Abstract

Background
Thyroid cancer affects over ½ million people in the U.S. and the incidence of thyroid cancer has increased worldwide at a rate higher than any other cancer, while survival has remained largely unchanged. The aim of this research was to develop, calibrate and verify a mathematical disease model to simulate the natural history of papillary thyroid cancer, which will serve as a platform to assess the effectiveness of clinical and cancer control interventions.

Methods
Herein, we modeled the natural pre-clinical course of both benign and malignant thyroid nodules with biologically relevant health states from normal to detected nodule. Using established calibration techniques, optimal parameter sets for tumor growth characteristics, development rate, and detection rate were used to fit Surveillance Epidemiology and End Results (SEER) incidence data and other calibration targets.

Results
Model outputs compared to calibration targets demonstrating sufficient calibration fit and model validation are presented including primary targets of SEER incidence data and size distribution at detection of malignancy. Additionally, we show the predicted underlying benign and malignant prevalence of nodules in the population, the probability of detection based on size of nodule, and estimates of growth over time in both benign and malignant nodules.
Conclusions
This comprehensive model provides a dynamic platform employable for future comparative effectiveness research. Future model analyses will test and assess various clinical management strategies to improve patient outcomes related to thyroid cancer and optimize resource utilization for patients with thyroid nodules.

Introduction
Thyroid cancer affects over ½ million people in the U.S. and the incidence of thyroid cancer has increased worldwide at a rate higher than any other cancer[1–3]. Over 90% of cases are papillary thyroid carcinoma (PTC) and the vast majority of the increase in incidence has been observed among PTC < 1 cm (papillary thyroid microcarcinoma, PTmC) [2]. Moreover, the number of patients affected by thyroid cancer is steadily increasing because of the relatively young age of patients at diagnosis, and because thyroid cancer is associated with a 5-year disease-specific survival rate of 98% [4].

Given that there has not been a similar increase in PTC mortality, it has been argued that clinicians are identifying tumors that would otherwise never have become symptomatic or caused harm. The argument for over-diagnosis is supported by autopsy series, showing a large subclinical reservoir of disease of PTC [5,6]. Of a large group of low-risk patients undergoing active surveillance of PTmC in Japan, few patients developed nodal metastases and no patient died of thyroid cancer over a median follow-up of ten years [7]. In the U.S., the mainstay of treatment of PTC has been total thyroidectomy and adjuvant radioactive iodine, despite evidence that less aggressive treatment generates similar outcomes [8]. This suggestion of potential over-treatment of PTC on a large scale has led to a focus among experts on the effectiveness of current treatment and surveillance strategies. This is reflected in the recent changes in the revised American Thyroid Association (ATA) guidelines for the management of adult patients with thyroid nodules and differentiated thyroid cancer published in late 2015 [9].

While there may be a shift towards less aggressive treatment, it is essential that we develop methods of accurately identifying those patients who do require more aggressive treatment. Over prolonged follow-up, nearly 1/3 of PTC patients have recurrence and 9% die from disease, making effective risk-stratification critical [10]. Given the longevity of patients who carry a diagnosis of PTC, survival alone does not suffice as an outcome measure and clinical trials are prohibitively time consuming and expensive. The physical, psychological, and financial costs of diagnosis and treatment over the prolonged course of survivorship are, therefore, increasingly relevant.

Mathematical simulation modeling utilizing best available clinical and epidemiological data provides a comprehensive framework with which to objectively assess current and future standards of care for patients with thyroid cancer. Herein we present the construction of the Thyroid Cancer Policy Model including the structure, primary data inputs, calibration techniques and targets, and estimates of goodness of fit. As a verification exercise, we use our natural history model to estimate the projected number of thyroid nodules that would be found with a hypothetical screening program and compare it to existing screening ultrasound data. The detailed presentation of the methodological rigor in the development of the TCPM is with the goal of providing transparency and reproducibility or model integrity, a critical issue to establish this comprehensive model as a foundation and platform for future comparative effectiveness research. Our ultimate goal for the TCPM is to use it to perform analyses that will provide
pressing evidence on quality of care, patient outcomes and optimize resource utilization to inform decision making for patients with papillary thyroid cancer.

**Methods**

**Human subject research**

Approved by the Kuma Hospital Ethics Committee, protocol #20130905. Informed (verbal) consent protocol was approved and performed (see Tumor growth and progression kinetics section).

**Model overview**

The TCPM is a microsimulation model that depicts the natural history of thyroid nodules with the purpose to develop a comprehensive platform for future comparative effectiveness research. Microsimulation is a type of computer-based analytic tool that, distinct from a cohort study, operates at the level of the individual or smaller. We model each patient individually, starting from birth; tracking the number of cells in each thyroid nodule that is developed to inform nodule volume. Each simulated individual has unique sets of attributes (i.e. age, sex) to which a set of potential events are applied (“transition probabilities”) such as chance of dying from various causes or chance of tumor growing or a distinct rate of tumor growth within a given time period. Individual lifetimes provide clinical details and population heterogeneity, but they are aggregated to assess overall outcomes. Data sources for model inputs include the US national cancer registry (Surveillance Epidemiology and End Results, SEER), published literature, and primary longitudinal data from a large clinical cohort.

We describe the methodological processes of model development including: identifying essential model parameters, assumptions, and key pre-clinical and clinical health states; defining calibration targets; and assessing model fit to calibration targets. Estimation of pre-clinical disease and course is essential to assess the effect of clinical interventions. We use accepted model calibration techniques to estimate unknown or unknowable transition probabilities between health states and tumor growth characteristics.

**Model structure and assumptions**

The Thyroid Cancer Policy Model (TCPM) is built in C++. It is a simulation of the natural history of thyroid nodules among women (thyroid cancer is three times more common in women than men)[4] followed from birth to age 100 or death (whichever comes first). All-cause mortality probabilities are based on cross sectional CDC life-tables from 2010–2012 [11]. There are four primary, overarching health-states in the model: no nodules present, subclinical nodule, detected nodule, and death (Fig 1). Fig 2 depicts the annual decision tree wherein each year (cycle length of the model) patients have a chance of developing new (subclinical) nodules, of detecting existing nodules (detected nodule), and of death. Simulated patients in the population have the potential to develop multiple nodules, each of which can be

![Fig 1. State transition diagram.](https://doi.org/10.1371/journal.pone.0177068.g001)
benign or malignant, unilateral or bilateral to replicate realistic clinical presentation. Additionally, each cycle tumors may grow, shrink, or remain stable in size.

In this pre-clinical natural history model, we define detection of a nodule to be at the point of clinical presentation. Clinical detection of thyroid nodules occurs commonly on physical exam or through incidental discovery from an unrelated imaging study. Simultaneous modeling of benign nodules is necessary, as, in practice, work-up of and treatment of potentially larger and/or benign nodules can lead to the incidental detection of a malignant nodule.

**Tumor growth and progression kinetics**

Thyroid carcinogenesis is distinct from most other cancers in that thyroid carcinomas are not thought to evolve from benign thyroid nodules [12]. Regardless, benign thyroid nodules need to be considered when attempting to model the diagnostic and treatment course of thyroid...
disease given the coincident location, growth, and imperfect diagnostic tests (i.e. of fine-needle aspiration biopsy and thyroid ultrasound). All thyroid nodules, both benign and malignant, can grow, remain stable, or shrink; cross-sectional data provides the proportion of benign nodules that fall into each category [12–15]. The analogous proportions for malignancies we derived from primary data (Y.I., A.M.): Patients at Kuma Hospital in Japan, under an approved study protocol, were informed of the risks and benefits of immediate surgery versus active surveillance for biopsy-proven low-risk PTmC (tumors < 1 cm) [16]. The current protocol was approved by the Kuma Hospital Ethics Committee (#20130905). We analyzed the de-identified primary data on the tumor size and growth rates (based on ultrasound) of 221 patients (age 21–80) with low-risk PTmC who underwent observation alone over a median follow-up of 9.7 years (S1 File). We assumed that the Japanese data approximates proportions of growth behavior (i.e. how tumors many grow, shrink, or stay the same size) for PTmCs to be comparable for all malignant nodules [7]. We found that in the group of tumors that grew, they did so in an exponential manner over the time intervals measured. However, the rate of growth in the observed data was too slow to account for the presence of large nodules that are seen in clinical practice. This is likely because, in this cohort of patients, tumors that grew at a faster rate passed a size threshold to be referred for surgery. To extrapolate the primary data over a longer time interval and to include the possibility of larger tumors, we needed to account for biological size limitations seen in vivo (i.e. symptomatic compression of surrounding structures in the neck adjacent to the thyroid) and the slowing of growth towards the upper (biological) limit of thyroid nodule size.

Although multiple growth models were attempted for nodule growth, our model best fit with a logistic growth model. Shrinking nodules were assumed to shrink exponentially; each nodule was characterized based on a random distribution with an average rate equal to that found in the analysis of the longitudinal data of Japanese patients with PTmCs. Because the true biological reasons for spontaneous shrinking in thyroid nodules are unknown, and that it is shown in both benign and malignant nodules, we assumed that malignant and benign nodules shrank at the rate found in the analysis of the Japanese patients with shrinking PTmCs. Results of the analysis of the Japanese data used in this work are provided in Table 1.

| Input Parameter Description (Abbreviation) | Base-Case Value | Source |
|---------------------------------------------|-----------------|--------|
| Probability a nodule is benign \(p_{\text{benign}}\) | 0.90 | [18] |
| Malignant Nodule Growth Characteristics | | |
| Probability of Growing \(p_{\text{malig\_growth}}\) | 0.301 | * |
| Probability of Shrinking \(p_{\text{malig\_shrink}}\) | 0.252 | * |
| Probability of Remaining Stable \(p_{\text{malig\_stable}}\) | 0.447 | * |
| Benign Nodule Growth Characteristics | | |
| Probability of Growing \(p_{\text{ben\_grow}}\) | 0.111 | [12] |
| Probability of Shrinking \(p_{\text{ben\_shrink}}\) | 0.131 | [12] |
| Probability of Remaining Stable \(p_{\text{ben\_stable}}\) | 0.758 | [12] |
| Rate of Shrinking Nodules (Exponential Shrinking) \((r, \text{Eq 3})\) | 0.0170 (0.0016)** | * |
| Slope of Stable Nodules (Linear Stability) \((r, \text{Eq 4})\) | 0.0094 (0.0096)** | * |
| Initial Tumor Cell Size (Diameter in millimeters) \((V_0, \text{Eq 2})\) | 0.012407 | [22] |
| Minimum Nodule Size Detection (min_size_detect) | 3.0 mm in diameter | [19–21] |
| Probability a detected patient has a malignancy \(p_{\text{detected\_nod\_is\_malig}}\) | 0.164 | [18] |

*Primary data from Kuma Hospital, Kobe, Japan.

**Format: Mean (standard deviation)

https://doi.org/10.1371/journal.pone.0177068.t001
We used established mathematical models for modeling tumor growth [17]. The logistic growth model used for tumor growth satisfies the differential equation below:

\[
\frac{dV}{dt} = rV(t) \left( 1 - \frac{V(t)}{K} \right)
\]

(1)

where \( r \) is the rate of growth, \( V \) is volume, \( t \) is time, and \( K \) is the carrying capacity. The solution is then

\[
V(t) = \frac{KV_0 e^{rt}}{K + V_0 (e^{rt} - 1)}
\]

(2)

where \( V_0 \) is the initial tumor volume. In our model, we fixed the initial tumor volume to be the volume of one cell, or, \( 10^{-6} \) mm\(^3\). For the carrying capacity, we assumed that nodules are spherical in nature and take the largest possible nodule to be 20 cm in diameter. With these assumptions, our only unknown parameter in the model was the rate of growth, which we assumed to be log-normally distributed. We then calibrated the mean and standard deviation, assuming a separate distribution for both malignant and benign nodules in addition to an age-based effect. For tumor shrinking, we used the following model:

\[
V(t) = V_0 e^{-rt},
\]

(3)

where \( V_0 \) is the initial size of the nodule when starting to shrink. Stable nodules develop over time in the form

\[
V(t) = V_0 + rt.
\]

(4)

For both shrinking and stable nodules, we assumed that benign and malignant nodules acted similarly. In addition, there is limited data to model when growing stops occurring; we assume then that the decision to potentially shrink or remain stable occurs five years after nodule development.

Parameters

Our natural history parameters include both calibrated (unknown) transition probabilities and those derived from literature (input). We assume that our calibrated parameters are dependent on age and stratify them by the calibrated age groups. We calibrate the probability of developing a nodule, a rate of clinical detection, and initial nodule growth rate, dependent on if the nodule’s true state as benign or malignant. Each nodule is assigned a true state upon development. We write the rate of detection as:

\[
r_i(V) = B_{i1} + B_{i2} V,
\]

(5)

where \( i \) is each age group, \( V \) is the volume of the largest nodule, and \( r \) is the rate of detection. Both \( B_1 \) and \( B_2 \) are calibrated for each age group. Thus, the rate of detection is independent of the number of nodules and the location in the thyroid, and is only dependent on age and volume.

In order to account for diagnosis and treatment of benign nodules that frequently occurs in clinical practice and subsequent incidental finding of malignancies in smaller nodules during work-up or on surgical pathology, our model includes the possibility of detection of benign nodules inferred by a relative risk of detection of benign versus malignant nodules from the literature [18]. For a person to be detected, there must exist a nodule greater than 3 mm, which represents a conservative limit of sonographic technology [19–21]. The model input parameters (prior to calibration) are shown in Table 1.
Calibration

There are two SEER calibration targets for the model: 1) Cross-sectional SEER thyroid cancer incidence data from 2010–2012, 2) SEER tumor data regarding malignant thyroid nodule size and age of detection for primary tumors diagnosed from 1975–2012. The model is calibrated to the tumor size by age, stratified by 5-year age groups (from 15–85) and one centimeter (cm) size intervals at diagnosis. We grouped tumor sizes greater than 6 cm into a single classification due to the limited data availability for nodules of this size. In order to set a target for patients detected that have only an underlying benign disease, we derived a proportion of patients that are diagnosed with a nodule that have a true underlying malignancy [18]. From this, we approximated benign incidence. However, there is limited data regarding size distribution of benign nodules on diagnosis; therefore, we assumed it to follow the same distribution as malignant nodules. However, because of the limited data in the benign size distribution, we did not weigh it heavily in the evaluation of model fit. Calibrated parameters were stratified by age and sex.

Model outputs using different possible calibrated parameter sets were quantitatively compared to expected targets using a weighted Chi-Squared goodness of fit (GOF) function and a visual assessment. The unknown parameter space was explored with simulated annealing and a greedy refinement of local minimum solutions [23]. A solely greedy approach–where steps are only accepted if they are strictly lower than the comparison–is limited by convergence to a non-ideal local minimum, whereas simulated annealing (in the initial phase) allows for steps to worse solutions in order to potentially escape local minima. Each calibration run explored over 20,000 unique parameter sets. All local minima parameter sets and goodness of fit results were recorded with the lowest GOF indicating the best fitting parameter set. After the calibration run, all local minimum parameter sets within a 5% range of the best goodness of fit value were fine-tuned using a greedy descent in the neighborhood of the solution. Calibrated parameters are shown in Table 2.

Hypothetical screening analysis: Illustrative example of future TCPM application

Screening for thyroid cancer is not currently recommended in the U.S. Analysis of changes in incidence before and after implementation of increased screening for thyroid cancer in South Korea showed direct correlation between screening and incidence for PTC [24]. As an application of our model to assess preclinical disease (i.e. underlying reservoir), we used the TCPM to assess the number of nodules and the number of cancers that would be detected if screening was implemented. This was compared to a cross sectional study of the German population who underwent screening thyroid ultrasound.[15]

Table 2. Calibrated parameter sets.

| Calibrated Parameter | Description |
|----------------------|-------------|
| Rates of nodule development | Constant, stratified by age* |
| Initial malignant growth rate | Calibration of the mean and standard deviation of a lognormal distribution, stratified by age* |
| Initial benign growth rate | Calibration of the mean and standard deviation of a lognormal distribution, stratified by age* |
| Nodule detection rate | Calibration of $\beta_1$ & $\beta_2$ in Eq 5, stratified by age* |

*5-year age intervals from 15 to 85. Ages below 15 use the calibrated values for ages 15–20, and ages greater than 85 use the calibrated values for ages 80–85.

https://doi.org/10.1371/journal.pone.0177068.t002
Results

Model fit

Model fit to our primary calibration targets are shown: The incidence proportion of thyroid cancers is plotted as a function of age category is provided below in Fig 3 and fit of size distribution in comparison to data from the SEER registry is depicted in Fig 4. Additionally, we present the model’s estimated distributions of sub-clinical thyroid nodules (a metric that includes benign and malignant nodules) (Fig 5). Our estimates of undetected nodules and the proportions are consistent with estimates regarding prevalence and size as detected by ultrasound or autopsy [6,25,26]. Fig 6 illustrates the probability of detection based on the size of the nodule with variation shown based on age. Fig 7 shows TCM estimates of benign and malignant nodule growth over time (excluding nodules that stay the same size or shrink).

Model verification

As an initial test and verification of the model, we simulated the effects of screening all 50-year-old women in the population with ultrasound. Our model predicted an underlying prevalence of any thyroid nodule at 50.01% for 50-year-old women with 6.44% having at least one malignant nodule (pre-clinical). Lastly, a simulation following females from age 15 to 85 estimates that in the interval 1.88% will develop thyroid cancer, consistent with SEER predictions. However, over 98% of the nodules would be less than 10 mm and non-palpable. When
compared to an external cross sectional study with screening ultrasound, the Thyroid Cancer Policy Model approximates the prevalence of patients with detectable nodules at all ages (Fig 8).

Discussion

The incidence of papillary thyroid carcinoma has been increasing worldwide, likely in large part because of increased awareness and improved imaging technologies. Survival with thyroid cancer remains stable, and the increase in incidence is attributable to small, indolent PTC. The clinical relevance of these small tumors is the subject of debate among experts in the field and has led to an overarching shift to less aggressive treatment and a primary focus on better risk-stratification [9,27,28]. Moreover, thyroid cancer patients are relatively young at diagnosis and frequently incur substantial associated health care costs as they undergo surveillance and treatment for recurrent disease over a lifetime, experiences that are a detriment to quality of life, and can cause financial hardship [29–32]. Given the excellent survival outcomes and numbers of patients required to be informative, clinical trials are impractical. Comparative effectiveness has been highlighted as a key area for research [9]. Therefore, a mathematical model to simulate the natural history of disease becomes valuable. The TPCM provides the framework to assess appropriateness, effectiveness, and cost-effectiveness of treatment.

We present details of the methodological process used in the development of the TPCM, with the goal of transparency to provide assurances regarding model integrity and validity. The primary strength of our model is the comprehensive and rigorous methodology we used.
to develop and validate it, with pre-determined calibration targets, calibration using an established automated search algorithm, and quantitative assessment of model output fit to calibration targets. Additional model strengths include the inclusion of both benign and malignant nodules, which is essential to inform comparative effectiveness in the clinical realm. The model is able to quantify and assess the underlying reservoir of disease that was informed by cross sectional ultrasound series. This is crucial in future comparative effectiveness work in including the costs and potential overtreatment downstream of an incidental finding.

Through reported longitudinal observations as well as cross sectional autopsy and ultrasound series, wherein incidental PTC were not age or gender specific, we have learned that some nodules remain clinically insignificant indefinitely [5,6,15,33,34]. Starting in the early 1990’s, our colleagues (Y.I., A.M.) at Kuma Hospital in Japan began offering active surveillance or surgery for low-risk PTmC. During extended follow-up, no patients died of thyroid cancer and <10% ultimately demonstrated evidence of significant growth of their tumors [7]. In another Japanese cohort, Sugitani et al found similar results. After a mean follow-up of five years, during which time only seven patients were lost to follow-up, 7% of lesions grew, and only 4% eventually underwent surgery [14]. Both Japanese studies found that younger patients’ tumors were more likely to progress, and that rescue surgery was successful. These findings have motivated changes in the most recent American Thyroid Association guidelines to allow
Fig 6. Probability of nodule detection by diameter of nodule (mm) with variation in probability range based on age as predicted by the model.

https://doi.org/10.1371/journal.pone.0177068.g006

Fig 7. Model estimates of growth over time stratified by benign versus malignant and by age groups.

https://doi.org/10.1371/journal.pone.0177068.g007
for the consideration of active surveillance of low-risk PTmCs [9,27]. While U.S. trials to assess the safety of active are being initiated, informative results will take many years to accumulate. Experts have outlined stratification for active surveillance but many are concerned about non-compliance or a loss to follow up among patients who agree to undergo surveillance alone.

In addition to estimating over diagnosis and treatment, TCPM will provide the foundation to assess which clinical interventions are effective in identifying and treating appropriate patients. After surgery for PTC, 10–28% of patients develop recurrent disease [10,35]. Simulations of large numbers of patients will allow us to objectively assess if conventional risk-stratification algorithms, use of known and future molecular diagnostics [36–39], post-operative adjuvant therapy, and individually tailored-approaches to the frequency and intensity of surveillance for tumor recurrence are cost-effective [40].

We chose SEER data as the primary calibration target as this is the highest quality data available in the US. An essential component to model thyroid cancer is the consideration of all thyroid nodules given the colocation and difficulty in definitive pre-operative diagnosis of malignancy. Clinical and cost implications of all nodules must be considered. In an attempt to capture the natural history of thyroid nodules, it is imperative that we include growth of both malignant and benign nodules. However, empirical data regarding sizes of benign nodules as well as the ratio of benign to malignant nodules is limited; for this reason, future steps include analysis of existing databases to infer targets for benign nodules as well.

In conclusion, we present the results of the development and validation of our TCPM. In future modifications, we will integrate financial and quality of life effects of thyroid cancer survivorship into the model for future analyses. Our model can be used to identify pivotal data gaps to target future research. Additionally, the model can be modified to integrate new data.
as they become available in the future. Our ultimate goal for the TCPM is for it to serve as a platform for future analyses that will provide data to improve patient outcomes and optimize resource utilization for patients with papillary thyroid cancer.

Supporting information
S1 File. Primary longitudinal data on the tumor size and growth rates. (XLS)

Author Contributions
Conceptualization: CCL AA GSG CYK CW CH.
Data curation: AA TZ YI AM.
Formal analysis: AA CH CYK TZ.
Funding acquisition: CCL.
Investigation: CCL CW TZ AA YI AM.
Methodology: CCL AA CH CYK TZ.
Project administration: CCL CH.
Resources: CCL CH GSG CYK.
Software: AA CYK CW CH.
Supervision: CCL YI AM GSG CH.
Validation: CCL AA CW.
Visualization: TZ.
Writing – original draft: CCL AA.
Writing – review & editing: CCL AA TZ CW AM GSG CYK CH.

References
1. Davies L, Welch HG (2014) Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 140: 317–322. https://doi.org/10.1001/jamaoto.2014.1 PMID: 24557566
2. Society AC (2016) American Cancer Society: Cancer Facts and Figures 2016.
3. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R (2013) Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013: 965212. https://doi.org/10.1155/2013/965212 PMID: 23737785
4. (2016) National Cancer Institute at the National Institutes of Health: Thyroid Cancer Statistics. In: Health NCatNIo, editor. Bethesda, MD: National Cancer Institute.
5. Furmanchuk AW, Roussak N, Ruchti C (1993) Occult thyroid carcinomas in the region of Minsk, Belarus. An autopsy study of 215 patients. Histopathology 23: 319–325. PMID: 8300067
6. Furuya-Kanamori L, Bell KJ, Clark J, Glasziou P, Doi SA (2016) Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. J Clin Oncol.
7. Miyauchi A (2016) Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. World J Surg 40: 516–522. https://doi.org/10.1007/s00268-015-3392-y PMID: 26744340
8. Wang TS, Goffredo P, Sosa JA, Roman SA (2014) Papillary thyroid microcarcinoma: an over-treated malignancy? World J Surg 38: 2297–2303. https://doi.org/10.1007/s00268-014-2602-3 PMID: 24791670
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26: 1–133. https://doi.org/10.1089/thy.2015.0020 PMID: 26462967

10. Grogan RH, Kaplan SP, Cao H, Weiss RE, Degroot LJ, Simon CA, et al. (2013) A study of recurrence and death from papillary thyroid cancer with 27 years of median follow-up. Surgery 154: 1436–1446; discussion 1446–1437. https://doi.org/10.1016/j.surg.2013.07.008 PMID: 24075674

11. Control CIID (2012) United States Life Tables, 2012. pp. 65.

12. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciarone A, et al. (2015) The natural history of benign thyroid nodules. JAMA 313: 926–935. https://doi.org/10.1001/jama.2015.0956 PMID: 25734734

13. Ito Y, Miyachi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. (2010) An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 34: 28–35. https://doi.org/10.1089/wjs.2010.0018 PMID: 205072532

14. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y (2010) Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 34: 1222–1231. https://doi.org/10.1007/s00268-009-0359-x PMID: 20666418

15. Reiners C, Wegscheider K, Schicha H, Theissen P, Vaupel R, Wrbitzky R, et al. (2004) Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96,278 unselected employees. Thyroid 14: 926–932. https://doi.org/10.1089/thy.2004.14.926 PMID: 15671771

16. Ito Y, Uruno T, Nakano K, Takamura Y, Miyazaki K, Kobayashi K, et al. (2003) An observational trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 13: 381–387. https://doi.org/10.1089/105072503321669875 PMID: 12804106

17. Benzekry S, Lamont C, Beheshhti A, Tracz A, Ebos JM, Hlatky L, et al. (2014) Classical mathematical models for description and prediction of experimental tumor growth. PLoS Comput Biol 10: e1003800. https://doi.org/10.1371/journal.pcbi.1003800 PMID: 25167199

18. Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, et al. (2013) Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 98: 564–570. https://doi.org/10.1210/jc.2012-2968 PMID: 23275525

19. Lai X, Zhang B, Jiang Y, Li J, Zhao R, Yang X, et al. (2016) Sonographic and Clinical Features of Papillary Thyroid Microcarcinoma Less than or Equal to Five Millimeters: A Retrospective Study. PLoS One 11: e0148567. https://doi.org/10.1371/journal.pone.0148567 PMID: 26881783

20. Zhou L, Chen B, Zhao M, Zhang H, Liang B (2015) Sonographic features of medullary thyroid carcinomas according to tumor size: comparison with papillary thyroid carcinomas. J Ultrasound Med 34: 1003–1009. https://doi.org/10.7863/ultra.34.6.1003 PMID: 26014319

21. Gu WJ, Yan HX, Luo YK, Wang FL, Yang GQ, Guo QH, et al. (2015) Characterization of papillary thyroid microcarcinomas using sonographic features in malignant papillary thyroid cancer: a retrospective analysis. Medicine (Baltimore) 94: e841. https://doi.org/10.1097/MD.0000000000000841 PMID: 26020388

22. Chignola R, Foroni RI (2005) Estimating the growth kinetics of experimental tumors from as few as two determinations of tumor size: implications for clinical oncology. IEEE Trans Biomed Eng 52: 808–815. https://doi.org/10.1109/TBME.2005.845219 PMID: 15987530

23. Stout NK, Knudsen AB, Kong CY, McMahon PM, Gazelle GS (2009) Calibration methods used in cancer simulation models and suggested reporting guidelines. Pharmacoeconomics 27: 533–545. https://doi.org/10.2165/11314830-000000000-00000 PMID: 19663525

24. Ahn HS, Kim HJ, Kim KH, Lee YS, Han SJ, Kim Y, et al. (2016) Thyroid Cancer Screening in South Korea Increases Detection of Papillary Cancers with No Impact on Other Subtypes or Thyroid Cancer Mortality. Thyroid.

25. Mandel SJ (2004) Diagnostic use of ultrasonography in patients with nodular thyroid disease. Endocr Pract 10: 246–252. https://doi.org/10.4158/EP.10.3.246 PMID: 15310543

26. Popoveniuc G, Jonklaas J (2012) Thyroid nodules. Med Clin North Am 96: 329–349. https://doi.org/10.1016/j.mcna.2012.02.002 PMID: 22443979

27. Brito JP, Ito Y, Miyachi A, Tuttle RM (2016) A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma. Thyroid 26: 144–149. https://doi.org/10.1089/thy.2015.0178 PMID: 26414743

28. Lebouleux S, Tuttle RM, Pacini F, Schlumberger M (2016) Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? Lancet Diabetes Endocrinol 4: 933–942. https://doi.org/10.1016/S2213-8587(16)30180-2 PMID: 27550849
29. Applewhite MK, James BC, Kaplan SP, Angelos P, Kaplan EL, Grogan RH, et al. (2016) Quality of Life in Thyroid Cancer is Similar to That of Other Cancers with Worse Survival. World J Surg 40: 551–561. https://doi.org/10.1007/s00268-015-3300-5 PMID: 26546191

30. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, et al. (2013) The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev 22: 1252–1259. https://doi.org/10.1158/1055-9965.EPI-13-0242 PMID: 23677757

31. Lubitz CC, Kong CY, McMahon PM, Daniels GH, Chen Y, Economopoulos KP, et al. (2014) Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer 120: 1345–1352. https://doi.org/10.1002/cncr.28562 PMID: 24481684

32. Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, Fedorenko C, Snell K, et al. (2013) Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 32: 1143–1152.

33. Harach HR, Franssila KO, Wasenius VM (1985) Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer 56: 531–538. PMID: 2408737

34. Bondeson L, Ljungberg O (1984) Occult papillary thyroid carcinoma in the young and the aged. Cancer 53: 1790–1792. PMID: 6997317

35. Hay ID, Thompson GB, Grant CS, Bergstrahl EJ, Dvorak CE, Gorman CA, et al. (2002) 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 26: 879–885. https://doi.org/10.1007/s00268-002-6612-1 PMID: 12016468

36. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, et al. (2012) Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med 367: 705–715. https://doi.org/10.1056/NEJMoa1203208 PMID: 22731672

37. Giordano TJ (2016) Follicular cell thyroid neoplasia: insights from genomics and The Cancer Genome Atlas research network. Curr Opin Oncol 28: 1–4. https://doi.org/10.1097/COO.0000000000000248 PMID: 26569424

38. Lubitz CC, Parangi S, Holm TM, Bernasconi MJ, Schalck AP, Suh H, et al. (2016) Detection of Circulating BRAF(V600E) in Patients with Papillary Thyroid Carcinoma. J Mol Diagn 18: 100–108. https://doi.org/10.1016/j.jmoldx.2015.08.003 PMID: 26631873

39. Wylie D, Beaudenon-Huibregtse S, Haynes BC, Giordano TJ, Labourier E (2016) Molecular classification of thyroid lesions by combined testing for miRNA gene expression and somatic gene alterations. J Pathol Clin Res 2: 93–103. https://doi.org/10.1002/cpr.38 PMID: 27499919

40. Wang LY, Roman BR, Migliacci JC, Palmer FL, Tuttle RM, Shaha AR, et al. (2015) Cost-effectiveness analysis of papillary thyroid cancer surveillance. Cancer 121: 4132–4140. https://doi.org/10.1002/cncr.29633 PMID: 26280253