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Postoperative radioiodine therapy impact on survival in poorly differentiated thyroid carcinoma: a population-based study

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Purpose **The true impact of postoperative radioiodine therapy on survival has been controversial for patients with poorly differentiated thyroid carcinoma (PDTC). We aimed to determine the impact of postoperative radioiodine on survival in PDTC through a population-based study.**

Methods **Data on patients with PDTC were collected from the US SEER database (2004 to 2015). Patients were divided into the radioiodine group and nonradioiodine group. Survival comparison between groups was evaluated by Kaplan–Meier curves, log-rank test and multivariate Cox regression analysis. Akaike information criterion was used to select variables in the nomogram. The performance of the nomogram was assessed by discrimination (C-index) and calibration plots.**

Results **The radioiodine group had more aggressive features, such as advanced tumor node metastasis stage and radical surgery, compared to the nonradioiodine group. PDTC patients receiving radioiodine therapy had a significant survival advantage in terms of overall survival (OS) (P=0.001) but not in terms of cancer-specific survival (P=0.083). Multivariate analysis revealed radioiodine therapy was an independent favorable factor for OS in PDTC patients (hazard ratio=0.57; 95% CI, 0.44–0.75, P<0.001). Subgroup analysis identified patients' characteristics favoring radioiodine therapy. The nomogram (age, tumor size, extension, neck lymph nodes metastasis and radioiodine therapy) of OS for predicting 3-, 5- and 10-year OS probability showed good discrimination (C-index, 0.797) and calibration power.**

Conclusion **Postoperative radioiodine therapy can prolong the long-term OS in patients with PDTC, and is an independent favorable prognostic factor for those patients. Further prospective studies are warranted.** ***Nucl Med Commun*** **43: 145–151** **Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignant tumor. Of differentiated carcinomas, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) account for about over 90% of cases [1]. Generally, the majority of DTC have well-differentiated features of normal thyroid, they, therefore, progress slowly and have a favorable prognosis, with a 10-year survival of 90%. Poorly differentiated thyroid carcinoma (PDTC) is a rare entity of DTC, accounting for 2–15% of all thyroid carcinomas, variated by regional [2]. Unlike well-differentiated thyroid carcinoma (WDTC), PDTC contributes to aggressive features linked to a frequent locoregional spread, distant metastasis and recurrence, and lies an intermediate prognosis between WDTC and undifferentiated thyroid carcinoma, with a 5-year survival of 60–85% [3–5]. In the treatment, both are dominated by surgery and radioiodine therapy [4]. Despite the weak iodine uptake in PDTC, postoperative radioiodine therapy for PDTC is generally recommended given the potential benefit and low side effects of radioiodine [6].

PDTC is classified as the intermediate risk of recurrence by American Thyroid Association [7] and high risk of recurrence by European Thyroid association. Postoperative radioiodine therapy is used for adjuvant therapy or clearing metastasis. However, the benefit of radioiodine therapy for PDTC remains unclear. The fact that PDTC could retain a variable ability to uptake radioiodine had been observed in clinical studies [8,9], and some of tumors that received initial postoperative

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radioiodine therapy could achieve partial regression or stability in the short-term [10,11]. Limited data are suggesting that the postoperative radioiodine therapy could improve the survival of PDTC patients [12]. In contrast, other retrospective studies indicated that radioiodine therapy was not associated with prolonged survival [6,13]. In these studies, the rarity of PDTC and the heterogeneity of PDTC diagnosis are common factors that might limit the ability to accurately evaluate the impact of radioiodine therapy on survival in PDTC.

The Surveillance, Epidemiology and End Results (SEER) collects and publishes reliable cancers data from population-based cancer registries covering approximately 34.6% of the USA. Through extracting PDTC information spanning decades from the SEER database, we conducted a reliable population-based study to especially investigate the survival difference in PDTC with and without postoperative radioiodine therapy. The nomogram for predicting the prognosis of PDTC patients was also established.

Patients and methods

Patients' selection

A total of 134915 cases with primary site labeled C73.9 (thyroid gland) were selected ranging from 2004 to 2015 in the SEER database. The inclusion criteria for PDTC were referred mainly to the high grade of the tumor. We enrolled 1179 cases designated as PDTC in the poorly differentiated grade of PTC (8050/3, 8260/3 and 8340/3) and FTC (8330/3) and insular carcinoma (8337/3) based on the International Classification of Diseases for Oncology Third Revision histology codes. The remaining variables were extracted including age, sex, race, tumor node metastasis stage (TNM), surgery of the thyroid, neck lymph nodes dissection, radiation, tumor size, extension, survival in months, causes of death and vital status. Then cases were excluded with the following features: unknown race (10 cases), unknown T (45 cases), unknown N (35 cases), unknown M (12 cases), unknown surgery primary site (35 cases), unknown neck lymph nodes dissection (1 case), unknown tumor size (35 cases), beam radiation (81 cases), combination of the beam with implants or isotopes (18 cases), radioactive implants (13 cases) and unknown method of treatment (12 cases). Finally, a total of 882 PDTC cases were recognized and were divided into the radioiodine group (582 cases) and the nonradioiodine group (300 cases) based on the radiation recode.

Statistical analysis

Chi-square test and Student's *t*-test were used for categorical and continuous variables between the radioiodine and nonradioiodine groups, respectively. Kaplan–Meier curves were used to plot the survival curves and the log-rank test was used to evaluate the statistical difference between the radioiodine and nonradioiodine groups. Univariable Cox regression analysis was performed to explore the potential confounders. Subsequently, variables that were statistically significant in univariate analysis were selected into multivariate Cox regression to identify the independent predictors. Both step-down process based on the Akaike information criterion (AIC) [14] was used to select the final variables for constructing the nomogram. The concordance index (C-index) and calibration curves [15] were used to evaluate the discrimination and calibration ability of the nomogram, respectively.

All statistical analyses were performed with R software (v 4.0.0). Statistical significance was defined as $P<0.05$ (two-sided).

Results

Clinical characteristics of patients

A total of 882 patients fulfilled the eligibility criteria, of which 582 were in the radioiodine group and 300 were in the nonradioiodine group, respectively. The patients' demographics and clinicopathologic characteristics were summarized in Table 1. In the whole group, the male-to-female ratio was 1:1.7, the median age was 57 years and the white accounted for 77.8%. A higher proportion of the radioiodine group had aggressive characteristics such as advanced T stage, tumor size >1 cm, extrathyroidal extension and neck lymph nodes metastasis, and more patients underwent total thyroidectomy and neck lymph nodes dissection, compared with the nonradioiodine group.

Survival analysis

Figure 1a showed the Kaplan–Meier survival curves demonstrating that patients with PDTC receiving radioiodine therapy had better overall survival (OS) compared to patients not receiving radioiodine therapy ($P=0.001$). Although there was no significant statistical difference in cancer-specific survival (CSS) ($P=0.083$), the cumulative survival rate of the radioiodine group in the first 10 years was significantly higher than the nonradioiodine group (Fig. 1b).

Prognostic factors in patients with poorly differentiated thyroid carcinoma

In univariate Cox regression analysis, variables including age, race, sex, histology, neck lymph nodes dissection, tumor size, extension, regional and distant metastasis, and radioiodine therapy were significantly associated with OS. In multivariate Cox regression analysis, six variables including age, histology, extension, regional metastasis, distant metastasis and radioiodine therapy were identified as independent factors of OS for PDTC patients. All of above data are shown in Table 2. Notably, radioiodine therapy remained an independent protective factor for OS after controlling the confounders (hazard ratio = 0.57; 95% CI, 0.44–0.75; $P<0.001$). These results indicated that postoperative radioiodine therapy was significantly associated with improved OS in patients with PDTC.

Table 1 Demographics and clinical characteristics of eligible patients with poorly differentially thyroid carcinoma

Characteristics	non-radioiodine, *N*=300	Radioiodine, *N*=582	Total, *N*=882	*P* value
Age (median)	60.0 (12–94)	55.0 (11–97)	57.0 (11–97)	0.966
<55	117 (39.0)	288 (49.5)	405 (45.9)	<0.001
55–70	88 (29.3)	182 (31.3)	270 (30.6)	
>70	95 (31.7)	112 (19.2)	207 (23.5)	
Race, *n* (%)				0.788
White	230 (76.7)	456 (78.4)	686 (77.8)	
Black	32 (10.7)	54 (0.93)	86 (9.8)	
Other	38 (12.6)	72 (12.3)	110 (12.4)	
Sex, *n* (%)				0.132
Male	102 (34.0)	228 (39.2)	330 (37.4)	
Female	198 (66.0)	354 (60.8)	552 (62.6)	
Histology, *n* (%)				0.268
PTC (poor differentiation)	211 (70.3)	395 (67.9)	606 (68.7)	
FTC (poor differentiation)	43 (14.3)	73 (12.5)	116 (13.2)	
Insular carcinoma	46 (15.3)	114 (19.6)	160 (18.1)	
Stage, *n* (%)				0.952
I	99 (33.0)	202 (34.7)	301 (34.1)	
II	33 (11.0)	59 (10.1)	92 (10.4)	
III	89 (29.7)	169 (29.0)	258 (29.3)	
IV	79 (26.3)	152 (26.1)	231 (26.2)	
T, *n* (%)				0.043
T1	64 (21.3)	87 (14.9)	151 (17.1)	
T2	55 (18.3)	117 (20.1)	172 (19.5)	
T3	126 (42.1)	287 (49.4)	413 (46.8)	
T4	55 (18.3)	91 (15.6)	146 (16.6)	
N, *n* (%)				0.015
N0	224 (74.7)	388 (66.7)	612 (69.4)	
N1	76 (25.3)	194 (33.3)	270 (30.6)	
M, *n* (%)				0.729
M0	270 (90.0)	528 (90.7)	798 (90.5)	
M1	30 (10.0)	54 (9.3)	84 (9.5)	
Tumor size, *n* (%)				<0.001
<1 cm	40 (13.3)	25 (4.3)	65 (7.4)	
1–4 cm	131 (43.7)	307 (52.7)	438 (49.7)	
>4 cm	129 (43.0)	250 (43.0)	379 (43.0)	
Extension, *n* (%)				0.587
Intrathyroidal	173 (57.7)	323 (55.5)	496 (49.6)	
Extrathyroidal	127 (42.3)	259 (44.5)	386 (38.6)	
Thyroidectomy, *n* (%)				0.002
Partial resection	46 (15.3)	49 (8.4)	95 (10.8)	
Total resection	254 (84.7)	533 (91.6)	787 (89.2)	
Neck lymph nodes dissection, *n* (%)				0.001
No	156 (52.0)	234 (40.2)	390 (44.2)	
Yes	144 (48.0)	348 (59.8)	492 (55.8)	

FTC, follicular thyroid carcinoma; PDTC, poorly differentially thyroid carcinoma; PTC, papillary thyroid carcinoma.

Subgroup's analysis

To examine the characteristics of the population that may benefit from radioiodine therapy, we performed the subgroups analysis. The results are shown in Fig. 2a–b. For OS, patients with PDTC might benefit from postoperative radioiodine therapy with the following characteristics: over 55-year of age, female, FTC and PTC (poor differentiation), total resection, tumor size >4 cm, extrathyroidal extension and regional and distant metastasis. For CSS, PDTC patients might benefit from postoperative radioiodine therapy the following characteristics: over 55 years of age, female, tumor size >4 cm, extrathyroidal extension and distant metastasis.

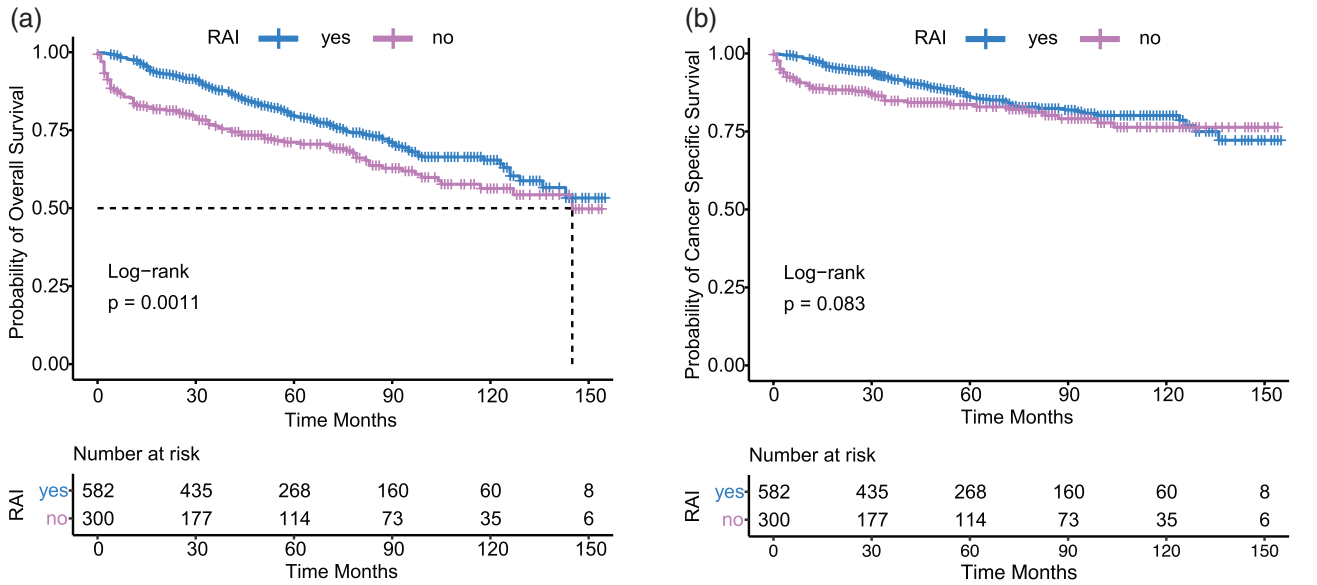
Construction and evaluation of the prognostic prediction nomogram

Based on the AIC results, age, tumor size, extension, neck lymph nodes metastasis and radioiodine therapy were integrated into a predictive model for OS, which was visualized into a nomogram predicting the probability of survival at 3, 5and 10 years (Fig. 3a). The C-index value to assess the discrimination power of the nomogram in OS was 0.797 (95% CI, 0.770–0.824). Calibration curves for the nomogram in OS showed good consistencies of survival probability between predicted and observed survival probabilities at 33, 5 and 10 years (Fig. 3b).

Discussion

Elucidating the impact of postoperative radioiodine therapy on survival of patients with PDTC is crucial to clinical decision making. In clinical practice, patients with PDTC are generally considered for postoperative radioiodine therapy even in the absence of proven definite efficacy. The rarity of PDTC and the heterogeneity of the diagnosis had been contributing to the controversial results in previous studies. In this study, we conducted a retrospective cohort study incorporating data from a reliable population-based database with the largest PDTC collection to date. The results showed that PDTC patients receiving postoperative radioiodine therapy had

Fig. 1



OS (a) and CSS (b) analysis of patients with PDTC between RAI and non-RAI group. CSS, cancer-specific survival; OS, overall survival; PDTC, poorly differentially thyroid carcinoma; RAI, radioiodine therapy.

improved long-term survival ($P = 0.001$). After controlling the confounders (age, race, sex, histology, neck lymph nodes dissection, tumor size, extension and metastasis), radioiodine therapy was an independent favorable factor for PDTC (OS, hazard ratio = 0.57; 95% CI, 0.44–0.75; $P < 0.001$).

The definition of PDTC is mainly based on the Turin criteria (based on solid/trabecular/insular growth pattern, mitotic index and necrosis) or Memorial Sloan Kettering Cancer Center (MSKCC) criteria (based on mitotic index and necrosis). Although the WHO classification adopts the Turin criteria as the diagnostic criteria for PDTC, the high-grade of tumor referenced by the MSKCC criteria can capture more intermediate prognosis of thyroid carcinomas, such as some of PTC [16]. In general, the agreement between PDTC diagnosed with the Turin criteria and those diagnosed with the MSKCC criteria was 75% [17]. Also, PDTC tumors defined according to the hyperproliferative grading were biologically more homogeneous compared to the Turin criteria. In this study, we collected patients with FTC and PTC, and insular carcinoma designated as poorly differentiated grade. As expected, the intermediate prognosis for patients with PDTC who underwent postoperative radioiodine therapy was 79.5% for 5-year OS and 64.2% for 10-year OS, while for patients who did not underwent radioiodine therapy was 70.5% for 5-year OS and 54.3% 10-year OS.

The use of postoperative radioiodine therapy in patients with PDTC had not been well established in past studies, and a favorable impact on survival was reported. PDTC represents a transitional phase between WDTC and undifferentiated thyroid carcinoma. Its ability to express thyroglobulin and uptake radioiodine reflects the partial well-differentiated features in thyroid carcinomas. Immunoreactivity to thyroglobulin had been reported in 86% of PDTC cases [18], and up to 80% of cases with the ability to uptake radioiodine was observed in clinical studies [9]. These tumors differentiated features are the theoretical basis for radioiodine therapy in PDTC patients and are potentially responsible for the benefit of radioiodine therapy. The current evidence studying the efficacy of radioiodine therapy are all retrospective studies with small numbers of patients and limited statistical power, which might yield false-negative results. Besides, different inclusion criteria for PDTC in studies often yielded different results. In the present study, we enrolled 882 patients who met the high-grade features in DTC and insular carcinoma. This retrospective cohort study is, to our knowledge, the largest number of PDTC patients who meet Turin criteria or MSKCC criteria by far. The results showed that the proportion of patients with more aggressive features in the radioiodine group than the nonradioiodine group, the survival curves in Fig. 1 remained higher overall. Age, histology, extension, regional metastasis, distant metastasis and radioiodine therapy were independent favorable factors of OS for PDTC patients. The risk of death was 43% lower in PDTC patients receiving radioiodine therapy than in those not receiving radioiodine. For CSS, there was no significant statistical difference ($P = 0.083$), but the cumulative survival rate of the

Table 2 Univariate and multivariate Cox proportional hazards analysis of overall survival

	Univariate logistic model			Multivariate logistic model		
Variables	Hazard ratio	CI 95%	*P* Value	Hazard ratio	CI 95%	*P* Value
			Age (years)			
<55		Reference			Reference	
55–70	3.91	2.65–5.75	<0.001	3.16	2.12–4.70	<0.001
>70	8.32	5.74–12.05	<0.001	6.24	4.25–9.16	<0.001
Race						
White		Reference			Reference	
Black	0.42	0.22–0.80	0.008	0.62	0.32–1.17	0.141
Other	0.97	0.66–1.44	0.886	0.82	0.56–1.22	0.340
Sex						
Male		Reference			Reference	
Female	0.68	0.53–0.89	0.004	0.92	0.70–1.20	0.536
Histology						
PTC (poor differentiation)		Reference			Reference	
FTC (poor differentiation)	1.67	1.17–2.38	0.005	1.52	1.04–2.21	0.030
Insular carcinoma	1.63	1.20–2.21	0.002	1.22	0.88–1.69	0.235
Thyroidectomy						
Partial resection		Reference				
Total resection	1.03	0.68–1.56	0.900			
Neck lymph nodes dissection						
No		Reference			Reference	
Yes	1.34	1.03–1.74	0.032	1.20	0.86–1.67	0.279
Tumor size						
<1 cm		Reference			Reference	
1–4 cm	2.24	0.91–5.51	0.080	1.53	0.60–3.91	0.371
>4 cm	4.84	1.98–11.81	< 0.001	2.07	0.80–5.53	0.135
Extension						
Intrathyroidal		Reference			Reference	
Extrathyroidal	2.88	2.20–3.77	< 0.001	2.09	1.55–2.81	<0.001
Neck lymph nodes metastasis						
No		Reference			Reference	
Yes	2.23	1.72–2.89	<0.001	1.44	1.03–2.03	<0.001
Distant metastasis						
No		Reference			Reference	
Yes	5.67	4.16–7.75	<0.001	3.37	2.40–4.74	<0.001
RAI therapy						
No		Reference			Reference	
Yes	0.65	0.50–0.84	0.001	0.57	0.44–0.75	<0.001

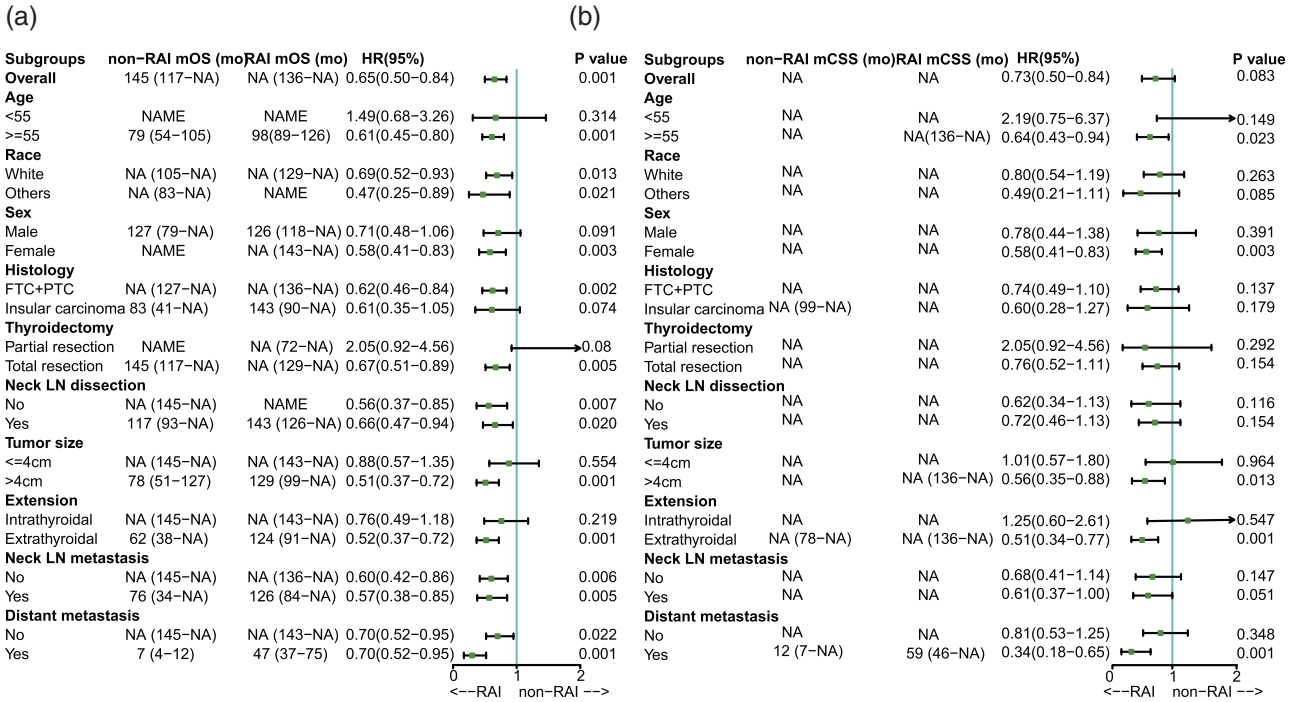
FTC, follicular thyroid carcinoma; PDTC, poorly differentially thyroid carcinoma; PTC, papillary thyroid carcinoma; RAI, radioiodine therapy.

radioiodine group in the first 10 years was higher than the nonradioiodine group. Also, the proportion who died of thyroid carcinoma was only 14.7% which might limit the statistical power and obtained false-negative results. Subgroup analyses were performed to further determine population characteristics that could benefit from postoperative radioiodine therapy, and results showed that aggressive characteristics such as older age, large tumor size and metastasis could benefit more from postoperative radioiodine therapy in OS and CSS, which was consistent with the guidelines recommending for radioiodine therapy.

In clinical practice, PDTC is not paid enough attention and the individualized prognosis is unclear. We conducted a nomogram through enrolled significant six variations to predict individualized survival probabilities at 3, 5 and 10 year. Nomograms as prediction tools can help patients and physicians make important treatment decisions and can be used to predict cancer outcomes or assess risk based on specific characteristics of a patient. Currently, nomograms have been used for a variety of cancers, such as hepatocellular cancer [19], colorectal cancer [20] and breast cancer [21]. To date, no nomogram has been reported for predicting the probability of survival in PDTC. In this study, we established a nomogram to predict PDTC survival, and the nomogram we conducted had a higher C-index (0.797; 95% CI, 0.770–0.824) compared with the TNM stage (0.739; 95% CI, 0.706–0.772). Therefore, this nomogram serves as a simple but vital tool for evaluating accurate prognostic prediction of patients with PDTC, quantifying treatment benefits and assisting clinicians in decision-making.

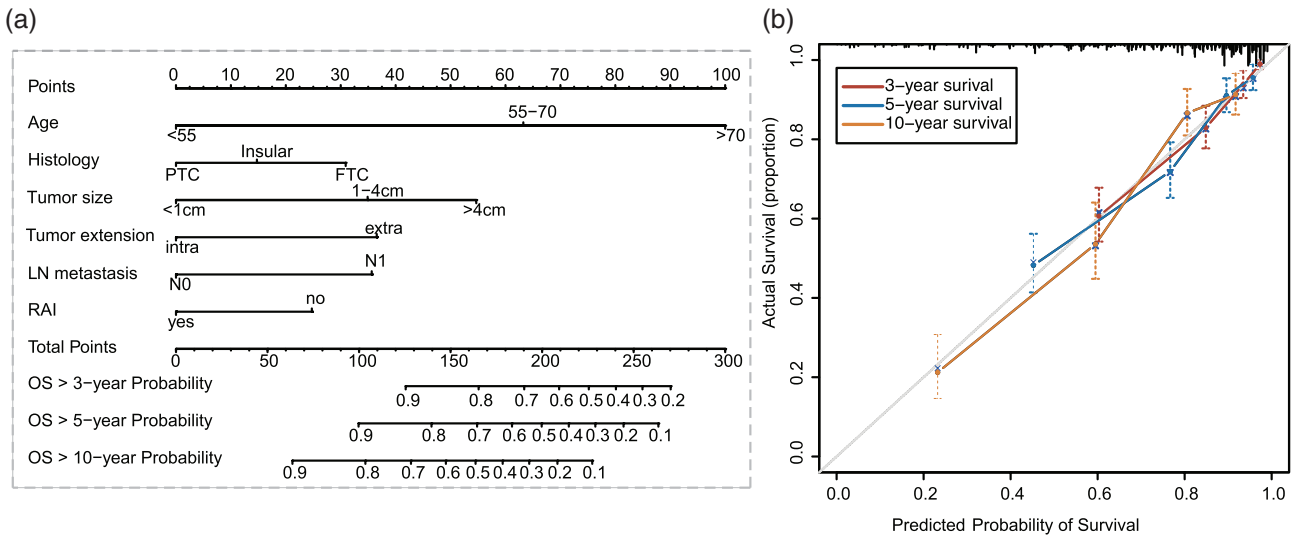
Given the infrequent incidence of PDTC, it is difficult to perform a prospective study with standardized treatment regimens. As a retrospective cohort study, our study has several limitations. First, coding errors are inherent in the SEER database. Second, factors that influencing the efficacy of radioiodine for PDTC patients are not recorded, including doses and times of radioiodine therapy, performance status of patients, resection situation and the level of thyroglobulin. These confounders may limit to accurately evaluate the impact of postoperative radioiodine therapy on survival for patients with PDTC. Besides, the response and the recurrence after initial radioiodine

Fig. 2



Forest plots of OS (a) and CSS (b) for patients with PDTC. CSS, cancer-specific survival; OS, overall survival; PDTC, poorly differentially thyroid carcinoma.

Fig. 3



Nomogram of predicting OS for patients with PDTC (a). Calibration plots for predictions in the 1-, 3- and 5-year survival (b). OS, overall survival; PDTC, poorly differentially thyroid carcinoma.

therapy are not recorded, which limits to fully investigated efficacy of postoperative radioiodine therapy for patients with PDTC.

In conclusion, our results indicate that postoperative radioiodine therapy can prolong the long-term OS for patients with PDTC, and is an independent favorable

prognostic factor for those patients. Further prospective studies are warranted.

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The data from the SEER database are publicly available. Thus, the present study was exempted from the approval of ethics committee of the third affiliated hospital of Sun Yat-sen university.

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The data directly downloaded from the SEER website in keeping with SEER requirements. We thank the open access to the database from SEER.

The present data are summarized in this article. The complete dataset can be retrieved from the SEER database or obtained from the authors upon formal request from interested readers.

Y.Z. and L.X. provided ideas for the study. L.X. and Q.Z. contributed to study design, performed patient data collection and data statistical analysis. J.J. and Y.Z. contributed to the interpretation of the data. All authors contributed to manuscript preparation. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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