BRAF mutation in papillary thyroid cancer: A cost-utility analysis of preoperative testing

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Background. *Papillary thyroid carcinoma (PTC) with BRAF mutation carries a poorer prognosis. Prophylactic central neck dissection (CND) reduces locoregional recurrences, and we hypothesize that initial total thyroidectomy (TT) with CND in patients with BRAF-mutated PTC is cost effective.*
Methods. *This cost-utility analysis is based on a hypothetical cohort of 40-year-old women with small PTC [2 cm, confined to the thyroid, node(−)]. We compared preoperative BRAF testing and TT+CND if BRAF-mutated or TT alone if BRAF-wild type, versus no testing with TT. This analysis took into account treatment costs and opportunity losses. Key variables were subjected to sensitivity analysis.*
Results. *Both approaches produced comparable outcomes, with costs of not testing being lower (−$801.51/patient). Preoperative BRAF testing carried an excess expense of $33.96 per quality-adjusted life-year per patient. Sensitivity analyses revealed that when BRAF positivity in the testing population decreases to 30%, or if the overall noncervical recurrence in the population increases above 11.9%, preoperative BRAF testing becomes the more cost-effective strategy.*
Conclusion. *Outcomes with or without preoperative BRAF testing are comparable, with no testing being the slightly more cost-effective strategy. Although preoperative BRAF testing helps to identify patients with higher recurrence rates, implementing a more aggressive initial operation does not seem to offer a cost advantage. (Surgery 2014;156:1569-78.)*

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Papillary thyroid carcinoma (PTC) represents the most common thyroid malignancy and has a rapidly increasing worldwide incidence.[1] PTC generally displays slow growth rates and a benign natural history of disease. Despite an overall excellent prognosis and 5-year survival rates of >95%, there remain subtypes of PTC that display higher risk behavior with increased recurrence rates, distant metastases, and mortality.[2,3]

Clinical risk factors suggestive of more aggressive PTC have historically included extrathyroidal extension, tumor size, variant, older age at diagnosis, and locoregional and distant metastases.[3] More recently, the BRAF V600E mutation has become a prominent molecular marker in PTC. It has been discovered in as many as 73% of PTCs and is associated with a more aggressive clinical course.[4-7] BRAF mutation positivity has been associated with an increased likelihood of node positive disease, higher recurrence rates, shorter intervals to recurrence, and increased cancer-related mortality among patients with PTC.[4,5] BRAF mutation positive tumors are also less likely to display iodine avidity, thus eliminating radioactive iodine (RAI) as a tool in the management of these patients.[8] Because of the association with worse outcomes, BRAF mutated PTCs may benefit from a more aggressive initial surgical treatment to limit morbidity and mortality.

Significant controversy remains around the role of prophylactic central neck dissection (CND) for PTC.[9] Although PTC follows a predictable pattern of metastases from central lymph nodes to the lateral compartment, there remains no clear benefit of prophylactic central lymph node dissection in patients with small primary tumors and clinically node-negative disease. There is no convincing evidence for the use of prophylactic central lymph node dissection in PTC mainly because of the low overall mortality, although

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there is a suggestion that it may be of clinical value with higher risk tumors.

A recent analysis suggests that the controversy of prophylactic neck dissection for PTC is not likely to be resolved owing to the indolent nature of the disease, the low mortality rate, and the large number of patients who would be required to adequately assess the better surgical option.[9] However, we believe that cost should play a role in the decision-making process and in formulating management plans for medical interventions. With the advent of the Affordable Care Act and subsequent changing patterns of health care coverage, cost containment has become increasingly relevant to medical care and should be an important part of the consideration.

We hypothesized that preoperative BRAF testing would identify a high-risk subset of early stage PTC patients. With a small added testing cost, they can be selected for prophylactic CND during the initial thyroidectomy, which would result in decreased lifetime costs and improvement in patient quality of life by limiting reoperative surgery. We used a decision tree analysis model to compare the long-term outcomes and costs between strategies of routine preoperative BRAF testing to identify patients for total thyroidectomy (TT) with central lymph node dissection (TT+CND) with no preoperative BRAF testing and initial surgery consisting of TT. TT alone was used as the standard operative procedure based on a recent cost-minimization study suggesting that it is more cost effective than TT+CND.[10]

METHODS

Study design. This is a cost-utility analysis from a societal perspective. The scope of our study was limited to a hypothetical cohort of 40-year-old women with seemingly low-risk PTC to minimize confounding variables. The population was defined to have stage I disease (T1b, N0, M0) that is 2 cm in size, and confined to the thyroid with clinically negative lymph nodes. The decision tree adhered to the 2009 revised American Thyroid Association treatment guidelines for patients with differentiated thyroid cancer.[2]

A state transition Markov decision model was constructed using decision software (TreeAge Pro Healthcare Module 2011; TreeAge Software, Inc, Williamstown, MA) to analyze the components of the decisions, potential consequences, and probable outcomes (Fig 1). This model compared preoperative BRAF testing by FNA versus no BRAF testing. Patients with BRAF mutation PTC were selected to undergo TT+CND, whereas BRAF wild-type patients underwent TT alone. Patients who did not undergo BRAF testing underwent TT as their initial operative treatment. Because BRAF-mutated tumors have been shown to have poor uptake of RAI,[8] a greater proportion of patients whose cancers were BRAF mutated did not undergo RAI for central neck or non–central neck recurrences, than compared with BRAF wild-type patients. Percentages of BRAF+/− patients as well as RAI avid/nonavid tumors were identical in each half of the testing and nontesting arms of the algorithm.

A 1-year cycle time frame was used to capture the initial surgery and acute postoperative hospitalization, as well as 3-, 6-, and 12-month follow-up visits per the American Thyroid Association guidelines.[11] The analytic horizon included the lifespan of the otherwise healthy 40-year-old women whose life expectancy was 82 years. This translated to 42 Markovian cycles, after which all states reached death. Life expectancy data were obtained from life tables from the US Centers for Disease Control and Prevention.[12]

Probabilities of clinical events. Probabilities of clinical outcomes and complications were derived from literature review (Table I). The proportion of patients testing positive for BRAF for this patient population was selected within a range from studies available in the literature. Recurrence rates for BRAF-mutated and BRAF wild-type patients were derived from a meta-analysis of 14 studies.[4] For equipoise in the decision model, recurrence rates for no BRAF testing were obtained from all-comers from the same studies. The rates were adjusted proportionally to account for the BRAF positivity rate. Complications of transient hypoparathyroidism, permanent hypoparathyroidism, transient dysphonia, and permanent single vocal cord paralysis were included in the model[13,14] (Table II).

Cost determination. Medical costs were derived from published studies as well as from Medicare reimbursement rates[15-18] (Table III). Societal costs such as income loss, opportunity loss, and costs of daily living were derived from public data.[19-21] All costs were measured in 2010 US dollars and discounted at a rate of 3% per year.

Utility determination. Utility data were obtained from studies analyzing patients undergoing total thyroidectomies and their complications[16] (Table IV). Patients who developed non-neck recurrences were considered to have chronic cancer and assigned a utility of 0.6 based on current literature.[22] Deceased patients were given a health state of 0. In the Markov model, health states were summed

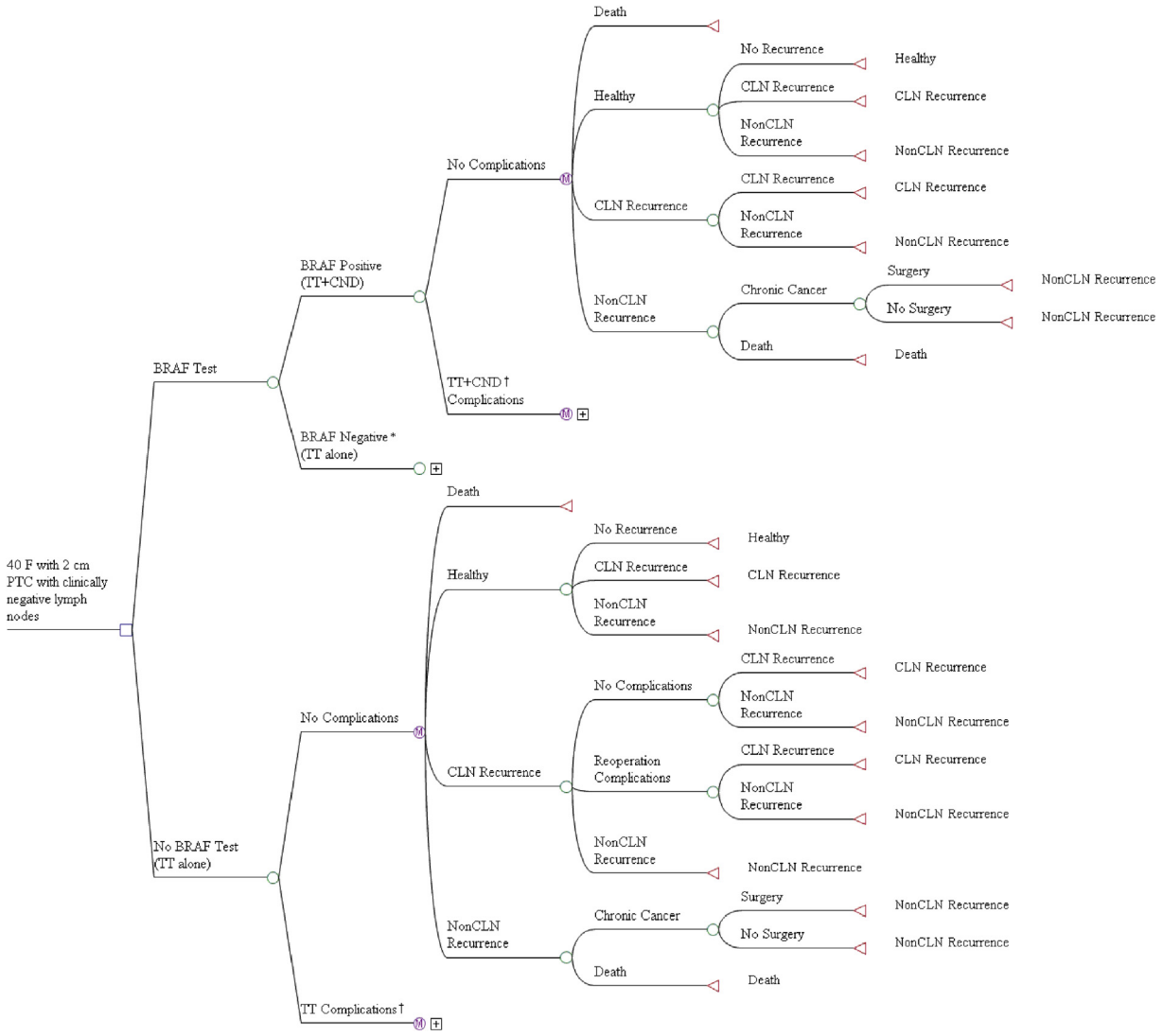

Fig 1. Simplified tree diagram of the decision tree model for the comparison of BRAF testing and no BRAF testing. *BRAF Negative arm is not expanded and is similar to No BRAF Test arm. †Complications arms are also not expanded and are similar to their corresponding No Complications arms. *CLN*, Cervical lymph node; *F*, female; *NonCLN*, noncervical lymph node; *PTC*, papillary thyroid cancer; *TT*, total thyroidectomy; *TT+CND*, total thyroidectomy with central neck dissection.

over 42 cycles to obtain the utility which was measured in quality-adjusted life-years (QALYs). Patients reaching the death state before the 42nd cycle were kept in the model to calculate opportunity loss. Utilities were discounted at a 3% annual rate.

Sensitivity analysis. Univariate sensitivity analysis was performed on all individual cost, incidence, and utility variables. The results of the model were said to be sensitive to any particular variable if the recommendation changed for the corresponding range of individual variables. Bivariate sensitivity analysis was performed on key variables to explore possible alternatives of the model conclusion.

Assumptions. Several assumptions were made in the construction of our decision model. (1) All recurrent laryngeal nerve injuries were unilateral. (2) Patients experiencing permanent vocal cord paralysis during TT did not experience contralateral recurrent laryngeal nerve injury if they required reoperation. (3) Patients did not experience >1 complication per operation. (4) There was no mortality associated with any operation. (5) All reoperations and debulking surgeries on patients with chronic cancer were assigned the same cost. (6) Costs were calculated from CPT codes based on Medicare payment information at a Northern California health care facility.[15] (7)

Table I. Incidence and probabilities of possible outcomes

Variable	*Incidence or probability (%)*	*Range (%)*
Incidence of BRAF mutation[4]	40	32–73
Death from cancer per year[5]	5	0–10
Cervical recurrence in BRAF mutation[4,13]	7	3.1–10.7
Cervical recurrence in BRAF wild type[4,13]	4.5	0.7–12.9
Cervical recurrence in all-comers[4,13]	5.8	1.9–11.6
Noncervical recurrence in BRAF mutation[4,13]	17.9	7.9–27.3
Noncervical recurrence in BRAF wild type[4,13]	8.1	1.3–23.1
Noncervical recurrence in all-comers[4,13]	11.7	4.2–22.7

Table II. Incidences and probabilities of side effects and complications

Variable	*Incidence or probability in TT only (%)*	*Range (%)*	*Incidence or probability in TT and CND (%)*	*Range (%)*
Hypothyroidism	100	NA	100	NA
Transient hypoparathyroidism[13]	16	5.6–5.8	30	14–86
Transient hypoparathyroidism after reoperation[14]	4	3–15	NA	NA
Permanent hypoparathyroidism[13]	1.3	0–5.6	1.5	0.8–6.6
Permanent hypoparathyroidism after reoperation[14]	3.5	0–5.6	NA	NA
Temporary RLN injury[13]	2.9	0–9	5	3.5–9.1
Temporary RLN injury after reoperation[14]	6	0–12	NA	NA
Permanent RLN injury[13]	1.3	0–3.1	1.5	0–6.6
Permanent RLN injury after reoperation[14]	3.5	0–25	NA	NA

CND, Central neck dissection; *NA*, not applicable; *RLN*, recurrent laryngeal nerve; *TT*, total thyroidectomy.

Because BRAF positive tumors demonstrated poor avidity to RAI, these patients did not receive RAI therapy for recurrences; however, the recurrence rates and survival for these patients were kept the same owing to poor data in the literature. (8) Recurrence rates were higher for BRAF positive patients compared with BRAF negative patients, which may be reflective of more aggressive disease and selection bias from available studies.

RESULTS

Treatment without preoperative BRAF testing was more cost effective than treatment with preoperative BRAF testing, resulting in cost savings of $801.51 per patient. Total costs per patient for the no testing strategy was $862,447.69, compared with $863,249.20 with BRAF testing. Overall utilities for the 2 strategies were essentially identical at 23.60 QALYs per patient. Preoperative BRAF testing carried the added expense of $33.96 per QALY.

Sensitivity analysis. Univariate sensitivity analysis was performed on key costs, outcome probability, and utility variables. Threshold analysis identified tumor recurrence rates that demonstrated equal cost effectiveness between BRAF testing and no BRAF testing. Equivalent costs between the 2 arms were found when the incidence of cervical recurrence in patients without BRAF testing increased from 5.8% to 8.0% or when incidence of noncervical recurrence increased from 11.7% to 11.9% in the no testing group. In patients testing negative for BRAF, equivalent costs occurred when the incidence of central neck recurrence decreased from 4.5% to 1.0% or when the incidence of noncervical recurrence decreased from 8.1% to 7.9%. Similarly, a decrease in noncervical recurrence rate from 17.9% to 17.6% in patients with the BRAF mutation would lead to equivalent cost between BRAF testing and not testing; however, central neck recurrence rates in BRAF-mutated patients were not sensitive within set ranges. A decrease in total recurrence rates in BRAF mutated patients equal to that of all-comers leads to the BRAF testing strategy to be more cost effective by $13,559.43. A 10% decrease in the recurrence in BRAF-positive patients compared with all-comers would lead to a cost savings of $16,281.56 with preoperative BRAF testing (Fig 2).

Additionally, univariate sensitivity analysis demonstrated equal cost effectiveness between the 2 strategies when the cost of TT increased to $12,607.76, or when the cost of TT with CND decreased to $11,734.24.

Table III. Cost variables and ranges

Variable	*Subtotal cost ($)*	*Range ($)*	*Total cost ($)*	*Range ($)*
BRAF testing[15,18]			97.45	55–123
TT[15,23]			10,604	8,000–13,738
TT with central neck dissection[15,23]			13,738	10,000–15,000
Reoperation for neck recurrence[15,23]			12,528	10,000–14,000
RAI[15]			379.22	366–449
Pre-RAI laboratory tests (β-HCG, TFTs)	75.42	72.17–79.97		
RAIU	91.71	90.04–95.78		
RAI treatment	158.00	154.00–214.46		
Office visit	54.09	49.82–58.36		
Hypothyroidism[15]			228.52	212–281
Office visit	54.09	49.82–58.36		
Laboratory tests (TSH, free T4, total T3, total T4)	64.93	62.10–72.45		
Levothyroxine (yearly costs)	109.50	100.00–150.00		
Neck ultrasonography[15]			149.77	139–250
Whole body scan[15]			396.54	200–500
Transient hypoparathyroidism (90 d)[15,16]			645.91	450–850
Office visit	54.09	49.82–58.36		
Laboratory tests (TSH, free T4, total T3, total T4)	64.93	62.10–72.45		
Laboratory tests (calcium, PTH)	64.87	62.10–72.45		
Calcium (90 d)	6.30	5.69–7.13		
Calcitrol (90 d)	217.80	202.13–267.51		
Permanent hypoparathyroidism (1st year costs)[15,16]			1,568.58	500–2,500
Office visit	54.09	49.82–58.36		
Laboratory tests (TSH, free T4, total T3, total T4)	64.93	62.10–72.45		
Laboratory tests (calcium, PTH)	64.87	62.10–72.45		
Calcium (per y)	25.55	24.00–67.00		
Calcitrol (per y)	883.30	853.27–993.56		
Permanent hypoparathyroidism (yearly costs)[15,16]			1,027.81	1,500–5,000
Office visit	54.09	49.82–58.36		
Laboratory tests (calcium, PTH)	64.87	62.10–72.45		
Calcium (per y)	25.55	24.00–57.00		
Calcitrol (per y)	883.30	853.27–993.56		
Transient RLN injury (180 d)[15,16]			118.82	50–250
ENT consult	34.52	34.01–43.31		
Laryngoscopy	56.92	51.55–62.17		
Office visit	54.09	49.82–58.36		
Permanent RLN injury[15,16]			202.29	50–500
ENT consult	34.52	34.01–43.31		
Laryngoscopy	56.92	51.55–62.17		
Office visit	54.09	49.82–58.36		
Voice reeducation treatment	83.47	80.22–105.00		
Debulking or other surgery for metastasis[15,23]			12,528	8,000–15,000
Cost of living[19]			29,149	20,000–50,000
Cancer death (final year costs)[17]			108,253	50,000–150,000
Death unrelated to cancer (final year costs)[17]			10,064	5,000–20,000
Yearly opportunity loss owing to premature death[20,21]			152,247	40,000–300,000

Costs are presented in US 2010 dollars ($).
βHCG, Beta-human chorionic gonadotropin; *ENT*, ear, nose, and throat; *PTH*, parathyroid hormone; *RAI*, radioactive iodine; *RAIU*, radioactive iodine uptake test; *RLN*, recurrent laryngeal nerve; *T3*, triiodothyronine; *T4*, thyroxine; *TFTs*, thyroid function tests; *TSH*, thyroid-stimulating hormone; *TT*, total thyroidectomy.

Sensitivity analysis of incidence of BRAF mutation was performed under the assumption that an increase of BRAF mutation would lead to a proportionate increase in the overall tumor recurrence rate. By concurrently adjusting both variables, the incremental cost effectiveness of BRAF testing approached zero when the rate of BRAF mutation decreased to 30%.

Bivariate sensitivity analysis was performed on key variables that were demonstrated to be

Table IV. Utility values and ranges

Variable	*Utility**	*Range*	*Short-term adjustment (d)†*	*Range (d)*
Total thyroidectomy[16]	1	0.9–1	15	7–20
Total thyroidectomy with CND[16]	1	0.9–1	20	15–27
Reoperation for neck recurrence[16]	1	0.9–1	8	7–27
Radioactive iodine[16]	1	0.9–1	7; 95 if after recurrence	0–180
Hypothyroidism[16]	0.99	0.9–0.99	NA	NA
Transient hypoparathyroidism (90 d)[16]	0.95	0.9–1	NA	NA
Permanent hypoparathyroidism[16]	0.95	0.9–0.99	NA	NA
Temporary recurrent laryngeal nerve injury (180 d)[16]	0.957	0.9–0.99	0.25	0–15
Permanent recurrent laryngeal nerve injury[16]	0.957	0.9–0.99	0.25	0–30
Cancer[22]	0.60	0.4–0.8	NA	NA
Death	0	NA	NA	NA

*Values represent long-term adjustments in utilities except where indicated. Utility measured in quality-adjusted life-years.
†Short-term adjustments represent a 1-time initial loss of utility for the duration indicated. Values calculated in days lost divided by 365 days in a year.
CND, Central neck dissection; *NA*, not applicable.

sensitive on univariate sensitivity analysis. Noncervical neck recurrence in all-comers was plotted against noncentral neck recurrence in BRAF-mutated patients with the base case reference point indicated (Fig 3). The line signified equal cost effectiveness, above which no BRAF testing strategy dominates and below which BRAF testing strategy dominates. Bivariate sensitivity analysis of cost of TT with TT with CND demonstrated a similar equal cost-effectiveness line with the base case reference point plotted (Fig 4).

Health care perspective. By eliminating income loss, opportunity loss, and costs of daily living, the model was analyzed from a health care perspective, with all other variables being equal. The overall cost per patient for BRAF testing ($28,213.49) was higher than the cost of no BRAF testing ($27,084.48), leading to an incremental cost of $1,129.01 per patient. The overall utilities of the 2 strategies did not change from the societal perspective; thus, preoperative BRAF testing carried the added expense of $47.84 per QALY.

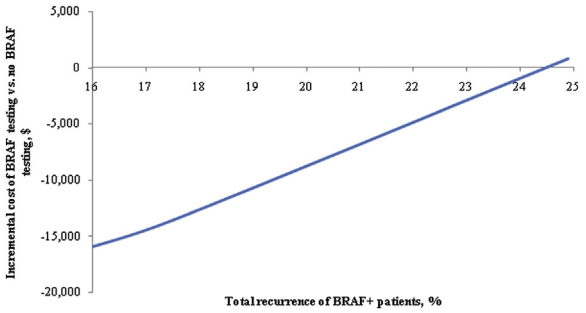

Fig 2. Total recurrence among BRAF-positive patients versus incremental cost of BRAF testing compared with no BRAF testing. This graph demonstrates the cost effectiveness of BRAF testing compared with no BRAF testing by varying the total tumor recurrence in BRAF-positive patients. At an incidence of total BRAF positive recurrences below 24.6%, the strategy of BRAF testing becomes more cost effective. When the BRAF positive recurrences is decreased to a rate equal to that of all-comers not undergoing BRAF testing (17.5%), the strategy of BRAF testing is $13,559.43 less expensive per patient than not testing.

DISCUSSION

In this cost-utility analysis, we aimed to determine whether preoperative BRAF testing to triage patients to receive prophylactic central lymph node dissection at their initial operation would yield a long-term cost benefit and improvement in quality of life. We hypothesized that a more aggressive initial operation in the higher risk BRAF mutation–positive subset of PTC patients would lead to a relative decrease in reoperative surgery, resulting in reduced costs from surgical complications and ultimately lower long-term costs with higher QALYs over the lifetime of the patient. However, we found the reverse to be true and that routine BRAF testing was more costly without improving patients' quality of life. Despite the higher complication rates and expenses of reoperative surgery, TT with CND remained more costly than TT alone. Rather than a cost savings, our data displayed higher costs of $801.51 per patient and an increase of $33.96 per QALY with preoperative BRAF testing.

Higher accrued expenses of the preoperative BRAF testing group were multifactorial, beginning with a BRAF testing price of $97. Increased costs of the initial TT+CND versus TT alone ($13,738 and $10,604, respectively) were the result of added operative times, increased hospital costs and duration of stay, and higher complication rates from

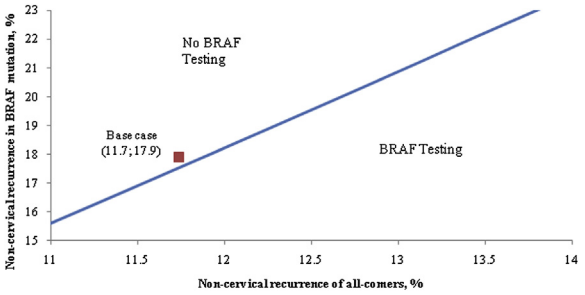

Fig 3. Bivariate sensitivity analysis of noncervical recurrence in all-comers versus in BRAF mutation. This figure shows the base case reference point of noncervical recurrence in all-comers versus in BRAF-mutated patients in relation to the line of equal cost effectiveness between BRAF testing (*below the line*) and not BRAF testing (*above the line*). A decrease in BRAF mutation recurrence and/or an increase in all-comers' recurrence would lead to BRAF testing as the dominant strategy.

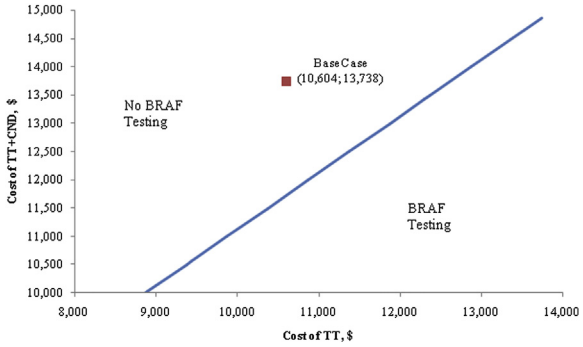

Fig 4. Bivariate sensitivity analysis of cost of total thyroidectomy versus cost of total thyroidectomy with central neck dissection. This figure demonstrates the base case reference point of the costs of TT alone versus TT+CND. The line represents equal cost effectiveness between BRAF testing (*below the line*) and no BRAF testing (*above the line*). An increase in cost of TT alone and/or a decrease in cost of TT+CND would approach equivalent costs between the 2 strategies. *TT*, Total thyroidectomy; *TT+CND*, total thyroidectomy with central neck dissection.

the primary operation with the addition of CND.[15,23] The increased complication rates of TT+CND versus TT alone[13] resulted in a significant cost difference in those patients who received CND during their initial operation.

Cost effectiveness and QALYs were affected significantly by the high incidence of BRAF positivity and the high recurrence rates in BRAF mutation–positive patients. Rates of BRAF mutation positivity in PTC and the aggressiveness of BRAF mutated tumors remain controversial with reported rates ranging from 32 to 73%.[4] Our model extrapolates a 40% BRAF positivity rate based on compiled available literature, but the sensitivity analysis suggests that adjusting the positivity rate of <30% makes the BRAF testing strategy the more cost-effective option. The results of such a change lead to a lower rate of initial central lymph node dissections and decreases overall costs.

Noncervical recurrence rates of all-comers and BRAF positive PTC were a major source of costs and patient morbidity in the model. Cervical and noncervical recurrence rates for all-comers utilized were 5.8% and 11.7% (range, 1.9–11.6% and 4.2–22.7%), respectively. At these rates, preoperative BRAF testing lacks cost effectiveness, but as the noncervical recurrences rise above 11.9%, testing becomes cost effective. These data suggest that in a population with higher risks of recurrence, a more aggressive initial treatment is justified, limiting the need for reoperation and its resultant complications. If overall recurrence rates are low, as in our model, BRAF testing results in unwarranted initial neck dissections and complications leading to increased costs and decreased QALYs.

We acknowledge that there are several limitations to this study. First, the selection and estimation of probabilities of occurrences in our model are subject to debate. Widely available testing for molecular markers such as BRAF have only become available within the past 10 years; therefore, the natural history of BRAF mutated PTC over the lifetime of a patient has not been clearly elucidated. Despite an extensive literature search to help guide the treatment algorithm, several assumptions have been made. Incidence and timing of recurrences, role of RAI treatment, and long-term data regarding the natural history of treating BRAF-mutated PTC have not been clearly established. There are also significant variations in complication rates for TT, TT+CND, and reoperative surgeries reported in the literature.[13,14] Although selective reports suggest that TT+CND should yield similar complication rates to TT alone, larger studies and meta-analyses suggest that the complications are generally higher with the addition of CND and in reoperative neck surgeries. Although high-volume centers report complication rates that approach zero, the majority of thyroid operations are performed by surgeons without specialty expertise.

Second, available studies that predict recurrence rates are retrospective in nature and group prophylactic and therapeutic lymph node dissections together,[4] whereas several reports offer no correlation between BRAF positivity and more aggressive or recurrent disease.[24,25] In addition,

available studies frequently do not encompass the lifespan of the cohort. Owing to these confounders, BRAF data tend to skew toward high rates of recurrence. A meta-analysis of 2,470 cases found a 24.9% recurrence rate in BRAF-positive tumors (range, 11–40%).[4] Although this study represents the most thorough BRAF-positive recurrence data, the 12.6% recurrence rate in the BRAF-negative counterpart is significantly higher than the 6% that is historically reported. To realistically compare costs in our treatment algorithm, we favored these higher rates of recurrence in our model.

Third, the recurrence data from the meta-analysis was derived from 14 studies.[4] Although recurrence/persistence was broadly defined as "the absence of clinical or radiographic imaging evidence of tumor and undetectable serum thyroglobulin levels during thyroid stimulating hormone suppression and stimulation without interfering antibodies," the specific criteria for diagnosing recurrent disease was not uniform across all studies. For example, a lower threshold for detecting serum thyroglobulin level may lead to an higher reported incidence of recurrences.

Fourth, we acknowledge that BRAF positivity and recurrent disease tend to increase with patient age. Because of the inability to accurately estimate BRAF positivity and recurrence rates by age, we chose a hypothetical low-risk, 40-year-old woman with stage I disease, limiting the applicability of our study. As future data become available that better delineate the association between age and BRAF mutation, we may be able to more accurately widen the scope of the study.

Fifth, from an oncologic and surgical standpoint, it seems intuitive that a more aggressive initial approach would be favorable for higher risk tumors. An aggressive operative approach should lead to similar, if not decreased, recurrence and improved long-term survival when matched stage for stage against an initial conservative operation. However, higher rates of recurrence have been described in BRAF-positive patients who underwent CND compared with those patients who did not (34 and 8.2%, respectively).[6] This likely represents the selection bias of higher risk patients being subjected to more extensive operations, but ultimately translates into the high recurrence rates seen in the BRAF-positive arm of our model and even higher rates for those who undergo initial CND. The lack of available recurrence data represents the major limitation of the model. This is exemplified by the sensitivity analysis suggesting that, if recurrence rates of BRAF-positive patients can be reduced to equivalent rates of all-comers through prophylactic CND, cost data would then favor preoperative BRAF testing by $13,559.43. However, because available data do not suggest that recurrence rates can be reduced by prophylactic CND, the oncologic decision for an aggressive initial surgery should be based on an individualized determination. As noted in the published literature, the feasibility of a prospective, randomized, controlled trial comparing the use of TT alone versus TT+CND is all but impossible because of the large number of patients and extensive follow-up required.[9] Limited recurrence and long survival rates make such a study unlikely to yield convincing evidence in favor of either therapeutic option. Studies that perform routine CND such as that by So et al[7] begin to address gaps in the literature and better represent early stage disease. The study suggests increased local recurrence and increased node positivity with BRAF-mutated tumors, but it is not able to address long-term outcomes and survival. Perhaps a longitudinal investigation in these types of studies can lead us closer to the natural history of the disease.

Many surgeons believe that preoperative risk stratification of PTC is useful in planning treatment strategies. Although we think of early stage PTC patients as having low-risk tumors, BRAF testing as an independent stratification variable may allow us to more accurately classify a high-risk group of patients who are better served with a different treatment regimen that may include a more extensive initial operative approach. This stratification of BRAF-positive patients is combined with the fact that ≤77% of BRAF-mutated primary tumors and 94% of recurrent BRAF-mutated tumors lack iodine avidity.[8] The loss of RAI as an important postoperative treatment modality has implications in support of a more aggressive initial approach to these patients. Additionally, the advent of anti-BRAF inhibitor therapeutics such as vemurafenib could have a major effect on the treatment algorithm or selected BRAF-positive patients, opening a window for treatment earlier in their disease course.

In conclusion, although BRAF has a promising role in the management of early stage PTC, we found that preoperative testing to triage patients to CND at initial surgery results in slight increases in cost over TT alone. However, additional elaboration of the data and long-term follow-up of patients treated for BRAF-mutated PTC are required to guide future management of the disease.

REFERENCES

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. J Am Med Assoc 2006;295:2164-7.
2. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see comments]. Cancer 1998;83:2638-48.
3. Ward LS, Morari EC, Leite JL, Bufalo NE, Guilhen AC, Araujo PP, et al. Identifying a risk profile for thyroid cancer. Arq Bras Endocrinol Metabol 2007;51:713-22.
4. Tufano RP, Teixeira GV, Bishop J, Carson KA, Xing M. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine 2012;91:274-86.
5. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. J Am Med Assoc 2013;309:1493-501.
6. Alzahrani AS, Xing M. Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND. Endocr Relat Cancer 2013;20:13-22.
7. So YK, Son YI, Park JY, Baek CH, Jeong HS, Chung MK. Preoperative BRAF mutation has different predictive values for lymph node metastasis according to tumor size. Otolaryngology 2011;145:422-7.
8. Barollo S, Pennelli G, Vianello F, Watutantrige Fernando S, Negro I, Merante Boschin I, et al. BRAF in primary and recurrent papillary thyroid cancers: the relationship with (131)I and 2-[(18)F]fluoro-2-deoxy-D-glucose uptake ability. Eur J Endocrinol 2010;163:659-63.
9. Carling T, Carty SE, Ciarleglio MM, et al. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. Thyroid 2012;22:237-44.
10. Lang BH, Wong CK. A cost-minimization analysis comparing total thyroidectomy alone and total thyroidectomy with prophylactic central neck dissection in clinically nodal-negative papillary thyroid carcinoma. Ann Surg Oncol 2014;21:416-25.
11. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
12. US Centers for Disease Control and Prevention. National Vital Statistics Reports [cited 2012 Nov]. Available from: www.cdc.gov/nchs/data/nvsr/nvsr61/mvsr61_06.pdf.
13. Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S, Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope 2012;122:797-804.
14. Kim MK, Mandel SH, Baloch Z, et al. Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg 2004;130:1214-6.
15. American Medical Association. CPT code/relative value search [cited 2013 Feb 1]. Available from: https://ocm.ama-assn.org/OCM/CPTRelativeValueSearch.do.
16. In H, Pearce EN, Wong AK, Burgess JF, McAneny DB, Rosen JE. Treatment options for Graves disease: a cost-effectiveness analysis. J Am Coll Surg 2009;209:170-179.e1-2.
17. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 2011;103:117-28.
18. Illumina. Latest developments in molecular pathology rate setting [updated 2013; cited 2013 Oct]. http://res.illumina.com/documents/clinical/reimbursement-latest-developments-mopath.pdf.
19. US Bureau of Labor Statistics. Consumer expenditure survey tables [cited 2012 Jul]. Available from: ftp://ftp.bls.gov/pub/special.requests/ce/standard/2010/cusize.txt.
20. Expectancy Data. The dollar value of a day, 2010 edition. Shawnee Mission (KS); 2010.
21. US Bureau of Labor Statistics. Consumer expenditure survey [cited 2012 Jul]. Available from: http://www.bls.gov/cex/#tables.
22. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol 2002;55:1130-43.
23. US Agency for Healthcare and Research Quality. Welcome to HCUPnet (Healthcare Cost and Utilization Project) [cited 2012 Oct]. Available from: http://hcupnet.ahrq.gov.
24. Walczyk A, Kowalska A, Kowalik A, Sygut J, Wypiórkiewicz E, Chodurska R, et al. The BRAF(V600E) mutation in papillary thyroid microcarcinoma: does the mutation have an impact on clinical outcome? Clin Endocrinol (Oxf) 2014;80:899-904.
25. Barbaro D, Incensati RM, Materazzi G, Boni G, Grosso M, Panicucci E, et al. The BRAF V600E mutation in papillary thyroid cancer with positive or suspected pre-surgical cytological finding is not associated with advanced stages or worse prognosis. Endocrine 2014;45:462-8.

DISCUSSION

Dr Jack Monchik (Providence, RI): I have 2 of questions for you. In the group that was BRAF positive, you said you would do a central node dissection on all of those groups. Hypothetically, what percentage would you attribute to having no nodes positive by gross examination?

Dr Barnard J. Palmer (Oakland, CA): We are assuming that all of these patients had no positive nodes clinically or by ultrasonography, and this was a low-risk tumor, with the only high-risk feature being BRAF positivity.

Dr Jack Monchik: You talked about, in the group that had the central node dissection, debulking. I would also suggest that radiofrequency or alcohol ablation, which is considerably cheaper, could be used in that situation, where an experienced surgeon has already done a central node dissection.

Dr Ralph Tufano (Baltimore, MD): I think that this is the kind of work that needs to be done to look at the utility of the testing that we do and the impact as far as quality of life.

I do think, though, that you may be putting the cart before the horse because the BRAF as an indication to do central neck dissection. Especially, as you already mentioned, in the presence of a

preoperative screening study such as ultrasound, even with its limitations in the central neck, in the absence of gross nodal disease, finding that disease that's microscopic may be of little clinical significance.

We truly really do not know if BRAF would be associated with a higher risk of having micronodal metastases in the central neck. But I do applaud the study and the algorithms that you have used to look at this. I think it is so important.

Dr Linwah Yip (Pittsburgh, PA): I agree that these studies are very sorely needed. I just had a concern about your models in the variables. First of all, the variable that if you do BRAF testing and do a central compartment nodal dissection, it seemed like your rate of recurrence was actually higher than the BRAF-negative group or even the other control arm, where they only did a total thyroidectomy. So first of all, I do not know how a cost-utility analysis that proposes to do more surgery at more cost for higher risk with no outcome benefit can actually ever have any proven positive utility.

My second comment is that I do not think we have those data. I sort of agree that we do not know yet that if you are BRAF positive, if you do a CND, which usually has a higher risk of nodal recurrence, which we have shown in other studies, whether that really makes a difference in long-term outcomes. I think that if your variables are not accurate, it really sort of questions the translation of that cost data to real practice.

Dr Barnard J. Palmer: I agree. Those are definitely 2 of the concerns we had. With respect to the higher recurrence rate in the BRAF-positive patients, that was difficult. And we used whatever the best available data were. We actually used Dr Tufano's paper as the basis of this, and looking back to find out exactly why this was the case is tough for us to understand. I do not know if it is the sample of patients that they are using, but the rates in those papers were higher actually overall, even in the non–BRAF-positive patients compared with what the historical literature is. So it is possible we are seeing a different type of disease maybe in the current century.

Dr Paolo Miccoli (Pisa, Italy): I agree that this is a very important paper. I just would object on the background, because you limited your study to the lymph nodes, assuming that lymph node recurrence or metastasis is very much linked with BRAF mutation. This is probably no longer so true, because there are several studies demonstrating that this linkage is not so active.

For example, there are several European and South American studies assuming that extrathyroidal extension, if you do an odds ratio of all the statistical analyses, the highest risk is for extrathyroidal extension much more than for lymph node recurrence. So this might be biased toward your paper, which a part of it is an excellent paper.

Dr Barnard J. Palmer: I agree. I think we probably are a little bit early in our cost analysis, not knowing the full natural history of what BRAF-positive tumors are going to do.

Dr Brad Mitchell (Morgantown, WV): As I understand it, you are looking at the positive value of the BRAF. Did you consider looking at whether it was BRAF negative and avoiding an ostensibly prophylactic central neck dissection, whether or not there would be any benefit? It did not seem that was calculated in your study.

Dr Barnard J. Palmer: Correct. We have not done that yet. We have actually been talking about doing the reverse, and maybe if all patients got prophylactic neck dissection unless they are negative, or if the standard patient received a prophylactic neck dissection, rather than only the higher risk people getting it.