A study of recurrence and death from papillary thyroid cancer with 27 years of median follow-up

Raymon H. Grogan, MD,[a] Sharone P. Kaplan, MSW,[b] Hongyuan Cao, PhD,[c] Roy E. Weiss, MD, PhD,[b] Leslie J. DeGroot, MD,[d,e] Cassie A. Simon, CTR,[f] Omran M. A. Embia, MBChB,[a] Peter Angelos, MD, PhD,[a] Edwin L. Kaplan, MD,[a] *and* **Rebecca B. Schechter, MD,[b]** *Chicago, IL, and Providence, RI*

Background. *Although recurrence and death can occur in patients with papillary thyroid cancer (PTC) several years after being diagnosed, the necessary duration of follow-up for these patients remains unclear.*

Methods. *This was a single-institution, retrospective review of 269 patients with PTC. Cox proportional hazards model and Kaplan-Meier curves were used to identify risk factors for recurrence and death. Risk predictors included age, sex, radiation exposure history, extent of operation, radioactive iodine treatment, follicular variant of PTC (FVPTC), extrathyroidal invasion, multifocality, TNM status, and stage.*

Results. *Median follow-up was 27 years. Of 269 patients, 180 (66%) were female, and 196 (73%) were ≤45 years of age. Recurrence and cancer-specific death rates were 28% and 9%, respectively. Time to recurrence (±SD) was 8.1 (± 8.3) years and to cancer-specific death was 9.0 (± 11.0) years; however, 11% of recurrences and 17% of deaths occurred after 20 years. Risk factors for recurrence were older age, FVPTC, T4 tumors, cervical lymph node involvement, metastases, and stage ≥ 4a. Predictors of death from PTC were older age, metastases, and stage ≥ 3.*

Conclusion. *Both recurrences and death from PTC can occur more than 30 years after being treated, thus lifelong follow-up of patients with PTC is necessary. (Surgery 2013;154:1436-47.)*

From the Department of Surgery, Endocrine Surgery Research Program,[a] Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism,[b] Department of Health Studies, Section of Biostatistics,[c] University of Chicago Pritzker School of Medicine, and Professor Emeritus,[d] University of Chicago, Chicago, IL; Research Professor, University of Rhode Island-Providence,[e] Providence, RI; and Cancer Registry,[f] University of Chicago Medicine, Chicago, IL

After treatment for papillary thyroid cancer (PTC), prolonged follow-up is necessary because recurrence and death can occur years after diagnosis.[1-3] Three frequently cited long-term studies on PTC have median follow-up times of only 11,[4] 15,[5] and 15.7[1] years. Thus, our understanding of the extended long-term morbidity and mortality of PTC decades after the initial diagnosis is uncertain. Investigating the long-term risks associated with PTC may lead to improved tailoring of treatments and surveillance testing for those at greatest risk from their cancers while potentially limiting unnecessary therapy and monitoring of patients at less risk. In an environment of uncontrolled health care costs and finite resources, better knowledge of risk predictors associated with poor outcome should lead to more appropriate, cost-effective care.

In 1990, DeGroot et al[4] published a landmark article on the natural history, treatment, and course of PTC of 269 patients treated at the University of Chicago between 1968 and 1988 with a median follow-up period of 11 years from diagnosis. The study found that 25% of PTC patients had recurrent disease and that 8.2% died from PTC. Cervical lymph node involvement and less than total/near total thyroidectomy were associated with increased risk of recurrence. Extrathyroidal invasion, distant metastases, less than

Funding provided by internal sources from the University of Chicago Department of Surgery Endocrine Surgery Research Program, and the Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism and the Rabbi Esformes Endowment.

Accepted for publication July 3, 2013.

Reprint requests: Raymon H. Grogan, MD, Department of Surgery, Endocrine Surgery Research Program, University of Chicago Pritzker School of Medicine, 5841 S. Maryland Ave, MC 4052, Chicago, IL 60637. E-mail: rgrogan@surgery.bsd.uchicago.edu.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2013.07.008

total/near total thyroidectomy, and age >45 years of age increased the risk of death. In addition, the study provided strong but not conclusive data that radioactive iodine (RAI) remnant ablation benefited patients with intrathyroidal tumors greater than 1 cm and those with cervical lymph node metastases.

Not all studies have supported the findings in this original analysis. Perhaps most controversial are the risks associated with cervical metastases and postoperative RAI. Although some studies have corroborated that cervical metastases increase cancer recurrence, others have not.[6] Recent data suggest that larger, clinically apparent, and abundant cervical lymphadenopathy or a high ratio of metastatic to total lymph nodes may increase risk of recurrence, whereas small-volume lymphadenopathy may confer lesser risk.[7,8] In addition, the presence of extranodal extension may negatively impact disease-specific survival.[8,9]

The benefit of RAI remnant ablation is still debated, particularly in low-risk patients. Although older, retrospective data suggest that patients with isolated tumors >1.5 cm may have a lesser risk of recurrence after RAI therapy,[1] in more recent studies researchers have concluded that RAI in low-risk patients has no benefit and may, in fact, have unacceptable side effects.[10,11] The benefits of RAI in greater risk patients are better established, but data are not entirely convincing.[12] The American Thyroid Association recommends RAI in many stage 3–4 cancers or when metastatic disease is present, although the American Thyroid Association guidelines acknowledge that there are inadequate or conflicting data in many clinical situations.[12]

We aimed to provide additional long-term follow-up on the original University of Chicago cohort of patients to ascertain a more accurate risk of recurrence and death over several decades and to further identify risk factors associated with poor clinical outcome. We report a median follow-up of 27 years on the University of Chicago cohort.

METHODS

Patients and follow-up. A database describing the nonconsecutive patient cohort from the original University of Chicago study was provided by DeGroot et al.[4] Data on demographics, tumor pathology, treatments, recurrences, and deaths were extracted. Pathologic diagnoses were based on the original evaluations. Additional follow-up was ascertained from the medical records and the University of Chicago Cancer Registry. The cancer registry confirmed specific data on death and recurrence via the social security death index, death certificates, obituaries, and direct patient follow-up. The study was approved by the University of Chicago Institutional Review Board.

Statistical analysis. Kaplan-Meier curves were used to demonstrate recurrence and survival rates, and their significance was determined with the log-rank test. We used Cox proportional hazards model with stepwise variable selection to examine the individual effects of risk predictors on cancer recurrence and cancer-specific death. No interaction terms were found to be statistically significant. Continuous data are either expressed as median values or mean ± SD. Potential risk predictors were age, sex, radiation exposure history, extent of operation, RAI treatment, follicular variant of PTC (FVPTC), extrathyroidal invasion, multifocality, TNM status, and stage. Age was evaluated as both a continuous variable and as a categorical variable divided into three groups: <45 years of age, 45–60 years of age, and >60 years of age. The categorical age variable was used in the multivariate analysis. We studied cervical lymphadenopathy by number of positive nodes: 0, 1–5, or >5 lymph nodes and by location according to the TNM classification: central neck (N1a) or lateral neck (N1b). Patients with Nx status were considered to have no clinically apparent lymphadenopathy based on preoperative evaluation and were considered N0 in the Cox models. Mx status was treated as unknown data because this information was undetermined most commonly at the time of operation and was not included in the Cox models. Tumor staging was done according to the 7th edition of the American Joint Committee on Cancer TNM (Tumor-Node-Metastasis) guidelines.[13] We defined recurrence as either development of new disease or progression of existing disease. We treated deaths from other causes as censoring.

Twenty-six patients were excluded from the analysis because of incomplete staging. Stage also was excluded from the final analysis because cancer stage is derived from other intrinsic variables such as age and tumor characteristics. The hazard ratios from the marginal model were considered the final model for stage.

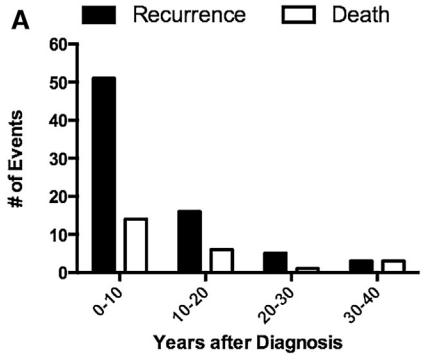
RESULTS

Cohort demographics (Table I). The study cohort consisted of 269 patients, 180 (67%) females and 89 (33%) males. Mean age was 35.9 ± 15.5 years. A total of 196 (73%) patients were <45 years of age at diagnosis, 52 (19%) patients were between 45 and 65 years, and 21 (8%) patients were >65 years of age. The cohort was notable for a large number of patients with low-dose radiation exposure (99 patients, 37%).

Table I. Study cohort characteristics with total numbers, deaths from thyroid cancer, and recurrences grouped by risk factor

	N	*Death*	*Recurrence*
Characteristic/risk factor	n *(% of total*)*	n *(% of subgroup†)*	
Patient			
Age, y, mean ± SD	35.9 ± 15.5		
<45	196 (73)	6 (3)	51 (26)
45–60	51 (19)	8 (16)	12 (23)
>60	22 (8)	10 (45)	12 (57)
Female	180 (67)	13 (7)	47 (26)
Male	89 (33)	11 (12)	28 (31)
Radiation exposure (+)	99 (37)	7 (7)	29 (29)
Radiation exposure (−)	170 (63)	17 (10)	46 (27)
Treatment			
Thyroidectomy			
Total/near-total	178 (66)	11 (6)	39 (22)
Less than total	83 (31)	11 (13)	32 (39)
Unknown	8 (3)	2 (25)	4 (50)
RAI therapy (+)	141 (52)	11 (8)	35 (25)
RAI therapy (−)	128 (48)	13 (10)	40 (31)
Surgery at University of Chicago	162 (60)	10 (6)	34 (21)
Surgery not at University of Chicago	107 (40)	14 (13)	41 (38)
Tumor			
Papillary	118 (44)	11 (9)	22 (19)
Papillary-follicular variant	151 (56)	13 (9)	53 (35)
Extrathyroidal invasion (+)	34 (13)	7 (21)	21 (62)
Extrathyroidal invasion (−)	235 (87)	17 (7)	54 (23)
Unifocal	148 (55)	14 (10)	41 (28)
Multifocal	121 (45)	10 (8)	34 (28)
No. positive lymph nodes			
0	164 (61)	15 (9)	36 (22)
1–5	65 (24)	5 (8)	22 (34)
>5	40 (15)	4 (10)	17 (43)
T1a	71 (26)	3 (4)	7 (10)
T1b	61 (23)	1 (2)	15 (25)
T2	51 (19)	2 (4)	11 (22)
T3	32 (12)	11 (34)	14 (44)
T4	29 (11)	5 (17)	18 (62)
T Unknown	25 (9)	2 (8)	10 (40)
Nx	154 (57)	14 (9)	32 (21)
N1a	58 (22)	6 (10)	20 (35)
N1b	57 (21)	4 (7)	23 (40)
Mx	120 (45)	7 (6)	32 (27)
M0	132 (49)	7 (5)	28 (21)
M1	17 (6)	10 (59)	15 (88)
Stage			
Stage 1	211 (78)	5 (2)	47 (22)
Stage 2	12 (5)	1 (8)	4 (33)
Stage 3	10 (4)	2 (20)	2 (20)
Stage 4a	17 (6)	4 (24)	7 (41)
Stage 4b	13 (5)	11 (85)	12 (92)
Stage unknown	6 (2)	1 (17)	3 (50)
Total	269 (100)	24 (9)	75 (28)

*Percentages of the total 269 cohort; example: 73% of the cohort was <45 years of age.
†Percentages of the subgroup; example: of the 196 patients <45 years of age, 26% recurred and 3% died.
RAI, Radioactive iodine.



B

Time (Years)	Recurrence n (%)	Death
0-10	51 (68)	14 (58)
10-20	16 (21)	6 (25)
20-30	5 (7)	1 (4)
30-40	3 (4)	3 (13)
Total	75 (100)*	24 (100)*

*9% death rate and 28% recurrence rate overall

Fig 1. *(A)* Actual number of recurrences or deaths by decade from the time of cancer diagnosis. *(B)* The majority of PTC recurrences and deaths occur within the first 10 years after diagnosis, but 11% of recurrences and 17% of deaths occurred after 20 years of follow-up. This observation suggests that lifelong surveillance for patients with PTC is necessary to dectect recurrences quickly.

Most of the patients had their initial operation [162 (60%)] at the University of Chicago, whereas the remainder came to the University for further management after operation. A total of 178 (66%) of patients had total/near-total thyroidectomies, 83 (31%) had less than total/near-total thyroidectomies, and 8 (3%) had unknown extents of thyroidectomy. At least one dose of postoperative RAI was administered to 141 (52%) of patients.

On final pathology, 151 patients (56%) had FVPTC; the remainder had classic PTC. No other subtypes of PTC were reported in the original cohort. After staging the cohort according to the 7th edition of the AJCC Staging Manual, 71 (26%) patients had T1a tumors, 61 (23%) had T1b tumors, 51 (19%) had T2 tumors, 32 (12%) had T3 tumors, and 29 (11%) had T4 tumors. Lymph node status included 154 (57%) Nx, 58 (22%) N1a, and 57 (21%) N1b. Seventeen (6%) patients had metastatic disease, and gross extrathyroidal invasion was observed in 34 (13%) cases. A total of 211 patients (78%) had Stage 1 disease, 12 (5%) had Stage 2 disease, 10 (4%) had Stage 3 disease, 17 (6%) had Stage 4A disease, 13 (5%) had Stage 4B disease, and 6 (2%) were stage unknown.

Long-term follow-up. We were able to obtain additional follow-up information on 204 patients (76%) of the original University of Chicago cohort, increasing the median follow-up from 11 years to 27 years. During the additional follow-up years, six cancers recurred, increasing the total number of recurrences from 69 (25%) to 75 (28%). The mean time to recurrence increased from 7.6 years to 8.1 (± 8.4) years (median 4.6 years). A total of 96 patients (36%) died, 24 (9%) from thyroid cancer, 35 (13%) from other causes, and 37 (14%) of unknown causes. The mean time to thyroid cancer death was 9.0 (± 11.0) years (median 3 years). The overall risk of death from thyroid cancer increased from 8.2% to 9.0% with the additional follow-up.

Of the 75 cases of recurrence, 51 (68%) recurred within the first 10 years, and 16 (21%) recurred between 10 and 20 years after diagnosis (Fig 1). In addition, we identified five cases of recurrence (7%) 20–30 years after diagnosis and three cases (4%) between 30 and 40 years after diagnosis. Of the 24 cases of thyroid cancer deaths, 14 (58%) occurred within the first 10 years, 6 (25%) occurred between 10–20 years, 1 (4%) occurred between 20–30 years, and 3 (13%) occurred between 30 and 40 years after the cancer was diagnosed.

Factors influencing recurrence. The complete Cox analysis on cancer recurrence is in Table II. On univariate analysis, the only patient characteristic associated with increased risk of recurrence was age. We found a trend toward greater recurrence rates with increasing age as a continuous variable. This trend is statistically significant when the cohort is divided into three age groups: <45 years of age, 45–60 years of age, and >60 years of age, with a hazard ratio of 3.88 (95% confidence interval 2.0–7.56) for the oldest age group compared with the youngest age group (Fig 2, *A*)

Univariate analysis of treatment characteristics shows that recurrence risk was decreased by total thyroidectomy (Fig 3, *A*) but was not decreased by RAI therapy [hazard ratio 0.82 (95% confidence interval 0.51–1.34); Fig 3, *B*]. Patients who had their first thyroid cancer operation at the University of Chicago also recurred less than those who had their operation elsewhere, but this could be a reflection of the extent of surgery (Fig 3, *C*).

Unfavorable tumor characteristics that increased the risk of recurrence on univariate analysis included: FVPTC (Fig 4, *A*), gross extra-thyroidal

Table II. Hazard ratios for predictors of survival and recurrence of papillary thyroid cancer, including the univariate model and final parsimonious model

	Survival analysis				*Recurrence analysis*			
	Univariate model		*Final model*		*Univariate model*		*Final model*	
*Risk predictor**	*Hazard ratio (95% CI)*	P *value*	*Hazard ratio (95% CI)*	P *value*	*Hazard ratio (95% CI)*	P *value*	*Hazard ratio (95% CI)*	P *value*
Age (continuous)	1.1 (1.06–1.13)	<.001			1.02 (0.98–1.0)	.07		
Age, y								
45–60	5.44 (1.81–16.35)	.003	73.61 (9.01–601.46)	<.001	0.91 (0.46–1.8)	.78	5.54 (1.98–15.47)	.001
>60	29.32 (9.60–89.59)	<.001	25.50 (2.76–235.56)	.004	3.88 (2.0–7.56)	<.001	4.88 (1.55–15.37)	.007
Male	1.51 (0.65–3.54)	.34			1.29 (0.78–2.13)	.33		
History of radiation (+)	0.55 (0.22–1.41)	.21			0.94 (0.57–1.55)	.81		
Thyroidectomy, less than total	2.17 (0.9–5.55)	.08			2.09 (1.27–3.44)	.004		
RAI therapy (+)†	1.04 (0.45–2.43)	.92			0.82 (0.51–1.34)	.43		
Papillary-follicular variant‡	0.77 (0.34–1.79)	.55			1.83 (1.09–3.09)	.02	5.93 (2.19–16.05)	<.001
Extrathyroidal invasion (+)	3.21 (1.31–7.9)	.01			4.32 (2.56–7.28)	<.001		
Multifocal tumor	1.04 (0.45–2.41)	.93			1.16 (0.71–1.89)	.55		
No. positive nodes								
1–5	1.09 (0.38–3.15)	.87			1.97 (1.11–3.52)	.02		
>5	1.42 (0.45–4.46)	.55			2.47 (1.31–4.64)	.005		
Tumor								
T1b	0.35 (0.04–3.39)	.37	1.42 (0.11–18.75)	.79	2.58 (1.05–6.32)	.04	4.23 (1.09–16.42)	.04
T2	0.97 (0.16–5.82)	.98	0.43 (0.03–6.52)	.54	2.53 (0.98–6.54)	.05	0.36 (0.07–1.87)	.23
T3	10.53 (2.92–37.99)	<.001	3.11 (0.52–18.44)	.22	6.20 (2.5–15.39)	<.001	1.57 (0.44–5.6)	.49
T4	4.07 (0.97–17.02)	.06	6.87 (0.84–55.99)	.07	8.74 (3.65–20.97)	<.001	5.65 (1.64–19.43)	.006
Node								
N1a	1.32 (0.5–3.52)	.58	16.21 (2.52–104.19)	.003	2.10 (1.16–3.79)	.01	6.78 (2.15–21.35)	.001
N1b	0.87 (0.28–2.7)	.81	2.07 (0.51–8.44)	.31	2.47 (1.38–4.44)	.002	10.82 (3.69–31.76)	<.001
Metastasis								
M1	19.84 (7.13–55.22)	<.001	74.46 (9.25–600.97)	<.001	8.64 (4.09–18.27)	<.001	58.43 (14.79–230.79)	<.001
Stage§								
2	5.54 (0.61–50.0)	.13			1.37 (0.42–4.4)	.6		
3	19.96 (3.3–120.91)	.001			1.15 (0.28–4.76)	.85		
4a	21.66 (5.11–91.78)	<.001			2.91 (1.3–6.5)	.01		
4c	200.83 (53.46–754.47)	<.001			20.85 (10.09–43.1)	<.001		

*Reference groups: age <45 y, female, history of radiation exposure (−), thyroidectomy total/subtotal, RAI therapy (−), unifocal tumor, no. positive nodes 0, Stage 1, Node Nx, Metastasis M0.
†RAI therapy.
‡Papillary thyroid cancer, follicular variant.
§Stage is not included in the final multivariate model because it is a derived factor. The univariate hazard ratios for stage are considered the final model for both recurrence and survival.
CI, Confidence interval; *RAI*, radioactive iodine.

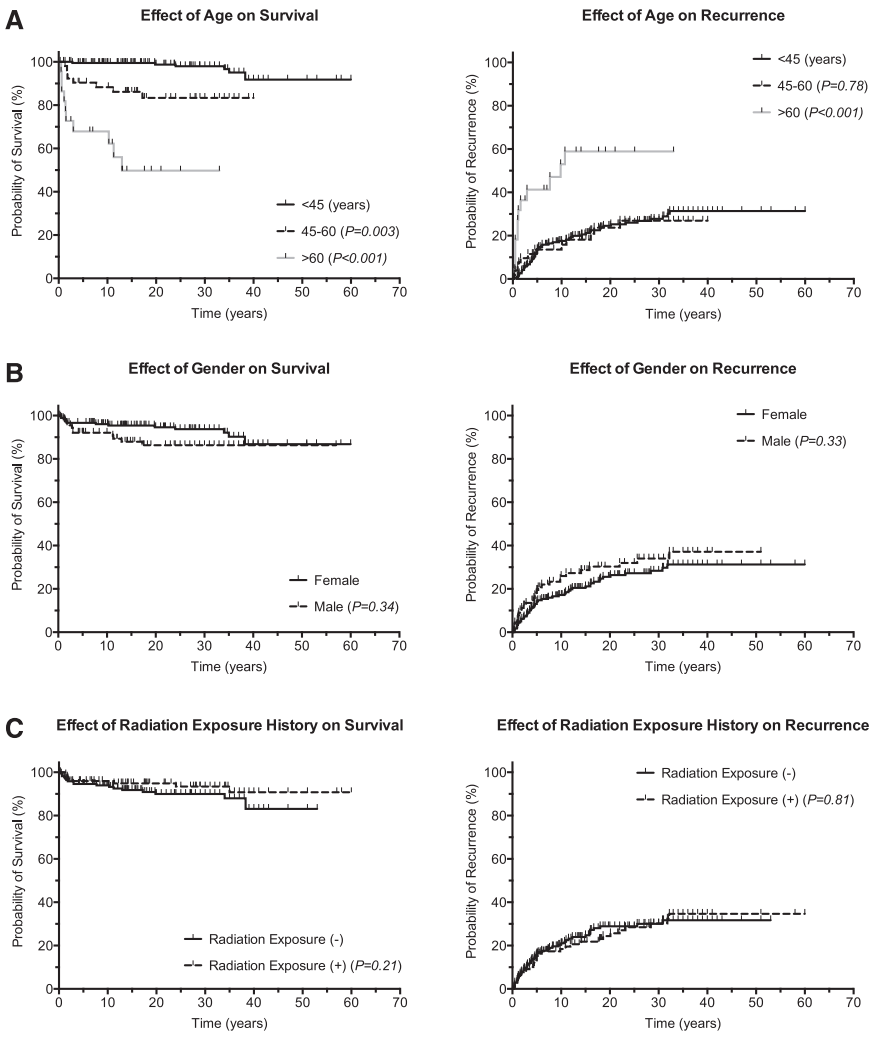


Fig 2. Effect of patient risk factors on PTC recurrence and survival. Risk factors intrinsic to the patient included age (*A*), sex (*B*), and previous history of radiation exposure to the head and neck (*C*). The Kaplan-Meier curves in (*A*) suggest that a three age group model is better than a two age group model at predicting death from PTC. The curves in (*B*) show that male sex does not increase the risk of recurrence or death. Thyroid cancer as a consequence of radiation exposure might be less aggressive than traditional PTC (*C*).

invasion (Fig 4, *B*), and having any positive lymph nodes (Fig 4, *D*). A direct correlation existed between the number of positive nodes found and the risk of recurrence (Fig 4, *D*). Each of the AJCC TNM anatomic sites (tumor, node, and metastasis) showed a direct correlation with recurrence risk (Fig 5, *A–C*). In the final combined stage, however, only stage 4A and 4C tumors showed a significant increase in recurrence risk (Fig 5, *D*). Sex, history of radiation exposure, RAI therapy, and multifocality had no effect on recurrence on univariate analysis (Fig 2, *C*; Fig 3, *B*; and Fig 4, *C*).

The final Cox model showed that age 45–60, age >60, FVPTC, T1b and T4 tumors, N1a or N1b lymphadenopathy, and distant metastases were each associated with significantly increased rates of recurrence (see Table II for hazard ratios). The only risk factor associated with a low risk of recurrence was T1a tumors. All other risk factors had a recurrence rate of at least 20% (Table I).

Factors influencing survival. The complete Cox analysis on thyroid cancer-specific deaths are in Table II. Univariate analysis showed that older age (as a continuous variable and in age groups 45–60 and >60) was associated with increased risk of cancer-specific death (Fig 2, *A*). There were no other patient specific characteristics that changed survival. The only treatment characteristic that improved survival was having the initial surgery at the University of Chicago (Fig 3, *C*). Total thyroidectomy trended toward increased survival [Less than total hazard 2.17 (95% confidence interval 0.9–5.55)].

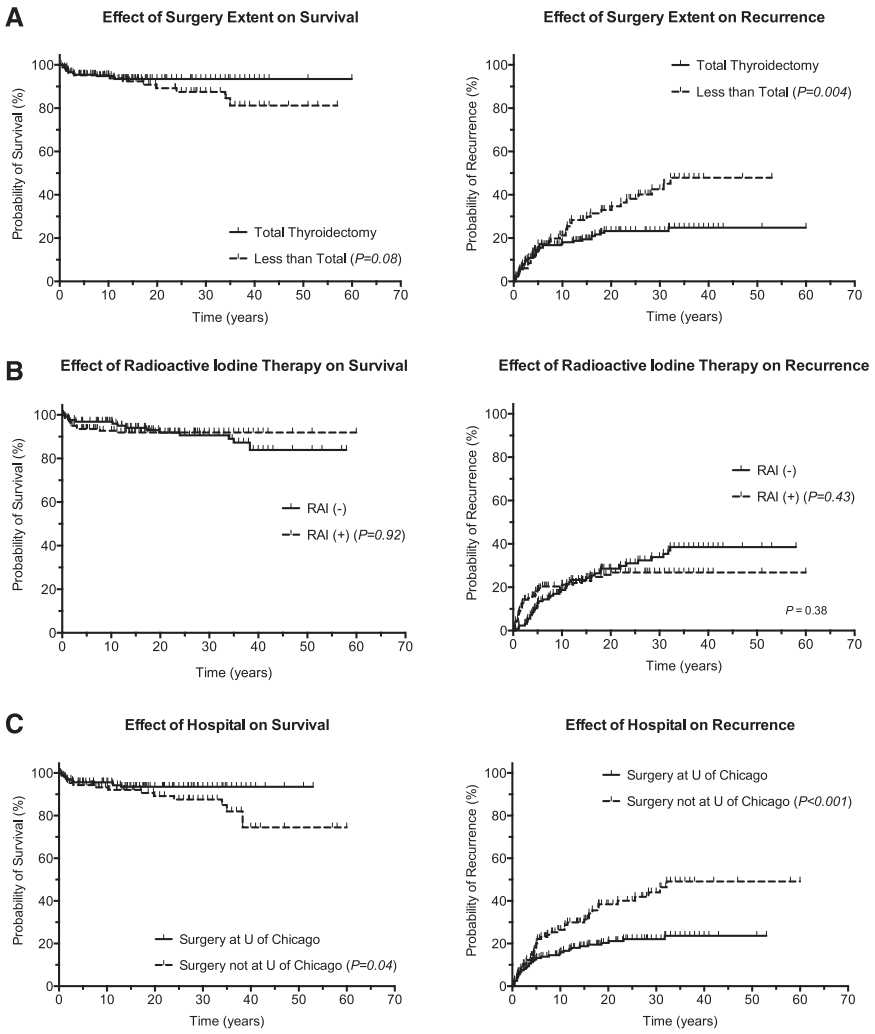


Fig 3. Effect of treatment on PTC recurrence and survival. Treatment modalities studied were extent of operation (*A*), RAI therapy (*B*), and the hospital at which the first operation was performed (University of Chicago versus other). Total thyroidectomy (*A*) improved recurrences and trended toward improved survival. Overall, RAI therapy (*B*) did not show any statistical improvement in recurrence or survival. Both RAI curves show a benefit after several years, suggesting that RAI does improve both recurrence and survival in the long-term. Those patients that had their first operation for PTC at the University of Chicago had better outcomes than those that did not (*C*). High-volume centers might have an impact on overall thyroid cancer outcomes.

Tumor characteristics that were associated with increased risk of death on univariate analysis included gross extrathyroidal extension (Fig 4, *B*), T3 tumors (Fig 5, *A*), and distant metastases (Fig 5, *C*). Stage 3, 4a and 4c cancers also were associated with decreased cancer-specific survival (Fig 5, *D*). Several factors had no effect on survival on univariate analysis, including: gender, history of radiation exposure, RAI therapy, FVPTC, multifocality, and cervical lymphadenopathy (Fig 2, *B* and *C*; Fig 3, *B*; Fig 4, *A*, *C*, and *D*; and Fig 5, *B*).

The final Cox model revealed that patients aged 45–60 years at diagnosis and those greater than 60 years of age had an increased risk of dying from PTC. Those diagnosed between 45 and 60 years of age were at the greatest risk. Patients with N1a cervical lymph node metastases and those with distant metastases were also found to have an increased risk of dying from PTC. There were deaths in every risk factor group, including those under age 45 and T1a tumors. Three patients with T1a tumors died from thyroid cancer, however these patients had distant metastasis at the time of presentation.

DISCUSSION

We present here long-term follow-up data on a thyroid cancer cohort with a median follow-up of 27 years. To our knowledge, this is currently the

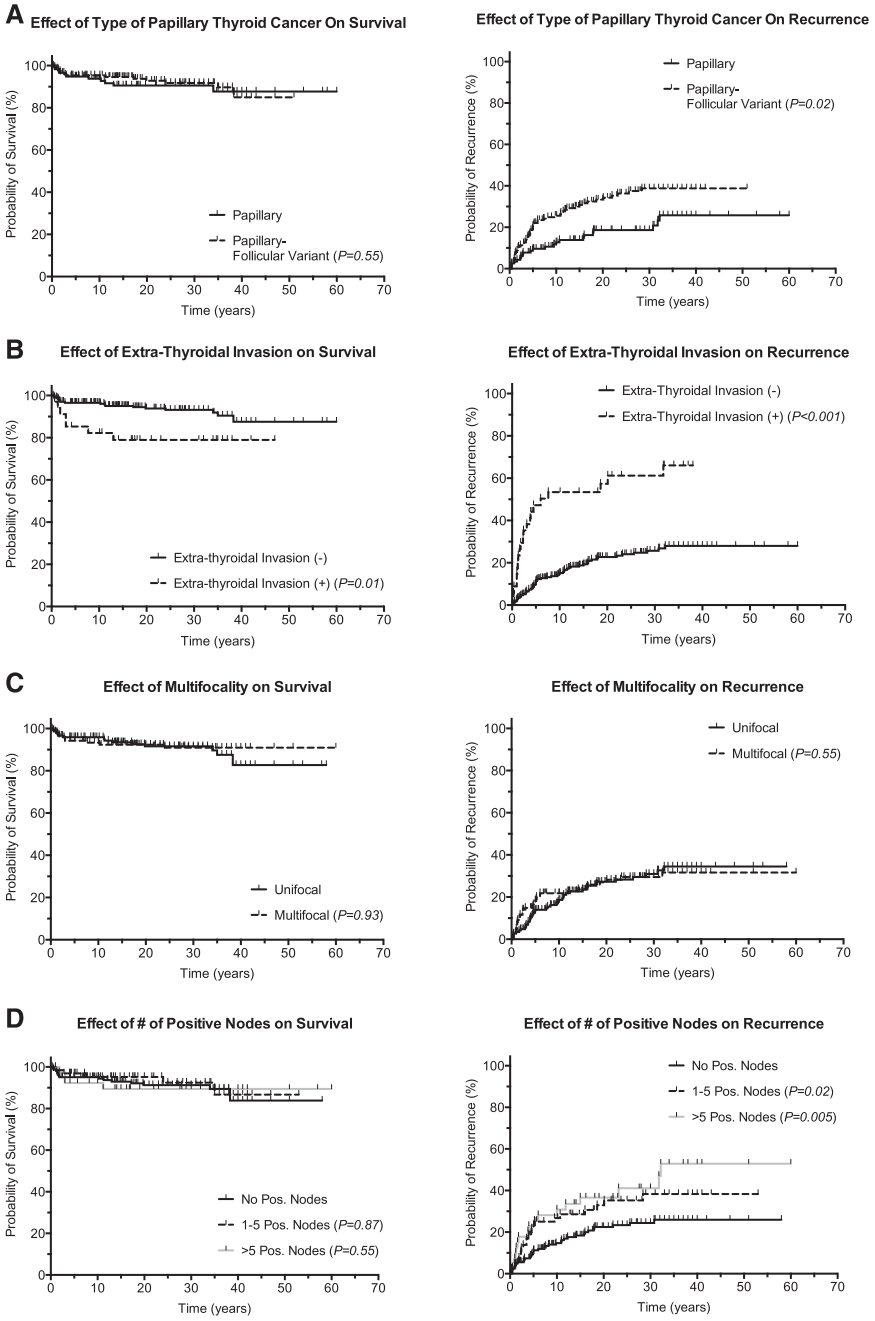


Fig 4. Effect of tumor characteristics on PTC recurrence and survival. Tumor characteristics included follicular variant of PTC (*A*), gross extra-thyrodial invasion (*B*), multifocality (*C*), and the number of nodes found to have cancer (*D*). In all cases, negative tumor characteristics had a greater impact on recurrence compared to survival.

longest follow-up period for PTC survival reported in the literature. Our longest follow-up was in a female operated on at 4 years of age for PTC. She was determined to be alive and well at age 64 years with no evidence of disease. The greater follow-up resulted in increased identification of recurrent disease and death from thyroid cancer. Although 67 of the 75 recurrences (89%) occurred within the first 20 years after diagnosis, we found an additional eight recurrences (11% of recurrences) and four deaths (17%) in the following two decades (Fig 1). These findings illustrate cancer recurrence and death can occur several decades after PTC is diagnosed and that prolonged surveillance is indicated. Our study also indicates that there are three risk factors that increase the risk of both recurrence and death, namely age >45, cervical lymph node involvement, and distant

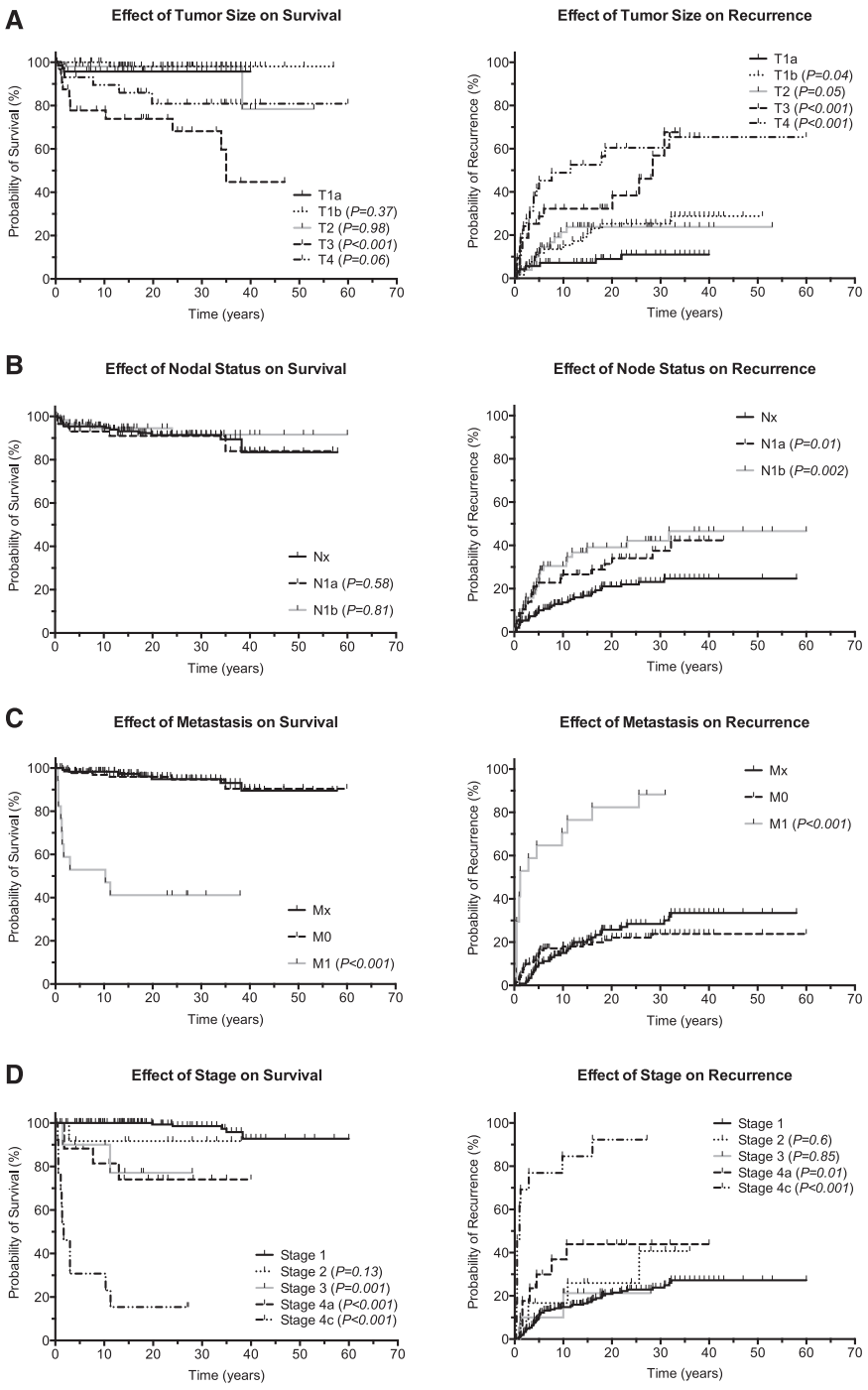


Fig 5. Effect of staging characteristics on PTC recurrence and survival. Each case was restaged according to the 7th edition of the AJCC staging manual. Kaplan Meier curves were generated for tumor (*A*), node (*B*), and metastasis (*C*), as well as for overall stage (*D*). In general the staging characterstics were better predictors of recurrence than survival. In particular, tumor (*A*), and final stage (*D*), did not correlate in a stepwise fashion as expected. T4 tumors appeared to have better survival than T3 tumors, and Stage 3 and Stage 4a survival was similar. This could be due to small sample size in our study, however a closer examination of the survival accuracy of the 7th edition staging manual may be warranted.

metastasis. No other risk factors were associated with increased risk of death. The three above risks factors plus FVPTC and large tumor size were associated with recurrence. This study also had several negative findings of interest. Male sex did not confer an increased risk of recurrence or death, and treatment with RAI did not decrease the risk of recurrence or death. Furthermore, multifocality,

extrathyroidal extension, and FVPTC also did not increase the risk of death.

Although the AJCC staging system divides thyroid cancer mortality risk between patients that are < or >45 years of age,[13] our data suggest mortality is better predicted with a three age group model: <45, 45–60, and >60 (Fig 2, *A*). The traditional two age group model is appropriate for predicting recurrence. Interestingly, we found that patients who were diagnosed between age 45 and 60 years of age had a greater relative risk of dying from thyroid cancer compared with patients >60 years at diagnosis. In general, older patients are at greater risk of death from other causes than their younger counterparts. We hypothesize that the decreased risk of PTC death in the oldest age group could be because as a group these older patients died from other diseases before they died from thyroid cancer, effectively lowering the relative risk of thyroid cancer death for the group.

We found that total/near total thyroidectomy decreases the risk of recurrence on univariate but not multivariate analysis. In addition, total/near-total thyroidectomy trended toward increased survival on univariate analysis. Because the cohort was small, subgroup analysis of thyroidectomy and tumor size or stage was not possible. A previous, large population-based study has shown that total thyroidectomy improves survival and recurrence in PTC when compared to lobectomy.[14] Because lobectomy falls under the umbrella of less than total/near-total thyroidectomy, this previous study is consistent with our findings that the extent of operation (thyroidectomy) may be important in outcome. Surrogates of completeness of operation, such as postoperative thyroglobulin measurements and/or postoperative percent uptake of RAI, were not available on many patients in the cohort and, therefore, could not be evaluated.

The benefits of RAI for remnant ablation, especially in low-risk patients, remain controversial. We did not find any statistically significant association between RAI treatment and recurrence or survival. Our Kaplan-Meier curves, however, suggest that the benefits of RAI are seen several years after treatment. Furthermore, we were unable to evaluate the benefits of RAI according to stage or tumor size due to limited sample size. On the basis of these data, we believe that RAI should be used judiciously in patients with thyroid cancer, especially those with small cancers confined to the thyroid gland. Given conflicting data in the literature, the decision to use RAI in those with cervical metastases should be individualized to consider all risk factors such as older age, tumor type, and quality and quantity of lymph nodes.[12]

Our finding that patients with FVPTC had greater risk of recurrence compared to PTC is consistent with some studies,[15] whereas other data suggest that recurrence rates in PTC and FVPTC are similar.[16,17] These conflicting data suggest that FVPTC is heterogeneous, with molecular variations likely affecting observed differences in tumor aggressiveness.[18] Furthermore, pathologic criteria for FVPTC have changed since the original cohort.[15] Because we relied on initial pathologic diagnoses, it is possible that some FVPTCs would now be reclassified as follicular thyroid cancer, which may be more aggressive than FVPTC.

The association between cervical lymphadenopathy and increased recurrence risk in our cohort is consistent with several studies in the literature.[7,8] We found that patients with N1b lymphadenopathy were at greater relative risk for recurrence compared to those with N1a lymphadenopathy. Because thyroid cancer is thought to metastasize to central lymph nodes before lateral lymph nodes, lateral neck disease may be associated with more aggressive cancer. Surprisingly, N1a but not N1b lymphadenopathy was associated with decreased survival, but the wide confidence interval for the N1b group (Table II) suggests great variation among this group. Differences in the extent of operation could explain these findings. Some lymphadenectomies were compartmental dissections, and some were just removal of suspected lymph nodes; it is possible that these distinctions could influence outcome. More data would help clarify these results, and we plan to further evaluate this in the future. Our data also suggested that the number of affected lymph nodes (1–5 or >5) was associated with increased recurrence on univariate analysis. These findings suggest that the quantity of nodal metastases may play a role in recurrence risk.

A great deal of thyroid cancer literature focuses on risk stratification based on staging to prevent overtreatment, provide optimal surveillance of low-risk patients, and adequately treat high-risk patients. Patients in our cohort considered high risk for recurrence and death based on stage were in many cases consistent with conventional risk stratification. Nevertheless, it should be noted that there were outliers. For example, five patients <45 years with Stage 1 disease went on to develop recurrent disease and die from cancer. These cases illustrate the heterogeneous nature of PTC and dispel a "one-treatment-plan-fits-all" model. The availability of genetic testing and a more thorough understanding of the genetics of thyroid cancer may provide guidance as to when presumably low-risk cancers require more intense treatment.[19] We

expect that genetic evaluation of PTC will someday prove more accurate for predicting cancer-specific mortality than our current staging systems.

Although our findings suggest that long-term surveillance for patients with PTC is necessary, the most effective method for monitoring remains unknown. We believe that lesser risk patients who achieve no evidence of disease status can be monitored with yearly thyroglobulin measurements and ultrasonography of the neck to avoid unnecessary radiation exposure. Those with greater risk of recurrence or those with unreliable thyroglobulin measurements due to antibody interference may also need intermittent diagnostic total body scanning. Further study is needed to determine the optimal surveillance testing and schedule.

Our study has limitations in terms of extrapolation to other patients with PTC. First, patients were not consecutive, and therefore, our cohort may have a selection bias. Second, because the University of Chicago is a tertiary referral center, patients referred to our institution may have more advanced disease than in the community. Third, our cohort had a high percentage of patients with radiation exposure. Finally, medical care such as operative technique, ultrasonography, and thyroglobulin assays have all improved in recent years; these modalities may change the natural history of PTC. Nonetheless, our findings provide insight into the long-term prognosis of PTC.

In conclusion, our findings demonstrate that most patients with PTC enjoy prolonged disease-free survival, but we found that 11% of recurrences and 17% of deaths occurred after 20 years. Furthermore, 4% of recurrences and 13% of deaths occurred more than 30 years after the diagnosis of thyroid cancer. Although most patients fit into standard risk stratification models, outliers do exist. Therefore, long-term and possibly lifelong surveillance is necessary and important.

REFERENCES

1. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
2. Mazzaferri EL. Long-term outcome of patients with differentiated thyroid carcinoma: effect of therapy. Endocr Pract 2000;6:469-76.
3. Hay ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19:545-76.
4. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.
5. Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, et al. Papillary thyroid carcinoma managed at the mayo clinic during six decades (1940-1999): Temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 2002;26:879-85.
6. Tuttle RM, Leboeuf R. Follow up approaches in thyroid cancer: a risk adapted paradigm. Endocrinol Metab Clin North Am 2008;37:419-35.
7. Schneider DF, Mazeh H, Chen H, Sippel RS. Lymph node ratio predicts recurrence in papillary thyroid cancer. Oncologist 2013;18:157-62.
8. Randolph GW, Duh Q-Y, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
9. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. Ann Surg Oncol 2013;20:1906-11.
10. Hay ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. J Surg Oncol 2006;94:692-700.
11. Iyer NG, Morris LGT, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer 2011;117:4439-46.
12. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
13. American Joint Committee on Cancer. Cancer staging manual. 7th ed. New York, NY: Springer-Verlag; 2010.
14. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375-81; discussion 381-4.
15. Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer 2006;107:1255-64.
16. Lang BH-H, Lo C-Y, Chan W-F, Lam AK-Y, Wan K-Y. Classical and follicular variant of papillary thyroid carcinoma: a comparative study on clinicopathologic features and long-term outcome. World J Surg 2006;30:752-8.
17. Passler C, Prager G, Scheuba C, Niederle BE, Kaserer K, Zettinig G, et al. Follicular variant of papillary thyroid carcinoma: a long-term follow-up. Arch Surg 2003;138:1362-6.
18. Gupta S, Ajise O, Dultz L, Wang B, Nonaka D, Ogilvie J, et al. Follicular variant of papillary thyroid cancer: Encapsulated, nonencapsulated, and diffuse: distinct biologic and clinical entities. Arch Otolaryngol Head Neck Surg 2012; 138:227-33.
19. Zheng X, Wei S, Han Y, Li Y, Yu Y, Yun X, et al. Papillary microcarcinoma of the thyroid: Clinical characteristics and BRAF(V600E) mutational status of 977 cases. Ann Surg Oncol 2013;20:2266-73.

DISCUSSION

Dr Ian D. Hay (Rochester, MN): In the prediction of disease-specific mortality, clearly, age and stage were the important factors. I think this comes as no surprise to anybody in this audience. I think it's interesting that you point out that the risk of death in stage III and IV is up four or five times more than usual.

In terms of prediction of recurrence, the follicular variant of papillary thyroid cancer seems to me to not quite jive with a lot of literature, and I would like your comments on that. Is this because these people are younger and have more neck nodal metastasis?

Could you comment on the peculiarity of the follicular variant of papillary cancer and verify that the radioiodine thing is not going to really improve at 45 or 70 years? We now have a study of 3,500 patients followed for 72 years. I'm not going to do it anymore. The same story was what we told everybody in 1986, and radioiodine, I don't think, makes a big difference.

Dr Raymon H. Grogan: We also were a little perplexed by the follicular variant of papillary thyroid cancer findings that we have. I think what we need to do is to have our pathologists go back and re-review how those were actually diagnosed as follicular variant of papillary thyroid cancer to really hone in on these data.

Our original paper tried to show that the radioactive iodine was effective for greater than T1 tumors. However, on our multivariate analysis (in our current study), we didn't find this to be an independent predictor of either improved survival or recurrence. And now we also have added these longer-term follow-up data to our original study, so we tend to currently believe the study that we have here, which shows that with the multivariate analysis, the radioiodine had no statistically significant effect. The Kaplan-meier curves do show a radioiodine effect after 30-40 years, however this did not reach statistical significance. Unfortunately the study cohort is not large enough for us to make any definitive statement about the radioiodine effect at the later timepoints.

Dr Quan-Yang Duh (San Francisco, CA): One, obviously this is not consecutive, which means that there is obviously going to be some selection bias. But the second part is that, over 40 years, how we follow these patients, and what we defined as recurrence must have changed. The patients that I see in the clinic right now with a 5-mm lesion that somebody wants to biopsy and call a recurrence, that patient, 40 years ago, would have been cured. Therefore, how did you define recurrences in this group of patients? Because you could see a later recurrence if that earlier follow-up was less sensitive.

Dr Raymon H. Grogan: One of the big limitations of our study is that it was difficult for us to follow these patients within our hospital setting within the medical record, because clearly this was such a long period of time. Many of these patients had moved all across the country. We even found patients that were outside of the country in this study. And I think that, if anything, we're underestimating our level of recurrence and death, because, essentially, when we were able to contact patients that were not within our university system, all we really had to go on was whether or not the patient had been told that they had a recurrence or not. So, in fact, if these patients were actually looked at with an ultrasound or biopsy, we may find that our recurrence rate may even be higher, although that may not be clinically significant.

Also, the treatment may have changed over time as well, which is maybe another bias. Because, again, these patients were first treated in 1960. And as we all know, as Dr. Duh pointed out, things have changed since that time.