BRAFV600E testing for low-risk papillary thyroid microcarcinomas – Computational model from a patient-oriented approach

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Abstract

Background: Given the good prognosis of low-risk papillary thyroid microcarcinomas (lrPTMCs) accurate risk stratification is valuable to optimize management: active surveillance vs. surgery. BRAFV600E testing was associated with increased recurrence risk, hence AS seems reasonable for mutation-negative lrPTMC. However, when considering AS, patient perception is highly important as adherence and emotional aspects are challenging. In this study, we aimed to model the contribution of BRAFV600E testing for the management of PTMCs when tailored to the patient perspective. Methods: We developed a Markovian model to predict the role of BRAFV600E in prioritizing between hemithyroidectomy (HT) and active surveillance (AS) for lrPTMCs. We used a simulated cohort of lrPTMCs, with probabilities of each strategy driven from previous literature. Outcomes were measured as quality-of-life years (QALYs). One- and two-way sensitivity analyses were conducted to ascertain model robustness. Results: We found that the optimal strategy (e.g., that would maximize QALYs) varies according to BRAFV600E status for patients without a preset predilection between AS to HT. Using one-way sensitivity analysis, we found that the two main variables that have the strongest impact on the decision are the utility of AS and the utility of a disease-free state after HT. Two-way sensitivity analysis demonstrated that BRAFV600E status can define the optimal strategy for patients in the middle zone of the utility range (e.g., patients without clear preference). Conclusions: Our model suggests that BRAFV600E status can facilitate decision-making regarding AS vs. HT for patients without preset predilection. Our model supports further real-life studies of BRAFV600E testing for PTMCs.

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Methods: We developed a Markovian model to predict the role of$BRAF^{V600E}$ in prioritizing between HT and AS for lrPTMCs. We used a simulated cohort of lrPTMCs, with probabilities of each strategy driven

from previous literature. Outcomes were measured as quality-of-life years (QALYs). One- and two-way sensitivity analyses were conducted to ascertain model robustness.

Results: We found that the optimal strategy (e.g., that would maximize QALYs) varies according to $BRAF^{V600E}$status for patients without a preset predilection between AS to HT. Using one-way sensitivity analysis, we found that the two main variables that have the strongest impact on the decision are the utility of AS and the utility of a disease-free state after HT. Two-way sensitivity analysis demonstrated that $BRAF^{V600E}$ status can define the optimal strategy for patients in the middle zone of the utility range (e.g., patients without clear preference).

Conclusions: Our model suggests that$BRAF^{V600E}$ status can facilitate decision-making regarding AS vs. HT for patients without preset predilection. Our model supports further real-life studies of $BRAF^{V600E}$testing for PTMCs.

Keywords: thyroid cancer; microcarcinoma; molecular testing; molecular diagnostic; thyroid surgery; active surveillance

Key Points

- Given the good prognosis of low-risk papillary thyroid microcarcinomas (lrPTMCs) accurate risk stratification is valuable to optimize management.
- This study aim to evaluate the possible contribution of molecular testing in the clinical decision-making regarding management of low-risk papillary thyroid microcarcinomas (lrPTMCs)
- Using a computed decision model, we analyzed the overall benefit resulting from the treatment strategies for lrPTMCs: active surveillance (AS) versus hemithyroidectomy (HT), measured by quality-of-life years (QALYs).
- We found that the optimal strategy that would maximize QALYs, varies according to $BRAF^{V600E}$ status for patients without a preset predilection between AS to HT.
- Our model suggests that when there is a dilemma between AS vs. HT for lrPTMCs, $BRAF^{V600E}$ status can facilitate decision-making, supporting further real-life studies of$BRAF^{V600E}$ testing for PTMCs.

Introduction

The incidence of thyroid cancer is growing in recent years, with an upsurge in the detection of microcarcinomas, defined as tumors < 1 cm in diameter. The abundant availability and continuous advances in imaging modality, mainly sonography, have contributed to the incidental identification of such tumors.[1]

Low-risk papillary thyroid microcarcinomas (PTMCs) were demonstrated to be less aggressive than larger tumors, to have low recurrence rates, and to carry a good prognosis with less than a 1% mortality rate.[1,2]Patients under active surveillance (AS) had similar survivals rates, and for those who eventually needed surgery, deferring surgery did not affect the chances for complete remission.[3] That has led to a shifting trend in the management of PTMCs from traditional surgical treatment to AS in selected cases.[2,4–6] The American Thyroid Association (ATA) guideline[7] states that the AS management approach can be considered for very low-risk papillary microcarcinomas, e.g. without clinically evident metastases or local invasion and no convincing cytologic evidence of aggressive disease. Other studies found a correlation between tumor aggressiveness and the location of the tumor; peripheral tumors and tumors which are attached to the trachea or located in the course of the recurrent laryngeal nerve are considered to express more aggressive behavior. These tumors were regarded as unsuitable for AS.[8]

Given the overall good prognosis of PTMCs and the increasing evidence of the benefits of AS, an accurate risk stratification process would be a valuable addition to the diagnostic workup.

In the past decade, molecular testing of thyroid nodules has rapidly evolved. *BRAF* point mutation at codon 600 ($BRAF^{V600E}$) is the most common alteration that is found in 40-70% of papillary thyroid cancers.$BRAF^{V600E}$ is strongly associated with more aggressive behavior of the tumor. It was also shown to be a predictor for aggressive features in studies and meta-analyses focusing on PTMC.[9–13] In these

reports,$BRAF^{V600E}$ positive nodules had a higher likelihood for recurrence.[9,10] Following this evidence, it has been suggested to use$BRAF^{V600E}$ testing for risk stratification, while $BRAF^{V600E}$- negative PTMC will be eligible for AS.[10] However, to date there is no real-life data testing this hypothesis nor data on the use of$BRAF^{V600E}$ pre-operatively for PTMC. In order to test its utility, we developed this stimulated model. Decision tree models are used to compare treatment strategies using computed data from previously published sources rather than an actual patient's cohort. The model results are based on chosen outcomes, such as cost, effectiveness, and quality of life. AS requires a high level of adherence from the patient. The patient's perception of his condition and his cooperation can highly influence the final decision. Therefore, we chose to perform this model from the patient's perspective, defining the optimal outcome as the strategy that will maximize quality of life.

Materials and Methods

We computed a decision tree model to assess the overall benefit resulting from each of the treatment strategies for lrPTMCs (surgical vs. AS), by incorporating the effect of$BRAF$ testing. We used Markov models, which are used for decision-making in health management to model the probabilities of different states and the rates of transitions among them. The model schematic is presented in Figure 1, and the detailed model can be found in the Supp. Materials. We compared the overall QALYs resulting from the management of patients with PTMC using the traditional surgical management with hemithyroidectomy (HT) compared to active surveillance (AS). We used TreeAge Software Pro version 2021 (TreeAge Software, Inc., Williamstown, MA USA) to construct the model. Additional analyses were performed using MATLAB (MathWorks 2020a). The analysis methodology and results are reported according to the Standards for QUality Improvement Reporting Excellence (SQUIRE 2.0).

Ethical approval: As the model is based on published data from previous studies and databases, review board exemption was accepted.

Outcome definitions

For each simulated case in the model, six possible outcomes were included: (1) under AS; (2) post-surgery with long-term complications; (3) Post-surgery without complications; (4) Cancer recurrence, defined as tumor recurrence or any appearance of new lymph nodes metastasis; (5) Cure, defined as no progression and no complication or recurrence in the surgery group after 20 years of follow-up; and (6) Death. The outcomes prevalence within each strategy were driven from previous literature[2,10,14] and are presented in Table 1.

For the AS strategy, patients were defined as 'treatment failure' in cases of [?] 3 mm increase in the size of the primary tumor or any new loco-regional metastasis was found, including involvement of cervical lymph nodes. Failure cases were assigned for hemithyroidectomy.

Model Structure

The model cycled annually and the transition probabilities were based on the rate of disease progression for the AS strategy (according to the treatment failure definition) and the recurrence rate for HT. Age-based probability of death was taken from the US Centers for Disease Control and Prevention (CDC) national vital statistics reports.[15] The Markov models for the possible health state following active surveillance and surgery are presented in Figure 2.

Disease progression

We considered two main factors affecting the tumor growth rate and the recurrence rate:

(1) *Patient age* [16]: The growth rate of the primary tumor was estimated to be 0.0091 (range 0.0082-0.01) for patients aged 40-59 years old and 0.004 (range 0.0036-0.0044) for patients more than 60 years old. The rate of locoregional progression during AS was 0.0023 (range 0.0021-0.0025) and 0.0005 (range 0.00045-0.00055) for patients aged 40–59 years and more than 60 years old respectively. The recurrence rate after HT was estimated to be 0.004 (range 0.003-0.005) independent from age.[14]

(2) $BRAF^{V600E}$*status* [10]: To calculate the recurrence rate following HT in patients with lrPTMC who are positive to$BRAF^{V600E}$ mutation we used the Kaplan-Meier curves for disease recurrence-free survival for a patient with low-risk conventional PTMC and $BRAF^{V600E}$ as presented by Kim et al.[10] We digitized the curves using GetData Software and fit the data to an exponential distribution, estimating the recurrence rate of $BRAF^{V600E}$ mutation-positive and $BRAF^{V600E}$ mutation-negative, respectively. We then calculated the hazard ratio (HR) of recurrence-free survival between the $BRAF^{V600E}$ mutation-positive and$BRAF^{V600E}$ mutation-negative patients. We assumed the same HR also for the tumor growth rate and the rate of progression to loco-regional disease. Lastly, we assumed that the patient $BRAF^{V600E}$ status is known.

Utility assessment

Outcomes were measured as quality-adjusted life years (QALYs), which is used to measure a disease burden, including both the effect on life quality and the quantity of life lived. Life quality is represented by utility weights given for each health state, ranging from 1 (best attainable health) to 0 (death). The utility values of the different health states were based on the study of Venkatesh et al.[3] We considered the utility value of patients with lrPTMC under AS as 0.88. This represents a disutility difference, e.g., lower quality-of-life, of AS compared to disease-free state post-HT, driven mainly from studies conducted in prostate cancer – another malignancy that can be treated by active surveillance. We have also considered a range of 0.88 to 1 in the sensitivity analysis, as utility of 1 was suggested in other studies.[17]

Sensitivity analysis

Sensitivity analyses were performed to examine the model's robustness considering possible real-life variations and uncertainties. In the sensitivity analysis, we assign a range, rather than a single value, to the model variables. One-way sensitivity analysis on all the model variables also was used to assess the contribution of each variable to the final results. To evaluate the influence of the genetic status on the utility profile of each strategy, we performed a two-way sensitivity analysis for the utility of AS state vs. the utility post-HT state, for both $BRAF^{V600E}$ positive and negative status.

Results

The study decision tree model is presented in Figure 1 and the Markov models for possible outcomes in Figure 2. We found that the overall benefit, as measured by QALYs, varies according to $BARF^{V600E}$ status; for patients with $BRAF^{V600E}$ positive tumors, the QALYs are 38.58 and 36.56 for HT strategy and AS respectively, with a difference of 2.02, and for patients with$BRAF^{V600E}$ negative tumors, the QALYs are 39.43 and 37.77 for HT and AS strategy respectively, with a difference of 1.66.

Using one-way sensitivity analysis, we found that the main two variables that have a strong impact on the decision are the utility of AS health state and the utility of disease-free state after HT without complication, as presented in the tornado diagrams (Figure 3).

To assess the influence of the genetic status on these two variables, we conducted a two-way sensitivity analysis of the two utility variables in the scenarios of$BRAF^{V600E}$ positive and negative tumors (Figure 1). The range of utility values in which HT will be the preferred strategy is wider in patients with positive$BRAF^{V600E}$ compared to patients with negative to$BRAF^{V600E}$ (Figure 4).

The model predictions indicate that in order to determine the optimal strategy for a specific patient, the physician needs to first assess the patient's perceived utility values for AS and post-HT without complication health states, and then to consider the need for genetic testing (see Figure 5 for the suggested management algorithm). According to this personalized approach, patients can fall into three groups with respect to their utility scores: (i) patients with high values for AS and low values for post-HT - would be recommended AS; (ii) patients with low values for AS and high values for post-HT - would be recommended surgery; (iii) patients with middle utility values - would be recommended genetic testing (Figure 4, grey area) to tailor each patient's optimal personalized management plan.

Discussion

With the accumulation of evidence regarding the excellent prognosis of lrPTMC, active surveillance is becoming a viable strategy.[3,18] In this study, we aimed to provide tools to optimize the risk stratification process, in order to allow physicians to tailor the most suitable strategy according to the patient's and nodule's specific characteristics.

Regional or distant metastases or other aggressive features such as tracheal or recurrent laryngeal invasion are clear indications for immediate surgery.[18]However, a broader approach to facilitate decision on AS was suggested for more complex cases, integrating sonography characteristics, tumor location, patient's demographics, comorbidities, and preferences, as well as the medical team's capabilities.[19] Our model adds to these factors input from $BRAF^{V600E}$molecular testing, one of the most common genetic etiologies in thyroid cancer which was shown to be associated with aggressive features.[9,11,20]

When considering the patient factors, patient-specific preferences and quality of life implications play a major role. While surgery has well-known risk and complication rates, it should be noted that AS requires repeated ultrasounds and visits to the clinic which may pose a burden to the patient and the health care system. In addition, AS may also be accompanied by emotional stress and potential anxiety in the face of uncertainty for some patients.[6,21] The fear of the "C-word" was also found to be a factor in the decision.[22] The extent of this stress may be affected by various factors, including the patient's personal perspectives, cultural norms, and social circumstances.[23]

We found that the first and most significant step in selecting the optimal strategy is the patient's attitude towards AS and surgery, which is reflected by the utility he would assign for "living with the tumor" (AS) vs. "going into surgery" (post-HT). This finding is supported by the analysis of the results from two previously published cost-effectiveness models comparing AS with hemithyroidectomy for PTMC.[17,24] These models have reached opposite conclusions, while the only remarkable difference between the two was the utility assigned to AS, thereby pointing out its major role. As no specific data exist for AS in PTMCs, estimation was driven from similar scenarios in other cancer types, mostly prostate, which resulted in a wide range of variability.

Hence, it is a great challenge for the physician to integrate the clinical features with the utility values for the individual patient in order to design the best-personalized treatment strategy. Quality tools to assist the physicians in establishing this value are currently lacking and could have a great value in facilitating the patient-doctor communication and the decision-making process.

Nodules features also play a key role in selecting treatment strategies. In addition to the current known low-risk criteria[18,19] that are the basic requirements to consider AS, our model incorporates the implication of$BRAF^{V600E}$ testing in risk stratification. This variant was found to be associated with tumor recurrent in PTMC cases, suggesting a more aggressive tumor behavior. However, there is currently yet to be tested in real-life studies and there is no evidence regarding the association between prognosis and the variant in patients under AS.

The major limitation of this study is its design – computational modeling rather than real-life patients. This type of model is commonly accepted before implantation of new methods, where it allows primary assessment of the potential benefits without is costs and risks. Our positive finding now can encourage further investment of resources in real-life studies.

As most of the data on molecular testing in PTMC focused on$BRAF^{V600E}$, we have presented this variant's influence on the model outcomes. However, in real life, molecular testing includes a wider profile of aggressive mutations, such as the$TERT$ mutations. This information may give us a more precise understanding of the tumor behavior and assist in further decision-making.

Conclusion

In this study, we have demonstrated that testing for$BRAF^{V600E}$ can dictate the optimal strategy for patients without preset preference. These patients pose the greatest challenge to physicians in the decision-making

prosses, hence additional evidence-based tools possess great added value. In light of our finding, performing a real-life study, with its costs and risks, is now better justified and encouraged.

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Figures

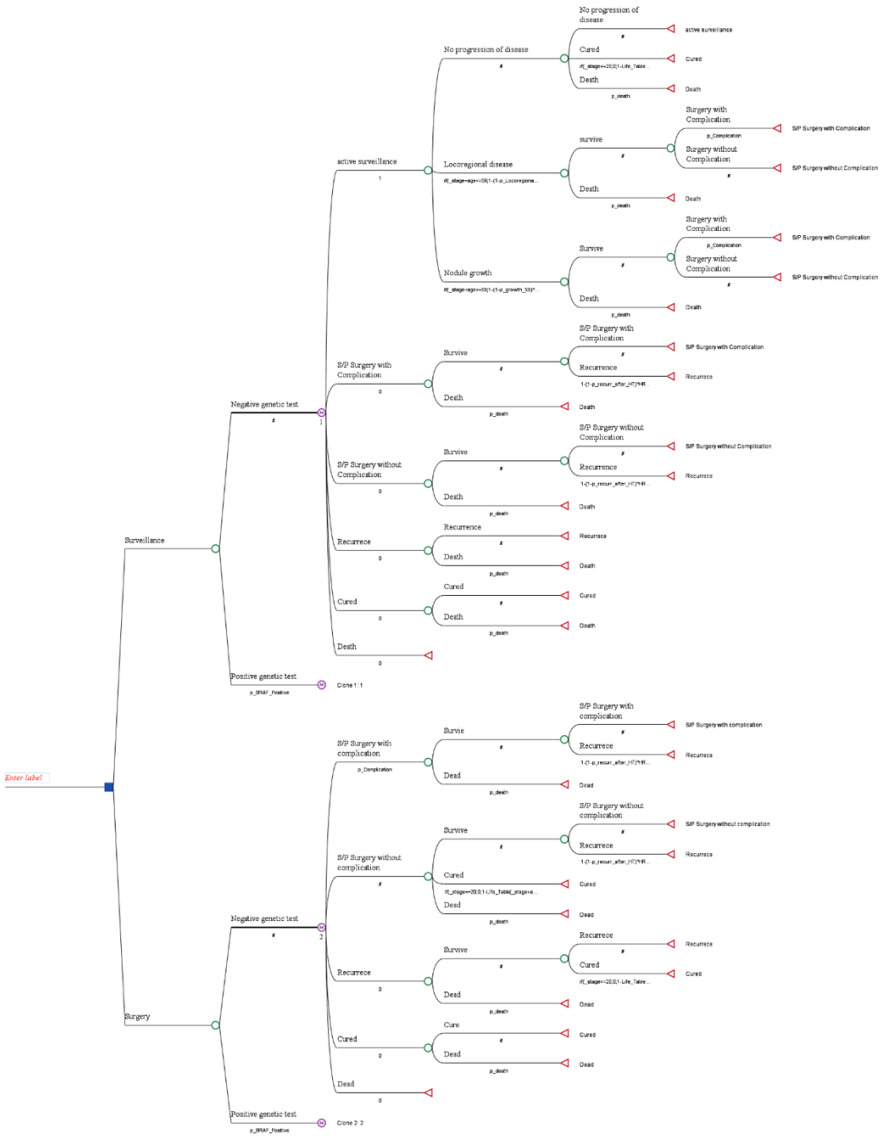

Figure 1: The model decision tree presenting the possible strategies and outcomes for low-risk PMCTs.

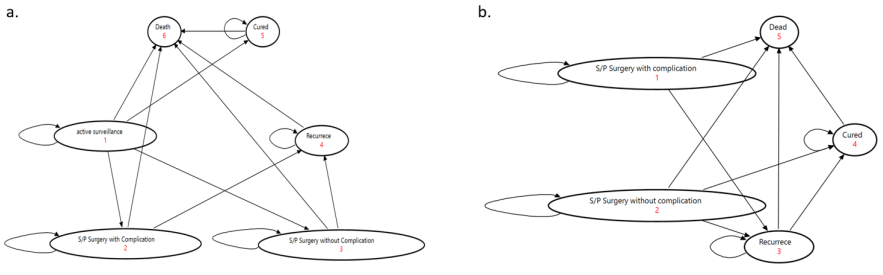

Figure 2: Markov models stimulating the possible outcomes of the treatment modalities. The model presents the possible health state following (a) active surveillance and (b) surgery, and the transitions

among them**.**

Figure 3: Tornado sensitivity analysis plot presenting the effect of the study variables, stratified by$BRAF^{V600E}$ status, (a) for patients with positive BRAF and (b) for patients with negative BRAF.

AS: active surveillance; HT: hemithyroidectomy.

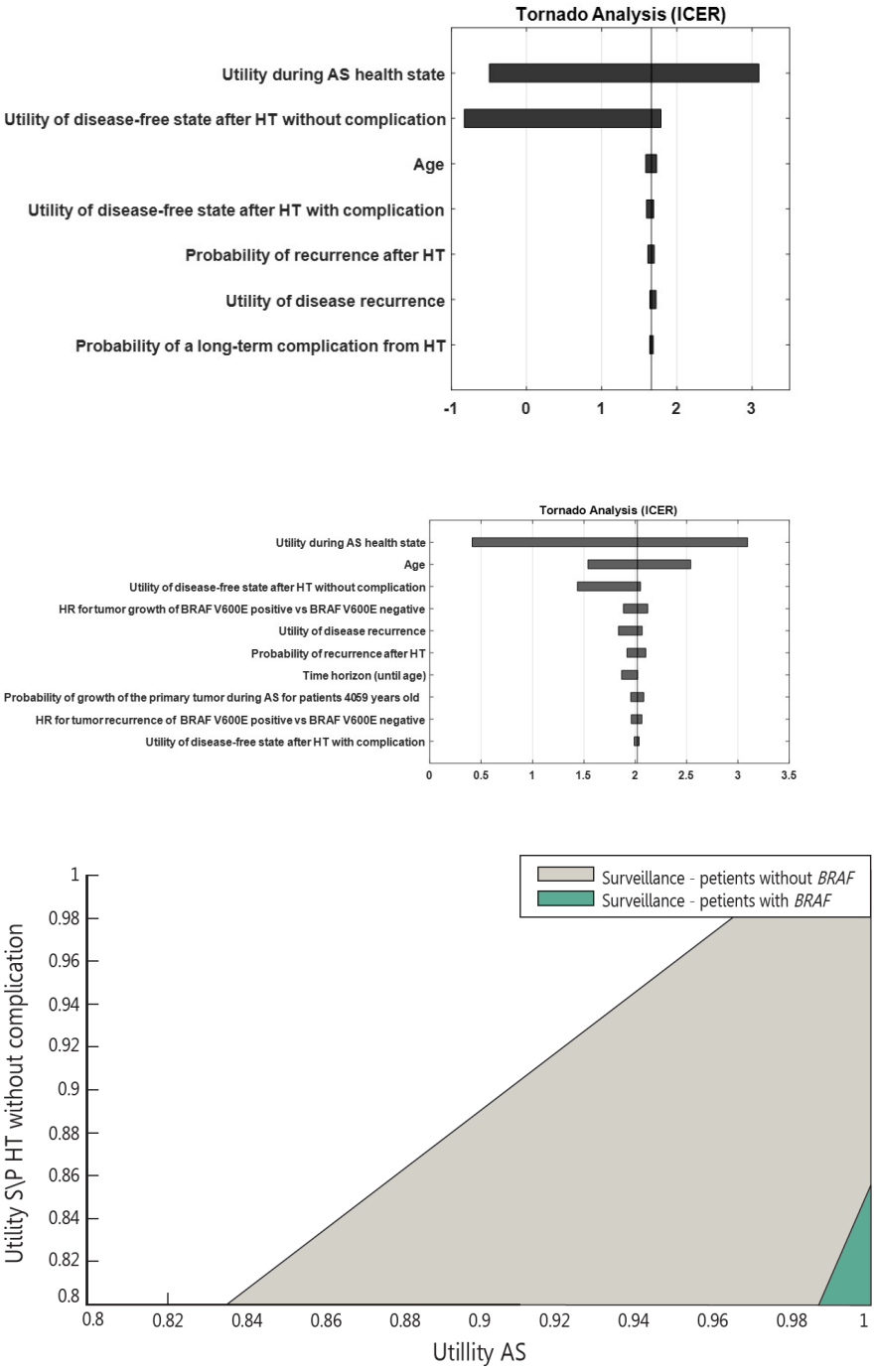

Figure 4: The preferred treatment by two-way sensitivity analysis of the utility variables . The

grey area highlights the range within the result which would differ according to the genetic status: active surveillance for$BRAF^{V600E}$negative and surgery for $BRAF^{V600E}$ positive.

AS: active surveillance; HT: hemithyroidectomy.

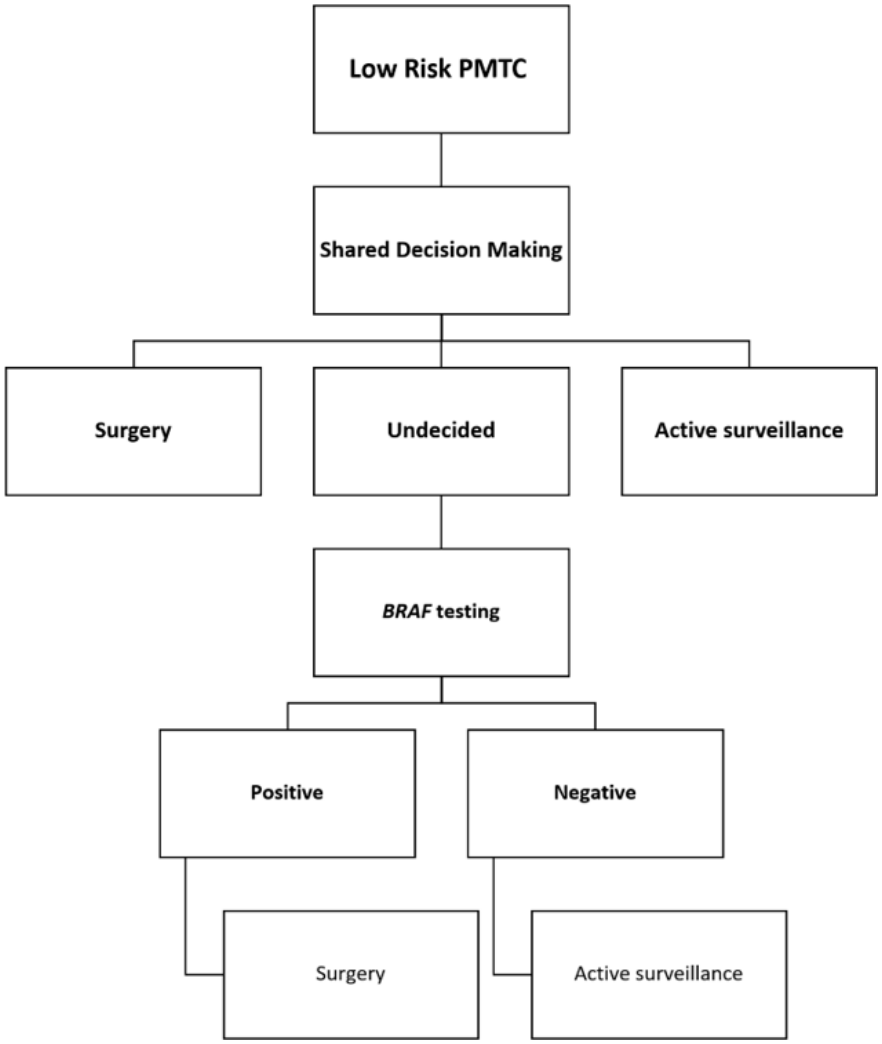

Figure 5: Suggestion for managemental algorithm integrating the patient's preference and the genetic status. In the case of lrPTMC (as defined in the ATA guidelines) a shared decision making is required, including a discussion between the patient and the physician, in order to inform the patient regarding the possible strategies and explore his/her preferred approach, which represents the utility he would assign to each strategy. That may include evaluating factors according to his/her perception, general medical state, and familial/social support. If there is no clear preference for one of the strategies,$BRAF^{\text{V600E}}$ testing would be recommended.

*Tables***Table 1.** Prevalence outcomes per strategy approach

DESCRIPTION	VALUE	LO
Probabilities	Probabilities	Pr

DESCRIPTION	VALUE	LO
HR for tumor growth of $BRAF^{V600E}$ positive vs. $BRAF^{V600E}$ negative	3.55	3
HR for tumor recurrence of $BRAF^{V600E}$ positive vs. $BRAF^{V600E}$ negative	3.55	3
Probability of a long-term complication from HT	0.0154	0.0
Probability of growth of the primary tumor during AS for patients aged 40–59 years old	0.0091	0.0
Probability of growth of the primary tumor during AS for patients more than 60 years old	0.004	0.0
Probability of loco-regional disease during AS for patients aged 40–59 years old	0.0023	0.0
Probability of loco-regional disease during AS for patients more than 60 years old	0.00050	0.0
Probability of recurrence after HT	0.00400	0.0
Model structure variables	Model structure variables	Mo
Age	40	35
Discount rate	0	0
Time horizon	100	90
Utilities values	Utilities values	Ut
Utility during AS health state	0.88	0.8
Utility of disease recurrence	0.54	0.5
Utility of disease-free state after HT with complication	0.63	0.5
Utility of disease-free state after HT without complication	0.99	0.8

HR – hazard ratio; HT – hemithyroidectomy; AS – active surveillance