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Knowledge of pathologically versus clinically negative lymph nodes is associated with reduced use of radioactive iodine post-thyroidectomy for low-risk papillary thyroid cancer

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Abstract

Cervical lymph node metastases are common in papillary thyroid cancer (PTC). Clinically negative lymph nodes confer uncertainty about true lymph node status, potentially prompting empiric postoperative radioactive iodine (RAI) administration even in low-risk patients. We examined the association of clinically (cN0) versus pathologically negative (pN0) lymph nodes with utilization of RAI for low-risk PTC. Using the National Cancer Database 1998–2011, adults with PTC who underwent total thyroidectomy for Stage I/II tumors 1–4 cm were evaluated for receipt of RAI based on cN0 versus pN0 status. Cut-point analysis was conducted to determine the number of pN0 nodes associated with the greatest decrease in the odds of receipt of RAI. Survival models and multivariate analyses predicting RAI use were conducted separately for all patients and patients <45 years. 64,980 patients met study criteria; 39,778 (61.2 %) were cN0 versus 25,202 (38.8 %) pN0. Patients with pN0 nodes were more likely to have negative surgical margins and multifocal disease (all $p < 0.001$). The mean negative nodes reported in surgical pathology specimens was 4; 5 pathologically negative lymph nodes provided the best cut-point associated with reduced RAI administration (OR 0.91, CI 0.85–0.97). After multivariable adjustment, pN0 patients with 5 nodes examined were less likely to receive RAI compared to cN0 patients across

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all ages (OR 0.89, $p < 0.001$) and for patients aged <45 years (0R 0.86, $p = 0.001$). Patients with <5 pN0 nodes did not differ in RAI use compared to cN0 controls. Unadjusted survival was improved for pN0 versus cN0 patients across all ages ($p < 0.001$), but not for patients<45 years ($p = 0.11$); adjusted survival for all ages did not differ ($p = 0.13$). Pathological confirmation of negative lymph nodes in patients with PTC appears to influence the decision to administer postoperative RAI if 5 negative lymph nodes are removed. It is possible that fewer excised lymph nodes may be viewed by clinicians as incidentally resected and thus may suboptimally represent the true nodal status of the central neck. Further research is warranted to determine if there is an optimal number of lymph nodes that should be resected to standardize pathological diagnosis.

Keywords

Introduction

Cervical lymph node status is used to determine a patient's prognosis and cancer stage, influencing both surgical care and postsurgical medical management for patients with papillary thyroid cancer (PTC). While cervical lymph node metastases are common, clinical assessment as defined by preoperative physical exam, thyroid ultrasound, or intra-operative assessment can miss lymph nodes that harbor metastatic disease [1–3]. Clinically negative lymph nodes in the setting of a surgical thyroid specimen that does not include lymph nodes for pathological review may leave clinicians uncertain about the patient's true lymph node status, potentially prompting empiric postoperative radioactive iodine (RAI) administration even in low-risk patients. Our objective was to examine whether clinically (cN0) versus pathologically negative (pN0) lymph nodes are associated with different utilization of postoperative RAI in the setting of low-risk PTC.

Low-risk thyroid cancer is defined as thyroid cancer which lacks local or distant metastases, aggressive histology, or vascular invasion; negative lymph node status is therefore a key component of low risk [4]. Current ATA guidelines do not recommend RAI for low-risk patients [4]. However, given that positive lymph nodes will upstage an otherwise low-risk patient aged 45 and older, we hypothesize that uncertainty regarding a patient's true lymph node status may influence clinical decision for RAI therapy post-thyroidectomy. Conversely, pathological confirmation of negative lymph nodes may reassure the clinician regarding the patient's true low risk, potentially decreasing RAI use.

Past research has examined how discovery of positive lymph nodes through prophylactic lymph node dissection upstages patients and influences subsequent care [5–7]. In contrast, our study focuses on how the resection of clinically benign-appearing nodes and confirmation of negative pathology impacts subsequent medical management. Specifically, this study includes patients with low-risk PTC who lacked clinical lymph node involvement to compare RAI use between patients with cN0 versus pN0 lymph nodes.

Methods

The National Cancer Database (NCDB) is maintained jointly by the National Cancer Society and the American College of Surgeons Commission on Cancer. It is a large, de-identified, nationwide sample that captures 85 % of incident thyroid cancer cases in the U.S. [8]. The NCDB Participant User File was used to identify cases between 1998 and 2011. International Classification of Diseases for Oncology, Third Edition (ICDO-3) codes 8050/3, 8260/3, 8340/3, 8341/3, 8342/3, and 8343/3 were used to identify patients with PTC. Data were coded according to the Commission on Cancer Registry Operations and Data Standards Manual, the American Joint Commission on Cancer (AJCC) Manual for Staging of Cancer and the *International Classification of Disease for Oncology*. Data were validated at local and NCDB levels, and de-identified and submitted to the NCDB in accordance with the Health Insurance Portability and Accountability Act (HIPAA) [9]. Since data analyzed are de-identified, this study was deemed exempt by our institutional review board.

Inclusion/exclusion criteria

The study population comprised adults 18 years with Stage I or II PTC and tumors 1–4 cm. Patients did not have lymphatic or distant metastases and had undergone total/near/subtotal thyroidectomy. Patients with more than one primary and aggressive variants of PTC were excluded. Patients with missing data for tumor size or RAI status also were excluded.

Low-risk patients were identified based on ATA risk criteria and AJCC staging, defined as T1-2, N0, Mx or M0 with tumor size 1–4 cm. Patients with clinically versus pathologically negative lymph nodes were identified based on the three separate NCDB lymph node variables available ("Regional lymph nodes positive, regional lymph nodes resected and scope of regional lymph node surgery"). Together, these variables capture whether lymph nodes were surgically resected or only clinically assessed and reported the number of negative lymph nodes that were removed in a surgical specimen and examined for pathological diagnosis.

Patient characteristics were reported as frequencies and proportions for categorical variables, and means and standard deviations for continuous variables. The mean and median number of lymph nodes examined and reported as negative on pathological review were calculated. Differences between patients who had clinically versus pathologically negative lymph nodes were examined using χ^2 tests and Student's T tests for categorical and continuous variables, respectively.

Patient demographic and clinical variables included age, gender, race, education, insurance status, and year of diagnosis; provider variables included hospital type and location. Pathological and clinical characteristics included tumor size, RAI administration (yes/no), and resection margin status. Patient comorbidity was represented by the modified Charlson/Deyo scoring system (1992) [10]. Socio-economic variables including education, income, and insurance status were defined as described in the NCDB user file dictionary [11].

Cut-point analysis

A cut-point analysis was conducted to determine the number of pathologically negative lymph nodes that was associated with the greatest decrease in the odds of receipt of RAI post-thyroidectomy [12]. This analysis was limited to patients with >1 pathologically negative lymph node. All values in the inner 50th percentile (25th to 75th percentiles) of the population density were considered for candidate cut-points. A logistic regression model was examined for each proposed cut-point, where a categorical number of pathologically negative lymph nodes variable with two possible values, less than the proposed cut-point and greater than or equal to the proposed cut-point, was the only predictor for the binary outcome of receipt of RAI. The proposed cut-points were then ranked separately by ascending odds ratio (OR) and p value (corrected for multiple comparisons). The best cut-point was the lowest combination of these two ranks.

Based on the best cut-point of 5 pathologically negative lymph nodes, the pathologically negative group was subgrouped into those with 1 lymph node, those with 2–4 lymph nodes, and those with 5 lymph nodes examined in the surgical specimen.

Univariate and multivariate analyses

Univariate logistic regression was used to compare the probability of RAI receipt between patients with clinically negative lymph nodes and the three subgroups of pathologically negative lymph nodes (1, 2–4, and 5 lymph nodes examined) for all patients and for the subset of patients aged <45 years.

Multivariate analysis was conducted to adjust for known covariates. The adjusted analysis compared the probability of RAI receipt between patients with clinically negative lymph nodes and the three subgroups of patients with pathologically negative lymph nodes, separately for all patients and then for those patients aged <45 years.

Overall survival

Overall survival (OS) was examined for all patients with pathologically negative versus clinically negative lymph nodes for all ages, and then for those patients aged <45 years using the Kaplan–Meier method and multivariate Cox proportional hazard models. For survival analysis, the data were limited to patients diagnosed in 2006 or earlier to allow for the minimum follow-up time of 5 years required to obtain access to survival data in NCDB.

A prespecified significance level of 0.05 was used for all statistical tests. Other than within the cut-point analysis, no adjustments were made for multiple comparisons. All statistical analyses were conducted with SPSS version 22 (IBM Corp., Armonk, NY) and SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 64,980 patients met study inclusion criteria; 39,778 (61.2 %) had cN0 nodes, and 25,202 (38.8 %) had pN0 lymph nodes. (Table 1) The mean number of negative lymph nodes examined in surgical specimens was 4 (standard deviation 5); the median was 2 (range 1–90), with an interquartile range of 1–5. More than one-third (35.5 %) of the pathologically

negative cases ($N = 25,202$) were diagnosed with just one lymph node examined on pathological review.

Patient demographics and clinical characteristics

Patients with pN0 lymph nodes were more likely to have negative surgical margins and multifocal disease compared to patients with cN0 lymph nodes (all p values < 0.001). (Table 1) Compared to patients with cN0 nodes, they were also more likely to be female, white, aged <45 years, and without comorbidities; they were more frequently from the Northeast or a metropolitan area, and more likely to receive care at an academic medical center (all p values < 0.001). 24,850 (62.5 %) patients with cN0 versus 15,492 (61.5 %) patients with pN0 lymph nodes received RAI. For patients ages <45 years, there was no difference in comorbidity score between groups. (Table 1).

Cut-point analysis

Pathological exam of five or more negative lymph nodes provided the best cut-point associated with less RAI utilization post-thyroidectomy (OR 0.91, confidence interval 0.85–0.97).

Univariate and multivariate models predicting use of RAI

On unadjusted analysis among patients of all ages, patients with 5 or more pN0 lymph nodes were 13 % less likely to receive adjuvant RAI as compared to patients with cN0 disease ($N = 64,225$, OR 0.87, CI 0.82–0.92, $p < 0.0001$). Patients younger than age 45 years were 18 % less likely to receive RAI after surgery if they had 5 or more pN0 lymph nodes as compared to cN0 controls ($N = 29,744$, OR 0.82, CI 0.76–0.89, $p < 0.0001$).

After multivariate adjustment for patient demographic, clinical, and other pathologic factors, patients with 5 or more pN0 lymph nodes were 11 % less likely to receive adjuvant RAI compared to those patients who had cN0 disease ($N = 43,112$ OR 0.89, CI 0.83–0.95, $p = 0.0003$); they were 14 % less likely to receive RAI after surgery if they were younger than age 45 years ($N = 18,944$, OR 0.86, CI 0.78–0.94, $p = 0.001$). (Table 2) In contrast, despite pathological confirmation of negative lymph nodes, there was no difference in RAI use for patients with cN0 versus pN0 nodes when fewer than 5 lymph nodes were examined by pathology.

Survival analysis

A total of 32,142 patients were analyzed for OS. 922 (4 %) patients with cN0 lymph nodes ($N = 21,820$) died, compared to 237 (2 %) patients with pN0 lymph nodes ($N = 10,322$). For the subgroup of patients younger than age 45 years, the event rate was very low. 125 (1 %) patients with cN0 lymph nodes ($N = 10,608$) died compared to 47 (1 %) patients with pN0 lymph nodes ($N = 5,679$). Unadjusted OS was improved for patients with pN0 compared to cN0 lymph nodes across all ages ($N = 32,142$, log rank $p < 0.001$) but not for patients aged <45 years ($N = 16,287$, log rank $p = 0.11$). Adjusted survival for patients of all ages did not differ between lymph node groups ($N = 15,427$, $p = 0.13$). Adjusted survival for patients aged <45 years was not performed due to their low event rate, highlighting the excellent prognosis of PTC for younger patients.

Discussion

Recent debate has centered on how malignant pathology in clinically benign-appearing lymph nodes alters prognosis and clinical management [1, 13, 14]. To our knowledge, no nationwide study has examined whether the confirmation of negative pathology for clinically benign-appearing nodes influences care, particularly with regard to the clinical decision to use RAI post-thyroidectomy. This is important for low-risk patients who are not generally recommended for RAI but who receive RAI based on additional risk factors and physician discretion.

Compared to patients with clinically negative lymph nodes, our study demonstrates that PTC patients are 11–14 % less likely to receive RAI if 5 or more lymph nodes are pathologically negative, with the greatest reduction in RAI utilization observed for patients who are aged <45 years. Younger patients aged <45 already have an excellent prognosis based on their age, thus reduction of RAI use in the low risk, young patient might be especially welcome, given that benefit of RAI therapy in this group has not been shown [15–17].

A possible explanation for the observed association between reduced RAI use and pathological confirmation of negative lymph nodes may involve a change in perceived disease risk. For older, low-risk patients, negative lymph node status is crucial to defining their disease Stage and risk [4]. Specifically, if positive lymph nodes are found, low-risk patients aged 45 years and older with Stage I and II disease are upstaged to Stage III disease and intermediate risk, thereby increasing consideration for RAI therapy. Negative node pathology potentially reassures clinicians that the patient is truly low risk, reducing the need for RAI. Due to their excellent prognosis, low-risk patients <45 years old are classified as Stage I, regardless of positive lymph nodes. (Stage II is reserved for distant metastases.) However, since low risk is defined in part by absence of lymph node involvement, patients <45 years with cN0 disease but without pathological "proof," may be regarded by clinicians as higher risk, thus potentially prompting increased RAI use for these patients.

Interestingly, in this study, the association between removal of negative lymph nodes and reduced RAI utilization post-thyroidectomy was observed only when 5 or more pathologically negative lymph nodes were examined. However, this study also reveals that the pathological diagnosis of negative lymph nodes is often made with fewer nodes. The median was 2 negative nodes examined, with more than one-third of patients diagnosed as pathologically negative based on exam of just 1 lymph node. In other words, the removal of 1 negative lymph node, likely an incidentally removed lymph node, results in a 'pN0' report for the surgical specimen. Based on our overall findings, it is possible that clinicians view excision of fewer than 5 lymph nodes as insufficient evidence to reflect true nodal status of the central neck.

In thyroid cancer, no established criteria exist for the minimum number of lymph nodes that constitute an adequate or robust lymphadenectomy, and/or that are required for optimal care and diagnosis. As observed in this study, just one lymph node can confer a "pathologically negative" resection; this in turn determines a lower stage in patients aged 45 and older. In contrast, minimum lymph node dissection criteria have been established for other cancers. In

colon cancer, for example, the Cancer Staging Handbook of the American Joint Committee on Cancer recommends that at least 12 lymph nodes draining the primary cancer should be resected and pathologically examined to ensure adequate staging [18].

While no established criteria exist for number of lymph nodes that constitute an acceptable resection, a review of literature on prophylactic lymph node dissection reveals that 5–12 lymph nodes constitute the typical number of lymph nodes resected within the central neck, higher numbers corresponding to bilateral central lymph node dissection [5, 13, 14, 19–21]. The number of lymph nodes resected depends on a number of factors, including the unique lymph node anatomy of the patient, and the skill and experience of the surgeon. Current data conflict regarding the impact of prophylactic central lymph node dissection on surgical morbidity, disease recurrence, and RAI use [2, 5–7, 14, 20, 22–27]. Long-term postoperative thyroglobulin levels appear similar for patients who undergo total thyroidectomy alone as compared to patients who additionally undergo prophylactic central lymph node dissection [6, 13].

Current ATA guidelines do not recommend routine central lymph node dissection for low risk, noninvasive, T1 or T2, clinically node negative disease [4]. It should be noted that while surgical intent is not captured by this study, the average number of clinically benign-appearing lymph nodes resected in this study is below the average number reported in prophylactic lymph node dissection. It is therefore possible that fewer lymph nodes resected may be viewed as inadequate, and potentially incidental, by some clinicians.

In a few small studies with limited sample size, prophylactic central lymph node dissection was noted to have the potential to either increase RAI use (due to upstaging of disease) or decrease RAI use (due to pathological confirmation of negative lymph nodes). In a retrospective cohort of 143 patients with Stage I–III PTC, >1 cm tumors, Hughes et al. found that bilateral central lymph node dissection upstaged 28.6 % of patients aged >45 years to Stage III, resulting in higher RAI dosing [6]. The median dose of RAI was greater in the thyroidectomy plus central lymphadenectomy group (150 mCi) as compared to thyroidectomy alone group (30 mCi), $p = 0.01$. Similarly, in a retrospective study of 115 patients with tumor size <2 cm, Bonnet et al. reported that bilateral central lymphadenectomy (in combination with prophylactic lateral lymph node dissection) resulted in altered clinical decisions regarding RAI use in 30.5 % of cases [5]. In contrast, in the prospective study of 181 patients with Stage I–IV PTC, Viola et al. found only 3 patients were upstaged, with only one change in subsequent therapy decision to give RAI [7]. The above studies examined how central lymph node dissection and discovery of positive lymph nodes affects RAI use and was not restricted to low-risk patients. In contrast, our nationwide study involved a large sample size and focused exclusively on low-risk patients who typically are not recommended for RAI, revealing an association between negative lymph node pathology and decreased RAI utilization.

Thyroid cancer is rare and has an excellent prognosis, requiring large sample sizes to detect associations between different management strategies and outcomes [28]. Clinical trials of prophylactic lymph node dissection are not feasible due to prohibitive cost and time [29]. In the absence of clinical trials, retrospective analysis using NCDB and other large

administrative databases is helpful, since they provide large sample sizes and substantial statistical power. Still, it should be noted that the NCDB represents an aggregate of a nationwide sample, and individual patient management decisions and outcomes may differ due to factors not captured by the NCDB.

Analyses of data from the NCDB are limited by the number of variables captured. Notably, surgeon's intention in resecting benign-appearing lymph nodes and the rigor of the pathologist in examining resected lymph nodes is not captured; as mentioned previously, the average number of lymph node resected in this study appears below the average number resected in reported intentional prophylactic lymph node dissection. Thyroglobulin levels and results of (pre- and posttreatment) RAI uptake scans, which could influence clinical decision-making regarding RAI use, or RAI dosage, are not captured in NCDB. Some NCDB variables of interest were incomplete for the years analyzed, including tumor multifocality and location in the thyroid; patient comorbidities data were available after 2003. Disease recurrence and disease specific survival are not available in the NCDB. Finally, NCDB may include coding errors. However, the Participant User File used to code these data is highly standardized, with numerous quality control measures in place [30].

In conclusion, knowledge of true negative lymph node status appears to be associated with a change in clinical decision-making regarding postoperative administration of RAI in low-risk PTC; specifically, lymph node dissection of benign-appearing nodes is associated with less use of RAI if ≥ 5 negative lymph nodes are confirmed on pathological review. While studies have focused on the clinical impact of positive lymph nodes discovered on prophylactic central lymph node dissection, our study is novel and demonstrates that the removal of 5 or more negative lymph nodes is associated with less use of RAI for low-risk PTC patients of all ages. It is possible that fewer excised lymph nodes are viewed by clinicians as incidentally resected and thus do not represent the true nodal status of the central neck.

It is unclear whether lessons learned from accurate staging in colon cancer with a minimum lymph node resection requirement can be applied to differentiated thyroid cancer. Further research is needed to better identify if an optimal or minimum number of lymph nodes should be resected to adequately represent the nodal status of the central neck in an effort to standardize pathological diagnosis. Studies to address whether pathologically negative lymph nodes affect the dosing of RAI in higher Stage disease could also be helpful. Additional research also could examine the percentage of patients with clinically negative lymph nodes (cN0) who are diagnosed as harboring malignant lymph nodes by pathologic evaluation (pN1). Finally, research is needed to investigate potential factors driving the use of adjuvant RAI in low-risk patients with excellent prognosis, particularly in patients aged <45 years.

Acknowledgments

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Table 1

Demographic and clinical characteristics of patients with clinically versus pathologically negative lymph nodes (1998–2011)

	All patients N = 64,980			Patients age <45 N = 30,132		
	Clinically negative LNs N (%)	Pathologically negative LNs N (%)	p value	Clinically negative LNs N (%)	Pathologically negative LNs N (%)	p value
Population size	39778 (61.2)	25202 (38.8)		17685 (58.7)	12447 (41.3)	
RAI therapy			0.01			0.02
No RAI	14928 (37.5)	9710 (38.5)		6563 (37.1)	4781 (38.4)	
RAI	24850 (62.5)	15492 (61.5)		11122 (62.9)	7666 (61.6)	
Age (years)			<0.001			
<45 (N = 30,132)	17685 (44.5)	12447 (49.4)				
45–64 (N = 27,187)	16838 (42.3)	10349 (41.4)				
65 (N = 7661)	5255 (13.2)	2406 (9.5)				
Mean (SD)	47 (14.0)	46 (13.0)		35 (7.0)	35 (7.0)	
Gender			<0.001			<0.001
Female	31614 (79.5)	21032 (83.5)		14947 (84.5)	10859 (87.2)	
Race			<0.001			<0.001
White	33616 (86.0)	22050 (89.7)		14816 (85.4)	10871 (89.5)	
Black	3243 (8.3)	1110 (4.5)		1397 (8.1)	480 (4)	
Other	2244 (5.7)	1435 (5.8)		1140 (6.6)	793 (6.5)	
Insurance			0.001			0.02
Insured	37998 (97.5)	24206 (97.9)		16757 (96.8)	11885 (97.3)	
Income			0.001			<0.001
High	27247 (73.4)	18257 (77.7)		12228 (73.9)	9007 (77.7)	
Education level			<0.001			<0.001
High	15408 (41.5)	10994 (46.8)		6908 (41.8)	5334 (46)	
Facility type			<0.001			<0.001
Community	3170 (8.0)	1362 (5.4)		1414 (8)	686 (5.5)	
Comprehensive	22380 (56.3)	12758 (50.6)		9889 (55.9)	6286 (50.5)	
Academic	13298 (33.4)	10689 (42.4)		5900 (33.4)	5260 (42.3)	
Other	930 (2.3)	393 (1.6)		482 (2.7)	215 (1.7)	
County			<0.001			0.002

	All patients N = 64,980			Patients age <45 N = 30,132		
	Clinically negative LNs N (%)	Pathologically negative LNs N (%)	p value	Clinically negative LNs N (%)	Pathologically negative LNs N (%)	p value
Metro	31429 (85.1)	20290 (87.3)		14129 (86)	10003 (87.4)	
Urban	4900 (13.3)	2603 (11.2)		2072 (12.6)	1284 (11.2)	
Rural	586 (1.6)	336 (1.4)		232 (1.4)	158 (1.4)	
Facility location			<0.001			<0.001
Northeast	9330 (23.5)	6877 (27.3)		3946 (22.3)	3292 (26.4)	
South	13661 (34.3)	7585 (30.1)		5887 (33.3)	3707 (29.8)	
Midwest	9291 (23.4)	5862 (23.3)		4338 (24.5)	3018 (24.2)	
West	7496 (18.8)	4878 (19.4)		3514 (19.9)	2430 (19.5)	
Comorbidity[a]			<0.001			NS
0	25470 (86.1)	18942 (88.3)		11296 (91.8)	9363 (91.8)	
1	3482 (11.8)	2178 (10.2)		917 (7.5)	755 (7.4)	
2	631 (2.1)	333 (1.6)		95 (0.8)	81 (0.8)	
Surgical margins			<0.001			<0.001
Negative	34516 (92.1)	22788 (93.5)		15425 (92.8)	11282 (93.9)	
Multifocality[b]			<0.001			<0.001
Yes	10396 (39.5)	8824 (44.3)		3901 (36.2)	3910 (41.7)	
Tumor size in cm			<0.001			<0.001
1	4261 (10.7)	2894 (11.5)		1661 (9.4)	1361 (10.9)	
>1–2	20561 (51.7)	13919 (55.2)		8843 (50)	6795 (54.6)	
>2–3	10256 (25.8)	6034 (23.9)		4960 (28)	3076 (24.7)	
>3–4	4700 (11.8)	2355 (9.3)		2221 (12.6)	1215 (9.8)	
Mean (SD)	2.4 (0.83)	2.3 (0.79)		2.7 (0.78)	2.4 (0.65)	

Values are presented as numbers (percentages) of the available sample size, excluding missing values

LNs lymph nodes, HS high school, SD standard deviation, IQR interquartile range, NS not statistically significant

[a] Charlson–Deyo comorbidity score: variable not collected in NCDB before 2003, values are presented as percentages of the known after 2003

[b] Variable not collected in NCDB before 2004, values are presented as percentages of the known after 2004

Table 2

Multivariate analysis of RAI use adjusted for lymph node status and other factors (1998–2011)

	All ages N = 43,112		Age <45 N = 18,944	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Negative lymph node diagnosis				
Clinically negative	1		1	
Pathologically negative 5 lymph nodes examined	0.89 (0.83, 0.95)	0.0003	0.86 (0.78, 0.94)	0.001
Pathologically negative 2–4 lymph nodes examined	0.96 (0.90, 1.01)	0.11	0.97 (0.89, 1.06)	0.49
Pathologically negative 1 lymph node examined	1.02 (0.96, 1.08)	0.53	1.01 (0.93, 1.10)	0.86
Tumor size (cm)				
3–4	1		1	
2–3	1.00 (0.93, 1.08)	0.96	0.92 (0.82, 1.03)	0.16
1–2	0.70 (0.66, 0.75)	<0.0001	0.65 (0.58, 0.71)	<0.0001
Margin status				
Positive	1		1	
Negative	0.55 (0.50, 0.60)	<0.0001	0.50 (0.44, 0.57)	<0.0001
Unknown	0.58 (0.47, 0.71)	<0.0001	0.60 (0.43, 0.85)	0.004
Patient age (years)				
<45	1			
45–64	1.04 (0.99, 1.08)	0.11		
65	0.82 (0.77, 0.88)	<0.0001		

Also adjusted for sex, race, education, income, health insurance, county type, facility type, year of diagnosis and comorbidity. OR reference = 1, OR <1 associated with reduced use of RAI OR >1 associated with increased use of RAI CI = confidence interval; statistical significance with $p < 0.05$