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RESEARCH

Novel scoring system guiding the incorporation of adjuvant RT for neuroendocrine neoplasms treated with surgical resection followed by chemotherapy

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Abstract

Purpose This study aimed to investigate the role of adjuvant radiotherapy (RT) in neuroendocrine tumors (NET) treated with primary resection and systemic chemotherapy and guide to incorporate adjuvant RT based on individualized prediction.

Methods We identified 4324 eligible patients using the SEER database. The most common histology was small cell carcinoma (SCC), followed by neuroendocrine carcinoma and carcinoid tumor. As the patients treated with RT were not randomly assigned, we performed propensity score matching (PSM).

Results RT was administered to 1693 (39.2%) patients who had more unfavorable features [higher proportion of SCC, N2/3 stage, and poorly/undifferentiated (PD) tumors]. After PSM, old age, male sex, SCC, advanced T or N stage, PD tumors, large tumor size, and no use of RT were all significantly associated with a poor prognosis. After multivariate analysis, the survival benefit of RT was preserved (HR 0.82, 95% CI 0.73−0.91, $p < 0.001$). Exploratory analysis suggested that primary site, PD tumors, SCC, tumor size < 2 cm, or LN negativity were the factors for which adjuvant RT appeared desirable. Further, we proposed a novel scoring system using aforementioned factors; site-thorax/genitourinary, PD tumor, tumor size < 2 cm, LN negativity. Based on individually calculated scores, we found that RT significantly increased survival in patients with scores of 2–4 but not in those with scores of 0–1.

Conclusions Our study highlights the necessity of guiding adjuvant RT for these rare types of cancer. We proposed a novel scoring system to carefully recommend RT in selected patients.

Keywords Radiotherapy · Neuroendocrine carcinoma · Surgery · Chemotherapy · SEER

Introduction

Neuroendocrine neoplasms include a heterogeneous group ranging from well-differentiated neuroendocrine tumors (NET) to poorly differentiated neuroendocrine carcinomas (NEC), which differ in origin, differentiation, and potential for metastasis (Rindi et al. 2018). Of these, the clinically relatively common one is the small cell carcinoma (SCC) of the lung, a type of high-grade NEC showing frequent distant metastases and poor survival rates. Other extrapulmonary NECs have been poorly studied due to their rarity. Therefore, therapeutic strategies for each NEC have not made significant progress to the present day (Cicin et al. 2007; Moon et al. 2021).

However, in a previously reported Surveillance, Epidemiology, and End Results (SEER) database analysis, Darasi et al. described the difference between lung NEC and extrapulmonary NECs to show that the primary site was significantly associated with overall survival (OS) even after adjusting various prognostic factors (Dasari et al. 2018). Xu et al. performed a similar analysis using the SEER database and showed that each treatment factor, such as surgery, radiotherapy (RT), and chemotherapy (CTx), was a prognostic factor for OS in the overall population (Xu et al. 2021). In a small institutional

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study for extrapulmonary SCC (EPSCC), Brennan et al. showed that definitive RT, limited disease, and prophylactic cranial irradiation were positive prognosticators and suggested that definitive chemoradiotherapy should be delivered whenever feasible (Brennan et al. 2010). Some studies have shown different response rates to platinum-based CTx respective to the primary site of origin (Terashima et al. 2012). However, there are very little data on the role of combining RT according to the primary origin sites of neuroendocrine neoplasms (Xie et al. 2017).

Moreover, incidentally found NECs may be observed in clinical situations after confirming the tumor type through resection (Sana and Saber 2015). In particular, preoperative diagnosis is difficult and often misclassified for extrapulmonary NEC (Sorbye et al. 2014). Therefore, adjuvant treatment can be considered after surgery for localized lesions because it has more curative potential than symptomatic unincidental tumors (Cheema et al. 2012). Based on the 2017 European Neuroendocrine Tumor Society guidelines, adjuvant chemotherapy may be considered in NETs in patients having unfavorable factors such as a high Ki-67 index, rapidly progressive disease, or tumors which radionuclide therapy is not indicated (Kaltsas et al. 2017). However, undertaking optimal adjuvant therapy is challenging due to scarce clinical data and recommendations in the literature (Cañizares Quisiguiña et al. 2021). For early-stage lung SCC resection, adjuvant treatment, such as systemic therapy alone for pN0, systemic therapy plus mediastinal RT for pN2, and with or without RT for pN1, is recommended (National Comprehensive Cancer Network. 2022). For other sites or grades of NEC, there are no specific guidelines other than the consideration of platinum-based CTx despite the lack of a high level of supporting evidence (Barrett et al. 2020). Especially for adjuvant RT in these cases, there is a complete lack of guidelines, thereby impeding clinical decisions.

Therefore, we conducted this study using the SEER database to investigate the role of adjuvant RT in incidentally found neuroendocrine neoplasms treated with primary resection followed by systemic CTx to reduce selection bias and include only those patients who were clinically considered available for CTx. Analysis was based on primary sites, grades, and other clinicopathologic variables. We proposed a novel scoring system to help clinicians decide on incorporating adjuvant RT based on individualized prediction. Our study could highlight the necessity of guiding adjuvant RT in the above rare situations, which remain to be elucidated.

Materials and methods

Study cohort selection process

We retrieved data from patients with non-metastatic neuroendocrine carcinoma based on the SEER 18 registry (1975–2016; Nov 2018 submission). We identified 294,810 patients with neuroendocrine carcinoma using the ICD-O-3 code list based on a previous study (Dasari et al. 2018). Of these patients, we excluded those with metastatic disease using the "Derived AJCC M stage" and selected those who received surgery at the primary site ($n = 48{,}526$). To reduce heterogeneity, 170 patients with rare histologic diagnosis, which accounts for less than 1% of the cohort, were excluded. To investigate the role of adjuvant RT in the context of receiving adjuvant CTx as routinely considered, only patients who underwent CTx were included, leaving a final total of 4324 patients for subsequent analyses. The patient selection process is shown in Supplemental Fig. 1.

Extraction of clinicopathological variables

We extracted information for the following clinicopathological variables from patient data: age at diagnosis, sex, race, marital status, insurance status, ICD-0-3 histology code, primary tumor site, tumor grade, tumor size, T and N stage according to the American Joint Committee on Cancer staging system 7th edition, number of lymph nodes examined, number of positive lymph nodes, RT, and survival. The primary tumor sites were classified into the following six groups: (1) Head and neck ("Gum and Other Mouth," "Hypopharynx," "Larynx," "Nasopharynx," "Nose, Nasal Cavity, and Middle Ear," "Oropharynx," "Salivary Gland," "Thyroid," "Tongue," "Tonsil"); (2) Thorax ("Lung and Bronchus," "Pleura," "Trachea, Mediastinum, and Other Respiratory Organs"), (3) Breast; (4) Abdomen/gastrointestinal (GI) ("Anus, Anal Canal, and Anorectum," "Appendix," "Ascending Colon," "Cecum," "Descending Colon," "Gallbladder," "Esophagus," "Hepatic Flexure," "Intrahepatic Bile Duct," "Large Intestine, NOS," "Liver," "Other Biliary," "Pancreas," "Peritoneum, Omentum, and Mesentery," "Rectosigmoid Junction," "Rectum," "Retroperitoneum," "Stomach," "Transverse Colon," "Splenic Flexure," "Sigmoid Colon," "Small Intestine"); (5) Genitourinary(GU)/gynecology(GY) ("Cervix Uteri," "Corpus Uteri," "Kidney and Renal Pelvis," "Other Female Genital Organs," "Other Urinary Organs," "Ovary," "Prostate," "Ureter," "Urinary Bladder," "Uterus, NOS," "Vagina," "Vulva"); (6) others ("Other Non-Epithelial Skin," "Soft Tissue including Heart," "Other Endocrine including Thymus"). A patient was considered to have undergone RT unless the radiation record

was "None/Unknown," "Refused (1988 +)," or "Recommended, unknown if administered."

Statistical analysis

χ^2 test and Student's *t*-test were used for comparing categorical and continuous variables between groups, respectively. Because the patients treated with RT were not assigned randomly, we used propensity score (PS) matching (PSM) after employing the multiple imputation method for missing values. The imputation process was repeated until ten different plausible datasets were obtained and pooled to stabilize the results. Using the imputed dataset, we calculated the PS to predict the likelihood that RT was administered to each patient. Based on the PS, the patients were matched at a 1:1 ratio (RT group vs. non-RT group) using nearest neighbor matching methods (caliper = 0.1).

OS was defined as the time from the date of diagnosis to the date of the last follow-up or death due to any cause. The Kaplan–Meier method was used to estimate the survival curves, and log-rank tests were used to compare the difference in survival rates in univariate analysis. The factors proven to have a significant impact on OS were included in the multivariate analysis (using the Cox proportional hazard model). To help shared decision in clinical setting, we developed the scoring system based on multivariate analysis results. The system was internally cross validated using a method of a k-fold validation. The model was applied in five folds and survival difference according to the receipt of RT was evaluated in each fold. A pooled effect size was estimated by mean hazard ratio (HR) and 95% confidence interval (CI) of five folds. A p-value less than 0.05 was considered statistically significant, and all statistical analyses were performed using R version 3.5.2 (http://www.r-project.org).

Results

Patient characteristics

The baseline characteristics of 4324 patients included in the study are presented in Supplemental Table 1. The median age of the cohort was 65 years (interquartile range [IQR], 55–72 years). The most common histology was small cell carcinoma ($n = 1971$, 45.6%), followed by neuroendocrine carcinoma ($n = 1268$, 29.3%), carcinoid tumor ($n = 440$, 10.2%). The majority of stages (available data) belonged to T1 or 2 (62.5%) and N0 (55.8%), reflecting the assumptions of our study, which intended to include incidentally confirmed cases after surgery. The mean tumor size was 2.6 cm. Most tumors were poorly differentiated/undifferentiated (78.8%), followed by well differentiated (11.3%) and moderately differentiated (9.9%). The median number of harvested and involved LNs was 10 (IQR, 0–15) and 1 (IQR, 0–3). The most frequently reported primary site was thorax ($n = 1505$, 34.8%), followed by abdomen ($n = 1344$, 31.1%) and GU/GY ($n = 1111$, 25.7%). According to our inclusion criteria, all patients received some form of CTx, but RT was administered to 1693 (39.2%) patients only.

Survival analysis

Three-year OS was 54.2% in the cohort (median follow-up 24 months, [IQR, 12–57 mo.]). Univariate analysis showed worse survival in patients with old age ($p < 0.001$), male sex ($p < 0.001$), small cell carcinoma ($p < 0.001$), advanced stage T ($p = 0.001$) or N ($p < 0.001$) stage, poorly/undifferentiated tumors ($p < 0.001$), large primary tumor size ($p < 0.001$), and tumor not originated from breast (Supplemental Table 2). In addition, the OS of the RT group was significantly inferior to the non-RT group (3-year OS 51.5% vs. 56.1%, $p = 0.011$, Fig. 1A). The results of the multivariate analysis were almost the same, except for T stage elimination from the final model through the forward step selection process. The statistical significance of the adverse impact of RT was maintained, despite the adjustment of other variables. (HR 0.82, 95% CI 0.74–0.92, $p < 0.001$, Supplemental Table 2).

Propensity-score-matched survival analysis

We noted multiple significant imbalances in comparing the baseline characteristics between the non-RT and RT groups (Table 1). Especially, RT group had more unfavorable features, including a higher proportion of SCC (56.8% vs. 38.4%), N2/3 stage (21.2% vs. 10.5%), and poorly/undifferentiated tumors (86.2% vs. 74.1%). Therefore, PS matching was used to adjust for the observed imbalances that resolved after matching (all standardized mean differences < 0.1), leaving 1273 patients in each group.

The results of the survival analysis in the PS-matched cohort are presented in Table 2. Old age ($p < 0.001$), male sex ($p < 0.001$), small cell carcinoma ($p < 0.001$, Supplemental Fig. 2), advanced T ($p < 0.001$) or N ($p < 0.001$) stage, poorly/undifferentiated tumors ($p < 0.001$, Supplemental Fig. 3), large primary tumor size ($p < 0.001$), and no RT ($p < 0.001$) were significantly associated with a poor prognosis. In particular, the 3-year OS rates were 47.8% in the non-RT group and 53.7% in the RT group ($p = 0.001$, Fig. 1B). After multivariate analysis, all the above factors, except T stage, retained statistical significance, and the

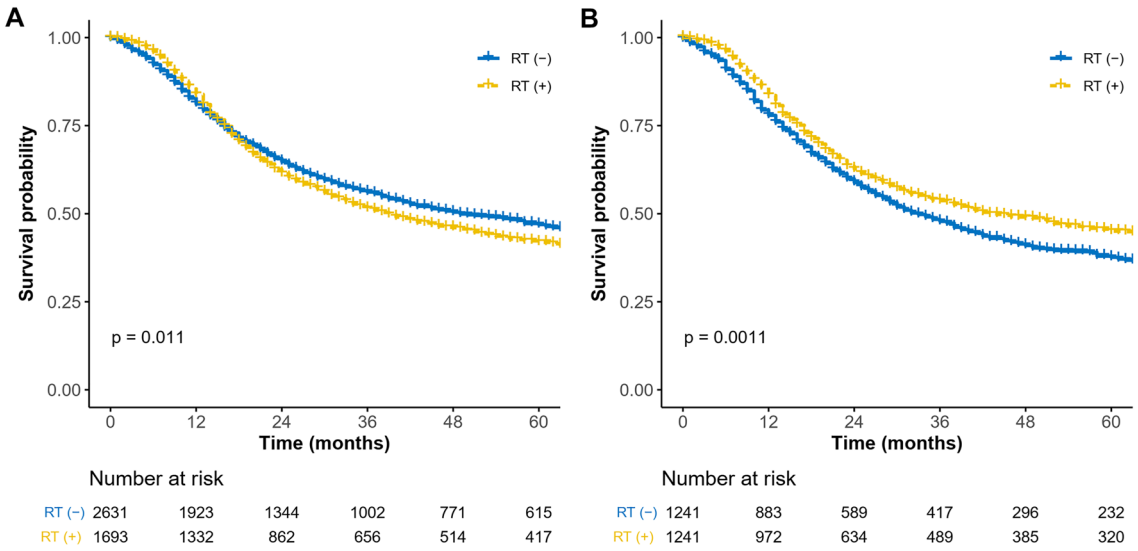

Fig. 1 Overall survival curves based on the receipt of radiotherapy in **A** all patients before matching and **B** the propensity-score-matched cohort

survival benefit of RT was also preserved (HR 0.82, 95% CI 0.73−0.91, $p < 0.001$, Table 2).

Subgroup analysis and a novel proposed scoring system for clinical application

Subsequently, we performed an exploratory subgroup analysis to identify patient groups that could benefit from adjuvant RT after the administration of CTx. Figure 2 shows exploratory analysis plotting HR and 95% CI comparing OS, based on the use of RT for each subgroup of patients.

The use of adjuvant RT had a favorable effect on SCC (HR 0.72, 95% CI 0.63–0.83, $p < 0.001$, $p < 0.0001$, Supplemental Fig. 4A), but not on other histologic types (Supplemental Fig. 4B–D). In the case of the primary site located in the thorax or GU/GY, the patients benefited from the use of RT (thorax, HR 0.81, 95% CI 0.69–0.96, $p < 0.017$; GY/GU, HR 0.82, 95% CI 0.68–0.99, $p < 0.036$), unlike the breast, head and neck, abdomen, or other sites. Site-specific exploratory forest plots are shown in Supplemental Fig. 5A–B. The benefits of RT were observed in patients with poorly differentiated tumors ($p = 0.0015$, Fig. 3A), but not in patients with low-to-intermediate grade tumors ($p = 0.24$, Fig. 3B). Older age > 65 years ($p = 0.007$), T1 ($p < 0.001$), N0 ($p = 0.001$), and tumor size < 2 cm ($p < 0.001$) were also predictors that significantly increased the OS with RT (Supplementary Table 3).

In summary, there are several experimental factors, such as primary site (thorax or GU/GY), poorly differentiated tumors, SCC, small tumor size (< 2 cm), or LN negativity, for which adjuvant RT seems desirable. To help clinical decision-making for RT, we proposed a novel scoring system based on the factors mentioned above. We stratified all matched patients by the proposed scoring system: 532 patients scored 0–1, 1665 patients scored 2–3, and 285 patients scored 4 (Fig. 4). On examining the benefits of administering adjuvant RT based on individually calculated scores, we found that RT increased survival in patients with scores 2–3 (3-year OS 46.5% vs. 51.9%, $p = 0.025$, Fig. 4C) and a score of 4 (3-year OS 47.8% vs. 71.4%, $p < 0.0001$, Fig. 4D), but not in patients with a score of 0–1 (3-year OS 51.6% vs. 51.0%, $p = 0.680$) (Fig. 4B). The scoring system was internally validated using whole dataset without PS matching. The RT benefit on OS was observed consistently in all of randomly selected five folds (HR [95% CI]; score 0–1 group, 1.01 [0.75–1.5], score 2–3 group 0.84 [0.70–1.01], score 4 group 0.75 [0.62–0.91], Supplemental Fig. 6).

Discussion

The potential benefit of incorporating adjuvant RT into primary surgery combined with systemic CTx in neuroendocrine neoplasms will probably remain controversial because these neoplasms are rare and poorly studied. Few institutional series and mainly case reports have dealt with adjuvant RT. However, considering the small number of patients in these studies and the existence of selection bias, it is still difficult to draw any definite conclusion. There is no report to date focusing on the role of adjuvant RT in these tumors. Therefore, our study is meaningful in the above respect, although there are some limitations. First, inevitable patient selection bias may have affected survival outcomes in our

Table 1 Comparison of patient characteristics according to receipt of radiotherapy before and after propensity score matching

Characteristics	Overall dataset			Propensity-score-matched group		
	RT not done ($N=2631$)	RT done ($N=1693$)	P-value	RT not done ($N=1273$)	RT done ($N=1273$)	SMD
Age						
Years, Median (IQR)	65 (56–73)	63 (53–71)	< 0.001	65 (56–72)	65 (54–73)	0.025
Sex						
Male	1380 (52.5)	800 (47.3)	0.001	638 (51.4)	611 (49.2)	0.044
Female	1251 (47.5)	893 (52.7)		603 (48.6)	630 (50.8)	
Marital status						
Single	666 (29.7)	428 (29.7)	1.0	374 (30.1)	341 (27.5)	0.059
Married	1573 (70.3)	1013 (70.3)		867 (69.9)	900 (72.5)	
Insurance						
Insured	1898 (88.1)	1135 (85.9)	0.158	1072 (86.4)	1078 (86.9)	0.04
Any medicaid	218 (10.1)	156 (11.8)		150 (12.1)	139 (11.2)	
Uninsured	38 (1.8)	30 (2.3)		19 (1.5)	24 (1.9)	
Race						
White	2240 (85.1)	1444 (85.3)	0.141	108 (8.7)	106 (8.5)	0.081
Black	243 (9.2)	139 (8.2)		65 (5.2)	86 (6.9)	
Other	141 (5.4)	109 (6.4)		1065 (85.8)	1048 (84.4)	
Unknown	7 (0.3)	1 (0.1)		3 (0.2)	1 (0.1)	
Histology						
Small cell carcinoma	1010 (38.4)	961 (56.8)	< 0.001	668 (53.8)	673 (54.2)	0.054
Carcinoid tumor	369 (14.0)	71 (4.2)		71 (5.7)	68 (5.5)	
Goblet cell carcinoid	95 (3.6)	5 (0.3)		6 (0.5)	5 (0.4)	
Mixed adenoneuroendocrine carcinoma	174 (6.6)	26 (1.5)		35 (2.8)	26 (2.1)	
Neuroendocrine carcinomas, NOS	777 (29.5)	491 (29.0)		352 (28.4)	364 (29.3)	
Atypical carcinoid tumor	65 (2.5)	41 (2.4)		37 (3)	35 (2.8)	
Adenocarcinoma c neuroendocrine differentiation	141 (5.4)	98 (5.8)		72 (5.8)	70 (5.6)	
T stage						
1	376 (29.0)	264 (34.0)	< 0.001	451 (36.3)	436 (35.1)	0.032
2	373 (28.8)	283 (36.4)		387 (31.2)	404 (32.6)	
3/4	548 (42.3)	230 (29.6)		403 (32.5)	401 (32.3)	
N stage						
0	774 (58.4)	413 (51.6)	< 0.001	683 (55)	676 (54.5)	0.016
1	412 (31.1)	217 (27.1)		374 (30.1)	383 (30.9)	
2/3	140 (10.5)	170 (21.2)		184 (14.8)	182 (14.7)	
Grade						
Well differentiated	295 (15.5)	56 (4.6)	< 0.001	80 (6.4)	73 (5.9)	0.032
Moderately differentiated	199 (10.4)	110 (9.1)		122 (9.8)	115 (9.3)	
Poorly/undifferentiated	1413 (74.1)	1040 (86.2)		1039 (83.7)	1053 (84.9)	
Primary tumor size						
< 2 cm	618 (23.5)	381 (22.5)	0.175	331 (26.7)	326 (26.3)	0.018
2–5 cm	1030 (39.1)	707 (41.8)		583 (47)	594 (47.9)	
≥ 5 cm	594 (22.6)	354 (20.9)		327 (26.3)	321 (25.9)	
Primary site						
Abdomen	1027 (39)	317 (18.7)	< 0.001	298 (24)	278 (22.4)	0.042
Breast	71 (2.7)	104 (6.1)		61 (4.9)	67 (5.4)	
Genitourinary/Gynecology	690 (26.2)	421 (24.9)		361 (29.1)	367 (29.6)	
Head and neck	29 (1.1)	125 (7.4)		29 (2.3)	29 (2.3)	

Table 1 (continued)

Characteristics	Overall dataset			Propensity-score-matched group		
	RT not done ($N=2631$)	RT done ($N=1693$)	P-value	RT not done ($N=1273$)	RT done ($N=1273$)	SMD
Thorax	802 (30.5)	703 (41.5)		480 (38.7)	488 (39.3)	
Others	12 (0.5)	23 (1.4)		12 (1)	12 (1)	
Number of						
Harvested LN, Median (IQR)	8 (0–17)	3 (0–8)	0.053	6 (0–13)	4 (0–13)	0.004
Involved LN, Mean (IQR)	1 (0–3)	1 (0–2)	< 0.001	0 (0–2)	0 (0–2)	0.02

RT radiotherapy, *SMD* standardized mean difference, *IQR* interquartile range, *LN* lymph node

study due to its retrospective nature. Second, unknown heterogeneity of CTx or RT regimens could have affected treatment outcomes, which could not be resolved due to limited information in the database. However, we used large-scale population-based data using PSM analysis to obtain a less biased comparison, and for the first time, we could show small but significant OS differences (HR 0.82, $p < 0.001$, 3-year absolute OS benefit of 5.9% in a matched cohort). Previous SEER data analysis of EPSCC by Xu and Guo similarly reported that RT resulted in better survival (HR 0.828, $p < 0.001$) after multivariate adjustment; however, they included whole patients, irrespective of resection or CTx (Xu and Guo 2021).

For decades, platinum-based CTx was considered the standard first-line treatment for neuroendocrine carcinomas (Moertel et al. 1991). However, their long-term survival was unsatisfactory, and the implementation of multimodality treatments increased. Mandish et al. reported an analysis of 5747 EPSCC patients using the National Cancer Database (Mandish et al. 2020). Overall median survival was only 1.2 years, and GI origin (HR 1.19, $p < 0.0001$) showed worse OS than GU. Notably, chemoradiation showed a decreased HR (HR 0.91, $p = 0.0363$) compared to CTx alone, consistent with our results. For organ preservation (not incidentally found), combined chemoradiation after transurethral resection of a bladder SCC provided reasonable control and preserved the quality of life (Bryant et al. 2016). Although RTx or CTx alone was beneficial, a combination of both resulted in better survival.

Although many previous studies focused on EPSCC with a poorer prognosis, another difference in our study is that we included all general NECs. Our exploratory subgroup analysis revealed that only SCC could benefit from adjuvant RT, and other histologic types may not. The need for RT may still be considered, depending on the primary site, the use of CTx, or other risk factors. Xie et al. reported 48 surgically resected NEC of the uterine cervix (Xie et al. 2017). In the entire cohort, CTx or RT was not a prognostic factor. However, trimodality therapy showed better survival than surgery alone in patients with tumors > 4 cm ($p = 0.006$). Moreover, RT for tumors with mixed histology achieved a better survival ($p = 0.01$), while an unfavorable tendency was observed for homogeneous neuroendocrine tumors. Tiffet et al. showed that adjuvant RT increased local control in a few cases of 12 thymic NET that did not receive CTx (Tiffet et al. 2003). Our supplemental data also support adjuvant RT for several experimental factors such as primary site (thorax or GU/GY) or poorly differentiated tumors. We developed a novel scoring system for comprehensively considering the desirable factors for adjuvant RT use. As shown in the Results section, our proposed scoring system could differentiate the patients who mostly derived the benefits of adjuvant RT (patients with a score equal to or more than 2) (Fig. 4). To the best of our knowledge, this is the first attempt to select a subset of patients who could be candidates for adjuvant RT after surgical resection. Interestingly, small tumor size (< 2 cm) and lymph node negativity score a point of 1 for adding adjuvant RT, which are opposite characteristics showing adjuvant RT benefit usually seen in solid cancers. Even for small and incidentally discovered lesions, the above results suggest the need for intensified adjuvant treatment because it is a tumor with a poor prognosis due to its inherent biological characteristics. If the tumor size is large or there is LN metastasis, the risk of subsequent distant metastasis is already too high, and hence, adjuvant RT may offer relatively small benefits. This aspect needs verification by various external data in the future.

In conclusion, adjuvant RT significantly improved OS rates in incidentally found neuroendocrine neoplasms treated with primary resection and systemic CTx. However, because the benefits may vary depending on various clinicopathologic characteristics, RT should be recommended for carefully selected patients (for example, patients with tumors consisting of small cell or poorly differentiated components

Table 2 Univariate and multivariate survival analysis in a propensity-score-matched group

Variables	3-year OS (%)	Univariate analysis, *P**	Multivariate analysis, *P*, HR (95% CI)†
Age			
As a continuous variable		< 0.001	0.01, 1.01 [1.00, 1.02]
≤ 65 years	58.8	< 0.001	Ref
> 65 years	42.1		0.001, 1.35 [1.14, 1.60]
Sex			
Male	44.5	< 0.001	Ref
Female	57.2		0.001, 0.82 [0.73, 0.92]
Marital status			
Single	49.2	0.492	NA
Married	51.4		
Insurance			
Insured	51.3	0.398	NA
Any medicaid	47.6		
Uninsured	43.9		
Race			
White	52.7	0.083	NA
Black	57.2		
Other	50.1		
Unknown	100.0		
Histology			
Small cell carcinoma	46.7	< 0.001	Ref
Carcinoid tumor	74.9		< 0.001, 0.46 [0.33, 0.63]
Goblet cell carcinoid	61.4		0.157, 0.49 [0.18, 1.32]
Mixed adenoneuroendocrine carcinoma	64.0		0.007, 0.55 [0.35, 0.85]
Neuroendocrine carcinomas, NOS			0.034, 0.86 [0.75, 0.99]
Atypical carcinoid tumor	50.7		< 0.001, 0.39 [0.24, 0.63]
Adenocarcinoma c neuroendocrine differentiation	77.3		0.082, 0.79 [0.60, 1.03]
T stage			
1	57.3	< 0.001	NA
2	50.3		
3/4	44.2		
N stage			
0	58.0	< 0.001	Ref
1	43.1		< 0.001, 1.83 [1.61, 2.08]
2/3	39.7		< 0.001, 2.06 [1.76, 2.40]
Grade			
Well differentiated	71.8	< 0.001	Ref
Moderately differentiated	68.1		0.149, 1.29 [0.91, 1.83]
Poorly/undifferentiated	47.4		< 0.001, 1.84 [1.37, 2.46]
Primary tumor size			
< 2 cm	57.7	< 0.001	Ref
2–5 cm	51.6		0.826, 1.02 [0.88, 1.17]
≥ 5 cm	42.5		0.002, 1.29 [1.10, 1.52]
Primary site			
Abdomen	51.4	< 0.001	Ref
Breast	83.6		< 0.001, 0.34 [0.22, 0.51]
Genitourinary/Gynecology	41.7		0.244, 1.11 [0.93, 1.34]
Head and neck	42.7		0.57, 0.90 [0.62, 1.30]
Thorax	80.3		0.454, 0.94 [0.79, 1.11]
Others	52.8		0.445, 0.76 [0.37, 1.55]
Radiotherapy			
No	47.8	0.001	Ref
Yes	53.7		< 0.001, 0.82 [0.74, 0.92]

Table 2 (continued)

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *Ref* reference, *NA* not available

**P*-value by log-rank test; †*P*-value by cox proportional hazard model with forward stepwise regression

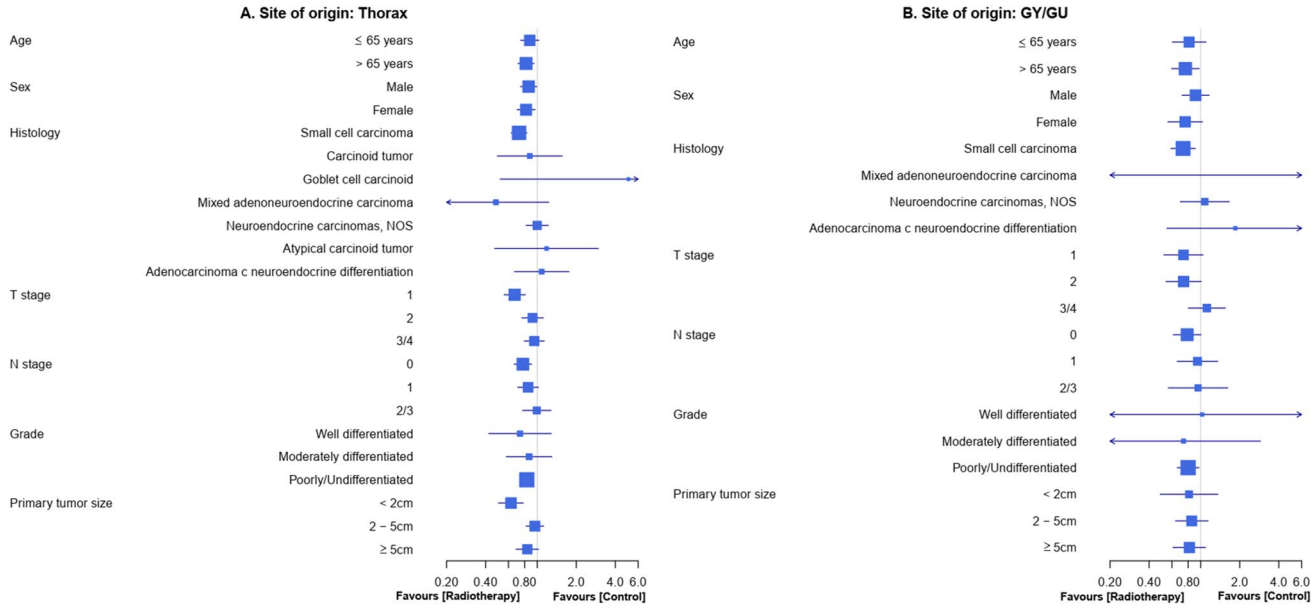

Fig. 2 Subgroup analysis evaluating overall survival benefit of adjuvant radiotherapy compared to no-radiotherapy, according to individual characteristics in the propensity-score-matched cohort

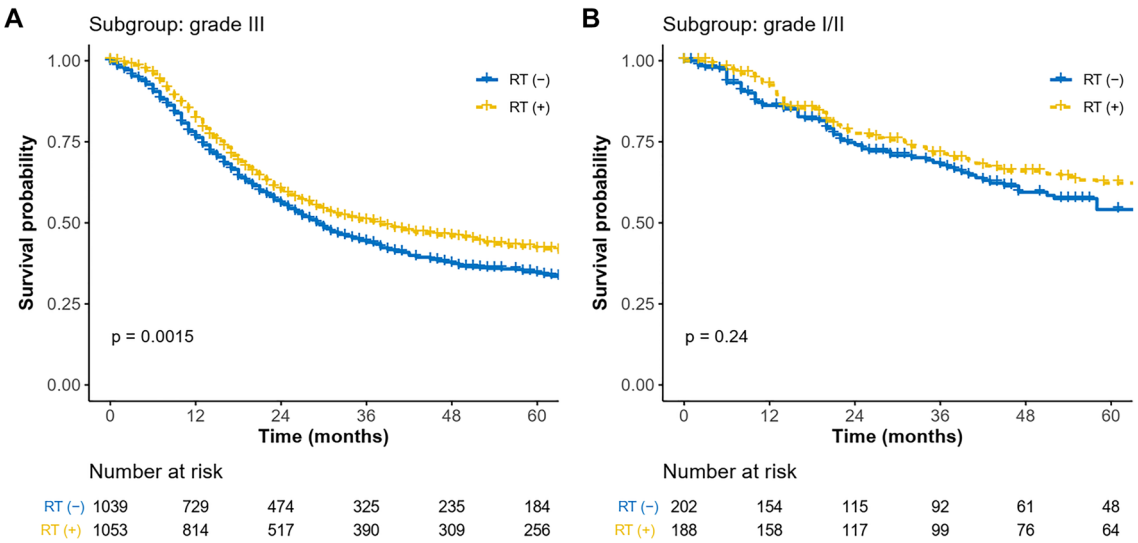

Fig. 3 Overall survival curves based on the receipt of adjuvant radiotherapy in **A** patients with grade III tumors and **B** patients with grade I–II tumors in the propensity-score-matched cohort

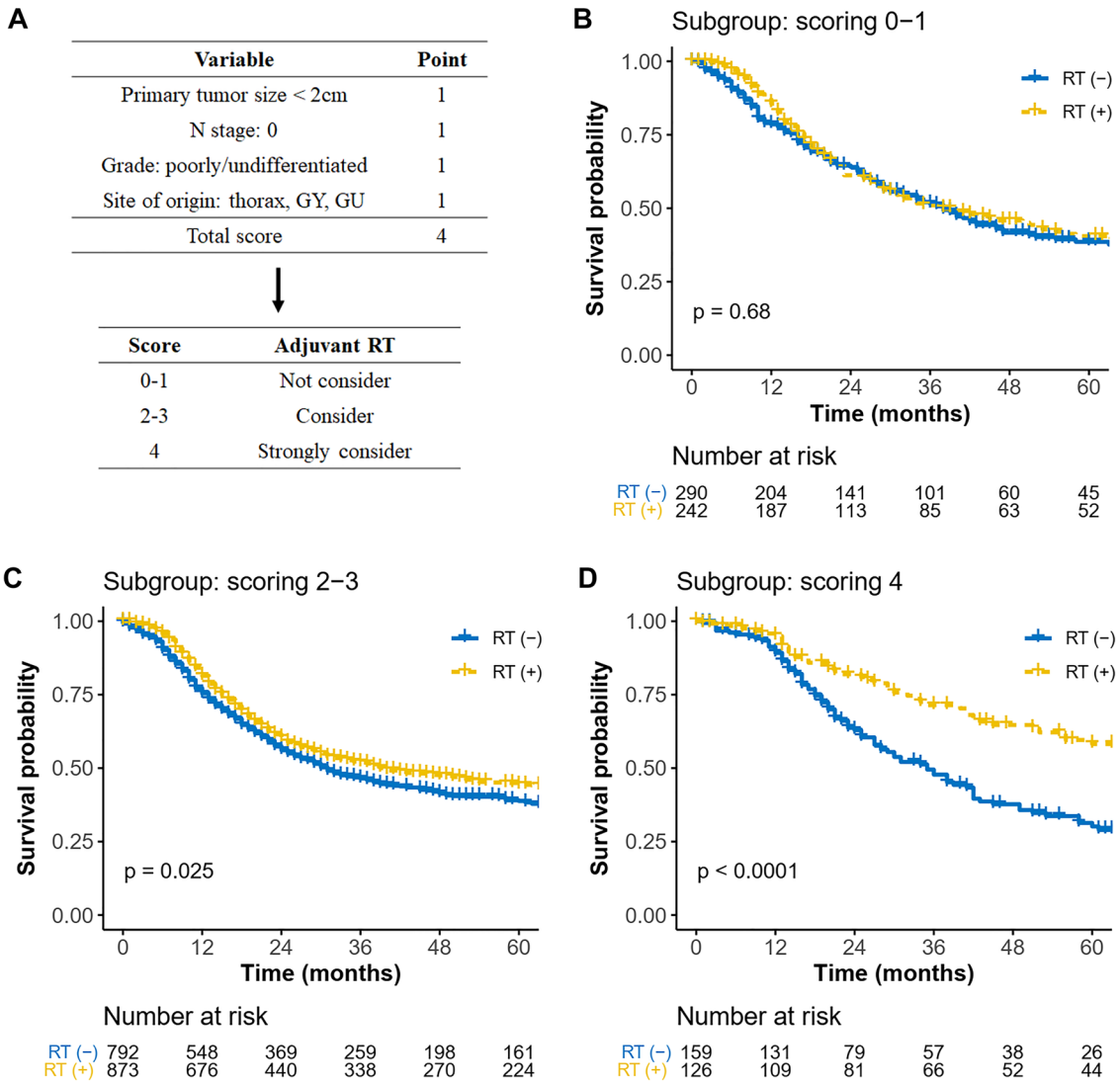

Fig. 4 Overall survival curves based on the proposed scoring system by the receipt of adjuvant radiotherapy **A** calculation of novel scoring system **B** subgroup of score 0–1, **C** subgroup of score 2–3, **D** subgroup of score 4 in the propensity-score-matched cohort

or tumors present in the thorax or GU/GY). We also successfully developed a novel scoring system that could predict survival benefits based on the administration of adjuvant RT to these rare types of cancer. Our results could be useful in practice and for designing possible related trials. This field requires multi-institutional and international cooperation to establish robust medical evidence with concerted efforts in the future.

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Data availability The datasets generated and/or analyzed during the current study are available in SEER database (SEER 18 registry (1975–2016; Nov 2018 submission).

Declarations

Conflict of interest The authors declare that no actual or potential conflict of interest exists.

Ethical approval This work was approved by the Institutional Review Board of Seoul Metropolitan Government Seoul National University Boramae Medical Center (IRB No. 07-2022-9) and performed according to the principles of the Declaration of Helsinki.

Consent to participate The informed consent was waived due to the retrospective and anonymized nature of the study by the same institutional committee of the Seoul Metropolitan Government Seoul National University Boramae Medical Center.

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