OncoTargets and Therapy

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ORIGINAL RESEARCH

The role of radioactive iodine therapy in papillary thyroid cancer: an observational study based on SEER

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Background: Papillary thyroid cancer (PTC) is a common endocrine malignancy with relatively good prognosis. Radioactive iodine (RAI) is considered effective for patients with total or nearly total thyroidectomy, but the beneficial effects of RAI are still controversial.

Materials and methods: To determine whether RAI therapy could improve the survival rates of PTC patients, we conducted a retrospective analysis using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Disease-specific survival (DSS) was obtained using multivariate Cox proportional hazard regressions.

Results: DSS was improved by RAI ablation in patients with tumor >2 cm, age >45 years and gross extrathyroidal or lymph node metastasis. In a further analysis, RAI therapy did not improve the DSS in patients with tumor <2 cm except those with distant metastasis. For patients with tumor >2 cm, those involving gross extrathyroidal extension, age >45 years or disease in the lymph nodes, DSS was improved after RAI therapy. Patients with distant metastasis always benefited from RAI ablation.

Conclusion: RAI ablation should be recommended to patients with tumor <2 cm and distant metastasis or patients with tumor >2 cm and one of the following risk factors: gross extrathyroidal extension, age >45 years, lymph node and distant metastases.

Keywords: RAI, prognosis, tumor size, metastasis, extension, age

Introduction

Thyroid cancer is a common endocrine malignancy. Over the past 3 decades, the incidence of thyroid cancer increased by 211% in the USA, driven mostly by the increase of papillary thyroid cancer (PTC). With the high incidence of thyroid cancer, mortality rate for advanced-stage PTC has also increased.[1,2]

It is widely agreed that PTC demonstrates relatively indolent clinical behavior. The improvements in diagnosis and treatment of PTC provide an excellent prognosis, with 90% survival rate at 10 years.[3–5] However, it remains a challenge to establish a standard treatment strategy for patients with PTC. To determine whether patients need more aggressive treatment, risk stratification systems were set up to stratify patients into low and high risk of recurrence or death of thyroid cancer.[6] In the current American Thyroid Association (ATA) Guidelines, radioactive iodine (RAI) is not routinely recommended after thyroidectomy for the low risk patients, but it is considered for ATA intermediate and high risk patients.[7] For patients with low risk factors, total thyroidectomy can remove the remnant, thus postoperative RAI ablation has no further effect on prognosis improvement.[8] It was reported that RAI only affected the survival of patients >45 years old with primary tumors >2 cm and lymph node and

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http://dx.doi.org/10.2147/OTT.S160752

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distant metastases.[9] Surgical resection followed by RAI is often advised for high risk tumors. While Mazzaferri and Jhiang demonstrated that RAI therapy significantly reduced recurrence rate and cancer-related death in patients with tumors >1.5 cm,[10] Jonklaas et al stated that RAI therapy benefited all patients except those with stage 1 disease.[11] No statistic differences of recurrence and death rates were reported between the ^{131}I group and the no-^{131}I group in a study recruiting 1,542 patients from Mayo Clinic.[12] RAI did not affect the survival rate in patients with small intrathyroid tumors. Therefore, RAI therapy was only recommended for patients with residual disease.[13,14] In most countries, postsurgical RAI ablation is recommended for PTC patients with tumors >1 cm. Due to the lack of long-term randomized trials and inconsistence of previous studies, the beneficial effects of RAI are still controversial.[15]

To further investigate the effects of RAI therapy on patients with PTC, we conducted a retrospective analysis using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The objective of this study was to determine whether RAI therapy could improve the long-term survival rates. Furthermore, we aimed to determine whether a cohort of patients with specific risk factors could be identified, and whether RAI therapy was associated with an improved survival rates for those patients.

Materials and methods

A retrospective cohort analysis using the SEER database from the National Cancer Institute was performed. Patients were selected between 2003 and 2013. Because of the different clinical behaviors between classical type and follicular variant of PTC, histologic subtypes of PTC were limited using the International Classification of Diseases for Oncology, 3rd edition[32] (ICD-O-3) as follows: 8050/3: papillary carcinoma, not otherwise specified (NOS); 8260/3: papillary adenocarcinoma, NOS; 8343/3: papillary carcinoma, encapsulated.

Patients whose information of tumor size, extension, lymph node and distant metastases was blank or unknown were excluded from this study. Cases with or without RAI ablation after total or nearly total thyroidectomy were eligible for further analysis.

Demographic data included sex (male and female), age at diagnosis (<45 or ≥45 years), race (white, black, Asian, other or unknown) and region (East, Northern Plains, Pacific Coast, Southwest or Alaska). Tumor size cutoffs from 1 to 4 cm were examined in 1 cm intervals to determine whether a tumor size threshold could be identified above which RAI therapy was beneficial to survival rates. The cancer characteristic of tumor extension was categorized as intrathyroidal (codes 100, 200, 300, 400), minimal extrathyroidal (code 450) and gross extrathyroidal (codes 480, 500, 520, 550, 600, 620, 650, 700, 720, 730, 800). Lymph node metastasis was classified into 2 groups: negative (code 000) and positive (codes 120, 135, 140, 155, 158, 160). Distant metastasis included no distant metastasis diseases (code 00) and distant metastasis diseases (codes 12, 40, 51, 60). Treatment characteristics included surgery (code 40: subtotal or nearly total thyroidectomy, code 50: total thyroidectomy) and radiation therapy (none or radioactive iodine therapy). All the variables were defined using the SEER specific codes.

To determine the tumor size threshold and assess the association between tumor size and RAI therapy, the analysis was firstly stratified by tumor size (by 1 cm intervals). We further stratified the patients based on tumor extension, age, lymph node and distant metastases to investigate the effects of RAI on patients with specific features.

Patient demographics, cancer- and treatment-related characteristics were compared between no RAI and RAI therapy groups using chi-square or Fisher's exact tests. In our study, the overall survival (OS) and disease-specific survival (DSS) were obtained using multivariate Cox proportional hazard regressions. A Cox proportion hazards model was used to assess the association between all the variables and survival. Stratified analyses were performed and Cox proportion hazards model was obtained to investigate the effects of RAI therapy. Adjusted hazard ratios (aHR) with 95% confidence intervals were generated to quantify the strength of the relative risk, and aHR>1.0 represented a worse prognosis than those <1.0. All the tests and performed were 2-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, NY, USA).

Ethics statement

This was a retrospective cohort analysis using data from the SEER database which was designed and maintained by the National Cancer Institute. Research was limited to secondary use of information previously collected in the course of normal care and data were anonymized before the conduction of statistical analyses. This article does not contain any studies with human participants or animals performed by any of the authors.

Results

Patient characteristics

A total of 41,287 cases were eligible for our study. The median follow-up time was 47.2 months. Among the total

death rate of 1,423 (3.4%), only 261 patients died from thyroid cancer (0.6%). Characteristics of patients are compared between the treatment subgroups in Table 1. Over half of the patients underwent postoperative RAI therapy. Patients with larger tumors, extrathyroidal extension, lymph node or distant metastases were more likely to be given RAI ablation after total or nearly total thyroidectomy.

Survival analysis

The aHRs for OS and DSS are listed in Table 2 to investigate the clinical significances. The multivariate models demonstrated that older age, larger tumor, extrathyroidal extension, lymph node and distant metastases had negative effects on the survival when controlling for the remaining variables ($P<0.05$). RAI therapy improved both OS (aHR = 0.586, $P<0.001$) and DSS (aHR = 0.600, $P<0.001$).

Table 1 Patient characteristics within subgroups

Variables	No RAI therapy N=18,222 (%)	RAI therapy N=23,065 (%)	*P*-value*
Median follow-up (months)	42.2	50.8	
Age at diagnosis, years			<0.001
<45	7,078 (38.8)	10,534 (45.7)	
≥45	11,144 (61.2)	12,531 (54.3)	
Sex			<0.001
Male	3,596 (19.7)	5,695 (24.7)	
Female	14,626 (80.3)	17,370 (75.3)	
Race			<0.001
White	14,995 (82.3)	18,972 (82.3)	
Black	1,116 (6.1)	903 (3.9)	
Asian	1,689 (9.3)	2,655 (11.5)	
Other	275 (1.5)	445 (1.9)	
Unknown	147 (0.8)	90 (0.4)	
Region			<0.001
East	7,255 (39.8)	7,532 (32.7)	
Pacific Coast	8,293 (45.5)	11,839 (51.3)	
Southwest	1,169 (6.4)	1,653 (7.2)	
Northern Plains	1,500 (8.2)	2,021 (8.8)	
Alaska	5 (0.0)	20 (0.1)	
Surgery			<0.001
Subtotal or near total thyroidectomy	991 (5.4)	642 (2.8)	
Total thyroidectomy	17,231 (94.6)	22,423 (97.2)	
Tumor size (cm)			<0.001
≤2	14,817 (81.3)	14,629 (63.4)	
>2	3,405 (18.7)	8,436 (36.6)	
Tumor extension			<0.001
Intrathyroidal	16,230 (89.1)	16,708 (72.4)	
Minimal extrathyroidal	851 (4.7)	2,651 (11.5)	
Gross extrathyroidal	1,141 (6.3)	3,706 (16.1)	
Lymph node metastases			<0.001
Negative	15,634 (85.8)	14,290 (62.0)	
Positive	2,588 (14.2)	8,775 (38.0)	
Distant metastases			<0.001
None	18,154 (99.6)	22,831 (99.0)	
Yes	68 (0.4)	234 (1.0)	
Status			<0.001
Alive	17,520 (96.1)	22,344 (96.9)	
Dead	702 (3.9)	721 (3.1)	
Thyroid cancer	94 (0.5)	167 (0.7)	
Other	608 (3.3)	554 (2.4)	

Note: *P-values were calculated by Pearson chi-squared or Fisher's exact testing.
Abbreviation: RAI, radioactive iodine.

Subgroup analysis of RAI therapy

We investigated the beneficial effects of RAI on patients with different features. Patients were stratified based on tumor size, age, extension, and metastasis. To determine the tumor size threshold for which RAI therapy could benefit the survival, tumor size was tested by 1 cm intervals between 1 and 4 cm. For patients with tumors <2 cm, RAI improved OS but did not benefit DSS. However, for those with tumors >2 cm, RAI therapy could significantly improve the OS and DSS. Similar results were found when patients were classified by age (<45 or ≥45 years), extension (intrathyroidal, minimal extrathyroidal or gross extrathyroidal), or lymph nodes metastasis (negative or positive). DSS was improved in older age, gross extrathyroidal, and lymph node groups but not the distant metastasis group (Table 3).

To further examine the associations between RAI therapy and DSS, patients were stratified (Figure 1). RAI therapy did not improve the DSS in all tumor <2 cm groups, except for patients with distant metastasis. For patients with tumors >2 cm, DSS benefited from RAI therapy only for those involving gross extrathyroidal extension, age >45 years or with disease in the lymph nodes; DSS was improved in tumor >2 cm whether or not patients had distant metastasis (Figures 2 and 3).

Discussion

Although postoperative RAI therapy is widely recommended for differentiated thyroid carcinoma,[15] the beneficial effects of RAI have been debated. In the current ATA Guidelines, RAI adjuvant therapy was not routinely recommended for low risk patients. It was considered after total thyroidectomy in ATA intermediate risk level differentiated thyroid cancer patients and high risk differentiated thyroid cancer patients.[7] The European Thyroid Association (ETA) guideline advised RAI for patients with T3/T4, N1 or M1 disease, while for young patients (<18 years) and patients with primary tumors between 1 and 2 cm without metastasis, it only gave a relative indication for RAI therapy.[16] The Society of Nuclear Medicine (SNM) Procedure Guideline recommended postoperative RAI for patients with tumor >1.5 cm, or tumor <1.5 cm with metastasis.[17] The European Association of Nuclear Medicine Guidelines considered RAI ablation as a standard procedure in patients with differentiated thyroid

Table 2 Cox proportional hazards regression model analysis of overall survival (OS) and disease-specific survival (DSS)

Variables	OS		DSS	
	aHR (95% CI)	*P*-value*	aHR (95% CI)	*P*-value*
Age at diagnosis, years				
<45	Reference		Reference	
≥45	6.730 (5.649, 8.018)	<0.001	20.332 (10.774, 38.368)	<0.001
Sex				
Male	Reference		Reference	
Female	0.567 (0.508, 0.633)	<0.001	0.656 (0.509, 0.844)	0.001
Race				
White	Reference		Reference	
Black	1.237 (0.988, 1.549)	0.064	1.065 (0.560, 2.026)	0.848
Asian	0.734 (0.599, 0.899)	0.003	0.844 (0.575, 1.238)	0.385
Other	1.231 (0.832, 1.821)	0.298	1.349 (0.628, 2.901)	0.443
Region				
East	Reference		Reference	
Pacific Coast	0.930 (0.826, 1.047)	0.229	1.087 (0.818, 1.445)	0.566
Southwest	0.909 (0.722, 1.143)	0.413	0.546 (0.279, 1.069)	0.077
Northern Plains	1.139 (0.948, 1.368)	0.165	1.113 (0.697, 1.776)	0.654
Alaska	1.453 (0.342, 6.173)	0.613	0.000 (0.000, 6.575E+266)	0.973
Surgery				
Subtotal or near total thyroidectomy	Reference		Reference	
Total thyroidectomy	0.815 (0.656, 1.012)	0.064	0.590 (0.354, 0.986)	0.044
RAI therapy				
None	Reference		Reference	
Yes	0.586 (0.525, 0.655)	<0.001	0.600 (0.461, 0.780)	<0.001
Tumor size (cm)				
≤2	Reference		Reference	
>2	1.493 (1.331, 1.674)	<0.001	3.704 (2.758, 4.975)	<0.001
Extension				
Intrathyroidal	Reference		Reference	
Minimal extrathyroidal	1.201 (0.985, 1.463)	0.070	2.325 (1.517, 3.562)	<0.001
Gross extrathyroidal	1.995 (1.740, 2.288)	<0.001	5.047 (3.682, 6.916)	<0.001
Lymph node metastases				
Negative	Reference		Reference	
Positive	1.290 (1.137, 1.463)	<0.001	2.103 (1.589, 2.784)	<0.001
Distant metastases				
None	Reference		Reference	
Yes	5.398 (4.291, 6.790)	<0.001	10.257 (7.422, 14.176)	<0.001

Note: **P*-values calculated by multivariate Cox analysis.
Abbreviations: aHR, adjusted hazard ratio (adjusted for age at diagnosis, sex, race, region, tumor size, extension, lymph nodes metastases, distant metastases, radiotherapy and surgery); RAI, radioactive iodine.

cancer after total or nearly total thyroidectomy, except for patients with unifocal PTC <1 cm without metastasis, thyroid capsule invasion, history of radiation exposure or unfavorable histology.[8] Due to the lack of long-term randomized trails and the use of different stratification systems, it is not easy to find the optimal treatment for patients.

In our study, we conducted a retrospective, population-based cohort analysis using the SEER database. Patients were stratified into different subgroups based on risk factors. DSS was improved by RAI only in patients with tumors >2 cm, gross extrathyroidal extension, older age (>45 years) and lymph node metastasis. Distant metastasis did not affect the outcomes of RAI due to the low percentage of patients with distant metastasis (0.7%). In patients with tumors >2 cm, RAI could improve the DSS for those with gross extrathyroidal extension, lymph node metastases, distant metastases or aged >45 years. Although patients without distant metastases in this group also benefited from RAI ablation, they should be further analyzed based on their characteristics (age, tumor extension, lymph nodes metastases), because the majority of patients did not have distant metastases. In patients with tumors <2 cm, DSS was not affected by the use of RAI regardless of age, extension, and lymph node metastasis, except for those with distant

Table 3 Cox proportional hazards regression model analysis of overall survival (OS) and disease-specific survival (DSS) of patients stratified by patients' features

	OS		DSS	
	aHR (95% CI)	*P*-value*	aHR (95% CI)	*P*-value*
Tumor size <2 cm				
No RAI therapy	Reference		Reference	
RAI therapy	0.651 (0.563, 0.752)	<0.001	0.785 (0.471, 1.823)	0.352
Tumor size ≥2 cm				
No RAI therapy	Reference		Reference	
RAI therapy	0.509 (0.430, 0.603)	<0.001	0.509 (0.430, 0.603)	<0.001
Age <45 years				
No RAI therapy	Reference		Reference	
RAI therapy	0.591 (0.418, 0.836)	0.003	1.846 (0.227, 14.978)	0.566
Age ≥45 years				
No RAI therapy	Reference		Reference	
RAI therapy	0.584 (0.520, 0.657)	<0.001	0.582 (0.445, 0.760)	<0.001
Intrathyroidal extension				
No RAI therapy	Reference		Reference	
RAI therapy	0.638 (0.557, 0.730)	<0.001	1.042 (0.648, 1.677)	0.856
MEE				
No RAI therapy	Reference		Reference	
RAI therapy	0.742 (0.493, 1.115)	<0.001	1.356 (0.512, 3.592)	0.541
GEE				
No RAI therapy	Reference		Reference	
RAI therapy	0.498 (0.395, 0.606)	<0.001	0.387 (0.278, 0.538)	<0.001
LNM negative				
No RAI therapy	Reference		Reference	
RAI therapy	0.623 (0.545, 0.713)	<0.001	0.700 (0.462, 1.062)	0.094
LNM positive				
No RAI therapy	Reference		Reference	
RAI therapy	0.539 (0.443, 0.654)	<0.001	0.498 (0.356, 0.697)	<0.001
No distant metastases				
No RAI therapy	Reference		Reference	
RAI therapy	0.603 (0.538, 0.676)	<0.001	0.644 (0.479, 0.865)	0.003
Distant metastases				
No RAI therapy	Reference		Reference	
RAI therapy	0.418 (0.262, 0.669)	<0.001	0.378 (0.209, 0.683)	0.001

Note: *P-values calculated by multivariate Cox analysis.
Abbreviations: aHR, adjusted hazard ratio (adjusted for age at diagnosis, sex, race, region, tumor size, extension, lymph nodes metastases, distant metastases, radiotherapy and surgery); MEE, minimal extrathyroidal extension; GEE, gross extrathyroidal extension; LNM, lymph nodes metastases; RAI, radioactive iodine.

metastasis. Podnos et al suggested that post-surgical RAI therapy could only improve the survival in PTC patients older than 45 years with tumors >2 cm, involving lymph node and distant metastases.[9] Some studies stated that surgery alone for small tumors (<1.5 cm) had favorable prognosis and RAI was not required. In addition, RAI did not influence the recurrence rates in papillary thyroid micro-carcinoma even for those with disease in lymph nodes.[18–20] Mazzaferri et al demonstrated that RAI therapy significantly reduced recurrence rate and cancer-related death in patients with tumors >1.5 cm.[10] Other studies revealed that RAI benefited patients with tumors >1 cm or residual and metastatic disease after surgery.[16,21] These results were consistent with ours. For patients with tumors <2 cm and without distant metastasis, total or nearly total thyroidectomy had favorable prognosis, and RAI ablation could not improve it, except for those with distant metastasis. Surgery alone could successfully remove the remnant, even in patients with extrathyroidal extension or lymph node metastasis. A recent study demonstrated that minimal extrathyroidal extension did not affect the survival in most well differentiated thyroid cancer, and those patients should have a more aggressive surgical or RAI treatment.[22]

In our study, RAI therapy did not show any benefits in patients with minimal extrathyroidal extension, but multivariate analysis demonstrated that minimal extrathyroidal extension was an independent risk factor for DSS.

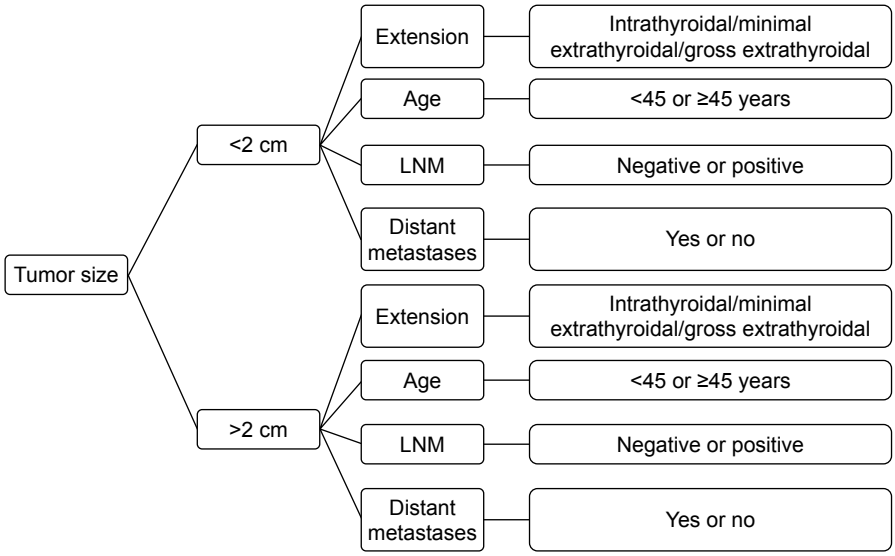


Figure 1 Stratification of patients based on tumor size, tumor extension, age, lymph node and distant metastases.
Abbreviation: LNM, lymph node metastasis.

For patients with tumors >2 cm, completeness of surgical resection is hard to achieve, especially when the tumor has invaded into the trachea, larynx or esophagus. Gross extrathyroidal extension has been regarded as a poor prognostic feature for many years.[13] It is reported that many patients with extrathyroidal extension responded very well to RAI.[23] However, it remains controversial whether the presence of lymph node metastasis is a risk factor of mortality.[24] Previous

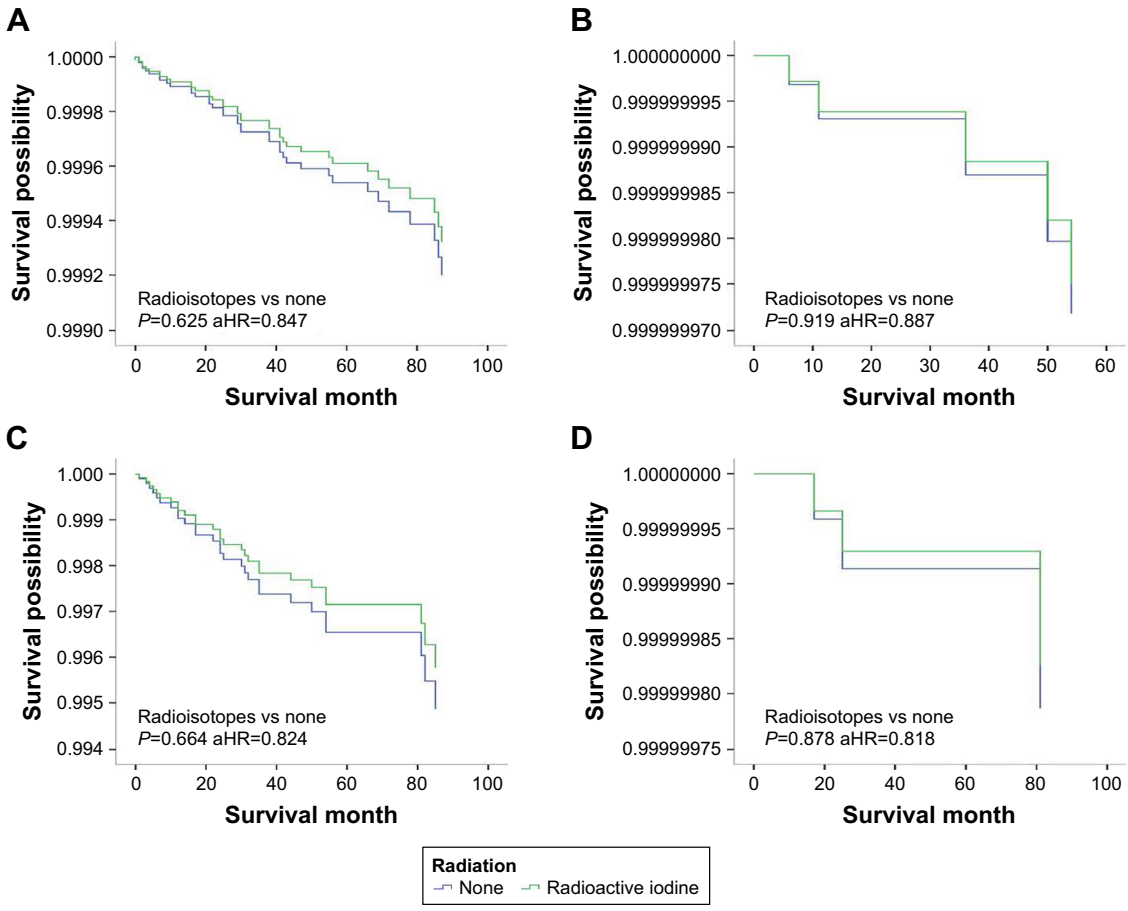


Figure 2 (*Continued*)

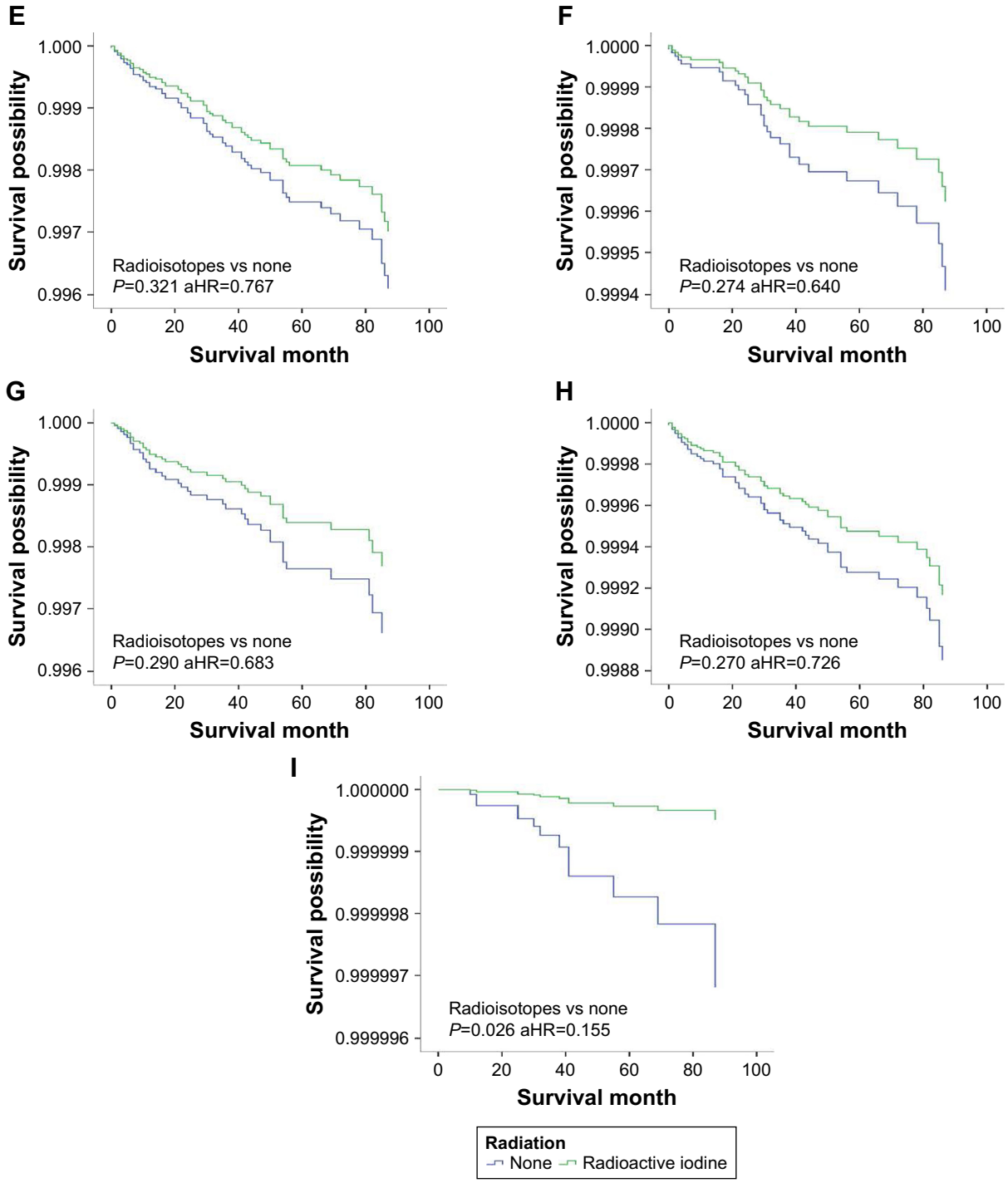


Figure 2 DSS curves of multivariate Cox analysis in the group with tumors <2 cm. DSS is based on radioactive isotope in (**A**) patients with intrathyroidal extension; (**B**) patients with minimal extrathyroidal extension; (**C**) patients with gross extrathyroidal extension; (**D**) patients younger than 45 years; (**E**) patients older than 45 years; (**F**) patients without lymph node metastases; (**G**) patients with lymph node metastases; (**H**) patients without distant metastases; (**I**) patients with distant metastases.
Abbreviations: aHR, adjusted hazard ratios; DSS, disease-specific survival.

studies showed that lymph node metastasis increased the recurrence rate and decreased the survival rate in patients older than 45 years.[25–27] In our study, patients with lymph node metastasis had poor OS and DSS. Recent ATA guidelines also recommended prophylactic central-compartment neck dissection in patients with PTC clinically involved lateral neck nodes.[7] RAI ablation eliminated potential tumor nest remnants in the lymph nodes after surgery, thus improving the DSS. Another study also considered lymph node metastasis as an indication of RAI.[28] Age was another risk factor of recurrence and death.[26,29] In our study, all patients older than 45 years benefited from RAI therapy.

Our goals with RAI therapy are to eradicate any normal residual thyroid tissue and locoregional or distant tumor deposits, thereby increasing the sensitivity and specificity of follow-up examinations of persistence or recurrence, such as thyroglobulin measurement and the whole-body radioiodine scan. However, treatment with ^{131}I may have dose-dependent adverse effects: dysfunction of salivary gland, reduction of tear production, transient dysfunction of male/female gonad, and higher risk of developing other cancers. It is important to consider these adverse effects when choosing RAI therapy in patients with PTC.[30] The adverse effects of RAI were not further examined in our study due to the lack of records of them in the SEER database.

There are several limitations in our study. We did not stratify patients into low- or high-risk groups using the current risk stratification systems. To determine whether RAI therapy benefited the survival, we classified patients into different groups with specific features, and we found that tumor size, extension, age, lymph node and distant metastases should be considered in RAI therapy. This retrospective

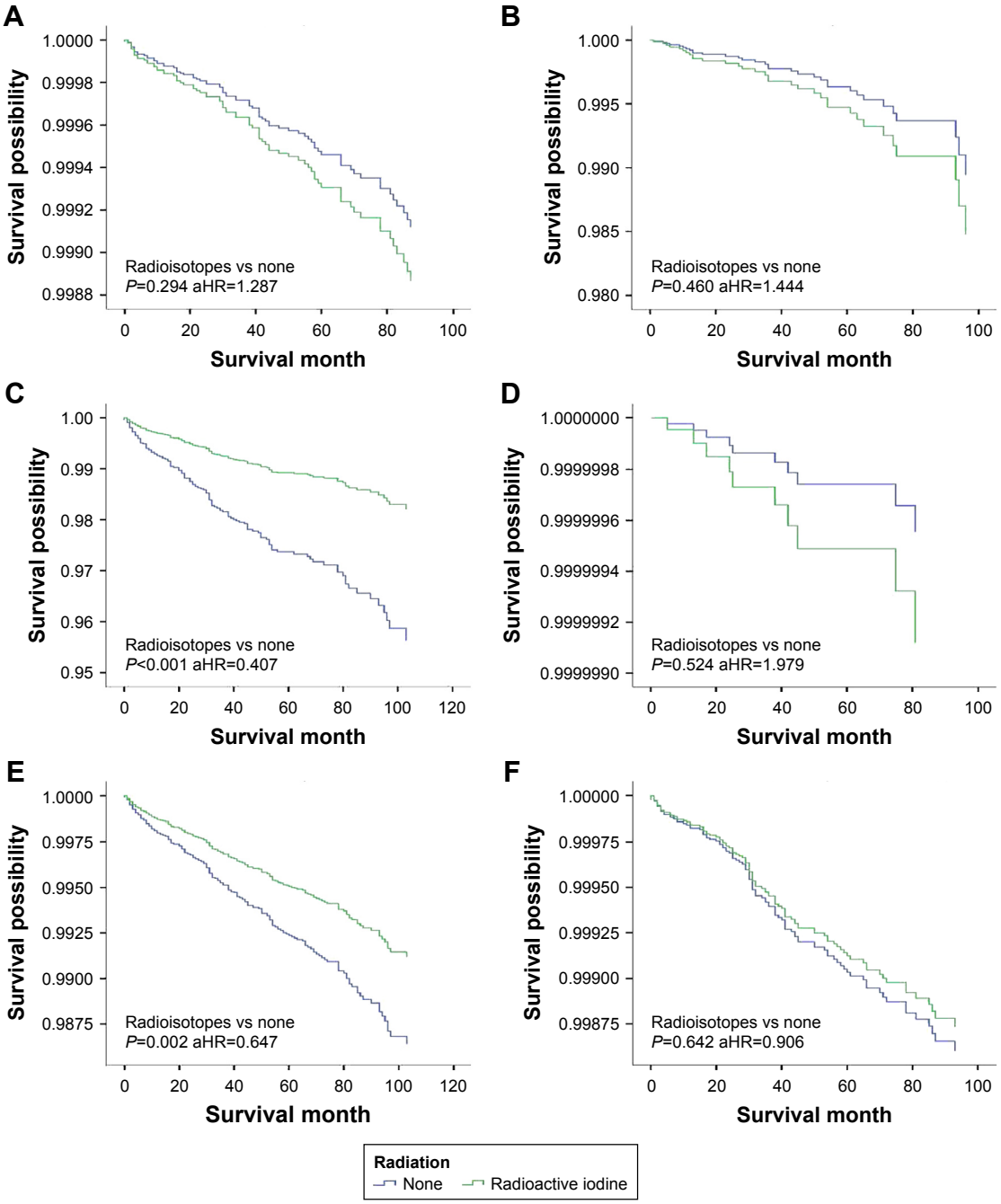


Figure 3 (*Continued*)

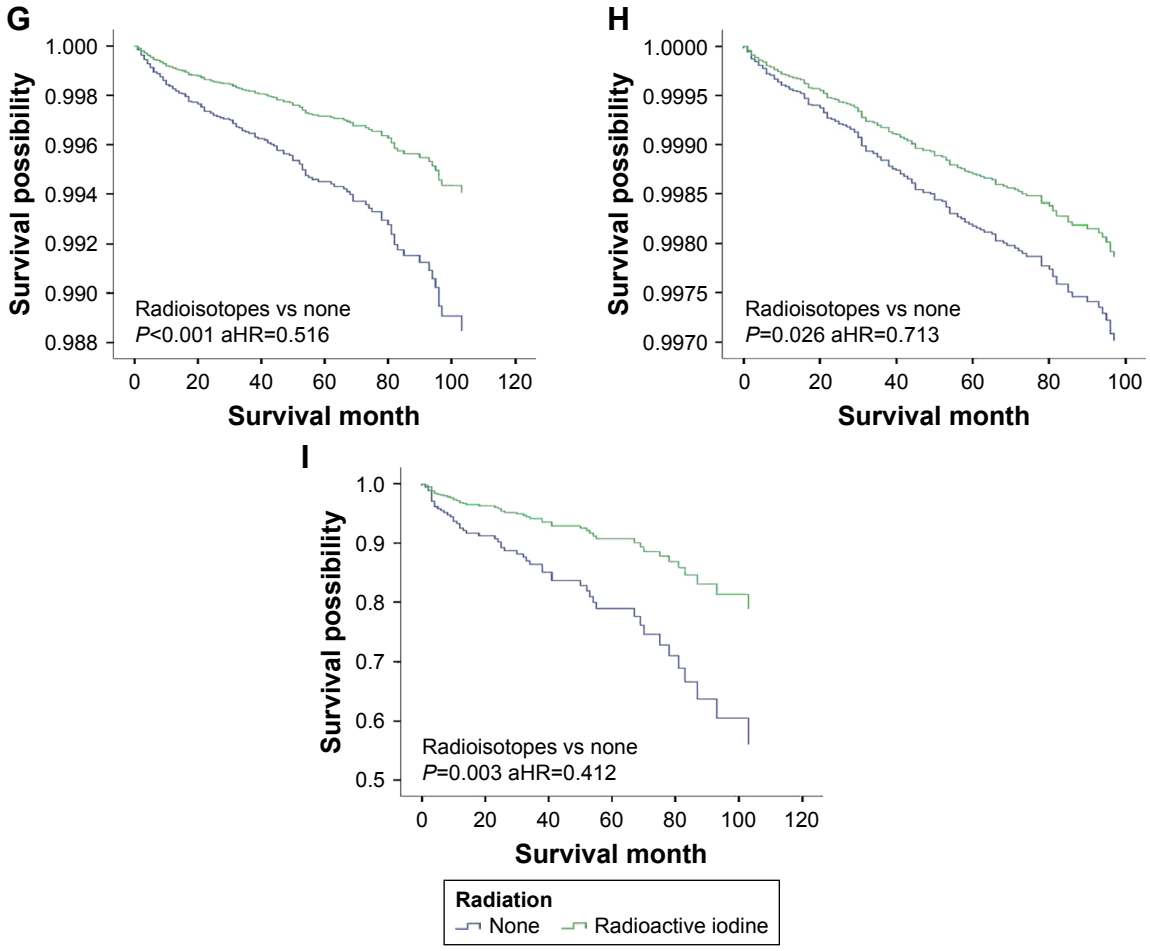


Figure 3 DSS curves of multivariate Cox analysis in the group with tumors >2 cm. DSS is based on radioactive isotope in (**A**) patients with intrathyroidal extension; (**B**) patients with minimal extrathyroidal extension; (**C**) patients with gross extrathyroidal extension; (**D**) patients younger than 45 years; (**E**) patients older than 45 years; (**F**) patients without lymph node metastases; (**G**) patients with lymph node metastases; (**H**) patients without distant metastases; (**I**) patients with distant metastases.
Abbreviations: aHR, adjusted hazard ratios; DSS, disease-specific survival.

analysis was potentially biased by prejudices: those receiving RAI had generally more risk factors (larger tumor size, extrathyroidal extension, lymph nodes and distant metastases) and a more advanced stage of disease; they tend to have a poorer prognosis, thus the survival benefit of RAI therapy would be cancelled by the worse disease features. To decrease the bias caused by patients' characteristics, we categorized patients into different groups (Figure 1), and we found that only those who had relatively high risk factors benefited from RAI therapy. In addition, molecular markers were not included in SEER. It is reported that *BRAF* had clinical value in planning the treatment strategy. *BRAF* was associated with more aggressive clinical behaviors, thus it predicted higher necessity of postoperative RAI ablation.[31] The SEER database has recorded no information about recurrence. Due to the indolent nature of PTC, recurrence is more meaningful than death. Despite these limitations, SEER is still important in understanding the associations between treatment outcomes and specific risk factors. Long-term randomized trials are needed for further study.

Conclusion

RAI ablation should be recommended to patients with tumors <2 cm with distant metastasis or tumors >2 cm with one of the following factors: gross extrathyroidal extension, age >45 years, lymph node and distant metastases. To optimize the treatment strategy for PTC patients, it is very important to consider all the risk factors.

Acknowledgment

We thank Qi Wu for assistance in improving the quality of language and revising the statistical methods.

Author contributions

All authors contributed toward data analysis, drafting and critically 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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