The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma

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Background. *The prognostic role of lymph node metastases in well-differentiated thyroid carcinoma remains controversial. We investigated impact of lymph node involvement on survival in patients with well-differentiated thyroid cancer.*
Methods. *We queried the Surveillance, Epidemiology, and End Results registry for patients diagnosed with well-differentiated thyroid carcinoma between 1988 and 2003. Cases were stratified by age (<45 vs ≥45 years) and pathology (papillary/follicular). Four separate Cox regression models were developed to test the effects of demographic and clinical covariates on survival.*
Results. *We identified 33,088 patients. 30,504 patients (49% ≥45 years) had papillary carcinoma and 2,584 patients (55% ≥45 years) had follicular carcinoma. Age affected survival in all models (*P *< .001). In patients with papillary carcinoma <45 years, lymph node disease did not influence survival (*P *= .535), whereas in patients ≥45 years, lymph node involvement was associated with 46% increased risk of death (*P *< .001). In patients with follicular carcinoma, lymph node involvement conferred increased risk of death in both age groups (*P *≤ .002). Effects of other covariates varied between models.*
Conclusion. *Cervical lymph node metastases conferred independent risk in all patients with follicular carcinoma and in those patients with papillary carcinoma aged ≥45 years, but did not affect survival in patients with papillary carcinoma <45 years. (Surgery 2008;144:1070-8.)*

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The incidence of thyroid carcinoma in the United States is increasing with an estimated 8.7 patients per 100,000 US population diagnosed in 2002.[1] Although this rise is attributed mostly to improved detection of subclinical papillary carcinoma, advances in diagnostic techniques have also led to increased preoperative detection of suspicious regional lymph nodes.[2,3] However, the management of lymph nodes in well-differentiated thyroid cancer remains controversial. A number of earlier single-center retrospective studies reported no difference in survival between patients with and without lymph node metastases.[4,5] Conversely, other single institution series demonstrated that cervical lymph node metastases have a deleterious effect on tumor recurrence and survival.[6,7] Moreover, large, retrospective population-based database studies have reached conflicting conclusions on the prognostic implications of cervical lymph node metastases. A review of the data included in the Surveillance, Epidemiology, and End Results (SEER) database in 2003 failed to identify cervical lymph node metastases as a risk factor for death in papillary and follicular thyroid cancer.[8] However, other investigators interrogating the same oncology database in 2005 determined that cervical lymph node involvement was a significant predictor of poor outcome.[9]

Current treatment guidelines from the American Thyroid Association recommend considering routine central compartment (level VI) neck dissection in patients with papillary carcinoma

Supported in part by the Institutional National Research Service Award T32 HS 013833 from the Agency of Healthcare Research and Quality, US Department of Health and Human Services.

Presented at the 29th Annual Meeting of the American Association of Endocrine Surgery, Monterey, California, April 6–8, 2008.

Accepted for publication August 20, 2008.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2008.08.034

regardless of whether cervical lymph nodes were suspicious for metastatic disease preoperatively.[10] Current tumor–node–metastasis (TNM) staging system endorsed by the American Joint Committee on Cancer emphasizes age as the primary determinant of prognosis in well-differentiated thyroid malignancies.[11] Those patients who are <45 years old are staged as either Stage I or II based on presence of distant metastases and irrespective of the presence or absence of lymph node involvement. However, patients ≥45 years of age with lymph node metastases have either Stage III or IV disease based on the presence and location of tumor positive lymph nodes and distant metastases. Given this age-specific approach to disease staging, we evaluated the effect of lymph node disease after stratifying by age (using the <45 vs ≥45 year threshold) to determine whether lymph node metastases conferred an independent risk for death in patients with papillary and follicular thyroid carcinoma.

METHODS

SEER Registry and study population. The SEER program is a United States population-based cancer registry supported by the National Cancer Institute and Centers for Disease Control and Prevention which was started in 1973. The current registry contains data from 18 sites and samples about 26% of the US population. SEER registrars routinely collect data including demographics, primary characteristics of the neoplasm, including tumor site and spread, primary course of treatment exclusive of chemotherapy, and follow-up for vital status.[12]

Data collection and management. This investigation was reviewed and approved by the Vanderbilt University Medical Center Institutional Review Board. We conducted a retrospective, population-based cohort analysis of patients reported in the SEER database who underwent resection for pathologically confirmed papillary and follicular thyroid carcinoma between 1988 and 2003. The following SEER-specific, ICD-O-3 codes were grouped as papillary: 8050 (papillary carcinoma), 8260 (papillary adenocarcinoma), 8340 (papillary carcinoma, follicular variant), 8342 (papillary carcinoma, oxyphillic), 8343 (papillary carcinoma, encapsulated), 8344 (papillary carcinoma, columnar), and 8450 (papillary cystadenocarcinoma). The following SEER-specific ICD-O-3 codes were grouped as follicular: 8330 (follicular adenocarcinoma), 8331 (follicular adenocarcinoma, well differentiated), and 8332 (follicular adenocarcinoma, trabecular).

Demographic data included age, gender, race, and ethnicity. Patients were stratified further as <45 or ≥45 years. Race was classified as Caucasian, African-American, or Other (Asian-Pacific Islander and Alaskan-Native American). Ethnicity was coded as a separate variable and classified as either Hispanic or non-Hispanic. Clinical staging data included Extent of Disease 10 (EOD-10) classification, which was available for 1988 to 2003. Information was categorized based on tumor size (≤2, 2–4, or >4 cm), lymph node involvement, and distant metastatic spread. Tumor extent was categorized as intrathyroidal or extrathyroidal. Only those patients with pathologically confirmed, node-positive disease were identified as having lymph node involvement. Patients without pathologically examined lymph nodes or without nodes present in the specimen were categorized as node negative. Data regarding extent of the thyroid-directed operation, presence of lymph node-directed dissection, treatment with radioactive iodine ablation (RAI), and survival were also recorded. Patients with missing staging information and patients who received external beam radiation as part of their treatment were excluded from the study.

Data analysis. Four patient groups were formed by stratifying the full cohort on the basis of age (<45 vs ≥45 years) according to the TNM staging paradigm and tumor histology (papillary or follicular thyroid carcinoma). Kaplan–Meier survival analysis with the log-rank test for between-group comparisons was used to quantify the effect of the 45-year age threshold on survival in patients with papillary and follicular thyroid carcinoma. Four separate Cox proportional hazard regression models were developed to test the effects of age, gender, race, ethnicity, radiation treatment, tumor size, tumor extent, and lymph node involvement on survival within each of the age-stratified groups. Age was included as a continuous covariate in each of the 4 stratified models to control for the potential effect of increasing age on all-cause mortality within each model.

Two secondary analyses were performed. Because tumor extent and distant metastases were coded under the same variable in the SEER database, they could not be expressed as mutually exclusive, independent measures in a single multivariate analysis. As such, in the first of the secondary analyses, we examined the impact of distant metastases on other covariates without modeling tumor extent. A second subsample analysis assessed the impact of thyroid and lymph node directed surgery in the multivariate regression models.

STATA 10 (Stata Corp., College Station, Tex) statistical software was used in data management and analysis. A type I error probability of <.05 was

Table I. Demographic and clinical data: SEER database, cases entered 1988–2003

	Papillary thyroid carcinoma (n = *30,504*)	*Follicular thyroid carcinoma* (n = *2,584*)
Age, yrs (mean ± SD)	45 ± 15	48 ± 17
Age ≥45	15,007 (49)	1,419 (55)
Female gender	23,882 (78)	1,892 (73)
Caucasian	25,275 (83)	2,056 (80)
African American	1,413 (5)	241 (9)
Hispanic ethnicity	3,915 (13)	249 (10)
RAI	14,918 (49)	1,263 (49)
Tumor size, median (IQR)	1.5 cm (0.8–2.5)	3.0 cm (2.0–4.5)
Tumor size ≤2 cm	19,918 (65)	704 (27)
2 cm < tumor size ≤ 4 cm	8,195 (27)	1,189 (46)
Tumor size >4 cm	2,391 (8)	691 (27)
Extrathyroidal spread	4,606 (15)	247 (10)
Lymph node metastases	6,768 (22)	61 (2)
Distant metastases	293 (1)	77 (3)

Table entries are *n* (%) unless indicated.
IQR, Interquartile range; *RAI*, radioactive iodine ablation; *SEER*, Surveillance, Epidemiology and End Results.

considered statistically significant. All confidence intervals (CI) are reported as 95% CI. Summary data are reported as mean ± standard deviation (SD), median with interquartile range (IQR), or percentages.

RESULTS

Demographics and survival analysis. There were 40,034 patients in the SEER registry who had been treated for well-differentiated thyroid carcinoma between 1988 and 2003. Among this group, 4,618 (11%) had missing information on tumor staging and 2,328 (6%) patients either had missing radiotherapy information or received external beam radiation as part of their treatment. These patients were excluded from the study. The remaining 33,088 patients comprised the complete cohort for further analysis. From this cohort, 30,054 patients (49% ≥45 years) had papillary carcinoma, and 2,584 patients (55% ≥45 years) had follicular carcinoma. 6,768 patients (22%) with papillary carcinoma had lymph node metastasis, and only 61 patients (2%) with follicular disease had lymph node involvement. The majority of the patients with both papillary and follicular lesions were Caucasian and female. African Americans comprised only 5% of patients with papillary cancer and 9% of patients with follicular cancer. Within both pathology groups, 49% of patients received RAI. Complete demographic and clinical data for this cohort are summarized in Table I. Tumor grade variable was populated in the SEER database for only 7,417 (22%) of the patients in our cohort. Of these patients, 70% had well-differentiated (Grade I) lesions, 24% had moderately differentiated (Grade II) lesions, 5% had poorly differentiated (Grade III) lesions, and 1% had anaplastic (Grade IV) disease.

Table II. Descriptive statistics for patients with lymph node involvement

	Papillary thyroid carcinoma (n = *6,786*)	*Follicular thyroid carcinoma* (n = *61*)
Age, median (IQR)	40 (30–52)	61 (45–72)
Female gender	4,676 (69)	36 (59)
Caucasian	5,658 (84)	51 (84)
Hispanic ethnicity	1,108 (16)	4 (7)
RAI	4,803 (71)	40 (66)
Tumor size, median (IQR)	2.0 cm (1.2–3.0)	3.5 cm (2.0–5.0)
Extrathyroidal spread	2,241 (34)	24 (44)
Distant metastases	177 (3)	6 (10)

Table entries are *n* (%) unless indicated.
IQR, Interquartile range; *RAI*, radioactive iodine ablation.

As shown in Table I, only 61 (2%) patients with follicular carcinoma had node-positive disease, and only 293 (1%) patients with papillary cancer and 77 (3%) patients with follicular cancer had distant metastases. Descriptive statistics for patients with positive lymph nodes are summarized in Table II. Of the 15 patients with follicular carcinoma age <45 years with lymph node involvement, 13 were Caucasian, 3 were Hispanic, 12 were female, 12 received RAI, only 3 had tumors >4 cm, 6 had extrathyroidal tumor spread, and none had distant metastatic disease. Descriptive statistics for all patients with metastatic disease are summarized in Table III.

Table III. Descriptive statistics for patients with distant metastatic disease

	Papillary thyroid carcinoma (n = *293*)	*Follicular thyroid carcinoma* (n = *77*)
Age, median (IQR)	55 (38–71)	69 (55–75)
Female gender	171 (58)	56 (73)
Caucasian	228 (78)	48 (62)
Hispanic ethnicity	61 (21)	11 (14)
RAI	216 (74)	59 (77)
Tumor size, median (IQR)	2.5 cm (1.2–4.0)	4.0 cm (2.5–6.5)
Lymph node metastases	177 (60)	6 (8)

Table entries are *n* (%) unless indicated.
IQR, Interquartile range; *RAI*, radioactive iodine ablation.

Univariate survival plots using the Kaplan–Meier method demonstrated improved survival in patients with node-negative papillary cancer ≥45 years (log-rank; $P < .001$) and all patients with follicular cancer (both log-rank; $P \leq .007$; Figs 1 and 2). Lymph node involvement did not affect survival in patients with papillary cancer <45 years (log-rank; $P = .354$; Fig 1).

Multivariate analysis. We developed 4 separate, multivariate Cox proportional hazard regression models in samples that were stratified by tumor histology (papillary or follicular) and age (<45 or ≥45 years). 15,497 patients were included in the papillary carcinoma <45 years (mean, 33.5 ± 7.4) multivariate regression model (Table IV). Age, African-American race, and Hispanic ethnicity had negative effects on survival (all $P < .001$). Extrathyroidal tumor extent had a negative effect on survival (hazard ratio [HR], 1.46; 95% CI, 0.99–2.16; $P = .057$). Female gender had a protective effect ($P < .001$); while the protective effect of RAI approached statistical significance (HR, 0.76; 95% CI, 0.56–1.03; $P = .078$). Presence of tumor-positive lymph nodes did not affect survival in this sample (HR, 1.11; 95% CI, 0.79–1.57; $P = .535$). The effects of the covariates differed in 15,007 patients with papillary carcinoma who were ≥45 years (mean, 58.2 ± 10.4; Table IV). Age, African-American race, tumor size >4 cm, extrathyroidal tumor extent, and lymph node involvement all had negative effects on survival (all $P < .001$). Specifically, lymph node metastases conferred a 46% increased risk of mortality in this population (HR, 1.46; 95% CI, 1.28–1.67; $P < .001$). Once again, female gender carried a protective effect ($P < .001$), whereas the effect of RAI was statistically marginal (HR, 0.90; 95% CI, 0.81–1.01; $P = .080$).

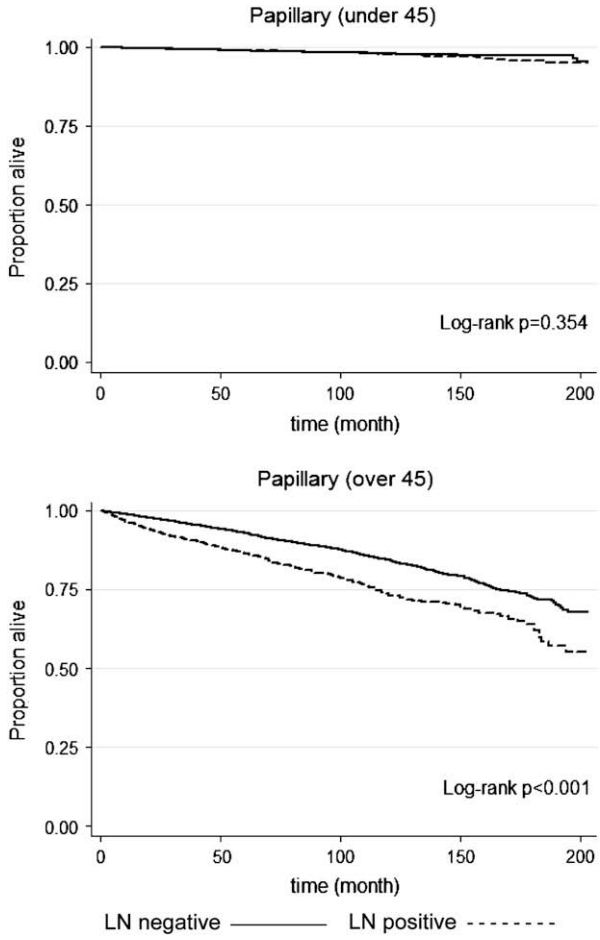

Fig 1. Survival by presence or absence of lymph node disease in patients with papillary carcinoma. Survival did not differ in patients <45 years (top). However, it was significantly worse in patients with lymph node involvement ≥45 years (bottom).

Results for the multivariate Cox analysis in the 1,165 patients with follicular carcinoma <45 years (mean, 32.6 ± 7.8) are reported in Table V. Age, tumor size >4 cm, and presence of lymph node metastases had effects on survival (all $P \leq .002$) in this patient cohort. Although only 15 patients in this cohort had lymph node involvement, their risk of death was increased 11-fold (HR, 11.2; 95% CI, 2.44–51.67; $P = .002$). Additionally, there was a statistically marginal effect suggesting increased risk with extrathyroidal tumor spread (HR, 2.72; 95% CI, 0.99–7.47; $P = .053$). Results for 1,419 patients with follicular carcinoma ≥45 years (mean, 61.1 ± 11.7) are reported in Table V. Age, African-American race, extrathyroidal tumor spread, and lymph node involvement all conferred independent risk (all $P \leq .041$). While only 46 patients in this cohort had lymph node disease, these patients had a greater risk of death (HR,

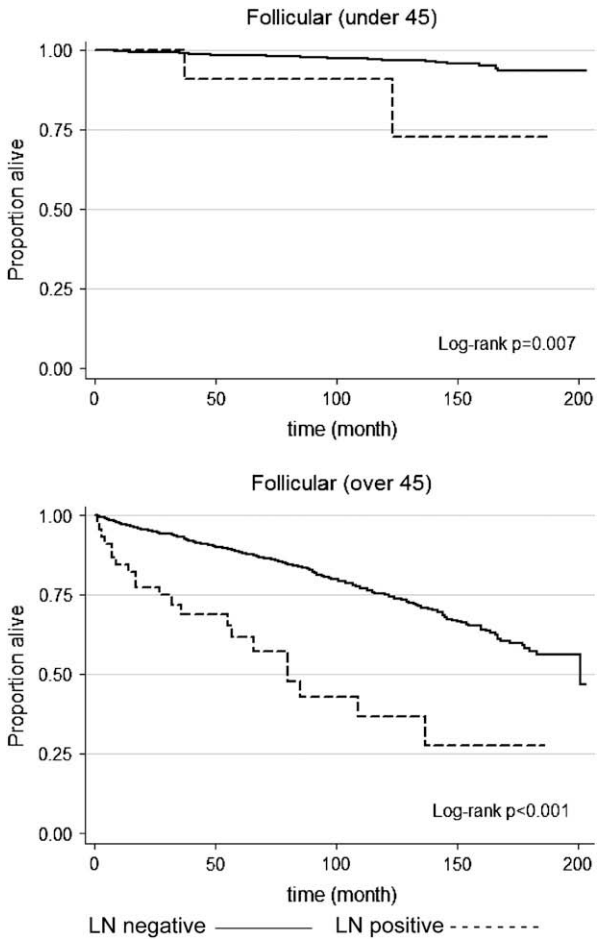

Fig 2. Survival by presence or absence of lymph node disease in patients with follicular carcinoma. Survival was significantly worse in patients with lymph node involvement in both patients groups <45 years (top) and ≥45 years (bottom).

2.86; 95% CI, 1.71–4.78; $P < .001$). An independent increased risk of tumor size >4 cm was suggested in this cohort ($P = .061$). RAI therapy was not associated independently with survival in all patients with follicular carcinoma of the thyroid ($P > .5$).

Secondary analyses. A secondary analysis examined the effects of distant metastases in lieu of tumor extent in the multivariate models. Unfortunately, the SEER registry coded these 2 separate staging parameters within the same variable, making it impossible to treat them as mutually exclusive, independent variables within a single multivariate model. After substituting metastatic spread for tumor extent variable, lymph node involvement was associated with increased risk of death in patients with papillary carcinoma ≥45 years of age and in all patients with follicular cancer (all $P \leq .001$). Lymph node metastases did not affect survival in patients with papillary cancer <45 years old ($P = .340$). Distant metastases had a negative impact on survival in all of the patients with papillary carcinoma and patients with follicular carcinoma ≥45 years ($3.87 \leq HR \leq 5.22$; all $P \leq .002$). The effect of metastatic spread could not be examined in patients with follicular carcinoma <45 years because there were only 4 patients in this category.

An additional analysis tested the effects of thyroid and lymph node directed surgery in the decreased number of patients (38–51% of the full cohort strata) with the information on the extent of operative resection. After adjusting for the effects of age, gender, race, ethnicity, radiotherapy, tumor size, tumor extent, and thyroid and lymph node directed surgery; lymph node metastases continued to confer an increased risk of death in patients with papillary carcinoma ≥45 years (HR, 1.96; 95% CI, 1.38–2.80; $P < .001$). Lymph node involvement did not influence survival in patients with papillary cancer <45 years in this model ($P = .624$). Too few patients and events remained in the follicular cancer models to generate any statistically meaningful results.

DISCUSSION

The generally indolent nature of papillary and follicular thyroid carcinoma renders prospective epidemiologic studies of risk factors associated with survival difficult. Numerous retrospective studies from high-volume institutions have influenced our understanding of risk factors for disease recurrence. Since the 1970s, the importance of age and tumor extent has been well described.[13] The current staging paradigm emphasizes age, tumor size, tumor extent, and metastatic spread as critical factors in postoperative disease staging. Our models confirm these findings. Even after stratifying patients by histology and the TNM staging system age threshold (45 years), age continued to carry a significant risk for death in all of our models. This observation is likely due, at least in part, to other causes of death which increase with age. Extrathyroidal tumor extent carried significant independent risk in all patients >45 years, whereas its independent risk in patients <45 years bordered on statistical significance ($.053 \leq P \leq .057$). Tumor size >4 cm was also an independent predictor of negative outcomes in a majority of the patients, but did not have a significant effect on survival in patients with papillary carcinoma <45 years old ($P = .177$). Moreover, in the secondary analyses, distant metastases had a 3- to 5-fold impact on survival in each of our stratified analysis (all $P \leq .002$) with the exception of patients <45

Table IV. Cox multivariate analysis of the effects of clinical and demographic covariates on survival in patients with papillary thyroid cancer

	<45 years (n = *15,497*)			*≥45 years* (n = *15,007*)		
	HR	*95% CI*	P	*HR*	*95% CI*	P
Age	1.04	1.02–1.07	<.001	1.09	1.08–1.09	<.001
Female gender	0.51	0.37–0.70	<.001	0.64	0.57–0.71	<.001
African American race	2.20	1.26–3.86	.006	1.55	1.24–1.93	<.001
Hispanic ethnicity	1.19	0.76–1.86	.446	1.01	0.84–1.21	.924
RAI	0.76	0.56–1.03	.078	0.90	0.81–1.01	.080
Tumor size > 4cm	1.40	0.86–2.29	.177	1.52	1.31–1.78	<.001
Extrathyroidal spread	1.46	0.99–2.16	.057	1.46	1.28–1.66	<.001
Lymph node metastases	1.11	0.79–1.57	.535	1.46	1.28–1.67	<.001

CI, Confidence interval; *HR*, hazard ratio; *RAI*, radioactive iodine ablation.

Table V. Cox multivariate analysis of the effects of clinical and demographic covariates on survival in patients with follicular thyroid cancer

	<45 years (n = *1,165*)			*≥45 years* (n = *1,419*)		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.20	1.11–1.29	<.001	1.08	1.07–1.09	<.001
Female gender	0.64	0.30–1.39	.261	0.80	0.61–1.06	.122
African American race	0.99	0.29–3.37	.990	1.50	1.02–2.22	.041
Hispanic ethnicity	0.69	0.16–2.98	.621	1.07	0.61–1.89	.799
RAI	1.22	0.60–2.49	.583	0.97	0.74–1.28	.841
Tumor size > 4cm	3.21	1.13–9.16	.029	1.45	0.98–2.15	.061
Extrathyroidal spread	2.72	0.99–7.47	.053	1.68	1.22–2.32	.001
Lymph node metastases	11.23	2.44–61.69	.002	2.86	1.71–4.78	<.001

CI, Confidence interval; *HR*, hazard ratio; *RAI*, radioactive iodine ablation.

with follicular cancer, in whom a meaningful statistical analysis could not be performed. Nevertheless, role of lymph node involvement in well-differentiated thyroid cancer remains controversial. Both retrospective single-center reviews and large population-based database studies have reached opposing conclusions regarding the prognostic implications of lymph node metastases.[8,9]

Although both papillary and follicular thyroid carcinomas are considered well-differentiated thyroid cancers, there are differences in tumor behavior, diagnosis, staging, and treatment between the 2 malignancies.[14,15] In addition, clinical staging, risk stratification, and treatment of papillary and follicular carcinoma are largely dependent on the 45-year threshold, employed in the TNM thyroid staging schema. As such, we stratified our analyses based on tumor histology and age. After adjusting for other demographic and clinical covariates, patients with papillary thyroid carcinoma <45 years and positive lymph node disease did not have an increased risk of death in our model (HR, 1.11; $P = .535$). In contrast, the multivariate model in patients ≥45 years with papillary cancer demonstrated that lymph node involvement conveyed a 46% increased risk of death (HR, 1.46; $P < .001$). While lymph node metastases occurred in 22% of the tumors with papillary histology, nodal metastases were present in only 2% of the patients with follicular carcinoma. This observation is not unexpected, given the largely hematogenous spread of follicular carcinoma. However rare presence of lymph node metastases conferred up to an 11-fold increased risk of death in these patients (<45 years: HR, 11.2; ≥45 years: HR, 2.86; both $P \leq .002$).

Our study included about 13,000 patients more than the last published series using the SEER database to examine the influence of lymph node metastases on survival.[9] We have analyzed an additional 2 years of data, which added about 9,000 patients, as well as a major pathologic diagnosis code for papillary adenocarcinoma (8260), which contributed an additional 6,500 patients. Other cohort size discrepancies between our studies and previous reports are largely a result of

differences in inclusion/exclusion criteria. Moreover, previous studies using the SEER registry did not stratify patients according to the 45-year threshold, which is an integral prognostic aspect of the TNM staging system. Because age is a crucial component of the staging system (where patients <45 years can only be Stage II or lower), we felt that it was clinically relevant and statistically meaningful to stratify our analyses by both tumor histology and patient age. The SEER registry includes mortality from all causes but does not provide cancer-specific mortality. Stratifying the models by the age threshold employed in the TNM staging system and then including age as a continuous variable in the individual models controls for the effect of aging within each of our analyses. Current practice guidelines recommend consideration for central compartment neck dissections for patient with papillary thyroid carcinoma and lymph node metastases.[10] Although our data suggest that lymph node involvement confers a significant risk to patients with follicular thyroid carcinoma, further studies are necessary to delineate optimal treatment practices for these patients.

A number of other risk factors and treatment modalities in papillary and follicular thyroid carcinoma need further evaluation. Tumor grade has been shown to be an important factor for prognosis in patients with well-differentiated thyroid carcinoma.[16] Unfortunately, only 22% of the patients in our entire cohort had information about tumor grade available in the SEER database. As such, it was not possible to adjust for this variable with multivariate techniques. Moreover, our models demonstrated a worse prognosis for majority of African-American patients. Indeed, because the outcome measure in our study is all-cause mortality, it is possible that racial differences in mortality reflect other causes of death in this patient population. Racial disparities in diagnosis and treatment of thyroid carcinoma have been suggested previously and more dedicated studies on this topic are required.[9,17]

Previously published studies from the SEER registry demonstrate a lack of survival benefit from radiotherapy in patients with well-differentiated thyroid cancer.[8,18] In our analysis, although there seemed to be 10% to 24% survival advantage in patients with papillary carcinoma who received RAI postoperatively, this improvement did not reach statistical significance ($P \geq .078$). Survival did not seem to be affected by RAI in patients with follicular carcinoma. Interestingly, although the current American Thyroid Association guidelines recommend RAI for most patients with Stage II disease or greater, only 66–77% of patients in our cohort with node-positive disease or metastatic spread received radioactive iodine.

Although this cancer registry is the standard for quality among cancer registries in the United States, some of the patient and treatment information is limited. The registry includes data from both community and academic hospitals; however, information is not stratified by hospital type or volume of head and neck operations. Moreover, data on specific tumor staging and operative procedure are frequently missing. Information on patient's comorbidities, performance status, tumor resection margin, and chemotherapy is not available. Data on tumor extent and metastatic disease is coded under the same variable for 1988 through 2003. As such, the models have to be constructed to include only one of these important variables. Despite these limitations, well-designed SEER registry studies have been able to provide clinicians with a wealth of information. Continuous improvements in SEER data collection and management will increase utility of this registry in study of quality and outcomes in cancer treatment. Our study based on population data captured by the SEER registry between 1988 and 2003 demonstrates lymph node status to be an independent predictor of survival in patients with follicular cancer of the thyroid and in patients with papillary carcinoma ≥45 years. Presence of lymph node metastases in patients with papillary carcinoma <45 years did not influence survival.

REFERENCES

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006;295:2164-7.
2. Solorzano CC, Carneiro DM, Ramirez M, Lee TM, Irvin GL III. Surgeon-performed ultrasound in the management of thyroid malignancy. Am Surg 2004;70:576-80.
3. Senchenkov A, Staren ED. Ultrasound in head and neck surgery: thyroid, parathyroid, and cervical lymph nodes. Surg Clin North Am 2004;84:973-1000.
4. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050-7.
5. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 1996;3:534-8.
6. McHenry CR, Rosen IB, Walfish PG. Prospective management of nodal metastases in differentiated thyroid cancer. Am J Surg 1991;162:353-6.
7. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005;90:5723-9.

8. Bhattacharyya N. A population-based analysis of survival factors in differentiated and medullary thyroid carcinoma. Otolaryngol Head Neck Surg 2003;128:115-23.
9. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg 2005;71:731-4.
10. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
11. Greene FLP, Fleming DL, Fritz ID, Balch A, Haller CM, Morrow M, editors. Thyroid. In: AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
12. National Cancer Institute. Surveillance, epidemiology and end results (SEER) program: Public use data (1973–2004). Available from: http://seer.cancer.gov/data/. Accessed July 2007.
13. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg 1976;184:541-53.
14. Sosa JA, Udelsman R. Papillary thyroid cancer. Surg Oncol Clin North Am 2006;15:585-601.
15. Phitayakorn R, McHenry CR. Follicular and Hurthle cell carcinoma of the thyroid gland. Surg Oncol Clin North Am 2006;15:603-23.
16. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control 2000;7:229-39.
17. Mitchell I, Livingston EH, Chang AY, et al. Trends in thyroid cancer demographics and surgical therapy in the United States. Surgery 2007;142:823-8.
18. Podnos YD, Smith DD, Wagman LD, Ellenhorn JD. Survival in patients with papillary thyroid cancer is not affected by the use of radioactive isotope. J Surg Oncol 2007;96:3-7.

DISCUSSION

Dr Ashok R. Shaha (New York, NY): I am very happy to see that you changed the title of your abstract, which said initially that lymph nodes negatively impact survival. They do not have an impact on younger people, and I think that is a major conclusion. We showed this from Memorial some 12 years back with a randomized study showing that in patients below the age of 45 there was no impact of lymph node metastases, but in older people positive nodes had an impact. What would be more interesting is what causes this impact? Why does it occur? Is it because the tumors are larger? Is it because there is more spread? Is it because the histology is worse in patients above the age of 45? I think that it would be more interesting to see why we think the nodal metastases have a negative impact. If we look at squamous cell carcinoma, the reason nodal metastases are bad is they recur in the neck nodes and patients die. We have not seen that in thyroid cancer, and I think that will be a very interesting study. I wanted to hear your thoughts on this.

Dr Victor Zaydfudim (Nashville, Tenn): I completely agree with you. In our study, we adjusted for tumor size, tumor spread, and presence of distant metastases, and we still found that lymph node involvement posed an independent risk in all patients over the age of 45 and in patients with follicular carcinoma even if they were under age of 45. Unfortunately, in the SEER database, tumor grade information was only available in about 20% of all patients included in our study and this did not allow us to adjust for it in the multivariate models.

Dr Geoffrey B. Thompson (Rochester, Minn): One of the things I have a little concern about is that there is really no mention both with the follicular and the papillary cancers of whether there was extrathyroidal extension. I think that that is very important. When we looked at our node-positive patients over the age of 45 several years ago, we found that it was really with those patients that had concomitant extrathyroidal extension of their primary tumor along with lymph node metastases where the lymph node metastases seemed to impart a worse prognosis. Also, in the follicular cancers, it has been our experience that the ones that tend to truly have lymph node metastases tend to be the more widely invasive type of follicular cancers. They are the larger, bigger tumors. But, say you have a patient with papillary cancer that is over the age of 45 and lymph node metastases, yet they still have an intrathyroidal papillary carcinoma; the lymph node metastases do not seem to impart a worse survival benefit or prognosis to those patients. Did you look specifically at extrathyroidal extension both in the papillary and follicular patients?

Dr Victor Zaydfudim (Nashville, Tenn): In the original manuscript that we submitted, we did not address the issue of extrathyroidal spread. We have since included this variable in the analyses shown at this meeting, as well as in our revised manuscript. Our initial concern with adjusting for extrathyroidal spread was because the SEER database coded tumor spread and distant metastatic spread under the same variable, and consequently we have separately adjusted for both tumor extent and metastases. Even after including extrathyroidal tumor spread in the multivariate models, positive lymph nodes carried an independent risk in patients with papillary cancer over 45 years, and in all patients with follicular cancer. Additionally, extrathyroidal tumor spread was a significant independent risk for negative outcome in all patients over 45 years of age. Risk was present, but did not quite achieve statistical significance in patients under 45.

Dr Shiro Noguchi (Oita, Japan): In the late 1960s, published in 1970s, I noted that particularly in the older patients the numbers of lymph nodes present was small. And in the younger patients—there were many lymph nodes. So, just looking for metastasis, younger patients, particularly teenagers, had more lymph nodes in their neck. So, I wonder if you have a proportion of metastatic lymph node to no metastatic lymph node.

Dr Victor Zaydfudim (Nashville, Tenn): We did not specifically look at the number of examined lymph nodes as a separate variable. Data on the number of lymph nodes examined are certainly available in the database, but because we were specifically interested in the effect of tumor positive lymph nodes, that is the variable we chose to examine in our analyses. Moreover, we thought we sufficiently adjusted for the effect of age by stratifying by age cutoff value of 45 and then including age as a continuous variable into every individual model.

Dr Shiro Noguchi (Oita, Japan): If lymph node harbors metastasis, it is bigger. And the numbers of lymph nodes in the neck between young people and old people and cadavers have to be compared.

Dr Victor Zaydfudim (Nashville, Tenn): Both age and lymph node status were included in all of our analyses. I think we have reliable data to show that in older patients lymph node metastases harbor a negative effect on survival.

Dr Bradford K. Mitchell (Morgantown, WV): If I understand correctly, you do not have cause-specific mortality. I didn't see that you excluded patients with other malignancies as an exclusion criterion. In light of the recent suggestion that radioactive iodine treatment may induce other malignancies, is it possible that is a confounding factor in your study?

Dr Victor Zaydfudim (Nashville, Tenn): I agree and think reporting all-cause mortality is a major limitation of the SEER database and a major limitation of our study. Unfortunately, it is the only end point provided by the database. That is one of the reasons we chose to adjust for age by using a stratification point of 45 years and including it in every multivariate model as a continuous variable. Only about 50% of the patients received radioactive iodine in our cohort. And after adjusting for effects of radioactive iodine, lymph node metastases still had a negative effect on survival in the patient populations that we have discussed.

Dr Bradford K. Mitchell (Morgantown, WV): So I think that radiotherapy dose needs to be controlled for in the data to know whether or not some of these bigger tumors got larger doses of radiation and may in fact have led to other malignancies.

Dr Victor Zaydfudim (Nashville, Tenn): We did adjust for tumor size; however, we could not adjust for the dose of radioactive iodine administered because that information is not available in the SEER database.