



The overuse of radioactive iodine in low-risk papillary thyroid cancer patients



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ABSTRACT

Background: The aim of this study was to use current American Thyroid Association (ATA) management guidelines to identify groups who might be at risk of overtreatment with radioactive iodine (RAI) ablation after surgery for low-risk papillary thyroid cancer (PTC).

Methods: PTC patients were identified using the Surveillance, Epidemiology and End Results database. Characteristics of low-risk patients (defined as T1 without metastasis) were compared to those not low-risk. Predictors of receiving RAI for low-risk disease were determined using logistic regression.

Results: Of 32,229 cases, 17,286 (53.6%) were low-risk. Low-risk patients, compared to others, were older (mean age 51.3 versus 48.5 years), and more often female (81.6% versus 71.7%), white (69.7% versus 62.0%), and insured (87.6% versus 85.6%) (all p-values < 0.001). Nearly 25% of low-risk patients received RAI. Predictors of overtreatment with RAI included age < 45 years (OR: 1.393; 95% CI: 1.250–1.552), age 45–64 years (OR: 1.275; 95% CI: 1.152–1.412), male sex (OR: 1.191; 95% CI: 1.086–1.305), Hispanic (OR: 1.236; 95% CI: 1.110–1.376) and Asian (OR: 1.306; 95% CI: 1.159–1.473) race, and extensive lymphadenectomy (OR: 1.243; 95% CI: 1.119–1.381).

Conclusion: Low-risk PTC patients were more likely to receive post-surgical RAI when not indicated under ATA guidelines if they were younger, male, Hispanic or Asian, or underwent extensive lymph node surgery. Identification of groups at risk for overtreatment can help impact practice patterns and improve the effective utilization of healthcare resources.

1. Introduction

The American Thyroid Association (ATA) guidelines task force published the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, which suggested that radioactive iodine (RAI) ablation is not routinely necessary for treatment of patients with low-risk thyroid cancer [1]. Specifically, postsurgical RAI is not indicated for the management of patients with T1a, N0/Nx, or M0/Mx disease [1]. Similarly, postsurgical RAI is not routinely indicated for the management of patients with T1b/T2, N0/Nx, or M0/Mx disease [1]. However, unwarranted variation in the use of RAI may occur, leading to the overtreatment of low-risk thyroid cancer patients with RAI [2,3].

The ATA treatment guidelines have provided guidance as to what may be regarded as overtreatment and excessive utilization of health care resources in the care of patients with low-risk thyroid cancer.

There is no survival benefit to receiving RAI among patients with low-risk thyroid cancer [4,5]. Furthermore, the use of RAI when not indicated may lead to unnecessary health risks (such as increased risk of secondary primary malignancies like leukemia and salivary gland cancer) and financial cost [2,4,6–9]. Thus it is important to identify patient groups who are at risk of overtreatment of low-risk thyroid cancer with RAI. Therefore, we sought to determine if disparities in the use of RAI ablation in low-risk thyroid cancer patients existed prior to publication of the most recent ATA guidelines in order to identify patient groups who may be more at risk of overtreatment with RAI after surgical treatment of low-risk thyroid cancer.

2. Methods

The Surveillance, Epidemiology and End Results (SEER) database was used to identify patients with thyroid cancer diagnosed between

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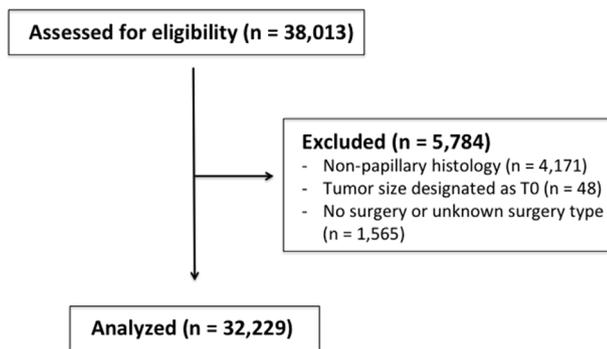


Fig. 1. Exclusion criteria and final analytic sample size.

2011 and 2013 [10]. SEER is a database maintained by the National Cancer Institute that contains information on patients with various types of cancer, and represents approximately 28% of the United States population [10]. The study period of interest was between 2011 and 2013, the most current SEER data available preceding publication of the ATA guidelines. We sought to assess current treatment patterns in order to identify patient groups at risk for overtreatment following publication of the current ATA guidelines. Patient demographics, tumor-and treatment-related data, and survival status were downloaded as a case-listing file, which was then transferred to the statistical analysis program for analysis. The initial sample size was 38,013 cases. Patients who did not have papillary histology, or had a tumor size designated as T0, or did not undergo surgery or underwent an unknown surgery type were excluded (Fig. 1). This left a final sample size of

Table 1
Characteristics of study population by risk category.

Characteristic	All, n (%)	Not Low Risk, n (%)	Low Risk, n (%)	Chi Square p-value
Total Study Population	32,229 (100)	14,943 (46.4)	17,286 (53.6)	
Mean Age in Years (standard deviation)	50.0 (14.8)	48.5 (15.6)	51.3 (13.9)	< 0.001*
Age Group in Years				< 0.001*
< 45	11,855 (36.8)	6301 (42.2)	5554 (32.1)	
45–64	14,644 (45.4)	6122 (41.0)	8522 (49.3)	
≥ 65	5730 (17.8)	2520 (16.9)	3210 (18.6)	
Sex				< 0.001*
Female	24,815 (77.0)	10,715 (71.7)	14,100 (81.6)	
Male	7414 (23.0)	4228 (28.3)	3186 (18.4)	
Race				< 0.001*
White	21,318 (66.2)	9263 (62.0)	12,055 (69.7)	
Black	2016 (6.3)	791 (5.3)	1225 (7.1)	
Hispanic	4981 (15.5)	2843 (19.0)	2138 (12.4)	
Asian	3368 (10.5)	1791 (12.0)	1577 (9.1)	
Other/Unknown	546 (1.7)	255 (1.7)	291 (1.7)	
Insurance				< 0.001*
Insured	27,933 (86.7)	12,794 (85.6)	15,139 (87.6)	
Uninsured	949 (2.9)	507 (3.4)	442 (2.6)	
Medicaid	2686 (8.3)	1371 (9.2)	1315 (7.6)	
Unknown	661 (2.1)	271 (1.8)	390 (2.3)	
Stage				< 0.001*
I	23,441 (72.7)	6248 (41.8)	17,193 (99.5)	
II	1990 (6.2)	1990 (13.3)	0	
III	4263 (13.2)	4263 (28.5)	0	
IVA	1570 (4.9)	1570 (10.5)	0	
IVB	160 (0.5)	160 (1.1)	0	
IVC	199 (0.6)	199 (1.3)	0	
IVNOS	26 (0.1)	26 (0.2)	0	
Unknown	580 (1.8)	487 (3.3)	93 (0.5)	
T Stage				< 0.001*
T1	20,219 (62.7)	2933 (19.6)	17,286 (100)	
T2	4671 (14.5)	4671 (31.3)	0	
T3	6080 (18.9)	6080 (40.7)	0	
T4	856 (2.7)	856 (5.7)	0	
TX	403 (1.3)	403 (2.7)	0	
N Stage				< 0.001*
N0	24,335 (75.5)	7199 (48.2)	17,136 (99.1)	
N1	7541 (23.4)	7541 (50.5)	0	
NX	353 (1.1)	203 (1.4)	150 (0.9)	
M Stage				< 0.001*
M0	31,987 (99.3)	14,701 (98.4)	17,286 (100)	
M1	242 (0.8)	242 (1.6)	0	
Surgery Type				< 0.001*
Lobectomy and/or Isthmectomy	4081 (12.7)	827 (5.5)	3254 (18.8)	
Partial Lobectomy	237 (0.7)	60 (0.4)	177 (1.0)	
Total/Near Total Thyroidectomy	27,911 (86.6)	14,056 (94.1)	13,855 (80.2)	
Lymph Nodes Removed				< 0.001*
0	14,405 (44.7)	4089 (27.4)	10,316 (59.7)	
1–3	8290 (25.7)	3756 (25.1)	4534 (26.2)	
≥ 4	8870 (27.5)	6707 (44.9)	2163 (12.5)	
Other/Unknown	664 (2.1)	391 (2.6)	273 (1.6)	
Radiation				< 0.001*
None	16,787 (52.1)	4368 (29.3)	12,419 (71.8)	
Radioactive Iodine	13,877 (43.1)	9577 (64.1)	4300 (24.9)	
Other/Unknown	1565 (4.9)	998 (6.7)	567 (3.3)	

*p-value significant at the < 0.05 level.

32,229 cases for analysis.

The age variable contained the following categories: age less than 45 years, age 45–64 years, and age at least 65 years. The purpose of this was to be consistent with age groupings denoted in the American Joint Committee on Cancer 7th Edition thyroid cancer staging (younger or older than 45 years), and to indicate when patients may become Medicare eligible by age (65 years) [11]. The stage variable referred to the 7th edition of the American Joint Committee on Cancer staging [11]. The race variable consisted of non-Hispanic white, non-Hispanic Black, Hispanic, non-Hispanic Asian and other/unknown. The insurance variable consisted of the following categories: uninsured, Medicaid, insured and unknown. The insured category included private insurance and Medicare.

Low-risk thyroid cancer was defined as T1, N0/Nx, M0/Mx disease. Based on current guidelines, patients with T1a tumors should not receive RAI, while patients with T1b or T2 tumors may be considered for RAI if certain high-risk features are present (aggressive histology, vascular invasion) [1]. Thus this analysis limited low-risk patients to those with T1 tumors, as the treatment guidelines are clearer.

Characteristics of patients with low-risk disease were compared to those who did not have low-risk disease. Chi-square analyses were used to compare categorical variables and two-sample t tests to compare mean age at diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) of presenting with low-risk disease were determined using logistic regression. The adjusted odds ratios of presenting with low-risk disease were determined by including the variables age, sex, race, and insurance type in the logistic regression model. These covariates were included because they demonstrated significant association with presenting with low-risk disease in chi-square analyses.

Among patients with low-risk disease, predictors of receiving RAI were determined using logistic regression. The adjusted odds ratios of receiving RAI among patients with low-risk disease were determined by including the variables age, sex, race, insurance type, surgery type and number of lymph nodes removed in the logistic regression model. These covariates were included because they demonstrated significant association with presenting with low-risk disease and/or receiving RAI in chi-square analyses.

All statistical analyses were performed using Stata version 12.1 (StataCorp LP, College Station, TX). A p-value of < 0.05 was used for all analyses to determine statistical significance. Because the SEER database contains de-identified data, institutional review board approval was not required to perform this study.

3. Results

The study sample included 32,229 patients with papillary thyroid cancer (PTC). The mean age at diagnosis was 50.0 years. The study sample included 24,815 (77.0%) female patients and 21,318 (66.2%) patients identified as white race (Table 1). Of all cases, 17,286 (53.6%) had low-risk disease. Low-risk patients, compared to others, were older (mean age 51.3 versus 48.5 years; $p < 0.001$), more often female (81.6% versus 71.7%; $p < 0.001$), more often white (69.7% versus 62.0%; $p < 0.001$), and more often insured (87.6% versus 85.6%; $p < 0.001$) (Table 1). Also, low-risk patients more frequently had stage I disease (99.5% versus 41.8%; $p < 0.001$), more frequently had 0 lymph nodes removed (59.7% versus 27.4%; $p < 0.001$), and less frequently underwent total thyroidectomy (80.2% versus 94.1%; $p < 0.001$) compared to patients who did not have low-risk disease (Table 1).

The adjusted odds of presenting with low-risk disease varied significantly by patient age, sex, race and insurance status (Table 2). Odds were greater among patients aged 45–64 years (OR 1.581; 95% CI: 1.504–1.662) and those aged ≥ 65 years (OR 1.479; 95% CI: 1.385–1.578) compared to patients aged < 45 years. Odds were greater among Blacks (OR 1.144; 95% CI: 1.040–1.258) and lower among Hispanics (OR 0.590; 95% CI: 0.553–0.629) and Asians (OR

Table 2
Odds of presenting with low-risk thyroid cancer.

Characteristic	Unadjusted Odds of Low Risk Disease, Odds Ratio (95% CI)	Adjusted [†] Odds of Low Risk Disease, Odds Ratio (95% CI)
Age in Years	1.013 (1.012–1.015)*	1.014 (1.012–1.015)*
Age Group in Years		
< 45	Reference	Reference
45–64	1.579 (1.504–1.658)*	1.581 (1.504–1.662)*
≥ 65	1.445 (1.356–1.540)*	1.479 (1.385–1.578)*
Sex		
Female	Reference	Reference
Male	0.573 (0.543–0.603)*	0.526 (0.498–0.555)*
Race		
White	Reference	Reference
Black	1.190 (1.084–1.307)*	1.144 (1.040–1.258)*
Hispanic	0.578 (0.543–0.615)*	0.590 (0.553–0.629)*
Asian	0.677 (0.629–0.728)*	0.679 (0.630–0.731)*
Other/Unknown	0.877 (0.740–1.040)	0.892 (0.750–1.061)
Insurance		
Insured	Reference	Reference
Uninsured	0.737 (0.647–0.839)*	0.834 (0.730–0.954)*
Medicaid	0.811 (0.749–0.877)*	0.885 (0.815–0.960)*
Unknown	1.216 (1.040–1.423)*	1.185 (1.010–1.391)*

*p-value significant at the < 0.05 level.

[†]Adjusted for age, sex, race, and insurance type.

CI = confidence interval.

0.679; 95% CI: 0.630–0.731) as compared to whites. Odds were lower among uninsured patients (OR 0.834; 95% CI: 0.730–0.954) and patients with Medicaid (OR 0.885; 95% CI: 0.815–0.960) compared to insured patients. Finally, odds were lower among males as compared to females (OR 0.526; 95% CI: 0.498–0.555)(Table 2).

Nearly 25% (4300) of low-risk patients were treated with RAI. Patients who received RAI for low-risk disease were younger (mean age 49.9 versus 51.8 years; $p < 0.001$), more often Hispanic (14.2% versus 11.8%; $p < 0.001$) or Asian (10.7% versus 8.6%; $p < 0.001$) and more often insured (88.9% versus 87.2%; $p < 0.001$) compared to those who did not receive RAI (Table 3). Also, patients who received RAI more frequently underwent total thyroidectomy (94.9% versus 75.3%; $p < 0.001$) and had lymph nodes removed (44.1% versus 37.0%; $p < 0.001$) compared to those who did not receive RAI (Table 3).

Predictors of overtreatment with RAI among low-risk patients included age less than 45 years (OR: 1.393; 95% CI: 1.250–1.552), age 45–64 years (OR: 1.275; 95% CI: 1.152–1.412), male sex (OR: 1.191; 95% CI: 1.086–1.305), Hispanic (OR: 1.236; 95% CI: 1.110–1.376) and Asian (OR: 1.306; 95% CI: 1.159–1.473) race, and more extensive lymph node removal surgery (OR: 1.243; 95% CI: 1.119–1.381) (Table 3).

Among low-risk patients, no patient who received RAI expired, and only 5 (0.04%) patients who did not receive RAI expired during the study period.

4. Discussion

According to the 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, low-risk cancer includes T1-T2, N0/Nx, M0/Mx tumors [1]. The current study used the SEER program, a large, nationally representative database, to identify factors associated with low-risk papillary thyroid cancer. We demonstrated that, among patients with PTC, predictors of presenting with low-risk disease (T1, N0/Nx, M0/Mx) included older age, female sex, Black race, and having insurance. Interestingly, patients of Hispanic or Asian race were less likely to present with low-risk disease.

These results regarding race and insurance are similar to prior research that has shown an association between socioeconomic status and

Table 3
Characteristics of low-risk patients by radioactive iodine (RAI) category.

Characteristic	All, n (%)	No RAI, n (%)	RAI, n (%)	Chi Square	p-value	Unadjusted Odds of Receiving RAI, Odds Ratio (95% CI)	Adjusted [†] Odds of Receiving RAI, Odds Ratio (95% CI)
Low Risk Population	17,286 (100)	12,986 (75.1)	4300 (24.9)				
Mean Age in Years (standard deviation)	51.3 (13.9)	51.8 (14.0)	49.9 (13.4)				
Age Group in Years							
≥ 65	3210 (18.6)	2556 (19.7)	654 (15.2)	< 0.001*		0.990 (0.988–0.993)*	0.992 (0.990–0.995)*
< 45	5554 (32.1)	4029 (31.0)	1525 (35.5)	< 0.001*		Reference	Reference
45–64	5522 (49.3)	6401 (49.3)	2121 (49.3)			1.479 (1.333–1.642)*	1.393 (1.250–1.552)*
						1.295 (1.173–1.430)*	1.275 (1.152–1.412)*
Sex				0.14			
Female	14,100 (81.6)	10,625 (81.8)	3475 (80.8)			Reference	Reference
Male	3186 (18.4)	2361 (18.2)	825 (19.2)	0.001*		1.068 (0.978–1.167)	1.191 (1.086–1.305)*
Race							
White	12,055 (69.7)	9138 (70.4)	2917 (67.8)			Reference	Reference
Black	1225 (7.1)	970 (7.5)	255 (5.9)			0.824 (0.713–0.951)*	0.851 (0.733–0.987)*
Hispanic	2138 (12.4)	1529 (11.8)	609 (14.2)			1.248 (1.126–1.383)*	1.236(1.110–1.376)*
Asian	1577 (9.1)	1116 (8.6)	461 (10.7)			1.294 (1.152–1.454)*	1.306 (1.159–1.473)*
Other/Unknown	291 (1.7)	233 (1.8)	58 (1.4)			0.780 (0.583–1.043)	0.860 (0.637–1.161)
Insurance Type				< 0.001*			
Insured	15,139 (87.6)	11,318 (87.2)	3821 (88.9)			Reference	Reference
Uninsured	442 (2.6)	338 (2.6)	104 (2.4)			0.911 (0.729–1.139)	0.824 (0.655–1.036)
Medicaid	1315 (7.6)	994 (7.7)	321 (7.5)			0.957 (0.839–1.091)	0.947 (0.826–1.086)
Unknown	390 (2.3)	336 (2.6)	54 (1.3)			0.476 (0.356–0.636)*	0.503 (0.374–0.676)*
Surgery Type				< 0.001*			
Lobectomy and/or Isthmectomy	3254 (18.8)	3043 (23.4)	211 (4.9)			Reference	Reference
Partial Lobectomy	177 (1.0)	167 (1.3)	10 (0.2)			0.864 (0.449–1.659)	0.894 (0.465–1.719)
Total/Near Total Thyroidectomy	13,855 (80.2)	9776 (75.3)	4079 (94.9)			6.017 (5.209–6.951)*	5.823 (5.036–6.734)*
Lymph Nodes Removed				< 0.001*			
0	10,316 (59.7)	7999 (61.6)	2317 (53.9)			Reference	Reference
1–3	4534 (26.2)	3320 (25.6)	1214 (28.2)			1.262 (1.165–1.368)*	1.090 (1.003–1.184)*
≥ 4	2163 (12.5)	1481 (11.4)	682 (15.9)			1.590 (1.436–1.760)*	1.243 (1.119–1.381)*
Other/Unknown	273 (1.6)	186 (1.4)	87 (2.0)			1.615 (1.247–2.092)*	1.355 (1.039–1.766)*

*p-value significant at the < 0.05 level.

[†]Adjusted for age, sex, race, insurance type, surgery type and number of nodes removed.

RAI = radioactive iodine ablation; CI = confidence interval.

cancer stage at presentation [12,13]. For example, factors such as minority race, lower socioeconomic status, and uninsured/Medicaid status have been associated with a greater likelihood of presenting with nodal involvement or metastatic disease [12,13].

Not only were there disparities among patients who presented with low-risk PTC, but also there were notable differences between the management recommended by the 2015 ATA guidelines and practice patterns that occurred just prior to the publication of these guidelines. The 2015 ATA guidelines do not recommend postsurgical RAI for T1a, N0/Nx, M0/Mx disease [1]. Nor is postsurgical RAI routinely indicated for the management of patients with T1b/T2, N0/Nx, M0/Mx disease [1]. The preceding ATA guidelines, published in 2009, did not recommend adjuvant RAI for T1a tumors, and recommended selective use of adjuvant RAI for T1b and T2 tumors [14].

Our analysis identified that patients with low-risk PTC were significantly more likely to receive RAI if they were younger, male, Hispanic or Asian race, or underwent more extensive lymph node surgery. Thus these particular patient groups appear to be over-treated with RAI according to both the current ATA guidelines and the preceding ATA guidelines.

Disparities in the management of thyroid cancer, specifically regarding RAI use, have been previously described [3,13]. Higher rates of RAI use have been associated with higher socioeconomic status [13]. Furthermore, in an analysis of patients with well-differentiated thyroid cancer in the National Cancer Database, the odds of receiving RAI were greater among patients who were younger than age 60 years or lacked comorbidities [3]. In addition, odds were lower among patients who were female, African American, uninsured or had Medicare/Medicaid, or were treated at a hospital with a low case volume (< 6 cases/year) [3]. Similar findings have been reported when specifically assessing patients with low-risk thyroid cancer [15].

Likewise, factors associated with lack of compliance with ATA management guidelines have also been previously reported [16,17]. Receipt of RAI in accordance with ATA guidelines has been associated with patients who are married, reside in the Southern United States, or underwent more extensive lymph node examination [17]. Evaluation of racial/ethnic differences revealed that appropriate receipt of RAI was more likely to occur among Black patients and less likely to occur among Hispanic patients compared to whites [18].

This study also demonstrated that patients who underwent more extensive lymph node surgery had an increased likelihood of receiving RAI. Some practitioners might perform a neck dissection in order to demonstrate that there is not a need for RAI. However, the performance of a neck dissection for negative nodes could also be a marker of an aggressive stance in treatment for that practice environment. The physician prescribing RAI is not usually the surgeon who is performing the operation, so they may not share a common plan. Often, the surgeon and endocrinologist or nuclear medicine specialist are not within the same practice group or institution. Future research could investigate in more detail the practice settings and characteristics of those practitioners who take a more aggressive practice pattern.

Identification of the type of patients at risk of receiving unnecessary RAI treatment will allow healthcare providers to be more aware of their practice patterns and consistently provide guideline-based care for optimal delivery of health care services. In the current study we specifically assessed low-risk PTC patients. We have identified those patients at risk of being over-treated with RAI when such therapy is not indicated under the most recent ATA guidelines. Moreover, there was no apparent survival benefit to receiving RAI for low-risk disease. Similarly, other studies have shown no difference in survival among low-risk patients who received RAI and those who did not [4,5].

Although this study has demonstrated that demographic and socioeconomic factors as well as the extent of lymph node surgery may play a role in the receipt of postsurgical RAI, other factors might be influential as well. Surveys of physicians who treat patients with thyroid cancer have suggested that in addition to the extent of thyroid

cancer and adequacy of surgical resection, a patient's age and willingness to receive RAI were the most important factors in determining whether a physician recommended RAI [19]. Surgeon and hospital-related factors may play a role as well. A survey of thyroid surgeons revealed that greater use of RAI for stage I thyroid cancer was associated with high versus low hospital case volume, less years of surgeon experience, general surgery versus otolaryngology specialization and surgeon preference for greater extent of surgical resection [20]. Thus it is clear that multiple factors affect the receipt of appropriate, guideline-based adjuvant RAI.

The current study has identified objective characteristics of patients at risk for overtreatment with RAI for low-risk PTC. Information from this study may be used to impact practice patterns so that all PTC patients receive ATA guideline-based care, and health care services are used most effectively and appropriately.

This is especially important since the use of RAI when not indicated may lead to unnecessary health risks and financial cost [2,4,6–9]. Al-Qurayshi et al. estimated that the cost of adjuvant RAI for patients with stage I PTC averaged approximately \$9.1 million per year [4]. In addition, RAI use has been associated with an increased risk of secondary primary malignancies such as leukemia and salivary gland cancer [2,6,7].

Limitations of this study include the fact that data was obtained from a national database, and thus may be associated with occasional coding errors and missing data. Also, because we chose to focus on cases diagnosed with thyroid cancer immediately prior to publication of the 2015 ATA guidelines, long-term survival data and analysis was limited. In addition, data regarding certain high-risk features (aggressive histology, vascular invasion) were unavailable.

5. Conclusion

Patients with low-risk papillary thyroid cancer were more likely to receive RAI after surgery when not indicated under current ATA guidelines if they were younger, male, Hispanic or Asian, or underwent extensive lymph node surgery. Identification of groups at risk for overtreatment can help impact practice patterns and improve the effective utilization of healthcare resources.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2019.05.011>.

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