Postoperative radioactive iodine-131 ablation is not necessary among patients with intermediate-risk differentiated thyroid carcinoma: a population-based study

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Keywords: Differentiated thyroid carcinoma -Intermediate risk -Surgery -Prognosis -Radioactive iodine ablation -End results (SEER) Programme

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Received:
25 February 2017
Accepted revised :
20 March 2017

Abstract

Objective: To assess the effectiveness of radioactive iodine (RAI) ablation among patients with intermediate-risk differentiated thyroid cancer (DTC) following surgery. **Subjects and Methods:** This population based study obtained information from the Surveillance, Epidemiology, and End Results (SEER) Program Research Data (1973-2013). National Cancer Institute, DCCPS, Surveillance Research Programme, Surveillance Systems Branch, released April 2016, based on the November 2015 submission. A total of 93,530 patients with primary thyroid cancer were identified in the SEER database during the period of 2004–2013 and focused on patients with DTC post-operatively treated or not treated with radioactive iodine (RAI). From these 9,127 patients were selected who had intermediate-risk DTC. A total of 8,601 patients were included in this study. For the overall population, the mean age of the population was 47.3 years and the majority were female (70.5%). **Results:** Kaplan-Meier analysis found the mean overall survival time (OS) for subjects with no radiation therapy which was 112.9 months and 114.9 months for those who received RAI ablation treatment (P< 0.001). However, thyroid cancer-specific survival was not significantly different between treatment groups (117.7 vs. 118.0 months, log-rank test P=0.164). Overall survival and thyroid cancer-specific 1 year, 5 years, and 10-years survival rates were ⩾89.8% and were similar between both treated groups. Multivariate analysis found age, gender, histologic type, and degree of lymph node metastases to be associated with OS, and age, gender, degree of lymph node metastasis and extra-thyroid tumor spread were independent factors for cancer-specific survival. In DTC patients with intermediate cancer risk multivariate analysis found that RAI was associated with a reduced risk of mortality compared with no radiation therapy (HR= 0.710, 95% CI: 0.562-0.897, P=0.004) but no significant difference was seen in cancer-specific survival, either based on whole study population or on tumor size category. **Conclusion:** In DTC patients with intermediate cancer risk although postoperative RAI ablation following surgery showed a benefit in overall survival, no significant difference was seen in cancer-specific survival, either based on whole study population or on tumor size category.

Hell J Nucl Med 2017; 20(1): 3-10 *Epub ahead of print: 20 March 2017* *Published online: 20 April 2017*

Introduction

Differentiated thyroid cancer (DTC), including papillary and follicular histotypes, make-up >90% of all thyroid cancers [1]. An increased incidence of DTC has been observed worldwide and may be attributable to better detection of early disease [1].

Differentiated thyroid cancer can be treated through complete surgical ablation, that is considered the ideal surgical treatment [2-4]. However, in a number of patients significant remnants are left in situ, and in such cases administration of radioactive iodine (RAI) is used. The goal of remnant ablation is to eliminate any normal thyroid tissue remaining after surgery, and to destroy suspected microscopic neoplastic cells with the idea of improving disease-free survival [5]. However, RAI is associated with several adverse events which negatively impact treatment outcomes [5]. In the past years, RAI ablation was indicated for almost every patient with DTC, however more recently, the management of DTC has changed in order to consider the individual risk of the patients for recurrent disease [5-8].

The individual risk of a patient depends upon a number of factors including gender, family history of the disease, tumor characteristics, presence of metastases, as well as serum thyroglobulin (Tg) levels and results of neck ultrasonography following surgery [5, 9-11]. Low risk patients undergo lesser surgery with or without RAI, and high-risk patients are managed aggressively with total thyroidectomy, compartment-based neck dissection, and high dose RAI [5, 6]. However, due to a paucity of clinical study data, the management of patients with intermediate-risk disease is not well defined. Intermediate risk

DTC is the second most common presentation which varies from 25% to 35% of all DTC [12]. Patients with intermediate disease are defined by the American Thyroid Association (ATA) as having one or more of the following characteristics: age >45 years, vascular invasion, microscopic extrathyroidal extension (T3), the presence of cervical lymph node metastases (pN1), and the presence of aggressive histological variants [5, 9]. To-date only four studies have evaluated treatment efficacy of RAI in intermediate-risk patients [12-15]. None of these studies evaluated the impact of RAI ablation therapy on the prognosis of patients with intermediate-risk DTC. The aim of this study was to investigate the prognostic effect of RAI ablation in intermediate-risk patients following surgery.

Subjects and Methods

Data source

This population based study obtained patient data information from the Surveillance, Epidemiology, and End Results (SEER) Programme (www.seer.cancer.gov) Research Data (1973-2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission. The SEER program is a population-based cancer registry covering approximately 30% of the population of the United States. The database is the largest available public and authoritative information source on cancer incidence and survival. All of the SEER data are de-identified, and hence, analysis of the data does not require Institutional Review Board approval or subject informed consent. We received permission to access the SEER database (reference number is 13765-Nov 2015).

Study population

Patients with a diagnosis of DTC (ICD-O-3 site C739) and histologic types of papillary thyroid carcinoma (ICD-O-3: 8050, 8340~8344) or follicular thyroid carcinoma (ICD-O-3: 8330~8332, 8335) were identified in the SEER database. All patients selected were in the postoperative state (cancer-directed surgery=10~80, 90). Intermediate-risk category was extracted based on the American Joint Committee on Cancer (AJCC) TNM classification system of T1/2 N1 M0 and T3 with/without N1 M0.

Study variables

The study endpoints were overall survival (OS) and overall mortality of cancer-specific death. Overall survival was calculated from the day of diagnosis to the date of death from any cause. Cancer-specific death designated that the person died of their cancer, and was calculated from the day of diagnosis to the date of death, which was indicated as "Vital Status" in the SEER database. Independent variables assessed included use of postoperative RAI and no radiotherapy. Relative variables collected included patient demographics (age at diagnosis, gender, race/ethnicity) and disease characteristics (histology, tumor size, degree of spread to regional lymph node, extrathyroidal spread of tumor and number of tumors observed).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, with independent sample t-test, categorical data were shown as count and percentage, with chi-square test or Fisher's exact test. Kaplan-Meier method with log-rank test was used to compare OS and cancer-specific survival between receiving no radiation therapy group and the RAI group. Univariate and multivariate Cox regression model were used to identify risk factors for survival outcomes. Variables that showed significant association with overall survival and cancer-specific survival by univariate analysis were selected for multivariate Cox regression analysis. For overall survival analysis, any cause of deaths was treated as events and survivors were treated as censored events. Among cancer-specific survival, deaths attributed to thyroid cancer were considered as events and deaths from other causes or survivors were treated as censored events. Statistical analyses were performed by IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, USA). And two-tailed $P < 0.05$ indicated statistical significance.

Results

Study subject

A total of 93,530 patients with primary thyroid cancer were identified in the SEER database during the period of 2004-2013. From these 9,127 patients were selected who had intermediate-risk DTC and histologic subtypes of papillary thyroid carcinoma or follicular thyroid carcinoma. Fifty-four patients who had no surgery performed and 472 patients who received non-RAI ablation therapy or whose therapy was unknown were exclude. A total of 8,601 patients were included in this study.

For the overall population, the mean age of the population was 47.3 years and the majority were female (70.5%). RAI ablation therapy was received by 67.6% of the population (Table 1). Patient and disease characteristics differed between treatment groups. The mean patient age was significantly higher in subjects with no radiation therapy then in the RAI group (48 vs. 47 years, $P = 0.008$). More patients in the RAI group were white had papillary thyroid carcinoma and a tumor size of T1/T2 compared with the non-radiation group. Fewer subjects in the RAI group had T3 tumors, no metastasis to regional lymph nodes (N0), localized tumors with no extra-thyroid extension (ETE), and solitary tumors (P values<0.001).

Overall survival

During the study period, a total of 294 patients died, 69 of which were attributed to thyroid cancer. Kaplan-Meier analysis found a significant difference in OS between no radiation therapy and RAI ablation; the mean OS time of subjects

Table 1. *Baseline of thyroid cancer patients in SEER database.*

Characteristics	Total (N=8601)	Radioactive iodine ablation		P-value
		No radiation therapy (N=2785)	Radioactive iodine ablation (N=5816)	
Age	47.34±15.47	48.0±16.10	47.03±15.15	0.008*
Gender				0.068
Male	2517(29.3)	779(28.0)	1738(29.9)	
Female	6084(70.7)	2006(72.0)	4078(70.1)	
Race				<0.001*
White	6888(81.1)	2178(79.5)	4710(81.8)	
Black	727(8.6)	290(10.6)	437(7.6)	
Others	881(10.4)	270(9.9)	611(10.6)	
Histologic type				<0.001*
Papillary thyroid carcinoma	7192(83.6)	2244(80.6)	4948(85.1)	
Follicular thyroid carcinoma	1409(16.4)	541(19.4)	868(14.9)	
Tumor size				0.001*
T1/T2	2344(27.3)	696(25.0)	1648(28.3)	
T3	6257(72.7)	2089(75.0)	4168(71.7)	
Degree of spread to regional lymph nodes				<0.001*
N0	4719(54.9)	1715(61.6)	3004(51.7)	
N1	499(5.8)	159(5.7)	340(5.8)	
N1a	2140(24.9)	608(21.8)	1532(26.3)	
N1b	1168(13.6)	258(9.3)	910(15.6)	
NX	75(0.9)	45(1.6)	30(0.5)	
Extrathyroidal spread of the tumor				<0.001*
Localized with no ETE	5150(62.5)	1759(66.3)	3391(60.7)	
Minimal ETE	1524(18.5)	438(16.5)	1086(19.4)	
Prominent ETE[1]	1568(19.0)	455(17.2)	1113(19.9)	

Number of tumors seen				<0.001*
No evidence of primary tumor, primary tumor in ectopic thyroid tissue	34(0.4)	17(0.6)	17(0.3)	
Solitary tumor	4331(51.0)	1564(56.9)	2767(48.2)	
Multifocal tumor	4126(48.6)	1167(42.5)	2959(51.5)	

Age was presented as mean ± standard deviation and other factors were expressed as frequency (%). ETE, extrathyroid extension Significant difference among the groups, P<0.051 Prominent ETE refers to tumor extension to pericapsular soft tissue/connective tissue, parathyroid, nerves, cricoid cartilage surrounding, and trachea*

with no radiation therapy was 112.9 months and was 114.9 months in patients who were given RAI (log-rank test, P< 0.001) (Figure 1). However, thyroid cancer-specific survival was not significantly different between treatment groups (117.7 for no radiation vs. 118.0 months for RAI; log-rank test P=0.164) (Figure 1). Overall survival 1 year, 5 years, and 10 years survival rates were: 98.5%, 95.0% and 89.8% for the subjects with no radiation therapy and 99.7%, 96.8% and 92.2% for the subjects with RAI ablation. For rates of cancer-specific survival, the 1 year, 5 years and 10 years survival rates were 99.5%, 98.8% and 98.2% for the subjects of no radiation therapy; 99.9%, 99.2% and 97.8% for the subjects of RAI ablation.

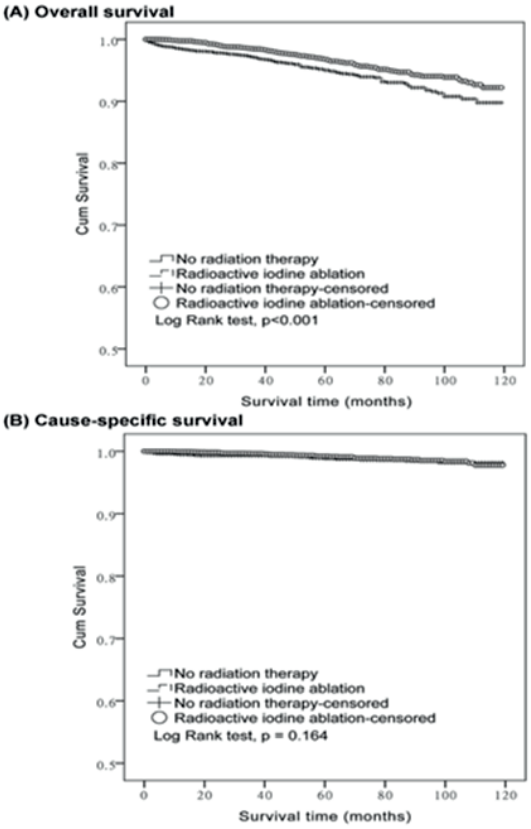

Figure 1. Comparison of differences between no radiation therapy and radioactive iodine ablation in the (A) overall survival and (B) cause-specific survival of patients with primary thyroid cancer.

Overall survival and cancer-specific survival based on tumor size

Overall survival and cancer-specific survival were evaluated by tumor size between no radiation and RAI ablation groups. No difference was observed between treatment groups for OS (114.4 months for no radiation vs. 115.8 months for RAI; log-rank test P=0.113) and cancer specific survival (118.6 months for no radiation vs. 118.5 months for RAI; log-rank test P=0.801) in subjects with T1/T2 size tumors. However, the RAI ablation group had significantly longer survival time than the no radiation therapy group in subjects with T3 stage cancer (114.7 vs. 112.4 months, respectively; log-rank test P<0.001) (Figure 2). No difference was seen between groups for cancer-specific survival in patients with T3 cancer (117.3 months for no radiation vs. 117.8 months for RAI, log-rank test P=0.154) (Figure 3).

Risk factors of mortality

Univariate Cox regression analysis found that age, gender, histologic types, RAI ablation, tumor size, and degree of spread to regional lymph nodes were significant factors for overall survival (P values < 0.05) (Table 2). It also indicated that age, gender, tumor size, degree of spread to regional lymph nodes and extrathyroidal spread of the tumor were significant factors for cancer-specific survival (P values <0.05) (Table 2).

The factors found to be significant in univariate analysis were used in the multivariate Cox regression models for OS and cancer-specific survival (Table 2) Multivariate analysis found that age, gender, histologic type, and degree of spread to regional lymph nodes were independent factors associated with OS (P= 0.043) (Table 2). Age, gender, degree of spread to regional lymph nodes and extrathyroidal spread of the tumor were independent factors associated with cancer-specific survival. Multivariate analysis also found the RAI ablation was associated with a reduced risk of mortality compared with no radiation therapy (HR=0.710, 95% CI: 0.562-0.897, P=0.004).

Discussion

The management of DTC has recently changed so that treat-

ment strategy is individualized based on risk stratification . This population based study investigated the effectiveness of RAI therapy following surgery among patients with intermediate-risk DTC. The study found that RAI ablation was associated with longer OS compared with radiation therapy (112.9 vs. 114.9 months, respectively). However, both treatments were similar with respect to cancer-specific survival. Age, being male, and degree of lymph node metastasis were associated with reduced OS and cancer-specific survival. Histological type and extra-thyroid tumor spread were also independent factors for OS and cancer-specific survival, respectively.

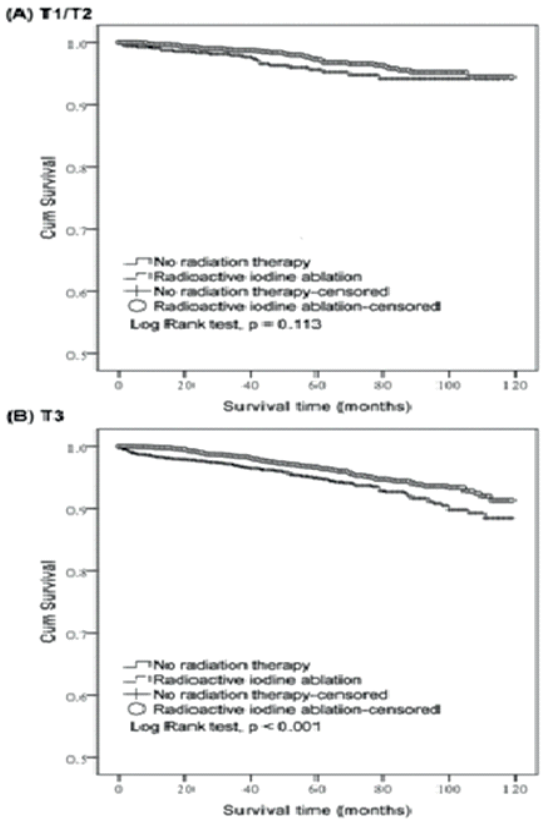

Figure 2. Differences in overall survival between no radiation therapy and radioactive iodine ablation in the (A) T1/T2 and (B) T3 "stage cancer", respectively.

Only a limited number of studies have evaluated the prognosis of the use of RAI ablation in patients with intermediate following surgery. A prior study assessed the use of adjuvant RAI therapy following surgery in patients with intermediate risk DTC [12]. Ballal et al. (2016) [12] included patients with DTC that either had surgical ablation (GR-1) or following surgery had significant remnant/nodal disease (GR-2). Only patients in the GR-2 group were treated with RAI therapy. Depending upon adjuvant RAI outcome, the GR-2 patients were separated into ablated (GR-2a) or not ablated (GR-2b). Over a median follow-up time of 10.3 years, 9.6% (12/125) of patients in the GR-1 groups had disease recurrence and 8% had persistent disease, and 5.9% (6/102) and 4.9% in the GR-2a group had disease recurrence or persistent disease, respectively. In patients that failed RAI therapy (GR-2a) 29.6% (8/27) had persistent disease (P=0.000). Overall survival was 100% for both groups, and disease-free survival were 92% for GR-1 and 90% for GR-2 groups. The authors concluded that RAI was not necessary patients whose DTC was surgically ablated, and that in patients who failed to achieve ablation after their first dose of RAI, perhaps should be considered to be in the high-risk category and treated aggressively.

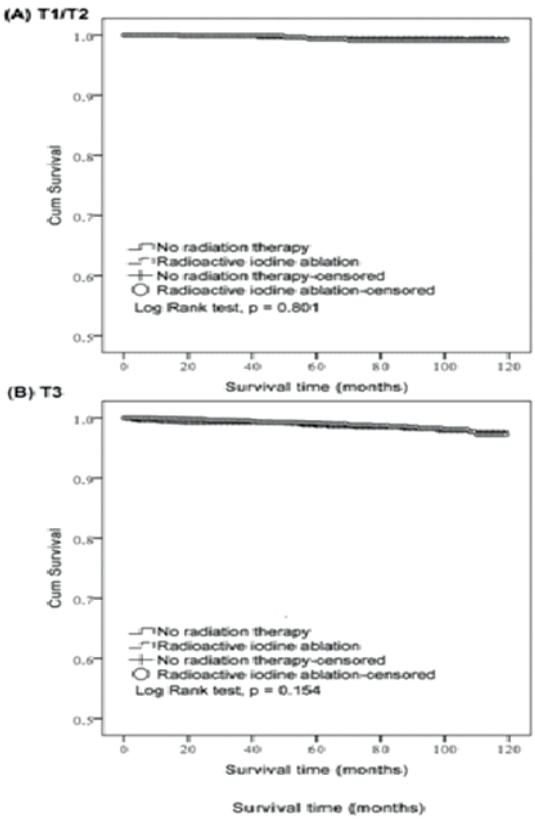

Figure 3. Differences in cancer-specific survival between no radiation therapy and radioactive iodine ablation in the (A) T1/T2 and (B) T3 "stage cancer", respectively.

Castagna et al. (2013) [15] evaluated the impact of low dose (1110-1850MBq) and high dose (⩾3700MBq) RAI therapy in patients with DTC classified as of intermediate risk. Of patients with low or high dose RAI therapy, 60% in each group had disease remission six to 18 months after ablation surgery. Persistent disease was observed in 18.8% of patients treated with low and in 14.3% of patients treated with high RAI dose, and metastatic disease was seen in 21.2% and 27.5% of patients, respectively (P=0.56). At 4.2 to 6.9 years, disease remission occurred in 76.5% of patients treated with low dose in 72.1% of those treated with high dose RAI, and death occurred in 2.4% and 2.1% of these patients, respectively. The authors conclude that in patients with DTC, high dose RAI therapy showed no advantage to low dose RAI therapy. The findings of Castagna et al. are supported by two earlier meta-analyses which found, using pooled data from randomized trials, that use of lower RAI doses was as effective as higher doses of RAI for thyroid remnant ablation [17, 18]. We did not evaluate the effect of dose on outcomes in our study.

However, Castagna et al. (2013) do not explain in the published paper the need for RAI remnant ablation therapy in the

Table 2. *Cox regression analysis of overall survival and cancer-specific survival*

Characteristics	Overall survival				Cancer-specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.087 (1.078,1.096)	<0.001*	1.087 (1.078,1.097)	<0.001*	1.088 (1.069,1.107)	<0.001*	1.090 (1.071,1.111)	<0.001*
Gender								
Male	Reference		Reference		Reference		Reference	
Female	0.482 (0.383,0.606)	<0.001*	0.621 (0.492,0.783)	<0.001*	0.486 (0.302,0.779)	<0.003*	0.596 (0.366,0.971)	<0.038*
Race								
White	Reference				Reference			
Black	1.478 (0.703,3.108)	0.303			1.478 (0.703,3.108)	0.303		
Others	1.316 (0.625,2.768)	0.469			1.316 (0.625,2.768)	0.469		
Histologic type								
Papillary thyroid carcinoma	Reference		Reference		Reference			
Follicular thyroid carcinoma	1.746 (1.348,2.262)	<0.001*	1.343 (1.009,1.786)	0.043*	1.592 (0.921,2.753)	0.096		
Radioactive iodine ablation								
No radiation therapy	Reference		Reference		Reference			
Radioactive iodine ablation	0.631 (0.501,0.795)	<0.001*	0.710 (0.562,0.897)	0.004*	0.712 (0.440,1.151)	0.166		

(continued)

Tumor size								
T1/T2	Reference		Reference		Reference		Reference	0.265
T3	1.415 (1.066,1.879)	0.016*	1.127 (0.774,1.642)	0.534	2.780 (1.330,5.810)	0.007*	1.758 (0.652,4.740)	
Degree of spread to regional lymph nodes								
N0	Reference		Reference		Reference		Reference	
N1	0.723 (0.445,1.175)	0.190	1.661 (0.960,2.872)	0.070	1.402 (0.623,3.154)	0.414	3.607 (1.489,8.743)	0.005*
N1a	0.713 (0.522,0.974)	0.033*	1.526 (1.030,2.260)	0.035*	0.545 (0.253,1.172)	0.120	1.039 (0.434,2.488)	0.931
N1b	1.059 (0.757,1.483)	0.737	1.907 (1.281,2.839)	0.001*	1.967 (1.091,3.546)	0.024*	3.285 (1.684,6.409)	<0.001*
NX	1.883 (0.834,4.248)	0.128	1.823 (0.805,4.131)	0.150	3.108 (0.748,12.913)	0.119	3.405 (0.816,14.209)	0.093
Extrathyroidal spread of the tumor			Reference					
Localized with no ETE	Reference				Reference		Reference	
Minimal ETE	1.155 (0.844,1.581)	0.368			2.099 (1.091,4.039)	0.026*	1.704 (0.813,3.576)	0.158
Prominent ETE[1]	1.266 (0.958,1.673)	0.098			3.527 (2.066,6.022)	<0.001*	2.585 (1.353,4.938)	0.004*
Number of tumors seen								
No evidence of primary tumor, primary tumor in ectopic thyroid tissue	Reference				Reference			
Solitary tumor	0.693 (0.172,2.795)	0.606			0.346 (0.048,2.515)	0.294		
Multifocal tumor	0.565 (0.140,2.287)	0.424			0.225 (0.030,1.663)	0.144		

** Significant factors, P<0.05. ETE, extrathyroid extension; HR, Hazard ratio; CI, Confidence interval. 1 Prominent ETE refers to tumor extension to pericapsular soft tissue/connective tissue, parathyroid, nerves, cricoid cartilage surrounding, and trachea*

patients who had complete surgical ablation [15]. It is of interest that the study of Ballal et al. (2016) indicated that adjuvant RAI therapy is not necessary in surgically ablated patients [12]. The findings of our study suggested that even in patients without complete surgical ablation, RAI showed benefit for OS but not for cancer-specific death, raising the questions of when it is necessary/advisable to use RAI following surgery.

Ballal et al. (2016) using univariate analysis found that prognostic factors associated with tumor recurrence in the intermediate-risk patients with DTC were being >45 years of age, TNM stage IVa, stimulated Tg levels at first follow-up >10 ng/mL, and failure to attain remission with the initial dose of RAI therapy [12]. These findings are similar to prior studies [19-22]. We also found that age, histologic type, and degree of lymph node metastasis impacted the prognosis of patients following RAI on OS and cancer specific survival.

Like other published studies that used SEER databases, our study has several limitations that should be considered. Although SEER conducts regular audits to evaluate both data completeness and quality, some misclassification of patient information (e.g., tumor size or subtype diagnosis) are inevitable. In addition, though the SEER database includes a large comprehensive database of patients with thyroid cancer, the database only captures a limited percentage (about 30%) of the U.S. population. Furthermore, populations in other countries may not behave the same and the occurrence of DTC in other populations may vary.

In conclusion, this population based study found that RAI improved OS but not cancer-specific survival following surgery in patients with DTC. It also showed that the impact of RAI on OS and cancer-specific survival were not dependent upon tumor size. Given the results of the present study, a clinician needs to assess the need of RAI ablation among DTC patients, especially of low and intermediate-risk.

Acknowledgements

The authors acknowledge the efforts of the Surveillance, Epidemiology and End Results (SEER) Program tumor registries in the creation of the SEER database. The interpretation and reporting of these data are the sole responsibility of the authors.

Funding source

This work was supported by Grant [2013]163 from Key Laboratory of Malignant Tumor Molecular Mechanism and Translational Medicine of Guarngzhou Bureau of Science and Information Technology; Grant KLB09001 from the Key Laboratory of Malignant Tumor Gene Regulation and Target Therapy of Guangdong Higher Education Institutes.

The authors declare that they have no conflicts of interest

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