survival and cancer-specific survival (CSS). A novel nomogram was constructed, and the results were evaluated using the concordance index.

Results: A total of 7,470 cases were identified between 2000 and 2019, among whom 1,429 were placed in the RT group and propensity-score matched with those in the no-RT group at a 1:1 ratio. Age, sex, marital status, disease extension, surgery, and RT were identified as independent prognostic factors of outcome. There was no significant difference in overall or CSS between RT and no-RT patients in the surgery group (P=0.22 and P=0.72, respectively). However, RT was associated with survival benefit in the no-surgery group. According to the concordance index, the nomogram could accurately predict the prognosis of patients with pNENs.

Conclusions: Our findings indicate that RT may provide a survival benefit for patients with pNENs, particularly for those who did not undergo surgery. The nomogram produced in this study may be a used to predict the prognosis of this patient group.

Keywords: Pulmonary neuroendocrine neoplasms (pNENs); radiation therapy; propensity score matching (PSM); survival benefit; nomogram

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^ ORCID: Jingtao Tong, 0000-0001-6948-5542; Kaitai Liu, 0000-0003-1757-5591; Guodong Xu, 0000-0001-8684-6485; Wei Shen, 0009-0003-1955-4353.

Introduction

Pulmonary neuroendocrine neoplasms (pNENs), a common type of neuroendocrine neoplasm (NEN) and originate from pulmonary neuroendocrine cells (1). They account for approximately 25% of all primary lung tumors and for 20–25% of primary NENs (2,3). According to the World Health Organization (2015), pulmonary NENs are mainly classified into four categories: typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC) (4). Moreover, carcinomas with both neuroendocrine carcinoma (NEC) and non-small cell carcinoma components have also been detected (4). Typical and atypical carcinoids are well differentiated and low-grade and intermediate-grade lesions, respectively. They are classified as carcinoid tumors, accounting for 2% of primary lung tumors (with typical-to-atypical ratio of 10:1). In contrast, LCNECs and SCLCs are high-grade and poorly differentiated tumors associated with poor prognosis and classified as NECs (4). However, an intermediate classification between neuroendocrine tumors (NETs) and NECs has recently been reported (5). Overall, SCLCs and LCNECs account for approximately 15%, and 3% of cases, respectively (6). In the United States, the incidence and prevalence of NENs continue to rise in a linear pattern due to the improvements in detection methods and diagnostic protocols (7).

The treatment of pNEN remains controversial and is generally determined according to the histologic type and stage. Typical carcinoids are usually slow-growing, and their treatment consists mainly of surgery in the early stage and somatostatin analogs (SSA) and everolimus for advanced disease (8,9). Unlike SCLC, for which there are established treatment options, atypical carcinoid tumors and LCNECs are managed with a variety therapeutic strategy due to the lack of large-scale clinical studies (10,11). Surgical resection is the mainstay of therapy for patients with localized pNENs (10-12). Systemic treatment options for metastatic pNENs include chemotherapy, targeted therapy, immunotherapy, SSA, and peptide receptor radionuclide therapy, among others (13,14). At present, there is a lack of consensus among the treatment guidelines regarding the appropriate treatment for locally advanced disease. Radiotherapy (RT) is a core treatment option for tumors; however, the role of RT in the treatment of pNENs remains unclear. A few prospective trials and meta-analyses involving patients with limited-stage SCLC have indicated that RT is effective against poorly differentiated tumors and useful as a radical therapy for local or advanced tumors (15,16). Yet, small-scale studies have yielded conflicting results regarding the optimal RT option for the other stages of SCLC, atypical carcinoid tumors, LCNECs, and combined carcinomas (10,17,18). In this study, we conducted a matched-pair analysis using data derived from the Surveillance, Epidemiology and End Results (SEER) database to evaluate the survival benefit of RT for patients with pNENs, particularly atypical carcinoid tumors and NECs, according to updated pathological classifications and modern radiological staging. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-2233/rc).

Highlight box

Key findings

- Radiotherapy (RT) may provide a survival benefit for patients with pulmonary neuroendocrine neoplasms (pNENs), particularly those who did not undergo surgery.

What is known and what is new?

- Radiation is a standard approach in non-small cell lung carcinoma and limited stage small cell lung carcinoma.
- RT may confer a survival advantage for patients with pNENs, particularly atypical carcinoid tumors and neuroendocrine carcinomas.

What is the implication, and what should change now?

- RT is an effective treatment option for patients with locally advanced pNENs, especially those ineligibles for surgery.

Methods

Patients

Data of patients diagnosed with pNENs between 2000 and 2019 were extracted from the SEER database (https://seer.cancer.gov/). The inclusion criteria were as follows: (I) pathological diagnosis of atypical carcinoid tumors and NECs (International Classification of Disease for Oncology, third edition, code 8013/3, 8244/3, 8246/3, 8249/3, and 8574/3); (II) availability of key clinicopathological data, including sex, race, age, marital status, and year of diagnosis; (III) availability of clinical and pathological information, including disease stage and treatment specifics; and (IV) absence of metastasis. Ultimately a cohort of 7,470 patients was included, among which patients with atypical carcinoid tumors was 739, and 2123 patients were LCNECs. And

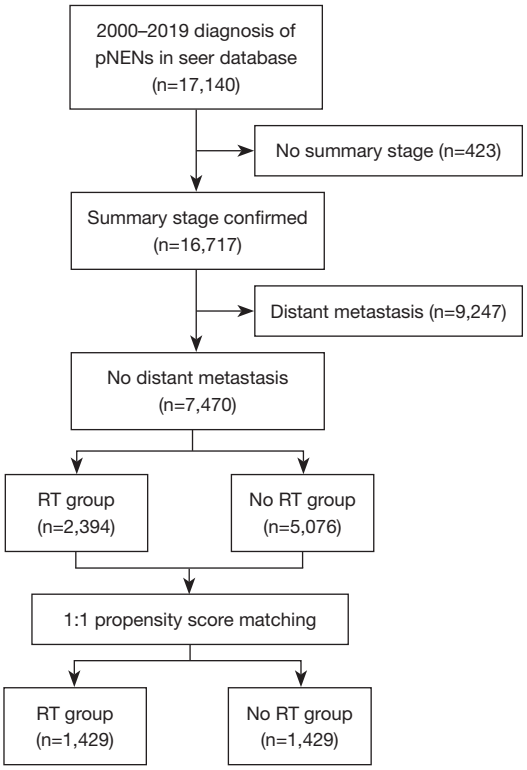

Figure 1 Flowchart depicting the patient selection process. pNEN, pulmonary neuroendocrine neoplasm; RT, radiotherapy.

among them, 2,394 patients received RT. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Covariates

The following variables were evaluated to identify the risk factors associated with atypical carcinoid tumors and NECs: age, sex, race, year of diagnosis, stage extension, marital status, surgery, chemotherapy, RT, and follow-up information. The prognostic factors for patients were determined through survival analyses. Overall survival (OS) was the primary endpoint, and cancer-specific survival (CSS) was the secondary endpoint. OS was defined as the period of time from diagnosis to death due to any reason. CSS was defined as the interval between the day of diagnosis and the day of death caused by atypical carcinoid tumors and NECs.

Propensity score matching (PSM)

PSM involves the conditional probability of assignment to a particular treatment given a vector of observed covariates (19). In this study, PSM was used to reduce the selection bias between the RT and no-RT groups of each subgroup. A logistic regression model was used to estimate propensity scores for all patients, including covariates that might have led to independent correlations between variables and RT status. The propensity score, ranging from 0 to 1, was determined using SPSS 26 (IBM Corp., Armonk, NY, USA). PSM was performed using 1:1 nearest-neighbor matching in the RT and no-RT groups to compare survival outcomes.

Statistical analyses

SPSS 26 (IBM Corp.) and R software version 4.2.3 (The R Foundation for Statistical Computing) were used for statistical analyses. A P value <0.05 indicated a statistically significant difference. The Kaplan-Meier method was used to estimate the survival rates of patients, and log-rank tests were used to assess differences between groups. Univariate and multivariate Cox proportional hazards regression analyses were used to examine the potential risk factors. Variables with a P value <0.05 or previously identified as prognostic factors were included in the multivariate analysis conducted via SPSS 26. In addition, a novel diagnostic nomogram was constructed using R software version 4.2.3 based on the independent risk factors.

Results

Patient characteristics before and after PSM

A total of 7,470 cases with complete information were enrolled in this study. Patients were further divided into RT (n=2,394) and no-RT (n=5,076) groups. After 1:1 PSM, each group comprised 1,429 patients (*Figure 1*). *Table 1* shows that PSM helped to balance the covariates and minimize the potential confounders, thus enhancing the comparability of the study groups.

Prognostic factors for survival after PSM

Univariate analysis of patients for both OS and CSS was conducted with baseline characteristics and with selected variables. The results of Cox regression analysis identified six related variables: age, sex, marital status, disease extension, surgery, and RT (*Table 2*). Kaplan-Meier curves of OS indicated that the younger patients or those with

Table 1 Baseline characteristics before and after PSM

Variable	Before PSM, n (%)			After PSM, n (%)		
	RT (n=2,394)	No RT (n=5,076)	P	RT (n=1,429)	No RT (n=1,429)	SMD
Age (years)			<0.001			0.38
<60	614 (34.67)	1,157 (65.33)		286 (48.98)	299 (51.02)	
60 to <80	1,520 (31.81)	3,258 (68.19)		945 (49.97)	946 (50.03)	
≥80	259 (28.15)	661 (71.85)		198 (51.83)	184 (48.17)	
Gender			<0.001			0.88
Male	1,230 (34.15)	2,372 (65.85)		728 (49.86)	732 (50.14)	
Female	1,164 (30.09)	2,704 (69.91)		701 (46.43)	697 (53.57)	
Race			0.02			0.51
White	1,983 (31.30)	4,353 (68.70)		1,225 (50.18)	1,216 (49.82)	
Black	289 (38.03)	471 (61.97)		135 (50.00)	135 (50.00)	
Others	122 (32.62)	252 (67.38)		69 (46.94)	78 (53.06)	
Marital status			0.52			0.68
Married	1,266 (34.15)	2,644 (67.62)		756 (50.37)	745 (49.63)	
Others	1,128 (31.69)	2,432 (68.31)		674 (49.67)	683 (50.33)	
Diagnosis year			0.002			0.71
<2010	1,343 (33.57)	2,654 (66.43)		749 (49.67)	759 (50.33)	
≥2010	1,051 (30.24)	2,424 (69.76)		680 (50.37)	670 (49.63)	
Disease extension			<0.001			0.87
Local	471 (16.22)	2,432 (83.78)		348 (50.22)	345 (49.78)	
Regional	1,437 (41.41)	2,033 (58.59)		791 (50.00)	791 (50.00)	
Distant	486 (44.30)	611 (55.70)		290 (49.74)	293 (50.26)	
Surgery			<0.001			0.42
Yes	509 (15.04)	3,393 (84.96)		457 (51.12)	437 (48.88)	
No	1,885 (52.83)	1,683 (47.17)		972 (49.49)	992 (50.51)	
Chemotherapy			<0.001			0.44
Yes	1,851 (57.81)	1,351 (42.19)		916 (50.55)	896 (49.45)	
No	543 (12.72)	3,725 (87.28)		513 (49.04)	533 (50.96)	

PSM, propensity score matching; RT, radiotherapy; SMD, standard mean deviation.

early-stage disease had better survival than did the older patients or those with late-stage disease. Moreover, married patients and female patients had better OS than did those with other marital statuses or male patients. Furthermore, patients who received RT or who underwent surgery received greater survival benefit than those who did not (*Figure 2*). Additionally, the Kaplan-Meier curves for CSS yielded similar results; however, the survival benefits were reduced in patients with regional disease after surviving for 75 months (all P values <0.05) (*Figure 3*).

In the multivariate analysis, all six variables were associated with survival. Moreover, RT was the intervention associated with better survival (OS: hazard ratio =0.793, 95% confidence interval: 0.733–0.857, P<0.001; CSS:

Table 2 Univariate analyses for prognostic factors after propensity score matching

Variable	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
<60	Reference		Reference	
60 to <80	0.562 (0.491–0.644)	<0.001	1.148 (1.029–1.281)	0.01
≥80	0.704 (0.628–0.789)	<0.001	1.546 (1.328–1.799)	<0.001
Gender				
Male	Reference		Reference	
Female	0.814 (0.753–0.880)	<0.001	0.797 (0.731–0.870)	<0.001
Race				
White	Reference		Reference	
Black	1.104 (0.919–1.327)	0.29	1.041 (0.852–1.271)	0.69
Others	1.168 (0.937–1.455)	0.12	1.204 (0.950–1.527)	0.12
Marital status				
Married	Reference		Reference	
Others	1.180 (1.091–1.276)	<0.001	1.156 (1.059–1.261)	0.001
Diagnosis year				
<2010	Reference		Reference	
≥2010	0.979 (0.904–1.061)	0.60	1.076 (0.985–1.175)	0.10
Disease extension				
Local	Reference		Reference	
Regional	0.490 (0.435–0.552)	<0.001	0.385 (0.335–0.441)	<0.001
Distant	0.674 (0.611–0.744)	<0.001	0.655 (0.589–0.728)	0.001
Surgery				
Yes	Reference		Reference	
No	2.082 (1.908–2.272)	<0.001	2.130 (1.930–2.352)	<0.001
Chemotherapy				
Yes	Reference		Reference	
No	1.065 (0.982–1.156)	0.13	0.949 (0.865–1.041)	0.27
Radiotherapy				
Yes	Reference		Reference	
No	0.844 (0.781–0.913)	<0.001	0.850 (0.779–0.928)	<0.001

CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

hazard ratio =0.797, 95% confidence interval: 0.731–0.870, P<0.001) after PSM (all P values <0.05) (*Figure 4*).

Additionally, we used Cox proportional hazards models to create nomograms that incorporated six key variables for OS and CSS. These nomograms were used to predict the 6-, 12-, and 24-month OS rates (*Figure 5*). The concordance index was applied to assess the discriminative ability of the models. The concordance index for the prediction of OS

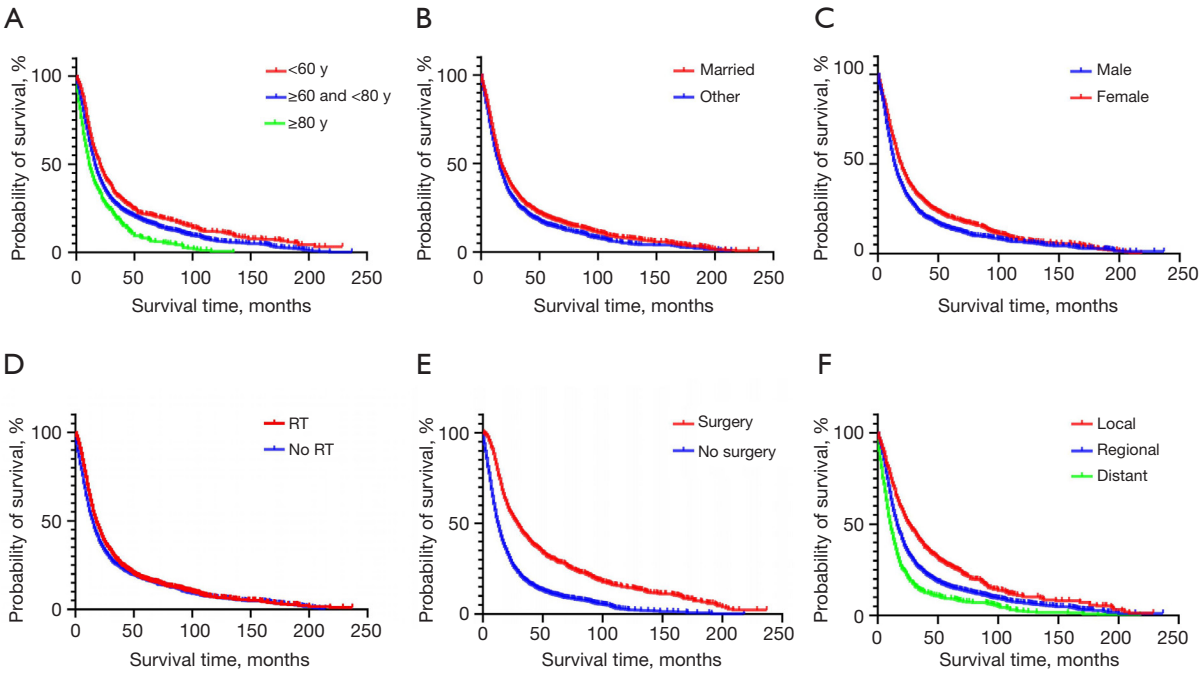

Figure 2 Kaplan-Meier OS estimates for patients grouped by (A) age, (B) marital status, (C) sex, (D) RT, (E) surgery, and (F) disease extension. OS, overall survival; RT, radiotherapy.

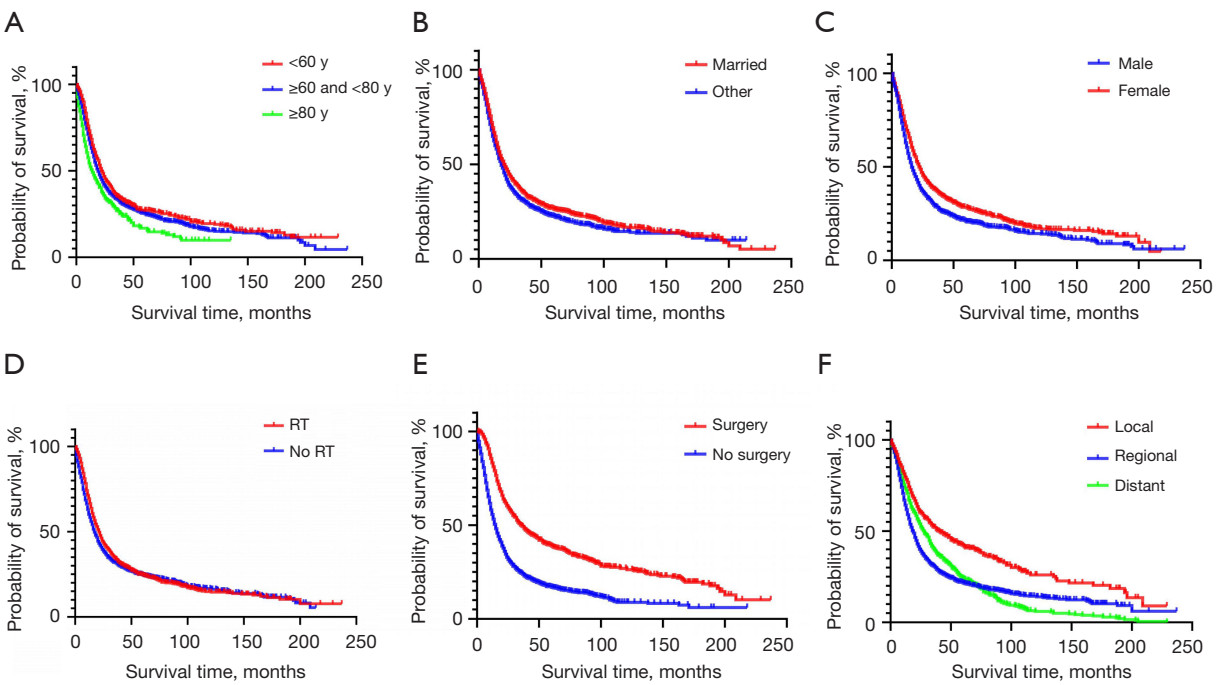

Figure 3 Kaplan-Meier CSS estimates grouped by (A) age, (B) marital status, (C) sex, (D) RT, (E) surgery, and (F) disease extension. CSS, cancer-specific survival; RT, radiotherapy.

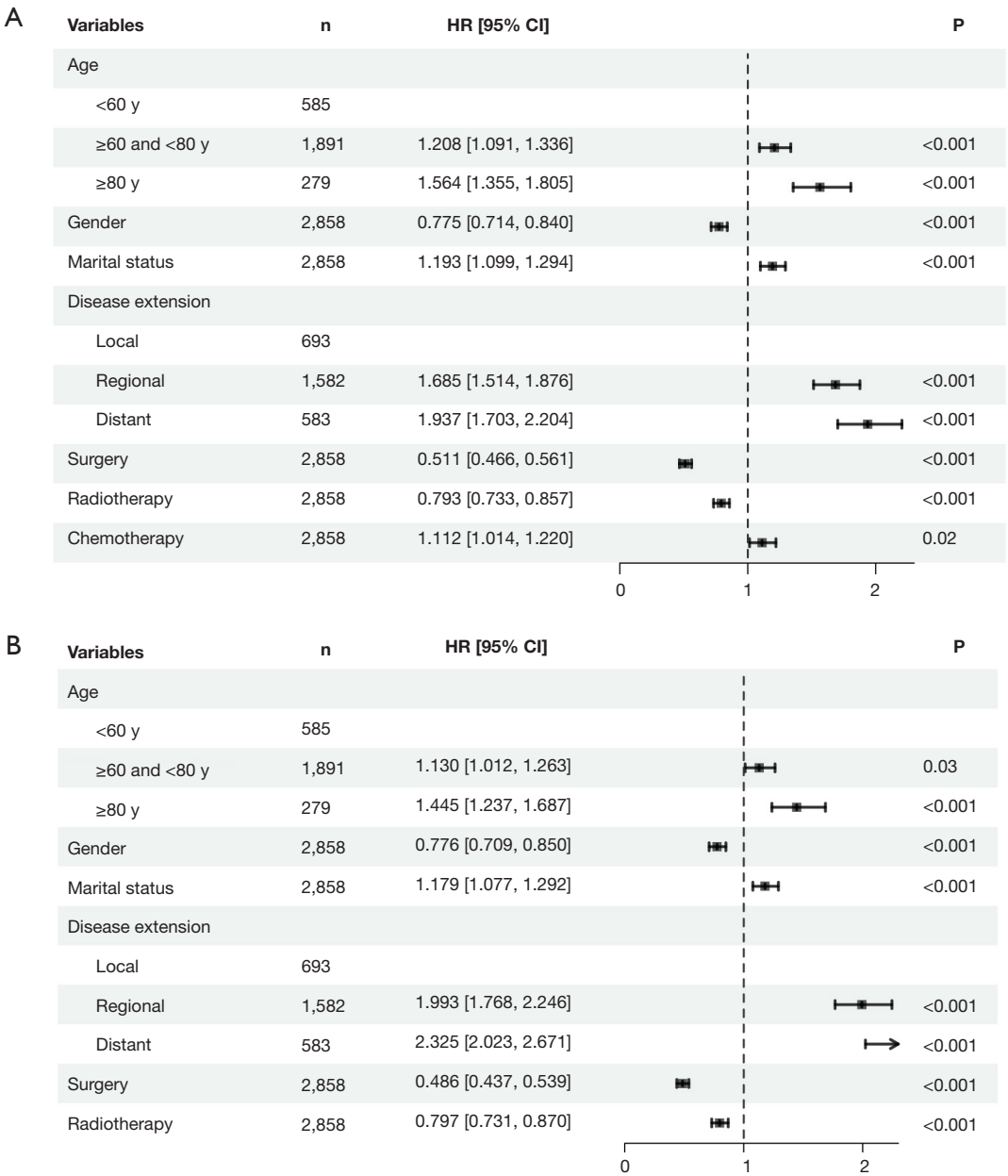

Figure 4 Forest plot of subgroup analysis for OS (A) and CSS (B) after 1:1 PSM. CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival; PSM, propensity score matching.

and CSS was 0.667 and 0.675, respectively. The nomograms demonstrated value for prognostic prediction in clinical practice, suggesting that RT is an important predictor of OS and CSS in patients with pNENs.

Subgroup analysis for OS and CSS after PSM

We further investigated the survival benefits of RT with or without surgery. Subgroup analyses of OS and CSS indicated that the patients who underwent surgery combined with RT had slightly greater survival benefits than did those without RT, both in terms of OS (OS: 32 *vs.* 27 months; P=0.22) and CSS (38 *vs.* 35 months; P=0.72). In patients without surgery, RT was associated with greater survival benefit as compared to no RT, both in terms of OS (15 *vs.* 11 months; P<0.001) and CSS (17 *vs.* 12 months;

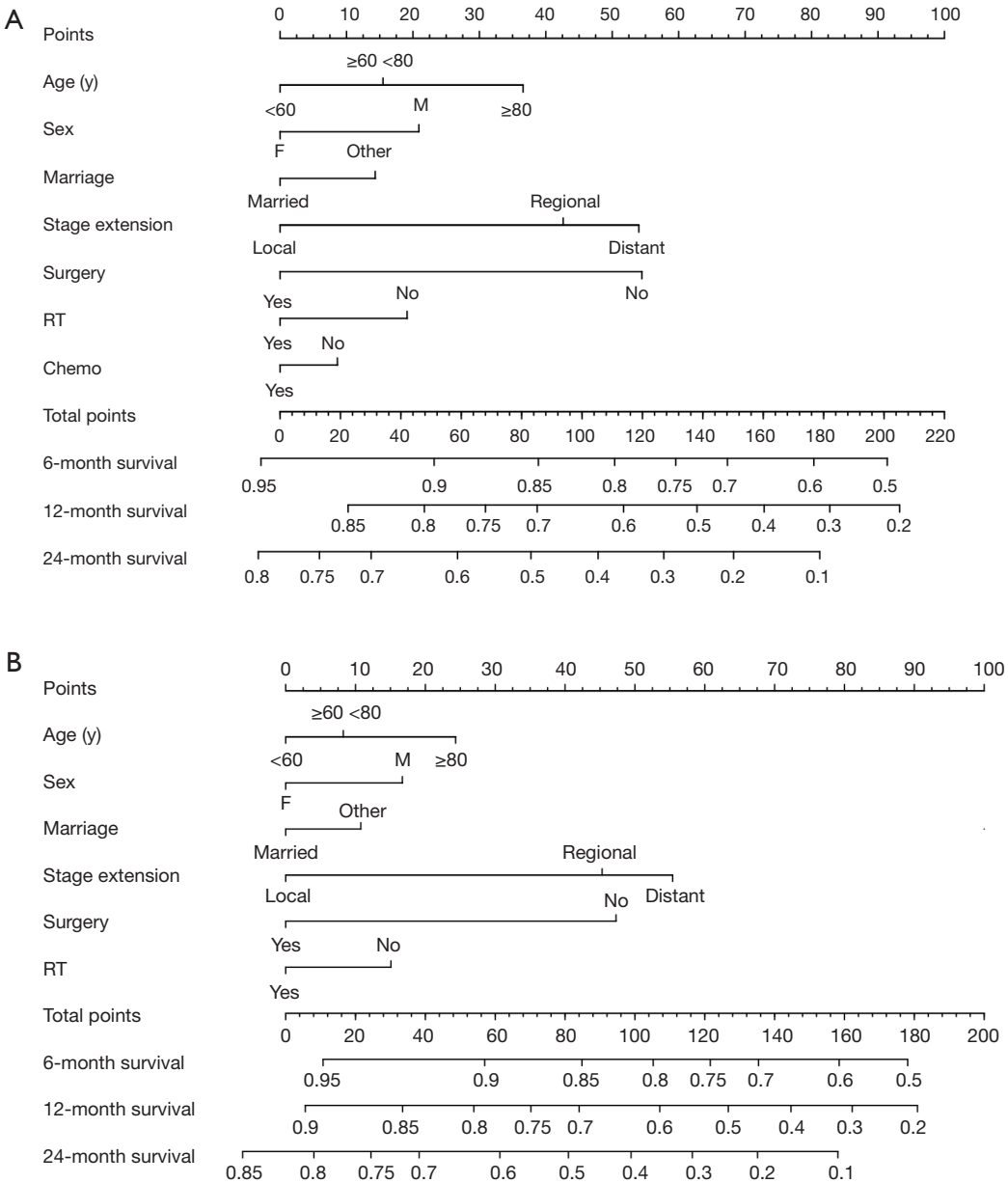

Figure 5 Nomogram for estimating the risk of overall survival (A) and cancer-specific survival (B) in patients with pulmonary neuroendocrine neoplasms. RT, radiotherapy.

P<0.001) (*Figures 6*,*7*).

Discussion

pNENs are a family of heterogeneous pulmonary neoplasms showing neuroendocrine morphology and immunophenotype, and there is limited evidence or accumulated knowledge regarding their management. RT is a common treatment option for tumors, but its role in pNENs has not been thoroughly investigated. Retrospective studies involving small samples with different classifications have reported contradictory findings (20,21). Moreover, there is no consistency across the different guidelines or an expert consensus regarding pNENs, except in SCLC. To the best of our knowledge, this is the first study that investigated the role of RT in pNENs in atypical carcinoid

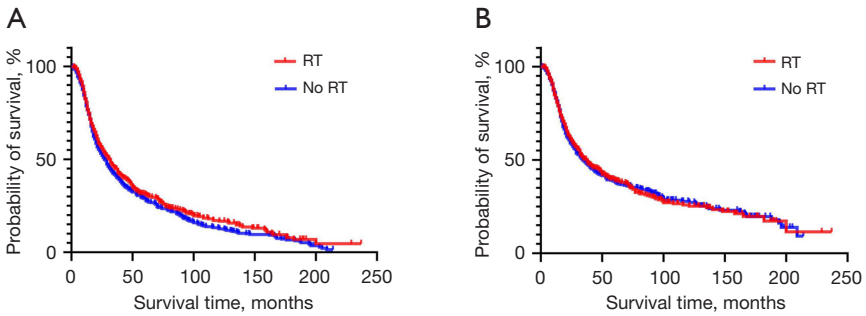

Figure 6 Kaplan-Meier (A) overall survival and (B) cancer-specific survival estimates for patients with and without RT who underwent surgery. RT, radiotherapy.

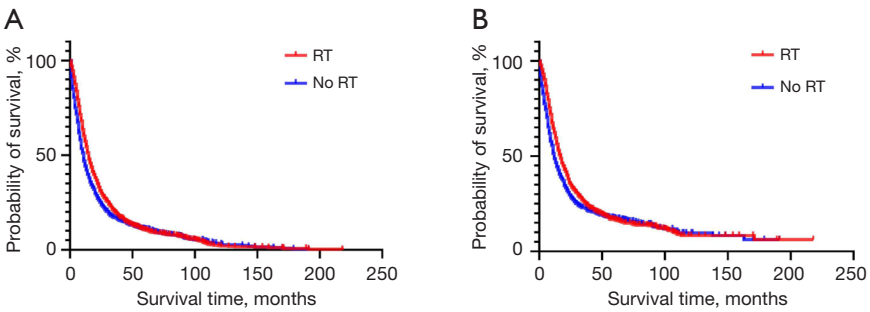

Figure 7 Kaplan-Meier (A) overall survival and (B) cancer-specific survival estimates for patients with RT and without RT who did not undergo surgery. RT, radiotherapy.

tumors and NECs using PSM. The findings demonstrated that RT offers significant benefits for patients with atypical carcinoid tumors and NECs, particularly for those who did not undergo surgery.

For resectable pulmonary atypical carcinoids, surgery is the only curative option recommended by the relevant guidelines and consensus statement. The European Neuroendocrine Tumor Society (ENETS) suggests using adjuvant RT or chemotherapy in patients with atypical carcinoids and positive lymph node status (22). However, The North American Neuroendocrine Tumor Society guidelines do not support the implementation of adjuvant RT or chemotherapy owing to a lack of evidence (22,23). A similar situation exists or pulmonary LCNECs, and the role of RT in patients with resected or regional LCNEC remains undefined (24,25). Lo *et al.* reported comparable survival outcomes of survival with surgery or stereotactic body RT in patients with early-stage pulmonary LCNEC. In their study, among patients who meet the surgical criteria, patients who underwent surgery had better survival than those who received stereotactic body RT (26). Findings based on the data obtained from SEER database suggest that RT may provide a survival benefit in patients with pulmonary LCNEC but not in those after surgery (27,28). In-depth analysis has been conducted on the genetic susceptibility and molecular pathology of SCLC (29), and prospective research studies and consensus statements have been established for its treatment. RT is critical to the treatment of local disease (2). In this study, we examined the role of RT in atypical carcinoid tumors and NECs. We found that RT was significantly associated with improved survival, particularly in patients who did not undergo surgery. Besides, we also constructed a nomogram to predict the OS of patients, which showed that in the same situation, patients who have undergone surgery, radiation therapy, chemotherapy, or combination therapy will have a longer survival time, while patients who have undergone surgery or radiation therapy will have a longer tumor related survival time.

However, there were certain limitations to our study that should be noted. First, despite the use of the PSM method, bias was inevitable due to the observational nature

of the study design. Second, we did not independently analyze the outcomes for different pathological types due to an imbalance in the number of cases. Finally, the details of RT implementation (e.g., times and fractional doses) and updated radiation techniques were not available in the database. Thus, further investigation in larger prospective studies is warranted to validate our findings.

Conclusions

Our cohort study indicated that RT may provide survival benefit in patients with atypical carcinoid tumors and NECs, particularly in those who do not undergo surgery.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-2233/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-2233/coif). R.A.R. has received consulting fees paid to him from ITM Radiopharma, Regeneron, TerSera Therapeutics, Exelixis, Novartis and Lantheus; has served on a speaker's bureau for AstraZeneca; is an unpaid Board of Directors member for the North American Neuroendocrine Tumor Society. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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