ORIGINAL ARTICLE

Thyroid Cancer Survival in the United States

Observational Data From 1973 to 2005

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Objective: To compare the survival rate of people with papillary thyroid cancer limited to the thyroid gland who have not had immediate, definitive treatment for their thyroid cancer with the survival rate of those who have had such treatment.

Design: Cohort study of incident cancer cases and initial treatment data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Data on cause of death was taken from the National Vital Statistics System.

Patients: Patients with papillary thyroid cancer limited to the thyroid gland.

Main Outcome Measure: Cancer-specific survival.

Results: Of all eligible people in the data (n=35 663), 1.2% did not undergo immediate, definitive treatment (n=440). The life table estimate of their 20-year cancer-specific survival rate was 97% (95% confidence interval [CI], 96%-100%). The corresponding estimate for the patients who did receive treatment was 99% (95% CI, 93%-100%). Among those who did not receive immediate, definitive treatment, 6 died from their cancer. This number is not statistically different from the number of thyroid cancer deaths in the treated group over the same period (n=161) (*P*=.09).

Conclusion: Papillary thyroid cancers of any size that are limited to the thyroid gland (no extraglandular extension or lymph node metastases at presentation) have favorable outcomes whether or not they are treated in the first year after diagnosis and whether they are treated by hemithyroidectomy or total thyroidectomy.

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PAPILLARY THYROID CANCER IS A common incidental autopsy finding. Studies published as early as 1947 demonstrated it,[1] and more recently, a report has shown that nearly every thyroid gland might be found to have a cancer if examined closely enough.[2] The advent of ultrasonography and fine-needle aspiration biopsy has allowed many previously undetected cancers to be identified, changing the epidemiology of the disease. Over the past 30 years, the detected incidence of thyroid cancer has increased 3-fold, the entire increase attributable to papillary thyroid cancer, and 87% of the increase attributable to tumors measuring less than 2 cm.[3] Tumors that are 2 cm or smaller would not be expected to be palpable by most clinicians.[4]

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As this reservoir of subclinical disease is uncovered, the clinician faces difficult questions: How aggressive should treatment be for these newly detected cancers confined to the thyroid gland? Do they need to be treated immediately, or can they be watched over time to assess their behavior? Because the natural history of papillary thyroid cancer has not been systematically studied, the answers to these questions are not known. Using National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data, we compare the cancer-specific survival of the cohort of patients who did not receive immediate, definitive treatment for their papillary thyroid cancer confined to the thyroid gland (ie, had no lymph node metastases or extraglandular extension at the time of diagnosis) with that of those who did receive immediate, definitive treatment.

See Invited Commentary at end of article

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METHODS

DATA SOURCE

We examined the natural history of untreated papillary thyroid cancer using the SEER 17 registries, which include information on all tu-

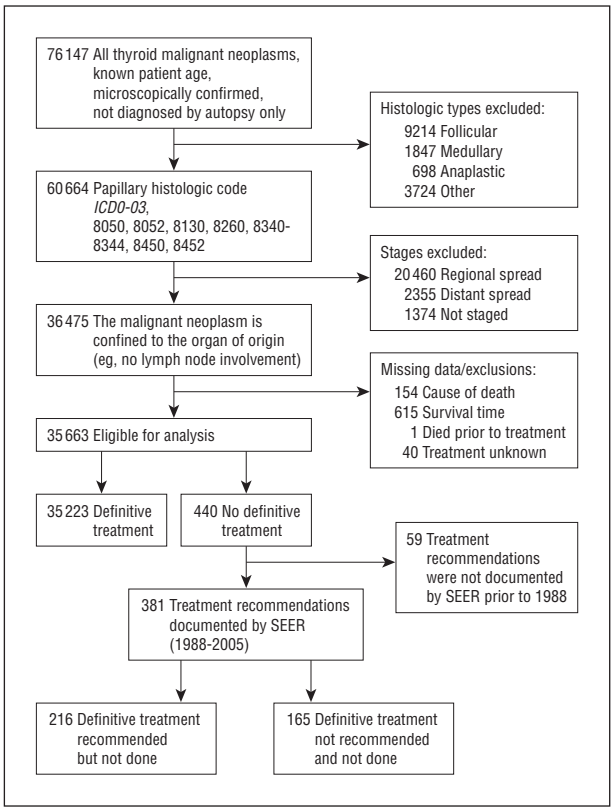

Figure 1. Case selection. All data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 17 database (1973-2005). The rounded rectangles with bold print are the groups included in the analysis.

Table 1. Distribution of Cancer Sizes, by Treatment Received[a]

Cancer Size	Immediate, Definitive Treatment Administered, No. (%) of Patients	
	Yes	No
Microscopically confirmed, but no tumor found in specimen	11 (<1)	0
<1.0 mm	2389 (7)	8 (2)
2.0 mm to 1.0 cm	11 114 (32)	49 (11)
1.1-2.0 cm	8154 (23)	77 (18)
2.1-3.0 cm	4561 (13)	58 (13)
3.1-4.0 cm	1823 (5)	22 (<1)
4.1-5.0 cm	830 (2)	13 (<1)
5.1-6.0 cm	342 (<1)	6 (<1)
6.1-7.0 cm	169 (<1)	2 (<1)
7.1-8.0 cm	98 (<1)	0
8.1-9.0 cm	45 (<1)	0
>9.0 cm	64 (<1)	2 (<1)
Size not documented	5623 (16)	203 (46)

[a] Data are from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 17 database from 1983 to 2005. Size data were recorded beginning in 1983. Prior to that date, cancers were described according to behavior only. Although cases included in the analysis for these years do not have size data, all were known to be limited to the thyroid gland without extension into or beyond the capsule of the gland.

mors diagnosed within the states of Connecticut, Hawaii, Iowa, New Mexico, Utah, Georgia, California, Kentucky, Louisiana, New Jersey; the metropolitan areas of Detroit, Michigan, Seattle–Puget Sound, Washington, and San Francisco–Oakland, California; and among Alaska Natives and Arizona Indians.[5] The SEER program began in 1973 with 9 registries initially contributing data, and 8 additional registries have been added over the years (the most recent in 2000). The SEER 17 registries represent 26% of the US population and are reasonably matched demographically to the United States population as a whole.[6]

EXPOSURE DEFINITIONS

All available cases within the SEER database that met inclusion criteria and had complete data were included. **Figure 1** shows our selection process to identify the 35 663 localized papillary thyroid cancers with complete data. The term *localized* comes from the SEER variable used in the analysis: "SEER Historic Stage A." This variable divides cancerous tumors into 4 categories: in situ, localized, regional, and distant. We included only those categorized as localized. The definition of localized for thyroid cancer is that the tumor can be of any size but must be confined to the thyroid gland and have no lymph node metastases or extraglandular extension at the time of diagnosis.

In addition, cases had to be microscopically confirmed, not diagnosed at autopsy only, and show papillary histologic characteristics (*International Classification of Diseases for Oncology, 3rd Revision* [*ICDO-03*],[7] codes 8050, 8052, 8130, 8260, 8340-8344, 8450, and 8452). There were no age or sex restrictions. We excluded cases that met these criteria but were missing cause of death, survival time, or treatment received. **Table 1** lists the distribution of tumor sizes among included cases, where those data were available.

Our primary interest was to learn the natural history of cases of papillary thyroid cancer confined to the thyroid gland that did not receive immediate, definitive treatment. The SEER database documents the first course of treatment for all patients in the registry and documents cases for a year or more before concluding that the patient did not receive treatment. Therefore, the definition of *immediate* in this setting is as long as a year or more after diagnosis. The mainstay of treatment for papillary thyroid cancer is surgery (hemithyroidectomy or total thyroidectomy) with or without postoperative irradiation (via external beam or ingested iodine). The definition of *definitive treatment* in this study is hemithyroidectomy or total thyroidectomy with or without postoperative irradiation.

The definition of *no immediate, definitive treatment* is that none of the definitive treatments was administered. A potential limitation exists within this group because the SEER database does not document the exact tissue specimen used to obtain the microscopic confirmation. Since the diagnosis of papillary thyroid cancer might not always be accurately reached through fine-needle aspiration and cytologic analysis (the best diagnostic test available), it is possible that some patients in the no immediate, definitive treatment group underwent an open procedure to do a biopsy or remove a nodule, which might be considered a sort of ad hoc partial treatment. Since this is not the standard of care, and none of these tissue samples indicated hemithyroidectomy or total thyroidectomy, all of these patients were considered not to have received definitive treatment.

In 1988, SEER began recording more detail about the reasons people did not receive immediate, definitive treatment of cancers. Because these data afford some insight into the reasons that some cancers are definitively treated while others are not, we examined the data from 1988 to 2005 under its own classification (**Table 2**). Among patients who did not receive immediate, definitive treatment between 1988 and 2005, if treatment was thought by the physician not to be prudent, SEER (and we) classified the case as "definitive treatment not recommended and not done." If definitive treatment was thought

Table 2. Thyroid Cancer–Specific Survival for Patients Diagnosed While Treatment Recommendations Were Documented[a]

Group	Patients, No.	Patients, % (95% Confidence Interval) 5 Year Survival	10 Year Survival
Definitive treatment recommended but not administered	216	98.1 (95.9-100)	98.1 (95.9-100)
Definitive treatment not recommended and not administered	165	99.3 (97.8-100)	99.3 (97.8-100)
Immediate, definitive treatment administered	29 789	99.8 (99.7-99.8)	99.5 (99.4-99.6)

[a]Data are from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 17 database from 1988 to 2005. Log-rank test findings of survival equality among the 3 groups are significant ($P<.001$).

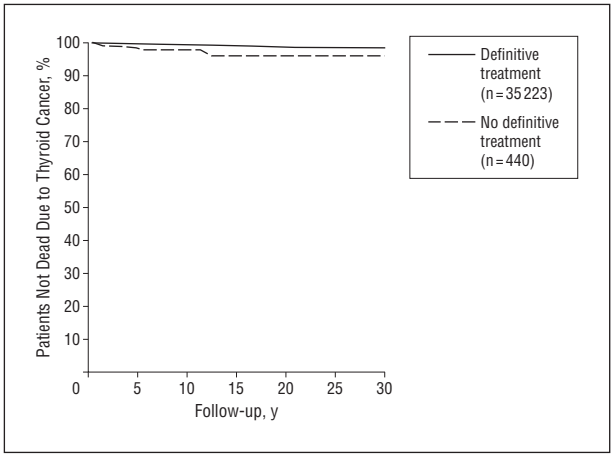

Figure 2. Thyroid cancer–specific survival among patients with localized papillary thyroid cancer. Data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 17 database (1973-2005). Log-rank test findings of survival equality are significant ($P<.001$).

to be appropriate by the physician but was declined by the patient, the case was classified as "definitive treatment recommended but not done."

OUTCOME MEASURES

The primary outcome was death, measured via cause-specific survival. Cause-specific survival (in this case, localized papillary thyroid cancer) is the probability over time of surviving the cancer (**Figure 2**). For example, a person who had the cancer and died 20 years later of pneumonia would be censored at death, having contributed 20 person-years of survival to the analysis. A person who had the cancer and died 20 years later of the cancer would contribute an event—a death due to the cancer—having also contributed 20 person-years of survival time. A 90% cancer-specific survival at 20 years would mean that 90% of patients had not died from their thyroid cancer, while 10% had died from their thyroid cancer.

We also examined overall survival of the cohort, which is the probability over time of avoiding death due to any cause (**Figure 3**); thus, all deaths are counted, whether due to the cancer or other causes. The purpose of testing for this outcome was

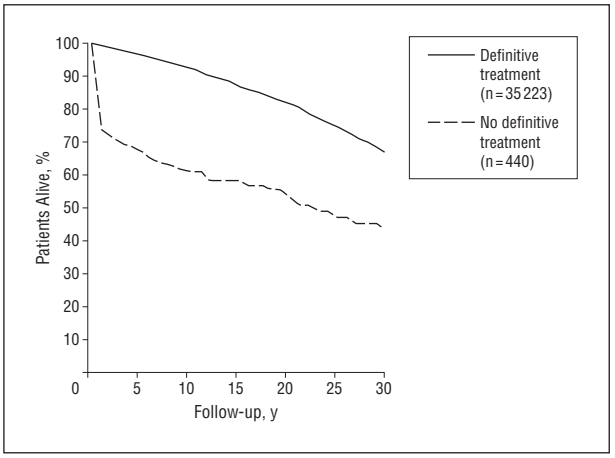

Figure 3. Overall survival among patients with localized papillary thyroid cancer. Data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 17 database (1973-2005). Log-rank test findings of survival equality are significant ($P<.001$).

to check the validity of the no immediate, definitive treatment group variable. It is unusual for a person to not undergo definitive treatment for a cancer; thus, we hypothesized that people in this group were likely to be substantially different from those who did undergo immediate, definitive treatment. If the data contained in this variable were valid, a greater proportion of the people in this group would be very ill and would have a lower overall survival than those who did undergo treatment.

STATISTICAL ANALYSIS

All data used in this study were analyzed using a combination of SEER*Stat,[8] the statistical software created by the Surveillance Research Program, and Stata 9 (StataCorp LP, College Station, Texas). The Kaplan-Meier survival function was used to determine both thyroid cancer–specific and overall survival.[9] Calculations were made for each of the 31 years of data available, and summary statistics for 5, 10, and 20 years are reported. An estimate of the 95% confidence intervals (CIs) was obtained by multiplying the SEER*Stat-generated SEs by –1.96 and +1.96. Tests of survival equality were performed during the survival analysis by the log-rank test.

RESULTS

From 1973 to 2005, SEER recorded 35 663 thyroid cancer cases that were eligible for our analysis. Included cases had a diagnosis of papillary thyroid cancer confined to the thyroid gland (ie, no lymph node metastases or extraglandular extension at the time of diagnosis). Of all the patients in this group, 1.2% did not undergo immediate, definitive treatment (n=440). The no immediate, definitive treatment group differed from the definitive treatment group by age—those who were not treated were older (mean age, 51 vs 46 years) ($P<.001$)—but not by sex (23% male in the treatment group vs 19% male in the no treatment group) ($P=.06$).

The mean follow-up time available for the 35 223 patients in the data set who received definitive treatment was 7.6 years (median, 5.3 years; range, 0-32 years). Mean follow-up time available for the 440 people in the data set who did not undergo immediate, definitive treatment was 5.9 years (median, 3.6 years; range, 0-31 years).

The difference in follow-up time was statistically significant ($P < .001$).

THYROID CANCER DEATHS

Of those who received immediate, definitive treatment over the course of the 32 years of data, 161 died of thyroid cancer (0.45%). Among people in this group who died of thyroid cancer despite treatment, mean survival was 7.4 years (median, 6 years; range, 0-23 years). The *t* test showed no significant difference in the number of thyroid cancer deaths observed in the immediate, definitive treatment group (161 deaths among 35 223 people) compared with those in the no immediate definitive treatment group (6 deaths among 440 people) ($P = .09$).

In the 1988-2005 subset of the no immediate definitive treatment group, there were 4 thyroid cancer deaths among the 216 patients for whom definitive treatment was recommended but not done and 1 thyroid cancer death among the 165 patients for whom definitive treatment was not recommended and not done. The number of deaths was not significantly different between the 2 groups ($P = .10$).

THYROID CANCER–SPECIFIC SURVIVAL

As shown in Figure 2, the long-term thyroid cancer–specific survival rates for papillary thyroid cancers confined to the thyroid gland (ie, without lymph node metastases or extraglandular extension at the time of diagnosis) were nearly identical whether the patient received immediate, definitive treatment or not. Those who did not receive immediate, definitive treatment had a 97% survival at 20 years. Twenty-year survival for the definitive treatment group was only 2% better (99% survival).

The data listed in Table 2 show that survival among those who did not receive immediate, definitive treatment was affected little by whether treatment had been recommended or not. Because these data have only been available since 1988, survival statistics can only be calculated over a shorter period. Among those patients who declined treatment despite recommendations to have it, 10-year thyroid cancer–specific survival was 98%. It was nearly the same (99%) among those patients for whom treatment had been recommended.

OVERALL SURVIVAL

The purpose of testing for overall survival was to check the validity of the no immediate, definitive treatment group as a variable. It is unusual for a person to not undergo definitive treatment for a cancer, and we hypothesized that people in this group were more likely to be too ill to undergo treatment. Figure 3 both illustrates this hypothesis and shows the overall survival difference between the 2 groups. A survival difference does appear almost immediately as the survival lines diverge in the first 1 to 2 years after diagnosis, but then the survival lines become nearly parallel. The divergence pattern supports the validity of the no immediate, definitive treatment variable. While the competing risk of death from other causes for this group was relatively high, the parallel lines following the initial divergence indicate that the overall survival of the 2 groups becomes the same once a small number of very ill patients are removed, suggesting that the health status of the remaining members of the 2 groups is comparable.

COMMENT

The cancer-specific survival of patients with papillary thyroid cancer confined to the thyroid gland (ie, without lymph node metastases or extraglandular extension at the time of diagnosis) who did not receive immediate, definitive treatment was 97% at 20 years. Twenty-year survival for people who did receive immediate, definitive treatment was only 2% better (99% survival). These data help put management decisions about localized papillary thyroid cancer in perspective: papillary thyroid cancers of any size that are confined to the thyroid gland, have no lymph node metastases at presentation, and do not show extraglandular extension are unlikely to result in death due to the cancer. Thus, clinicians and patients should feel comfortable considering the option to observe for a year or longer cancers that fall into this category. When treatment is elected, the cancers in this category can be managed with either hemithyroidectomy or total thyroidectomy, and the prognosis will be the same.

LIMITATIONS

As with all database research, we are dependent on the accuracy of the coding of secondary data. The validity of this study rests on the trustworthiness of the no immediate, definitive treatment variable. We used 2 different approaches to check the main issue of concern—whether the no immediate, definitive treatment group was "real" (ie, whether the patients in this group actually had not received immediate, definitive treatment). First, given that the diagnosis of papillary thyroid cancer might not always be accurately reached through fine needle aspiration and cytologic analysis, we consulted the tumor registries directly to find out what types of tissue samples were used to obtain microscopic confirmation of a diagnosis in the case of the people who were categorized as not having received treatment. In reviewing individual cases with the registries that contributed these patients, we learned that the modes of diagnosis varied: some of the cancers were diagnosed by cytologic analysis or core needle biopsy, while others were diagnosed by open biopsy or excision of a nodule. Some might consider this a sort of ad hoc partial treatment. However, since this is not the standard of care, and none of these tissue samples indicated hemithyroidectomy or total thyroidectomy, we felt comfortable following the SEER categorization of these patients as not having received definitive treatment.

Second, we examined general characteristics of the no immediate definitive treatment variable by testing the overall survival of people in this group compared with those who did receive immediate, definitive treatment. This analysis confirmed that the no definitive treatment group was distinct from the definitive treatment group and was thus likely to be a valid comparison group.

CONCLUSIONS

The outcomes of patients who have papillary thyroid cancer limited to the thyroid gland are extremely favorable. Survival is so good that it is appropriate to consider whether the risk of complications outweighs the benefits of treatment during discussions about when and how to treat the disease. The risk of permanent hypoparathyroidism and significant damage to laryngeal function have been reported to range from 3% to 5% in large case series,[10,11] which approximates the 2% and 4% disease-specific mortality we describe herein. These data provide a firm basis on which physicians and patients can begin to discuss the timing and aggressiveness of management plans for papillary cancers confined to the thyroid gland.

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INVITED COMMENTARY

Should Papillary Thyroid Carcinoma Be Observed?

A Word of Caution

We read with interest the analysis by Davies and Welch of over 35 000 patients with localized papillary thyroid carcinoma (PTC) within the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 17 registry comparing the outcomes of a selected subgroup who were not treated (n=440) with those undergoing definitive surgical treatment. While there was a significant survival advantage (both disease specific and overall) for those undergoing definitive treatment (log rank $P<.001$), the authors conclude that because the absolute difference was so small (2% at 20 years), (1) localized PTC can be safely observed without surgery and (2) the extent of surgery does not influence subsequent survival. In our practice, we certainly recommend observation for many patients with PTC, in particular those with severe medical comorbidities, more pressing malignant neoplasms, or small-volume recurrent PTCs; but we unfortunately also have to treat many patients with recurrent PTC (or dedifferentiated PTC), often resulting in significant morbidities and quality-of-life changes. Just as the authors point out the risks of permanent hypoparathyroidism and laryngeal dysfunction, we lament the suffering caused by recurrent PTC after an inadequate initial evaluation and/or treatment. What we truly need is not only appropriate observation for highly selected cases but also appropriate biopsy, evaluation, and treatment by an experienced multidisciplinary team.

In their landmark publication in *JAMA* in 2006, Davies and Welch[1] documented the dramatic rise in thyroid cancer incidence (particularly PTC) in the United States over the last 15 years. Others[2] have argued that while this

rise in incidence is partly an actual increase in disease incidence, most of the increase is likely attributable to a diagnostic and/or screening bias of more individuals having thyroid nodules detected by more prevalent use of various imaging and/or diagnostic techniques. In their article in this issue of *Archives*, Davies and Welch have followed up on issues they raised in their original *JAMA* publication[1(p2167)]:

> Because many of these cancers would likely never have caused symptoms during life, epidemiologists have labeled the phenomenon, "overdiagnosis. . . . " Overdiagnosis is a cause for concern because it makes it hard to identify which patients need treatment . . . Further studies will be needed to determine if a more cautious diagnostic approach—perhaps simply providing follow-up for symptomatic thyroid nodules—is worthwhile. In addition, papillary cancers smaller than 1 cm could be classified as a normal finding.

We completely agree with underlying concern that many PTCs (possibly clinically unimportant) are being detected and receiving invasive treatment when they perhaps should be managed more conservatively with observation only. However, as we explore this approach, we must keep in mind the existing body of literature that clearly defines which patients with PTC and which PTC tumors represent higher risk. We must also consider the shortcomings of population-based databases, the anxiety many patients will experience while the physician is "observing" a cancer, and the importance of clinician experience to the risk of treatment. Most importantly, we must remember that physicians treat individuals not populations.

The authors' conclusion, as specifically stated in their abstract, bears repeating:

> Papillary thyroid cancers of any size that are limited to the thyroid gland (no extraglandular extension or lymph node metastases at presentation) have favorable outcomes whether they are treated in the first year after diagnosis or not and whether they are treated by hemithyroidectomy or total thyroidectomy.

Taken literally, this conclusion suggests that an older male patient with a large tumor and a history of radiation exposure can be safely observed. The authors have not specifically analyzed by tumor size; patient age, sex, family history, or radiation exposure; or specific timing and/or type of treatment. Therefore, the reader is poorly informed and perhaps misinformed by the authors' conclusion, which is not fully backed by the data and ignores significant existing literature. These clear shortcomings point out the flaws of attempting to make inferences about the subtleties of cancer treatment using a population database that lacks sufficient information on medical history, cancer stage, histologic findings, and treatment details to allow multivariate adjustment or, as needed in this case, a complete description of the very select subset of 440 patients with PTC who apparently did not receive definitive treatment. For instance, the authors have not been able to provide the number of such patients who had some form of unorthodox primary treatment less than a lobectomy (eg, a lumpectomy, radioactive iodine treatment, external beam radiotherapy). Similarly, the authors have not provided comprehensive size data or information regarding prior radiation exposure. Welch and Black[3] and others[4,5] have reported significant misclassifications in cause of death and stage existing within the SEER registry. In addition to these misclassifications, it is certainly possible that a significant proportion of the 440 patients in the present study might have been misclassified as not having received definitive treatment when they actually did undergo surgery.

As the authors point out, occult PTC has long been known from autopsy series to be extremely prevalent. Similar to occult prostate cancer, these occult PTCs may represent a normal aging process of the thyroid gland. While it is possible that most occult PTCs are clinically insignificant and can be safely observed, with rare exceptions we currently do not know how to predict which of these tumors will progress with age to active, sometimes aggressive disease. However, once diagnosed, the observation of a previously occult PTC will lead to significant anxiety for many patients (and some clinicians) until it is formally treated. Clearly, 2 advances are needed: (1) a better understanding of which occult PTCs will progress to clinically relevant cancers; and (2) a consensus of which nodules should not be biopsied. The first advance will require a better understanding and/or classification of the molecular processes of PTC progression, such as the presence of the *BRAF* (V600E) mutation.[6,7] As for the second challenge, we encourage the adherence to and further refinement of the current American Thyroid Association Guidelines[8] for thyroid nodule management. Certainly, those with a family history of PTC, familial adenomatous polyposis syndrome, or a personal history of radiation exposure might require thyroid nodule biopsy, but for many small nodules, biopsy should be avoided in favor of serial ultrasonography. However, even some micro-PTCs (<1 cm) eventually lead to recurrence and sometimes even death.[9]

While the authors mention the surgical risk of permanent hypoparathyroidism and laryngeal dysfunction, they discuss neither an association with surgeon experience nor the fact that such risks increase with PTC size, extent, and recurrence. In several modern series, such risks are 0% to 3% for patients undergoing total thyroidectomy and 0% to 5% when central compartment neck dissection is included.[10] However, many if not most patients with micro-PTC will be treated with lobectomy, thus virtually eliminating the risk for permanent hypoparathyroidism and halving the risk for permanent laryngeal dysfunction. Furthermore, while the risks cannot be completely eliminated, they should be subject to open discussion between an individual clinician and patient, which Davies and Welch allude to in their conclusions and which we strongly encourage. Furthermore, as quality measures such as rates of permanent hypoparathyroidism and laryngeal dysfunction become incorporated into reimbursement schema, it is likely that patient access to such information will enhance such open discussions.

Finally, the apparent suggestion that a statistically significant "only 2% better survival" for those receiving definitive treatment is clinically similar to the survival of those not receiving definitive treatment must be taken skeptically in light of our discussions herein. Therefore, PTC observation should only be cautiously considered in the most carefully selected cases. While the observations from such a population-based database are clearly

relevant to epidemiologic studies or perhaps to bureaucrats managing population-level health care budgets, for the individual patient-physician discussion, it is quite different. For instance, if the 5-, 10-, and 20-year thyroid cancer–specific survival estimates are accurate and the entire 35 000 patients with PTC confined to the thyroid gland were observed, crudely (ie, without adjustment for loss to follow-up or other mortality), between 500 and 700 excess patients would have died of PTC. Certainly, most of these hypothetical 500 to 700 people would have wished their physicians had offered them the treatment that had "statistically" better survival (ie, surgery). We would wonder if the 6 people who died of their thyroid cancer in this real yet very selected and/or small "no treatment" group would have agreed that a statistically significant 2% difference in survival was not clinically relevant. We as individual clinicians must keep the individual patient's best interest at the center of our decision making, whether it be operating on, observing, or referring the patient.

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