

# Use of Radioactive Iodine for Thyroid Cancer

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**M**ORE THAN 40 000 INDIVIDUALS in the United States receive a thyroid cancer diagnosis each year, and the overwhelming majority of cases are well-differentiated thyroid cancer.<sup>1</sup> Standard treatment for well-differentiated thyroid cancer is thyroidectomy. To ensure full eradication of remnant thyroid tissue and to treat residual disease, in patients with visible, inoperable, iodine-avid metastases, radioactive iodine is often administered after total thyroidectomy. Previous cohort studies have shown improved survival and reduced tumor recurrence when iodine-avid, advanced-stage, well-differentiated thyroid cancer is treated with radioactive iodine.<sup>2-4</sup> There is little controversy concerning the value of radioactive iodine for these patients. In contrast, for very low-risk disease, in which prognosis is typically excellent, treatment with radioactive iodine is of uncertain benefit.<sup>5-8</sup>

Indications for use of radioactive iodine following surgery for the majority of well-differentiated thyroid cancers are hotly debated.<sup>9-11</sup> In the absence of randomized controlled trials evaluating the utility of radioactive iodine relative to disease severity, clinical guidelines have left radioactive iodine

**For editorial comment see p 762.**

**Context** Substantial uncertainty persists about the indications for radioactive iodine for thyroid cancer. Use of radioactive iodine over time and the correlates of its use remain unknown.

**Objective** To determine practice patterns, the degree to which hospitals vary in their use of radioactive iodine, and factors that contribute to this variation.

**Design, Setting, and Patients** Time trend analysis of radioactive iodine use in a cohort of 189 219 patients with well-differentiated thyroid cancer treated at 981 hospitals associated with the US National Cancer Database between 1990 and 2008. We used multilevel analysis to assess the correlates of patient and hospital characteristics on radioactive iodine use in the cohort treated from 2004 to 2008.

**Main Outcome Measure** Use of radioactive iodine after total thyroidectomy.

**Results** Between 1990 and 2008, across all tumor sizes, there was a significant increase in the proportion of patients with well-differentiated thyroid cancer receiving radioactive iodine (1373/3397 [40.4%] vs 11 539/20 620 [56.0%];  $P < .001$ ). Multivariable analysis of patients treated from 2004 to 2008 found that there was a statistical difference in radioactive iodine use between American Joint Committee on Cancer stages I and IV (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.31-0.37) but not between stages II/III and IV (for stage II vs stage IV, OR, 0.97; 95% CI, 0.88-1.07 and for stage III vs stage IV, OR, 1.06; 95% CI, 0.95-1.17). In addition to patient and tumor characteristics, hospital volume was associated with radioactive iodine use. Wide variation in radioactive iodine use existed, and only 21.1% of this variation was accounted for by patient and tumor characteristics. Hospital type and case volume accounted for 17.1% of the variation. After adjusting for available patient, tumor, and hospital characteristics, 29.1% of the variance was attributable to unexplained hospital characteristics.

**Conclusion** Among patients treated for well-differentiated thyroid cancer at hospitals in the National Cancer Database, there was an increase in the proportion receiving radioactive iodine between 1990 and 2008; much of the variation in use was associated with hospital characteristics.

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use to physician discretion in most scenarios.<sup>12-17</sup> Proponents argue that universal use of radioactive iodine increases the ease of following the tumor marker, thyroglobulin, and may destroy microscopic metastases. In contrast, opponents counter that mortality secondary to thyroid cancer is

sufficiently low, negating the need for the unnecessary health risks, including secondary cancer following radioactive iodine,<sup>18-30</sup> and the costs<sup>31</sup> associated with universal radioactive iodine use.

The recent increase in the incidence of small, low-risk thyroid can-

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cers<sup>32,33</sup> mandates an understanding of patterns of care in thyroid cancer. We hypothesized that there would be unwarranted variation in radioactive iodine use with factors other than disease severity predicting administration. In this study, we determined the recent change in practice patterns, examined the degree to which hospitals vary in their use of radioactive iodine, and assessed factors that contribute to this variation.

## METHODS

### Data Source and Study Population

The National Cancer Database, a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, is a US nationwide, facility-based oncology data set that currently captures 70% of all newly diagnosed malignant cancers, including close to 85% of all thyroid cancers, in the United States.<sup>34</sup> Once diagnosed and treated at a hospital with a Commission on Cancer–accredited cancer program, the remainder of a patient's disease course and treatment are documented by the hospital registrar even when care is transferred to another facility.<sup>34</sup> Data are coded and reported according to nationally established protocols coordinated under the auspices of the North American Association of Central Cancer Registries.<sup>35</sup> No patient, physician, or hospital identifiers were examined in this study, and exemption was granted for this study by the University of Michigan Institutional Review Board.

Data from 314 039 patients diagnosed as having primary thyroid cancers between January 1, 1990, and December 31, 2008, were queried from the National Cancer Database. To ensure a stable physician cohort over the period reviewed in this study, only currently accredited Commission on Cancer programs that had reported cases in 14 of the 19 years to the National Cancer Database were included. Patients with tumor histologies of papillary, follicular, or Hurthle cell cancer types were retained for analysis. Because total thyroidectomy is recom-

mended before radioactive iodine treatment, only patients who had undergone total thyroidectomy (n=189 219) at the 981 Commission on Cancer–accredited programs were selected for analysis. Correlates of radioactive iodine use were evaluated in the 85 948 patients with diagnoses between 2004 and 2008 to define the most contemporary practice patterns.

### Measures

Patient age was stratified into 3 biologically relevant groups: age 44 years or younger, age 45 to 59 years, and age 60 years or older. Patient race/ethnicity was categorized by the National Cancer Database as non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, and Native American. Due to smaller numbers, Hispanic, Asian/Pacific Islander, and Native American were collapsed into an "other" category. Race/ethnicity was included in the analysis because it has been shown to influence cancer treatment.<sup>36</sup> With data drawn from the 2000 US Census, we assigned 2008 100% poverty line, insurance type, percentage with college degree, and rural-urban continuum. We used the Charlson-Deyo Index to identify comorbid conditions within the cohort.<sup>37,38</sup>

Tumor size was categorized according to the definitions used by the American Joint Committee on Cancer (AJCC).<sup>39</sup> Tumor histology was limited to *International Classification of Diseases for Oncology* classification codes for papillary, follicular, and Hurthle cell cancer types.<sup>40</sup> Type of cancer program consisted of the following mutually exclusive categories: community hospitals, comprehensive community, teaching/research, and National Cancer Institute/National Comprehensive Cancer Network. Hospital volume was analyzed as a continuous and categorical variable. Case volume categories were created by computing a weighted average of the annual thyroid case volume at each reporting cancer program for the years 2004 to 2008 and dividing the distribution into equal-

sized quintiles of hospitals: 6 or fewer, 7 to 11, 12 to 19, 20 to 34, and 35 or more cases per year.

### Statistical Analysis

We performed a time trend analysis of radioactive iodine use relative to tumor size between years 1990 and 2008. The  $\chi^2$  test was used to assess the statistical significance of temporal trends in radioactive iodine use.

Next, we selected data from the most recent 5 years in this cohort, 2004–2008, for univariate analysis and multivariable logistic regression. Univariate associations between radioactive iodine use and patient and tumor characteristics were evaluated by  $\chi^2$  test.

We used hierarchical generalized linear models<sup>41,42</sup> to account for the clustering of thyroid cancer patients within hospitals while assessing the effect of comorbidity and sociodemographic (sex, age, race/ethnicity, poverty level, insurance, education, rural-urban continuum), tumor (histology, stage), and hospital (hospital type and case volume) characteristics. Specifically, we used a logit link to model the binary radioactive iodine use. Our model also included a random hospital-specific intercept to capture the heterogeneity across hospitals. 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: between patients (within hospitals):  $\text{logit}(P[Y_{ij}=1]) = \mu_{0i} + \theta'X_{ij}$

Level 2: between hospitals:

$$\mu_{0i} = \beta_{00} + \beta_{0i} + \gamma'Z_i$$

$$\text{Combined model: } \text{logit}(P[Y_{ij}=1]) = \beta_{00} + \beta_{0i} + \gamma'Z_i + \theta'X_{ij}$$

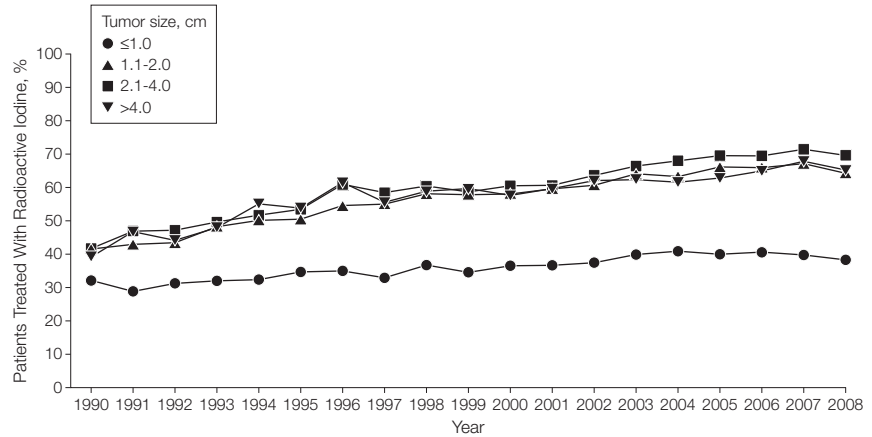
where  $\beta_{00}$  is the population-averaged log odds of radioactive iodine use,  $\beta_{0i}$  is the hospital-specific random effect, assumed to follow a normal distribution with mean zero and variance  $\sigma_{\text{hosp}}^2$ ,  $X_{ij}$  is the matrix of patient and tumor covariates,  $\theta$  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 for the  $i$ th hospital, and  $\gamma$  is the corresponding vector of coefficients. Model estimates were obtained using a likelihood-based approach in SAS PROC GLIMMIX. A hierarchical generalized linear model approach allows the estimation and partitioning of variance in radioactive iodine use between the patient and hospital levels. As a measure of the importance of the hospital effect on individual use of radioactive iodine, we estimated the percentage of the variance in radioactive iodine use attributable to hospitals using the intraclass correlation coefficient. The intraclass correlation coefficient was estimated based on the assumption of a threshold model that is appropriate for a binary outcome.<sup>41</sup>

Our initial null model contained only a hospital-specific random-effects term. Next, we fitted a series of adjusted models that, in addition to the hospital-specific random effect, included fixed patient characteristics (comorbidity, sociodemographic covariates), tumor characteristics, and hospital covariates (each covariate group at a time). These models were used to calculate the percentage of total variance attributable to patient, tumor, and hospital characteristics. The denominator for this calculation was total variance, which included the variance attributable to random (unmeasured) hospital effects after adjustment for the corresponding fixed-effects covariates in a given model, the variance attributable to the corresponding measured covariates (ie, fixed effects), and the variance attributable to unmeasured patient or tumor characteristics plus error. In this way, the relative importance of each component could be examined.

Finally, a fully adjusted model was fitted incorporating the available patient and hospital characteristics as fixed-effects covariates in the model. The residual intraclass correlation coefficient was calculated based on the fully adjusted model and represents the percentage of variance attributable to hospitals after adjustment for avail-

**Figure 1.** Percentage of Patients Treated With Radioactive Iodine Based on Tumor Size Between 1990 and 2008



The number of patients in each tumor category per year ranged from 570 to 7538 for tumors sized 1.0 cm or smaller, from 848 to 6001 for tumors sized 1.1 to 2.0 cm, from 874 to 4603 for tumors sized 2.1 to 4.0 cm, and from 330 to 1689 for tumors larger than 4.0 cm.

able patient and hospital characteristics. The denominator in the calculation of this percentage was composed of the variance attributable to unmeasured hospital effects, after adjustment for available patient and hospital variables, and the variance attributable to unmeasured patient or tumor characteristics plus error.

As another measure of hospital variation in use of radioactive iodine, hospital-specific radioactive iodine administration rates were calculated based on a hierarchical generalized linear model that was adjusted for patient and tumor characteristics. Hospital-specific rates were obtained using empirical Bayes predictions<sup>43</sup> and then plotted by hospital rank, from lowest to highest according to the empirical Bayes predictions. This method shrinks the estimate of hospital-specific radioactive iodine administration rate toward the average rate, as a factor of the number of thyroid cancer patients treated at the hospital. Hospitals treating a large number of thyroid cancer patients will have less shrinkage whereas hospitals treating a small number of thyroid cancer patients will have more shrinkage toward the average rate.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina). Two-

sided tests were used, with  $P < .05$  considered statistically significant.

## RESULTS

Between 1990 and 2008 there was a significant increase in the proportion of patients with well-differentiated thyroid cancer who received radioactive iodine as adjuvant therapy after total thyroidectomy ( $P < .001$ ). In 1990, 1373 (40.4%) of 3397 patients received radioactive iodine whereas in 2008, 11 539 (56.0%) of 20 620 received radioactive iodine. For tumors sized 1.1 to 2.0 cm, 2.1 to 4.0 cm, and larger than 4.0 cm, there was a 55% to 67% increase in the percentage of patients treated in 2008 compared with those treated in 1990. The proportion of tumors sized 1.0 cm or smaller treated with radioactive iodine was lower but has also increased steadily over time (FIGURE 1).

The TABLE summarizes the study population and proportion receiving radioactive iodine as adjuvant therapy following total thyroidectomy in 2004-2008. In multivariable analyses, younger age and absence of comorbidity were associated with a small but significantly greater likelihood of receiving radioactive iodine after total thyroidectomy (for younger age, odds ratio [OR], 2.15; 95% confidence in-

terval [CI], 2.04-2.26 and for absence of comorbidity, OR, 1.19; 95% CI, 1.07-1.35). Female sex (OR, 0.87; 95% CI, 0.84-0.91), African American race (OR, 0.83; 95% CI, 0.77-0.89), and absence of private/government insurance (OR,

0.84; 95% CI, 0.81-0.88) were associated with significantly less likelihood of receiving radioactive iodine. There was a statistically significant difference in radioactive iodine use between AJCC stages I and IV (OR, 0.34; 95% CI, 0.31-0.37), but not for stage II (OR, 0.97; 95% CI, 0.88-1.07) or stage III (OR, 1.06; 95% CI, 0.95-1.17) vs stage IV. When hospital case volume was analyzed as a categorical variable, there was an increased likelihood of radioactive iodine use as the volume category increased. Compared with high case volume, there was a significant difference in low case volume (OR, 0.44; 95% CI, 0.33-0.58) and low-medium case volume (OR, 0.62; 95% CI, 0.48-0.80). The effect of continuous case volume was also statistically significant in both the unadjusted and adjusted models. The adjusted OR was 1.006 (95% CI, 1.003-1.008;  $P < .001$ ), suggesting that for every 1 additional case a hospital treats, the odds of radioactive iodine use increase by 0.6% after adjusting for patient and tumor characteristics and hospital type.

The subgroup analysis of patients treated between 2004 and 2008 demonstrates substantial variation in use of radioactive iodine. Patient/tumor characteristics explain 21.1% of this variance and measured hospital characteristics 17.1%. These partitioned variances were obtained from a series of adjusted models so the relative importance of each component could be examined. After controlling for sex, age, race/ethnicity, comorbidity, poverty level, insurance, education, degree of ruralism/urbanism, tumor histology/size/stage, and hospital type and case volume, the residual intraclass correlation coefficient was 29.1%, indicating that substantial variation in radioactive iodine use still exists across hospitals.

After selecting patients without comorbidity and with consistent sociodemographic variables (white race, income above 100% poverty, private insurance, areas where  $\geq 12\%$  of the population has a college education, and metropolitan residence), evaluation of

**Table.** Multivariable Analysis of Participants and Hospital Characteristics, 2004-2008

Characteristics	No. (% of Participants)		Odds Ratio (95% CI)	
	Overall	Treated With Radioactive Iodine	Unadjusted	Adjusted
<b>Participant characteristics</b>				
Sex				
Male	19 754 (23.0)	12 079 (61.2)	1 [Reference]	1 [Reference]
Female	66 194 (77.0)	37 346 (56.4)	0.82 (0.79-0.85)	0.87 (0.84-0.91)
Age, y				
$\leq 44$	34 432 (40.1)	21 090 (61.3)	1.43 (1.38-1.48)	2.15 (2.04-2.26)
45-59	30 267 (35.2)	17 159 (56.7)	1.18 (1.14-1.22)	1.19 (1.14-1.26)
$\geq 60$	21 249 (24.7)	11 176 (52.6)	1 [Reference]	1 [Reference]
Charlson-Deyo comorbidity index score				
0	73 943 (86.0)	42 942 (58.1)	1.26 (1.15-1.39)	1.19 (1.07-1.35)
1	10 303 (12.0)	5593 (54.3)	1.08 (0.98-1.20)	1.07 (0.95-1.21)
$\geq 2$	1702 (2.0)	890 (52.3)	1 [Reference]	1 [Reference]
Race/ethnicity				
White	67 528 (78.6)	39 104 (57.9)	1 [Reference]	1 [Reference]
African American	5539 (6.4)	2816 (50.8)	0.75 (0.71-0.79)	0.83 (0.77-0.89)
Other	12 881 (15.0)	7505 (58.3)	1.02 (0.98-1.05)	1.06 (1.00-1.12)
Household income				
Above 100% poverty	41 877 (52.4)	24 011 (57.3)	0.99 (0.96-1.02)	1.04 (0.99-1.08)
Below 100% poverty	38 054 (47.6)	21 897 (57.5)	1 [Reference]	1 [Reference]
Insurance				
Private/government	64 070 (75.9)	38 013 (59.3)	1 [Reference]	1 [Reference]
Medicare/Medicaid/uninsured	20 359 (24.1)	10 776 (52.9)	0.77 (0.75-0.79)	0.84 (0.81-0.88)
College degree, %				
$< 12$	33 906 (42.4)	19 335 (57.0)	0.97 (0.94-1.0)	1.01 (0.97-1.05)
$\geq 12$	46 021 (57.6)	26 572 (57.7)	1 [Reference]	1 [Reference]
Rural-urban continuum				
Metropolitan population	67 852 (85.7)	38 810 (57.2)	0.94 (0.89-0.97)	1.02 (0.96-1.08)
Other	11 364 (14.4)	6685 (58.8)	1 [Reference]	1 [Reference]
<b>Tumor characteristics</b>				
Tumor histology				
Papillary	78 651 (91.5)	44 850 (57.0)	1 [Reference]	1 [Reference]
Follicular	4893 (5.7)	3084 (63.0)	1.29 (1.21-1.36)	1.09 (1.01-1.18)
Hurthle cell	2404 (2.8)	1491 (62.0)	1.23 (1.13-1.34)	1.03 (0.92-1.14)
Tumor size, cm <sup>a</sup>				
$\leq 1.0$	29 941 (36.4)	11 900 (36.4)	0.36 (0.34-0.38)	
1.1-2.0	24 771 (30.1)	16 201 (65.4)	1.04 (0.98-1.09)	
2.1-4.0	20 024 (24.3)	13 952 (69.7)	1.26 (1.19-1.33)	
$> 4.0$	7524 (9.1)	4862 (64.6)	1 [Reference]	
Lymph node involvement <sup>a</sup>				
N0	66 137 (77.0)	35 019 (53.0)	1 [Reference]	
N1	18 691 (21.7)	13 570 (72.6)	2.36 (2.72-2.44)	
NX	1120 (1.3)	836 (74.6)	2.62 (2.29-3.00)	
Distant metastases <sup>a</sup>				
M0	85 388 (99.3)	49 076 (57.5)	1 [Reference]	
M1	560 (0.7)	349 (62.3)	1.22 (1.03-1.45)	
AJCC TNM stage				
I	64 166 (75.6)	34 539 (53.8)	0.56 (0.52-0.59)	0.34 (0.31-0.37)
II	9018 (10.6)	6113 (67.8)	1.01 (0.93-1.09)	0.97 (0.88-1.07)
III	7843 (9.2)	5407 (68.9)	1.06 (0.98-1.15)	1.06 (0.95-1.17)
IV	3886 (4.6)	2630 (67.7)	1 [Reference]	1 [Reference]

(continued)



radioactive iodine use showed wide hospital-level variation in both lower-risk, young female patients with tumor size of 1.0 cm or smaller and stage I disease and higher-risk, older male patients with tumor size larger than 2.0 cm and stage III or IV disease. For the lower-risk profile, 246 (64.9%) of the 379 hospitals treating such patients had a radioactive iodine administration rate that was statistically significantly different from the mean of 37.4%, with 79 (20.8%) of the 379 hospitals having a rate below the mean rate and 167 (44.1%) of the hospitals having a rate above the mean (FIGURE 2). For the higher-risk profile, 63 (64.3%) of the 98 hospitals treating such patients had a radioactive iodine administration rate that was statistically significantly different from the mean rate of 74.9%, with 17 (17.4%) of the 98 hospitals having a rate below the mean rate and 46 (46.9%) of the hospitals having a rate above the mean (FIGURE 3).

**COMMENT**

The results of this study provide insight into the use of radioactive iodine for management of well-differentiated thyroid cancer. Between 1990 and 2008, there was an increase in radioactive iodine use across all tumor sizes. In addition to tumor characteristics, other patient and hospital characteristics were also associated with radioactive iodine use. There was wide between-hospital variation in radioactive iodine use, and much of the variance was attributable to unexplained hospital characteristics.

Previous studies have evaluated between-hospital variation in rates of surgical procedures<sup>44,45</sup> and the role of discretionary decision making on treatment intensity.<sup>46,47</sup> Germane to our study is a single-institution study that evaluated use of radioactive iodine over time and found an increase in use between 1940 and 1999<sup>48</sup> and a study of Surveillance, Epidemiology, and End Results data that found increased radioactive iodine use between 1973 and 2006.<sup>22</sup> However, our study is novel because it investigates not only treat-

ment trends but also correlates of radioactive iodine use and variation in use in a large and recently treated multicenter cohort of thyroid cancer patients.

The explanation for the increase in radioactive iodine use across all tumor sizes is not entirely clear, but it has

been hypothesized that increased detection of low-risk disease can lead to overestimation of treatment efficacy and a subsequent increase in use of therapy.<sup>49</sup> We know from previous population studies that well-differentiated thyroid cancer is increasing at a faster rate than any other malignancy,

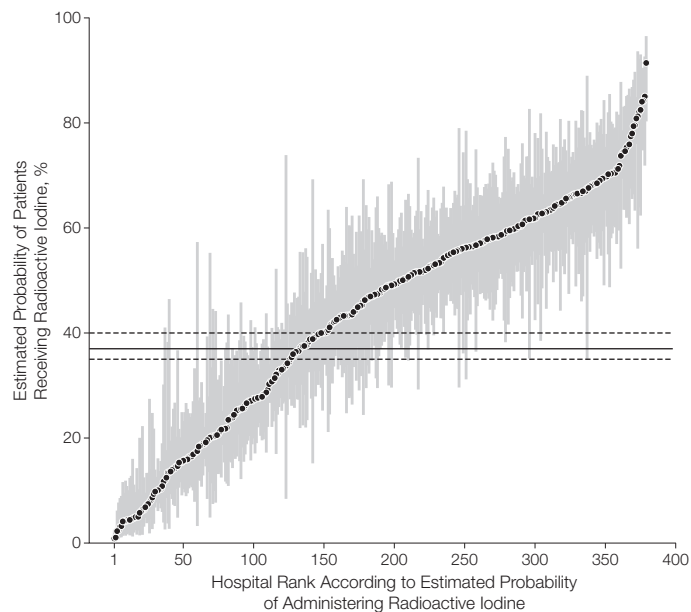
**Table.** Multivariable Analysis of Participants and Hospital Characteristics, 2004-2008 (continued)

Characteristics	No. (%) of Participants		Odds Ratio (95% CI)	
	Overall	Treated With Radioactive Iodine	Unadjusted	Adjusted
<b>Hospital characteristics</b>				
Hospital type				
Community/comprehensive community	48 532 (56.5)	27 773 (57.2)	0.93 (0.78-1.11)	1.18 (0.97-1.44)
Teaching/research/NCI-NCCN	37 416 (43.5)	21 652 (57.9)	1 [Reference]	1 [Reference]
<b>Case volume, cases/y</b>				
Low (≤6)	2415 (2.8)	1064 (44.1)	0.49 (0.38-0.64)	0.44 (0.33-0.58)
Low-medium (7-11)	6109 (7.1)	3098 (50.7)	0.69 (0.54-0.86)	0.62 (0.48-0.80)
Medium (12-19)	10 261 (11.9)	5604 (54.7)	0.87 (0.69-1.09)	0.82 (0.64-1.06)
Medium-high (20-34)	19 235 (22.4)	11 440 (59.5)	1.03 (0.82-1.29)	0.99 (0.79-1.27)
High (≥35)	47 928 (55.8)	28 214 (58.9)	1 [Reference]	1 [Reference]

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute.

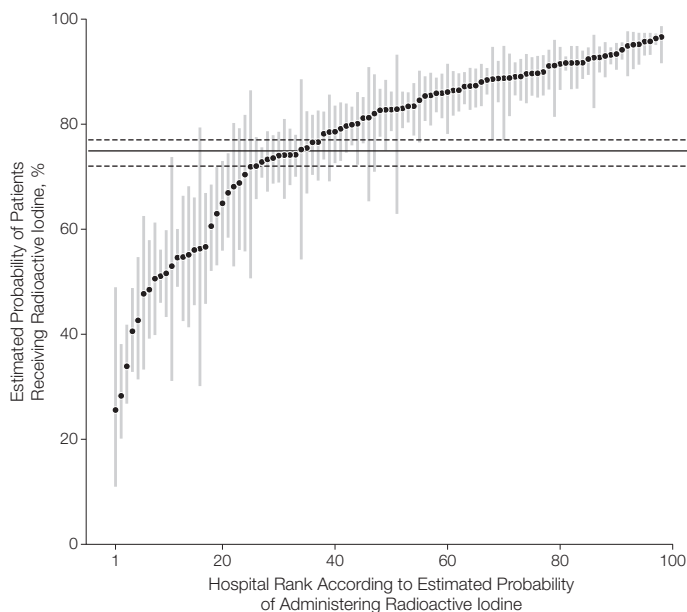
<sup>a</sup>Tumor size, lymph node involvement, and distant metastases were not included in the adjusted analysis because they are included in the AJCC TNM stage.

**Figure 2.** Variation in Hospital-Level Radioactive Iodine Use in Patients With Papillary Thyroid Cancer and Characteristics Associated With Low Risk of Death (n=379 Hospitals)



The horizontal line is the population mean (37.4%) and the dashed lines represent its 95% confidence interval. The vertical lines represent the 95% confidence intervals for the hospital-specific estimated probabilities of radioactive iodine use.

**Figure 3.** Variation in Hospital-Level Radioactive Iodine Use in Patients With Papillary Thyroid Cancer and Characteristics Associated With High Risk of Death (n=98 Hospitals)



The horizontal line is the population mean (74.9%) and the dashed lines represent its 95% confidence interval. The vertical lines represent the 95% confidence intervals for the hospital-specific estimated probabilities of radioactive iodine use.

with a 2.4-fold increase in incidence over the past 30 years.<sup>32,33,50</sup> The majority of the increase is due to detection of small, low-risk tumors,<sup>32,51</sup> and, in light of the 10% to 36% incidence of occult well-differentiated thyroid cancer in autopsy studies,<sup>52,53</sup> overdiagnosis of clinically irrelevant cancers may be occurring.<sup>49,54</sup> Thus, there is potential that increased detection of low-risk disease is spurring an increase in thyroid cancer treatment intensity.

In addition to identifying trends in radioactive iodine use and correlates of use, this study also found large hospital-based variation, with patient and tumor characteristics accounting for 21% of the variation and unknown hospital factors accounting for 29% of the variation. This finding suggests disease severity is not the sole determinant of radioactive iodine use.

Wide variation in radioactive iodine use was seen in both lower- and higher-risk patients. The low-risk patient profile depicted in Figure 2 is a profile in which use of radioactive iodine was left

to physician discretion<sup>13-15,17</sup> until the most recent clinical guidelines.<sup>12</sup> In contrast, almost all clinical guidelines would strongly recommend radioactive iodine after thyroid surgery in the high-risk patient profile depicted in Figure 3.<sup>12-17</sup> The variation demonstrated in both low- and high-risk patients suggests clinical uncertainty.<sup>55,56</sup> Some of this uncertainty may be explained by the lack of clinical trials evaluating the efficacy of radioactive iodine use for thyroid cancer and the conflicting single-institution studies. Because of limited clinical evidence, clinical guidelines have left radioactive iodine use to physician discretion in many cases.<sup>12,13</sup> A recent study has shown that when clinical guideline treatment recommendations are not supported by strong evidence, less guideline-concordant care occurs.<sup>57</sup>

Studies using a large database such as the National Cancer Database have inherent limitations. Specific to thyroid cancer, presence of extrathyroidal extension, postoperative serum

thyroglobulin level, and tumor iodine avidity are not recorded. In addition, treatment details such as dose of radioactive iodine and addition of prophylactic central lymph node dissection are not known. These missing details may be important because they can affect the indications for radioactive iodine<sup>58</sup> and, in the case of radioactive iodine dosing, affect assessment of intensity of care.

Even with the limitations inherent in a large database, the results of this study have implications for patients, physicians, and payers. Although it is appropriate therapy for certain well-differentiated thyroid cancers, the benefit of radioactive iodine may not always exceed the risks. There is a clear role for adjuvant therapy with radioactive iodine in iodine-avid, advanced-stage, well-differentiated thyroid cancer<sup>2-4,59</sup>; however, there is unclear benefit to radioactive iodine use in low-risk disease<sup>5-7,60-65</sup> because patients with low-risk disease have an excellent prognosis regardless of intervention.<sup>6,66,67</sup>

In addition to clear cost-saving benefits associated with not using radioactive iodine for low-risk disease,<sup>31</sup> limiting radioactive iodine use would decrease patients' risks of adverse effects. Not only are there transient adverse effects on quality of life with the hypothyroidism typically required before radioactive iodine treatment,<sup>68</sup> but radioactive iodine itself has long-term health risks. Recent studies have found increased risk of second primary malignancies after radioactive iodine treatment, even in the lowest-risk patients,<sup>22</sup> with the greatest risk being for leukemia, which increases 2.5-fold.<sup>19,20,69,70</sup> Radioactive iodine is also associated with additional adverse systemic effects<sup>17,18,27,28,30,71,72</sup> and damage to local tissue, such as the salivary glands and nasolacrimal ducts.<sup>21,23,25,26</sup> There are also potential public health risks if appropriate safety precautions are not taken at the time of radioactive iodine administration.<sup>73</sup> In contrast to the potential for overtreatment and greater harm than good when using radioactive iodine for low-risk disease, the

spectrum of radioactive iodine use in the high-risk patient profile suggests that undertreatment of some high-risk patients may be occurring. This has potential implications for patient health, such as increased risk of disease recurrence and mortality.<sup>4,6</sup>

The fact that disease severity appears to have a small influence on radioactive iodine use after thyroid surgery is concerning. In the interest of curbing the increasing health care costs and preventing both overtreatment and undertreatment of disease, indications for radioactive iodine should be clearly defined and disease severity should become the primary driver of radioactive iodine use.

In summary, in the United States, the incidence of small, low-risk thyroid cancers is increasing at a faster rate than any other malignancy.<sup>50</sup> Paradoxically, use of radioactive iodine is increasing in patients with all tumor sizes. The significant between-hospital variation in radioactive iodine use suggests clinical uncertainty about the role of radioactive iodine in thyroid cancer management. Of concern, for patients with thyroid cancer, the hospital where care is received has a substantial influence on treatment with radioactive iodine after total thyroidectomy, even after accounting for patient and tumor characteristics.

**Author Contributions:** Dr Haymart had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Haymart, Stewart.

**Acquisition of data:** Stewart, Birkmeyer.

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**Statistical analysis:** Banerjee, Stewart.

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