

Disease Severity and Radioactive Iodine Use for Thyroid Cancer

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Context: Although variation in radioactive iodine (RAI) use for thyroid cancer has been demonstrated, the role of region and nonclinical correlates of use within risk groups has not been investigated.

Objective: The objective of the study was to determine the correlates of RAI use within risk groups.

Design/Setting/Patients: Use of RAI was evaluated across 9 US regions in 85 948 patients with well-differentiated thyroid cancer diagnosed between 2004 and 2008 at 986 hospitals associated with the US National Cancer Database. Cancers were then categorized as low risk (tumor size ≤ 1 cm and American Joint Committee on Cancer stage I disease), medium risk (neither low nor high-risk), and high risk (American Joint Committee on Cancer stage III or IV). Within each risk stratum, the role of region and nonclinical correlates of RAI use were evaluated using hierarchical logistic regression.

Main Outcome Measure: Use of RAI was measured.

Results: Rates of RAI use varied across geographic regions from 49% to 66%. Regional differences persisted after controlling for patient and hospital characteristics and evaluating less vs more intensive regions within low-risk [odds ratio (OR) 0.36 (95% confidence interval [CI] 0.25–0.53)], medium-risk [OR 0.23 (95% CI 0.16–0.34)], and high-risk cancers [OR 0.30 (95% CI 0.19–0.49)]. Patterns of RAI use were similar in medium- and high-risk patients. The most nonclinical correlates of use were in low-risk patients.

Conclusion: Similar treatment patterns for the heterogeneous medium-risk thyroid cancer patients compared with the high-risk patients suggest more intensive management in patients with medium-risk disease. The large number of nonclinical correlates of RAI use, including region, imply controversy over indications for RAI. (*J Clin Endocrinol Metab* 98: 678–686, 2013)

There is large variation in radioactive iodine (RAI) use for thyroid cancer with much of the variation attributed to the hospital at which care is received (1). The general trend has been an increase in RAI use over time, both for small and large tumors (1, 2). These treatment trends have implications for patients and for the health care system. RAI is associated with damage to other iodine avid

tissues and, rarely, second primary malignancies (3, 4). In addition, the administration of RAI in patients with low-risk disease is more costly (5).

Although variation in the use of RAI has been documented, patterns of use within risk categories remain unknown. We hypothesized that there would be both regional variation in RAI use, most likely due to unmeasured

differences in provider knowledge, attitudes, and beliefs and that the correlates of RAI use would differ between low-, medium-, and high-risk patients. To test these hypotheses, we evaluated correlates of RAI use, including region of the United States, across risk strata in a large cohort of patients treated at 986 hospitals associated with the US National Cancer Database between 2004 and 2008.

Materials and Methods

Data source and study population

The National Cancer Database is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. Close to 85% of all thyroid cancers in the United States are included in this database (6). We selected the 85 948 patients diagnosed with well-differentiated thyroid cancer between 2004 and 2008 who underwent total thyroidectomy. The cohort of patients was selected from hospitals affiliated with the US National Cancer Database four of the 5 specified years. After a patient was diagnosed and treated at a Commission on Cancer-accredited cancer program, the hospital registrar was responsible for documenting care, even when the patient was transferred to another facility (7). The data were then coded and reported according to nationally established protocols coordinated by the North American Association of Central Cancer Registries (8). Because no patient, physician, or hospital identifiers were examined, the University of Michigan Institutional Review Board granted exemption for this study.

Measures

Hospitals were assigned to their corresponding US census region. States included in the New England region were Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, and Vermont. The mid-Atlantic region consisted of New York, New Jersey, and Pennsylvania. The South Atlantic region included Washington, DC; Maryland; Delaware; Florida; Georgia; North Carolina; South Carolina; Virginia; and West Virginia. The East North Central region involved Illinois, Indiana, Michigan, Ohio, and Wisconsin. The East South Central region included Alabama, Kentucky, Mississippi, and Tennessee. The West North Central region included Iowa, Kansas, Minnesota, Missouri, North Dakota, Nebraska, and South Dakota. The West South Central region consisted of Arkansas, Louisiana, Oklahoma, and Texas. The Mountain region encompassed Arizona, Colorado, Idaho, Montana, New Mexico, Nevada, Utah, and Wyoming. The Pacific region included Alaska, California, Oregon, Washington, and Hawaii.

We created 3 disease severity categories for subgroup analysis. Because recent clinical guidelines do not recommend RAI in tumors 1 cm or less unless there are additional high-risk features, tumors that are 1 cm or less and still American Joint Committee on Cancer (AJCC) stage I were included in the low-risk category. Because RAI is typically recommended for iodine-avid advanced stage disease, AJCC stage III or IV cancers were categorized as high risk. The medium-risk category was a heterogeneous population that did not belong in the low or high-risk categories. In many cases medium-risk thyroid cancer would be associated with a selective-use recommendation in the recent guidelines (9).

As previously described (1), hospital case volume categories were created by computing a weighted average of the annual thyroid cancer case volume at each reporting cancer program for the years 2004–2008 and dividing the distribution into equal-sized quintiles of hospitals. We then combined the lowest 2 and then the middle 2 quintiles to create 3 volume categories: low (≤ 11 cases per year), medium (12–34 cases per year), and high (≥ 35 cases per year). Patient age was stratified into 4 biologically relevant groups: age less than 20, 20–44, 45–59, and 60 years and older. Patient race/ethnicity was categorized by the National Cancer Database as non-Hispanic white, black, Hispanic, Asian/Pacific Islanders, and Native American. Due to smaller numbers, Hispanic, Asian/Pacific Islanders, and Native American were collapsed into the category, other. Race/ethnicity was included in the analysis because race/ethnicity has been shown to influence cancer treatment (10). With data drawn from the 2000 Census, we assigned insurance type and rural-urban continuum. We used the Charlson-Deyo Index to identify comorbid conditions within the cohort (11, 12). Tumor size was categorized according to the definitions used by the AJCC (13). Tumor histology was limited to the International Classification of Diseases for Oncology classification codes for papillary, follicular, and Hurthle cell cancer types (14). Lymph node status was classified as no lymph node metastases (N0), lymph node metastases (N1), or unknown lymph node status (NX). Distant metastases were either present or absent.

Statistical analyses

Our analytical cohort was comprised of patients diagnosed with well-differentiated thyroid cancer between 2004 and 2008 who underwent total thyroidectomy. To assess the role of region and nonclinical correlates of RAI use among low-, medium-, and high-risk patients, we performed stratified analyses. Within each disease severity category, hierarchical logistic regression models (15, 16) were fitted to obtain unadjusted and adjusted odds ratios (OR) for the use of radioactive iodine corresponding to region, hospital case volume, and patient clinical and nonclinical covariates. To account for the clustering of thyroid cancer patients within hospitals, we included a random hospital-specific intercept.

We let $Y_{ij} = 1$, if the j th patient seen at the i th hospital used radioactive iodine, and $Y_{ij} = 0$ otherwise. The probability of radioactive iodine use by the j th patient seen at the i th hospital can then be modeled as follows:

- Level 1 was between patients (within hospitals), logit [$P(Y_{ij} = 1) = \mu_{0i} + \theta' X_{ij}$];
- Level 2 was between hospitals: $\mu_{0i} = \beta_{00} + \beta_{0i} + \gamma' Z_i$;
- Combined model was logit [$P(Y_{ij} = 1) = \beta_{00} + \beta_{0i} + \gamma' Z_i + \theta' X_{ij}$]

where β_{00} is the population-averaged log odds of radioactive iodine use, and β_{0i} is the hospital-specific random effect that captures the heterogeneity across hospitals. The random intercept β_{0i} is assumed to follow a normal distribution with mean 0 and variance σ^2_{hosp} , X_{ij} is the matrix of patient clinical and non-clinical covariates, θ is the corresponding vector of fixed effects representing changes in the log odds of radioactive iodine use corresponding to each unit change in the covariate values, Z_i represents the vector of hospital-level covariates (hospital region and case volume) for the i th hospital, and γ is the corresponding vector of coefficients. We obtained the model estimates using the

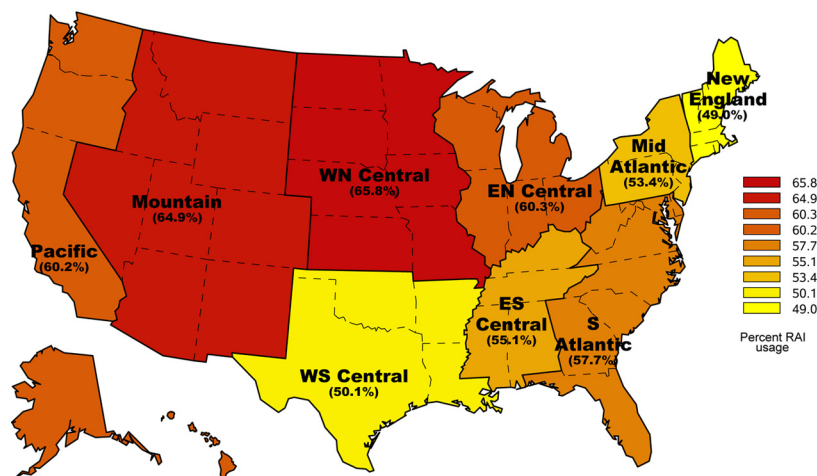


Figure 1. Use of RAI by region of the United States.

likelihood-based approach in SAS PROC GLIMMIX (SAS version 9.3; SAS Institute, Cary, North Carolina).

All statistical analyses were performed using SAS software (SAS version 9.3; SAS Institute). We calculated 95% confidence intervals (CI), and exclusion of the null value (1) was considered statistically significant.

Results

Region and RAI use

Figure 1 demonstrates the large regional variation in RAI use for thyroid cancer with the New England region treating 49% of patients and the West North Central region treating 66% of patients. As shown in Fig. 2, although the proportion of patients treated varies by disease severity category, regional variation is present in all 3 risk groups. The proportion of patients receiving RAI ranged from 28% to 47% of low-risk patients, 57% to 76% of medium-risk patients, and 60% to 76% of high-risk patients.

Low-risk thyroid cancer

Table 1 shows the correlates of RAI use in low-risk patients. There are significant differences in RAI use based on the region in which treatment is received. Relative to the West North Central region, New England is significantly less likely to treat low-risk patients with RAI [OR 0.36 (95% CI 0.25–0.53)] after controlling for hospital case volume, patient sex, patient age, comorbidity, race, insurance, rural-urban continuum, tumor histology, and lymph node involvement. The low-volume hospitals were slightly less likely to treat low-risk patients with RAI than the high-volume hospitals. Nonclinical patient correlates of less RAI use in low-risk patients included: age 60 years or older, 1 or more comorbidities, black race, Medicaid/uninsured, and Medicare insurance. Papillary thyroid cancer patients were less likely to receive RAI than follicular/Hurthle cell patients. Those without lymph node

metastases or with unknown metastases were less likely to receive RAI than those with lymph node metastases.

Medium-risk thyroid cancer

Table 2 shows correlates of RAI use in medium-risk patients. Although a larger proportion of patients with medium-risk disease receive RAI, similar to low-risk patients, region, low hospital case volume, Medicaid/uninsured, Medicare insurance, and absence of lymph node metastases were associated with less RAI use. In the adjusted model, there was a significant difference in RAI use based on region, with the greatest difference seen

between the mid-Atlantic and West North Central regions [OR 0.23 (95% CI 0.16–0.34)]. Similar to the other risk categories, RAI use in New England was still low.

High-risk thyroid cancer

Table 3 shows the factors that correlate with RAI use in high-risk patients. Similar to other risk categories, region and low hospital case volume still correlate with less RAI use. The maximum regional difference is between the New England and West North Central regions [OR 0.30 (95% CI 0.19–0.49)]. Nonclinical patient correlates of less use for high-risk patients include age 60 years or older and Medicare insurance. Both age and insurance status were independent predictors of RAI use. In contrast to low-risk disease, patients with papillary thyroid cancer are more likely to receive RAI than those with follicular/Hurthle cell cancer. Similar to low- and medium-risk patients, not having any lymph node metastases is associated with less RAI use.

Discussion

The proportion of patients across US regions receiving RAI was similar in medium- and high-risk patients. Regional treatment variation was seen in all risk categories, with a greater number of nonclinical correlates of RAI use in low-risk patients compared with medium- and high-risk patients.

It is known that some providers prefer more intensive management of thyroid cancer (17–19), and a previous survey study suggests that these treatment preferences differ by region (20). These physician-driven differences in treatment intensity may explain the regional variation seen in the management of low- and medium-risk disease. The persistence of this regional variation in high-risk patients was less expected. One contributing factor to re-

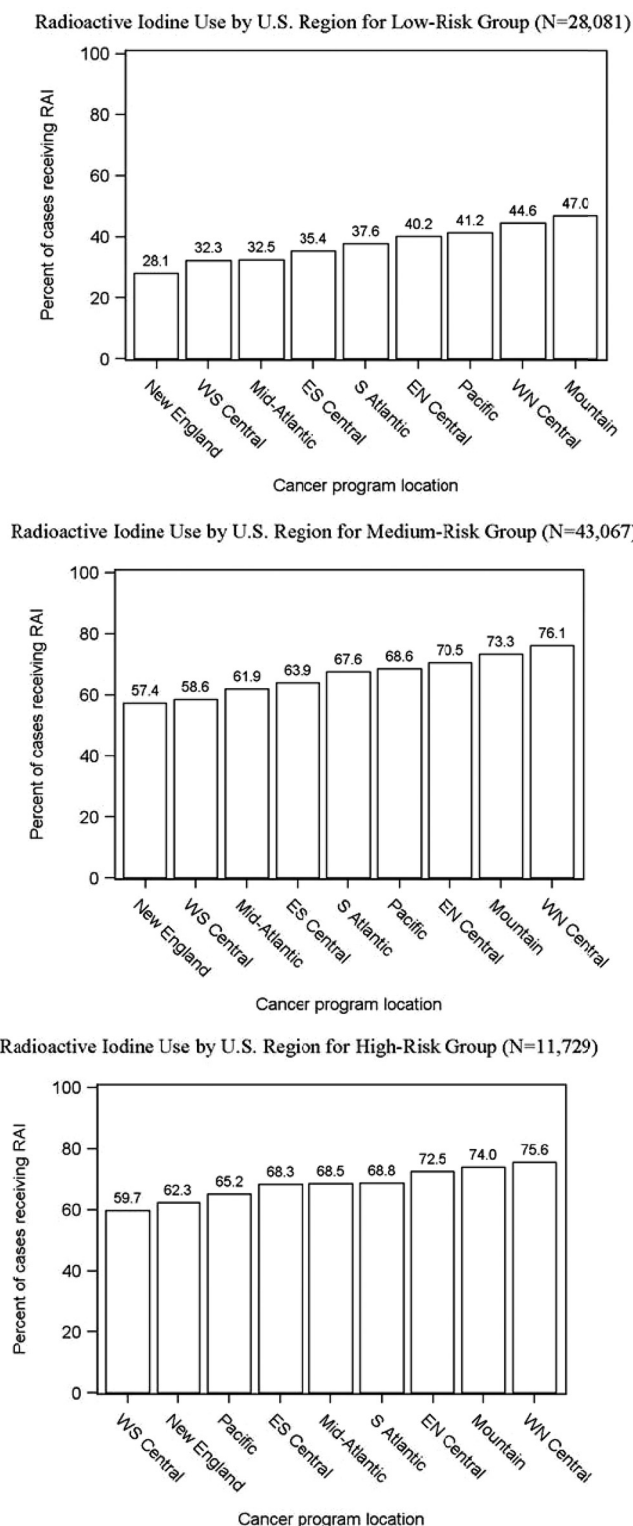


Figure 2. RAI use by region within low-, medium-, and high-risk patients.

gional variation in high-risk patients may be differences in provider beliefs regarding prophylactic central lymph node dissections and pretreatment scans, which can influence the perceived indications for RAI (21). For example, prophylactic central lymph node dissection can reveal occult lymph node metastases, which would subsequently

upstage as many as one third of patients over age 45 years to AJCC stage III (22, 23). Because some regions may be less likely to perform prophylactic central lymph node dissections, they may have fewer patients with occult micro-metastases in their stage III cohort, thus potentially influencing the proportion of patients treated with RAI. In addition, assuming no extrathyroidal extension, some providers would assume surgical cure after prophylactic lymph node dissection, whereas others would treat with RAI (22, 24, 25). In addition to differences in physician treatment intensity and variable use of interventions that expose more disease, there is a large body of work in medicine correlating regional variation in use to health care spending, with greater use seen in high-spending regions (26, 27). It is possible that similar to other diseases, health care spending correlates with thyroid cancer treatment intensity.

The medium-risk thyroid cancer cohort is very heterogeneous because it can include patients under age 45 years with distant metastases and patients over the age of 45 years with 1.1–2 cm unifocal, intrathyroidal tumors. In contrast, the high-risk cohort is more homogeneous. Assuming iodine avidity, RAI would typically be recommended for the high-risk cohort (9). Yet, as shown in Fig. 2, the proportion receiving RAI across regions is very similar in the medium and high-risk cohorts. This suggests a lower threshold for RAI administration than what is advocated in the most recent guidelines, with a tendency for more aggressive management when treatment choices are left to provider discretion.

The clinical correlates of use we identified were consistent with our expectations. For example, it is probable that there is less RAI use for low-risk papillary thyroid cancers vs low-risk follicular/Hurthle cell cancers because these small, potentially indolent papillary thyroid cancers are often incidental discoveries in postoperative pathology. These occult papillary thyroid cancers are seen in 4%–10% of surgical pathology specimens when surgery is performed for benign thyroid disease (28, 29), and because close to one third of people have occult papillary thyroid cancers on thorough autopsy (30), there may be no clinical consequence to their discovery (31). In contrast, we found that for high-risk patients, those with papillary thyroid cancer are more likely to receive RAI than those with follicular/Hurthle cell cancer. Hurthle cell cancers are known to be less iodine avid than papillary cancer, thus potentially partially explaining this finding (32). Similarly, it is not surprising that the presence of lymph node metastases is associated with greater RAI use in all risk categories because many physicians use lymph node status as an indication for RAI (21, 22). There are 2 reasons that RAI use may not differ in patients with distant metastases

Table 1. RAI Use for Low-Risk Thyroid Cancer

	Patients, n, %		OR (95% CI)	
	Overall	Treated With RAI	Unadjusted	Adjusted
Hospital characteristics				
Hospital region				
EN Central	4519 (16.1)	1816 (40.2)	0.75 (0.56–1.00)	0.75 (0.55–1.01)
ES Central	1688 (6.0)	597 (35.4)	0.60 (0.42–0.85)	0.64 (0.44–0.92)
Mid-Atlantic	4807 (17.1)	1562 (32.5)	0.47 (0.35–0.64)	0.48 (0.35–0.66)
Mountain	1930 (6.9)	907 (47.0)	1.13 (0.78–1.63)	1.02 (0.69–1.51)
New England	1798 (6.4)	505 (28.1)	0.39 (0.27–0.55)	0.36 (0.25–0.53)
Pacific	3345 (11.9)	1379 (41.2)	0.84 (0.62–1.14)	0.75 (0.55–1.03)
S Atlantic	5597 (19.9)	2106 (37.6)	0.66 (0.49–0.88)	0.68 (0.50–0.91)
WS Central	2267 (8.1)	733 (32.3)	0.58 (0.42–0.81)	0.58 (0.41–0.83)
WN Central	2130 (7.6)	950 (44.6)	1.0 (Reference)	1.0 (Reference)
Case volume (cases/y)				
Low (≤ 11)	2480 (8.8)	801 (32.3)	0.77 (0.63–0.93)	0.81 (0.66–0.98)
Medium (12–34)	9423 (33.6)	3679 (39.0)	1.03 (0.87–1.21)	1.04 (0.87–1.23)
High (≥ 35)	16 178 (57.6)	6075 (37.6)	1.0 (Reference)	1.0 (Reference)
Patient characteristics				
Sex				
Female	23 392 (83.3)	8703 (37.2)	0.89 (0.83–0.95)	0.94 (0.87–1.02)
Male	4689 (16.7)	1852 (39.5)	1.0 (Reference)	1.0 (Reference)
Age (y)				
<20	259 (0.9)	113 (43.6)	1.84 (1.41–2.41)	1.06 (0.78–1.43)
20–44	9982 (35.5)	4361 (43.7)	1.85 (1.72–1.98)	1.25 (1.14–1.37)
45–59	10 841 (38.6)	3960 (36.5)	1.34 (1.25–1.43)	1.17 (1.07–1.28)
≥ 60	6999 (24.9)	2121 (30.3)	1.0 (Reference)	1.0 (Reference)
Charlson-Deyo comorbidity index score				
0	23 855 (85.0)	9156 (38.4)	1.31 (1.22–1.42)	1.13 (1.04–1.23)
≥ 1	4226 (15.0)	1399 (33.1)	1.0 (Reference)	1.0 (Reference)
Race/ethnicity				
Black	1827 (6.5)	510 (27.9)	0.61 (0.55–0.69)	0.66 (0.58–0.75)
Other	3561 (12.7)	1412 (39.7)	1.08 (0.99–1.17)	1.00 (0.91–1.10)
White	22 693 (80.8)	8633 (38.0)	1.0 (Reference)	1.0 (Reference)
Insurance				
Insurance, NOS	4302 (15.6)	1661 (38.6)	0.97 (0.89–1.05)	0.96 (0.88–1.05)
Medicaid/uninsured	1586 (5.7)	556 (35.1)	0.81 (0.72–0.91)	0.78 (0.69–0.89)
Medicare	4614 (16.7)	1325 (28.7)	0.60 (0.55–0.64)	0.74 (0.67–0.82)
Private/government	17 125 (62.0)	6898 (40.3)	1.0 (Reference)	1.0 (Reference)
Rural-urban continuum				
Metro population	22 248 (85.9)	8363 (37.6)	1.05 (0.96–1.15)	1.04 (0.95–1.14)
Other	3663 (14.1)	1377 (37.6)	1.0 (Reference)	1.0 (Reference)
Tumor characteristics				
Tumor histology				
Papillary	27 614 (98.3)	10 313 (37.3)	0.51 (0.42–0.62)	0.47 (0.38–0.58)
Follicular/Hurthle cell	467 (1.7)	242 (51.8)	1.0 (Reference)	1.0 (Reference)
Lymph node involvement				
NX	195 (0.7)	86 (44.1)	0.32 (0.23–0.46)	0.39 (0.27–0.58)
N0	25 763 (91.7)	8949 (34.7)	0.17 (0.15–0.19)	0.19 (0.17–0.21)
N1	2123 (7.6)	1520 (71.6)	1.0 (Reference)	1.0 (Reference)

Abbreviations: EN, East North; ES, East South; NOS, not otherwise specified; S, south; WN, West North; WS, West South.

vs those without. One possibility is that the threshold for RAI use is lower (ie, the threshold is based on the tumor size and/or the presence or absence of lymph node metastases). The other possible explanation is that more patients with distant metastases have noniodine-avid tumors.

In contrast to the predictability of the clinical correlates, many of the nonclinical correlates of RAI use we identified were less expected. Although the relationship between low hospital case volume and less RAI has been

demonstrated in previous work (1), it is not clear why patients with Medicare insurance are less likely to receive RAI, regardless of disease severity. One possibility is that older patients are not being referred to high-volume facilities at the same rate as younger patients (33), thus also explaining the relationship between age 60 years and older and less RAI use in both low- and high-risk patients. Alternatively, because patient preference cannot be assessed with this data set, it is possible that for low-risk disease in

Table 2. RAI Use for Medium-Risk Thyroid Cancer

	Patients, n, %		OR (95% CI)	
	Overall	Treated With RAI	Unadjusted	Adjusted
Hospital characteristics				
Hospital region				
EN Central	6845 (15.9)	4826 (70.5)	0.52 (0.36–0.75)	0.55 (0.38–0.80)
ES Central	2672 (6.2)	1707 (63.9)	0.44 (0.28–0.70)	0.46 (0.29–0.72)
Mid-Atlantic	7250 (16.8)	4489 (61.9)	0.24 (0.16–0.36)	0.23 (0.16–0.34)
Mountain	2811 (6.5)	2060 (73.3)	0.85 (0.51–1.40)	0.73 (0.44–1.19)
New England	2958 (6.9)	1699 (57.4)	0.23 (0.15–0.36)	0.24 (0.15–0.38)
Pacific	5971 (13.9)	4094 (68.6)	0.55 (0.37–0.82)	0.50 (0.34–0.74)
S Atlantic	8040 (18.7)	5438 (67.6)	0.44 (0.30–0.64)	0.43 (0.30–0.63)
WS Central	3125 (7.3)	1831 (58.6)	0.35 (0.23–0.54)	0.33 (0.22–0.51)
WN Central	3395 (7.9)	2585 (76.1)	1.0 (Reference)	1.0 (Reference)
Case volume (cases/y)				
Low (≤ 11)	4460 (10.4)	2438 (54.7)	0.46 (0.37–0.59)	0.49 (0.39–0.62)
Medium (12–34)	14 980 (34.8)	10 007 (66.8)	0.87 (0.69–1.10)	0.85 (0.68–1.07)
High (≥ 35)	23 627 (54.9)	16 284 (68.9)	1.0 (Reference)	1.0 (Reference)
Patient characteristics				
Sex				
Female	33 541 (77.9)	22 288 (66.5)	0.95 (0.90–1.01)	0.96 (0.91–1.02)
Male	9526 (22.1)	6441 (67.6)	1.0 (Reference)	1.0 (Reference)
Age (y)				
<20	1144 (2.7)	822 (71.9)	1.50 (1.29–1.75)	1.10 (0.92–1.31)
20–44	21 553 (50.0)	14 697 (68.2)	1.30 (1.22–1.38)	1.05 (0.96–1.14)
45–59	12 046 (28.0)	7938 (65.9)	1.17 (1.09–1.25)	1.08 (0.99–1.18)
≥ 60	8324 (19.3)	5272 (63.3)	1.0 (Reference)	1.0 (Reference)
Charlson-Deyo comorbidity index score				
0	37 853 (87.9)	25 324 (66.9)	1.13 (1.06–1.22)	1.08 (1.00–1.16)
≥ 1	5214 (12.1)	3405 (65.3)	1.0 (Reference)	1.0 (Reference)
Race/ethnicity				
Black	2787 (6.5)	1748 (62.7)	0.92 (0.83–1.01)	1.01 (0.91–1.11)
Other	6994 (16.2)	4547 (65.0)	1.02 (0.95–1.10)	0.99 (0.92–1.07)
White	33 286 (77.3)	22 434 (67.4)	1 (Reference)	1 (Reference)
Insurance				
Insurance, NOS	6957 (16.4)	4611 (66.3)	0.94 (0.87–1.01)	0.93 (0.87–1.01)
Medicaid/uninsured	3354 (7.9)	2124 (63.3)	0.80 (0.73–0.88)	0.80 (0.73–0.88)
Medicare	5845 (13.8)	3632 (62.1)	0.73 (0.69–0.79)	0.84 (0.76–0.92)
Private/government	26 157 (61.8)	17 990 (68.8)	1 (Reference)	1 (Reference)
Rural-urban continuum				
Metro population	34 081 (86.0)	22 614 (66.4)	1.08 (1.00–1.17)	1.06 (0.98–1.16)
Other	5528 (14.0)	3770 (68.2)	1 (Reference)	1 (Reference)
Tumor characteristics				
Tumor histology				
Papillary	38 358 (89.1)	25 681 (67.0)	1.18 (1.10–1.27)	1.07 (0.99–1.16)
Follicular/Hurthle cell	4709 (10.9)	3048 (64.7)	1 (Reference)	1 (Reference)
Lymph node involvement				
NX	355 (0.8)	252 (71.0)	1.08 (0.81–1.45)	1.13 (0.83–1.55)
N0	34 687 (80.5)	22 521 (64.9)	0.58 (0.54–0.61)	0.59 (0.55–0.63)
N1	8025 (18.6)	5956 (74.2)	1 (Reference)	1 (Reference)

Abbreviations: EN, East North; ES, East South; NOS, not otherwise specified; S, south; WN, West North; WS, West South.

particular, patient preference may be different in younger vs older patients. Finally, it is possible that there is age disparity in physician treatment recommendations. Sosa and colleagues (34, 35) previously documented both age and race disparities in the management of thyroid cancer. In our data set, the relationship between both black race and Medicaid/uninsured status with less RAI use may suggest health disparity; however, the fact that this difference is not seen in the highest-risk patients is somewhat reassuring.

The greater number of nonclinical correlates of RAI use we identified for low- vs high-risk patients is supported by previous research showing that nonclinical correlates of use are more likely when there is discretionary decision making (36). The reliance on discretionary decision making in thyroid cancer guidelines is related to the fact that compared with other malignancies, such as breast cancer, there are fewer concrete data to support recommendations. It is well known that when clinical guidelines are not supported by strong evidence, physicians are less

Table 3. RAI Use for High-Risk Thyroid Cancer

	Patients, n, %		OR (95% CI)	
	Overall	Treated With RAI	Unadjusted	Adjusted
Hospital characteristics				
Hospital region				
EN Central	1774 (15.1)	1287 (72.5)	0.57 (0.38–0.84)	0.60 (0.41–0.89)
ES Central	624 (5.3)	426 (68.3)	0.47 (0.29–0.76)	0.48 (0.30–0.77)
Mid-Atlantic	2057 (17.5)	1410 (68.5)	0.31 (0.20–0.46)	0.31 (0.21–0.47)
Mountain	669 (5.7)	495 (74.0)	0.78 (0.47–1.30)	0.70 (0.43–1.17)
New England	816 (7.0)	508 (62.3)	0.27 (0.17–0.44)	0.30 (0.19–0.49)
Pacific	1738 (14.8)	1133 (65.2)	0.45 (0.30–0.68)	0.43 (0.29–0.64)
S Atlantic	2154 (18.4)	1481 (68.8)	0.43 (0.29–0.63)	0.42 (0.28–0.62)
WS Central	861 (7.3)	514 (59.7)	0.30 (0.19–0.46)	0.31 (0.20–0.48)
WN Central	1036 (8.8)	783 (75.6)	1.0 (Reference)	1.0 (Reference)
Case volume, cases/y				
Low (≤ 11)	1266 (10.8)	740 (58.5)	0.48 (0.38–0.61)	0.53 (0.41–0.67)
Medium (12–34)	3916 (33.4)	2586 (66.0)	0.74 (0.60–0.92)	0.77 (0.62–0.96)
High (≥ 35)	6547 (55.8)	4711 (72.0)	1.0 (Reference)	1.0 (Reference)
Patient characteristics				
Sex				
Female	6995 (59.6)	4790 (68.5)	1.05 (0.96–1.15)	1.06 (0.97–1.17)
Male	4734 (40.4)	3247 (68.6)	1.0 (Reference)	1.0 (Reference)
Age, y				
45–59	6497 (55.4)	4658 (71.7)	1.45 (1.33–1.59)	1.22 (1.09–1.38)
≥ 60	5232 (44.6)	3379 (64.6)	1.0 (Reference)	1.0 (Reference)
Charlson-Deyo comorbidity index score				
0	9434 (80.4)	6504 (68.9)	1.17 (1.05–1.31)	1.06 (0.94–1.19)
≥ 1	2295 (19.6)	1533 (66.8)	1.0 (Reference)	1.0 (Reference)
Race/ethnicity				
Black	713 (6.1)	431 (60.4)	0.79 (0.66–0.96)	0.92 (0.76–1.12)
Other	1773 (15.1)	1146 (64.6)	0.98 (0.86–1.12)	0.96 (0.83–1.12)
White	9243 (78.8)	6460 (69.9)	1.0 (Reference)	1.0 (Reference)
Insurance				
Insurance, NOS	1452 (12.6)	1011 (69.6)	0.87 (0.74–1.01)	0.86 (0.73–1.00)
Medicaid/uninsured	731 (6.4)	471 (64.4)	0.82 (0.67–0.99)	0.86 (0.70–1.06)
Medicare	3498 (30.4)	2214 (63.3)	0.63 (0.57–0.70)	0.76 (0.67–0.87)
Private/government	5822 (50.6)	4235 (72.7)	1.0 (Reference)	1 (Reference)
Rural-urban continuum				
Metro population	9114 (83.8)	6198 (68.0)	0.94 (0.81–1.08)	0.94 (0.81–1.09)
Other	1758 (16.2)	1250 (71.1)	1.0 (Reference)	1.0 (Reference)
Tumor characteristics				
Tumor histology				
Papillary	10 001 (85.3)	6992 (69.9)	1.60 (1.42–1.80)	1.21 (1.04–1.40)
Follicular/Hurthle cell	1728 (14.7)	1045 (60.5)	1.0 (Reference)	1.0 (Reference)
Lymph node involvement				
NX	58 (0.5)	39 (67.2)	0.94 (0.50–1.77)	1.13 (0.56–2.28)
N0	3749 (32.0)	2352 (62.7)	0.65 (0.59–0.71)	0.78 (0.70–0.88)
N1	7922 (67.5)	5646 (71.3)	1.0 (Reference)	1.0 (Reference)
Distant metastases				
M0	11 283 (96.2)	7769 (68.9)	1.42 (1.14–1.77)	1.18 (0.93–1.49)
M1	446 (3.8)	268 (60.1)	1.0 (Reference)	1.0 (Reference)

Abbreviations: EN, East North; ES, East South; M1, distant metastases present; M0, distant metastases absent; NOS, not otherwise specified; S, south; WN, West North; WS, West South.

likely to provide guideline-concordant care (37), and thus, one would expect more treatment variation and potentially differences in use based on nonclinical factors such as age, race, and insurance status. Although RAI has been recommended for high-risk, iodine-avid patients for many years, the pendulum has only recently swung toward less RAI use in the lowest-risk patients (9, 38). However, interestingly, despite being a cohort in

which even the most recent clinical guidelines still leave use of RAI to physician discretion in a large proportion of patients (9), the number of nonclinical correlates of use for the medium-risk cohort was similar and even lower than that of high-risk patients.

Strengths of this study include the large cohort of recently treated thyroid cancer patients, the exhaustive set of variables included in the analyses, and the representation

of patients treated across the United States. Limitations include a lack of detail on use of interventions that can change perceived indications for RAI, such as pretreatment scans and prophylactic central lymph node dissections, and a lack of pathological details that may influence physician decision making, such as micro- vs macrolymph node metastases and information on extrathyroidal extension. In addition, we cannot distinguish the role of physician vs patient preference.

Previously a rare cancer and still a cancer with a low mortality rate, it is no surprise that there are currently no randomized controlled trials evaluating patient outcome with and without RAI. Secondary to the lack of randomized controlled trials and conflicting observational studies (39–41), the clinical guidelines leave much of thyroid cancer management to provider discretion (9). However, because thyroid cancer is becoming an increasingly common cancer (42), there is now a need now to reevaluate the risks and benefits of RAI and the impact of current practice patterns on population health. Understanding the current correlates of RAI use is critical to recognize areas of controversy in thyroid cancer management and improve patient care. In the future, it is important that disease severity and extent of treatment benefit, not region, age, race, or insurance status, drive the use of RAI for thyroid cancer.

Acknowledgments

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This work was supported by the National Cancer Institute at the National Institutes of Health (Grant K07CA154595-02, to M.R.H.).

Disclosure Summary: The authors have nothing to disclose.

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