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# Cost-utility analysis of rhTSH for differentiated thyroid carcinoma from a societal perspective

## *Análise de custo-utilidade de TSH recombinante para carcinoma diferenciado de tireoide na perspectiva da sociedade*

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**ABSTRACT**

**Objective:** The treatment of individuals with differentiated thyroid carcinoma (DTC) includes thyroidectomy followed by radioiodine ($^{131}$I) ablation. For treatment effectiveness, elevated TSH levels are essential, which can be achieved through thyroid hormone withdrawal for 4-6 weeks after thyroidectomy. However, considering the limitations of withdrawal, the use of recombinant human TSH (rhTSH) could be an alternative. This study aims to evaluate whether rhTSH is cost-effective compared to the induction of endogenous hypothyroidism (IHE) by levothyroxine withdrawal, from the societal perspective. **Methods:** A cost-utility analysis was conducted following the Brazilian Ministry of Health's guidelines, using a Markov model with four health states (pre-ablation, ablation, post-ablation, and recovered). A 17-week time horizon (weekly cycles) was adopted from the societal perspective, including direct and indirect costs. Effectiveness was measured in quality-adjusted life years (QALYs). Probabilistic and deterministic sensitivity analyses were also performed. **Results:** The results showed that rhTSH treatment provides greater clinical benefit (0.2687 vs. 0.2602 QALYs) at an incremental cost (R$ 4,762 vs. R$ 4,135), with an incremental cost-utility ratio (ICUR) of R$ 73,662/QALY gained. The most impactful factors were the cost of rhTSH, lost workdays, and utility values. **Conclusion:** The findings suggest that rhTSH offers greater clinical benefits, spite of additional costs and could be a cost-effective alternative depending on the willingness-to--pay threshold for society's perspective. Brazil did not recommend a willingness-to-pay threshold for this perspective and if it coincided with the threshold adopted for the SUS, rhTSH would be cost-effective for a threshold of R$120,000/QALY gained.

**Keywords:** Thyroid Neoplasms; Thyrotropin Alfa; Cost-Effectiveness Analysis; Quality--Adjusted Life Years

**RESUMO**

**Objetivo:** O tratamento de indivíduos com carcinoma diferenciado de tireoide (CDT) inclui a tireoidectomia, seguida pela ablação com radioiodo ($^{131}$I). Para a eficácia, é fundamental que os níveis de TSH estejam elevados, podendo ser alcançado pela interrupção do hormônio tireoidiano por 4-6 semanas após tireoidectomia. Porém, considerando as limitações da interrupção, o uso de TSH humano recombinante (rhTSH) seria uma alternativa. Este trabalho avalia se rhTSH é custo-efetivo comparado à indução de hipotireoidismo endógeno, sob a perspectiva da sociedade. **Métodos**: Foi realizada uma análise de custo-utilidade utilizando modelo de Markov com quatro estados de saúde (pré-ablação, ablação, pós-ablação e recuperado), para horizonte temporal de 17 semanas (ciclos semanais), incluindo custos médicos diretos e custos indiretos. A efetividade foi mensurada em anos de vida ajustado pela qualidade (QALY). Também foram realizadas análises de sensibilidade probabilística e determinística. **Resultados**: Os resultados indicaram que o tratamento com rhTSH oferece maior benefício clínico (0,2687 vs 0,2602 QALYs) a um custo incremental (R$626,50), com razão de custo-utilidade incremental (RCUI) de R$ 73.662/QALY ganho. Os fatores mais impactantes foram o preço do rhTSH, dias de trabalho perdidos e utilidade. **Conclusão**: Conclui-se que o rhTSH oferece maiores benefícios clínicos, apesar dos custos adicionais, e pode ser uma alternativa custo-efetiva dependendo do limite de disposição a pagar para a perspectiva da sociedade. O Brasil não recomendou um limite de disposição a pagar para essa perspectiva e, se coincidisse com o limite adotado para o SUS, o rhTSH seria custo-efetivo para um limite de R$ 120.000/QALY ganho.

**Palavras-chave:** Neoplasias da Glândula Tireoide; Tirotropina Alfa; Análise de Custo-Efetividade; Anos de Vida Ajustados por Qualidade de Vida

## Introduction

Differentiated thyroid carcinoma (DTC) originates from the follicular or papillary cells of the thyroid, that play the role of producing and releasing hormones. DTC accounts for 90% of thyroid cancer cases, being the most prevalent endocrine malignant neoplasm worldwide.[1]

In recent years, although the worldwide incidence of DTC has increased, ranging from 1.2 to 2.6 cases per 100,000 men and from 2.0 to 3.8 cases per 100,000 women annually, patient survival remains high, especially when diagnosis and treatment are carried out early,[1,2] with annual mortality rate is 0.5/100,000 in men and women.[3-5]

The initial treatment of DTC is thyroidectomy, which involves the total or subtotal removal of the thyroid gland, depending on the extent of the tumor. After surgery, depending on the risk classification and the presence of residual tissue or metastasis, radioablation with $^{131}I$ (radiodine), aiming to destroy any remaining thyroid cells and reduce the risk of recurrence. The combination of these therapies offers a favorable prognosis, with high rates of survival and control of the disease, especially when performed early and adequately.[6]

To optimize radioiodine uptake, it is necessary to obtain elevated TSH levels, which can be achieved by temporarily stopping thyroid hormone replacement. However, this conduct can lead to the development of hypothyroidism, which impairs the quality of life of patients. In this context, recombinant human thyrotropin (rhTSH) emerges as an effective option, allowing thyroid hormone replacement and minimizing the adverse effects of the procedure that has a significant impact on absenteeism.[6-8] Thus, this study was conducted to determine whether rhTSH is cost-effective compared to the induction of endogenous hypothyroidism by levothyroxine suspension, from the perspective of society. The adoption of this perspective is justified by the fact that one of the main benefits linked to the use of rhTSH is the reduction of indirect costs, especially those resulting from absenteeism, which are not contemplated by the perspective of the Unified Health System (SUS). Thus, the approach from the perspective of society makes it possible to estimate the economic impact of technology in a more comprehensive way, incorporating both direct medical and indirect costs.

## Methods

The economic analysis was carried out according to the recommendations of the Methodological Guidelines for Economic Evaluation of the Ministry of Health (MS).

The target population for this analysis was adults diagnosed with DTC who require the use of radioiodine. The perspective of society was adopted, considering that the main objective of rhTSH is to reduce the impairment in quality of life and, consequently, absenteeism.

For this analysis, rhTSH (alpha-thyrotropin) was considered as an intervention. This is indicated for use as an adjunct treatment for radioiodine ablation of remaining thyroid tissues in patients who have undergone total or subtotal thyroidectomy for well-differentiated thyroid cancer.[9] The comparator consists of the interruption of the use of levothyroxine, inducing endogenous hypothyroidism (causing physiological increase in TSH).[10]

The time horizon established for the model was 17 weeks, considering cycles with weekly duration. The choice was established according to identified clinical trials,[11-20] that evidenced the short-term benefit (1 month after ablation) of the evaluated technology and in accordance with other studies of economic evaluation in the literature that demonstrated that this period is sufficient to capture the differences in resources used and associated costs between the 2 arms of the model.[21-25] In addition, no discount rate was applied for costs and outcomes, as recommended by the MH Methodological Guidelines for Physical Health for short-term studies.[26]

### *Model*

A Markov model was developed with four health states in order to capture the benefits, consequences and costs from the beginning of thyroidectomy treatment to the patient's complete recovery (after 17 weeks).

The health conditions covered were: (1) pre-ablation, (2) ablation, (3) post-ablation, and (4) recovery (Figure 1). The (1) **Pre-ablation** state refers to the phase in which the patient undergoes a successful thyroidectomy and prepares for ablation. The duration of this state can vary from one week (for the intervention) to four weeks (mean identified for the comparator in the literature studies).[21-25] In state (2) **Ablation**, the patient undergoes the radioiodine ablation procedure, lasting one week for both groups. The (3) **Post-ablation** status represents the recovery period in which the utility weights have not yet reached the level of complete recovery, reflecting a gradual recovery of the patient over eight weeks. Finally, the (4) **Recovered status** corresponds to the phase in which the patient has already fully recovered from thyroidectomy and ablation procedures. It is important to note that the model does not allow patients to return to their previous health status.

Furthermore, for both groups evaluated (rhTSH or levothyroxine suspension), It was assumed that thyroidectomy was successful, since clinical studies in the literature [11,14,15,17,18,20] indicated a success rate greater than 90% and did not observe significant differences between the technologies evaluated for this outcome.

The result is presented as the incremental cost-effectiveness ratio (RCEI) calculated by the difference between the costs and outcomes of the interventions (incremental actuals per year of life adjusted for incremental quality - R$/QALY).

### *Outcomes*

The outcome used to measure effectiveness in the model was the number of quality-adjusted life years (QALY). As no national studies were identified that provided specific utility data for DTC, utility estimates for each model cycle were drawn from a meta-analysis published by the *National Institute for Health and Care Excellence* (NICE).[23] In this analysis, the agency converted data obtained through the *Medical Outcome Study Short Form 36* (SF-36) into utility weights.

Additionally, the average reported utility for the Brazilian population between 40 and 44 years of age is $0.817 \pm 0.179$[27], a value lower than that observed in the meta-analysis conducted by NICE[23] for patients with DTC. To adjust for this discrepancy, the utility value was recalibrated considering the EQ-5D-3L health utility score for the English population[28] and adjusted for the Brazilian population according to the calculation presented in appendix 2 of the material published by the Ministry of Health[29] (multiplier factor = utility of the Brazilian population divided by the utility of the general population of the country of origin of the cohort for which the utility of health status was measured). The utilities adopted in the model are presented in Figure 2.

### *Costs*

For the analysis, direct medical costs and indirect costs were considered. The direct costs included hospital and outpatient expenses, including procedures, exams and patient monitoring, according to the guidelines of the PCDT of DTC.[10] The indirect cost included referred to the loss of productivity, measured by absenteeism, that is, absence from work due to health problems related to the disease or treatment with rhTSH and levothyroxine discontinuation. Further details of the costs included are presented in Table 1. All values were obtained in reais (BRL, R$) and reflect February 2024 prices, without conversion to other currencies.

**Figure 1.** Conceptual model of economic evaluation considering health states.

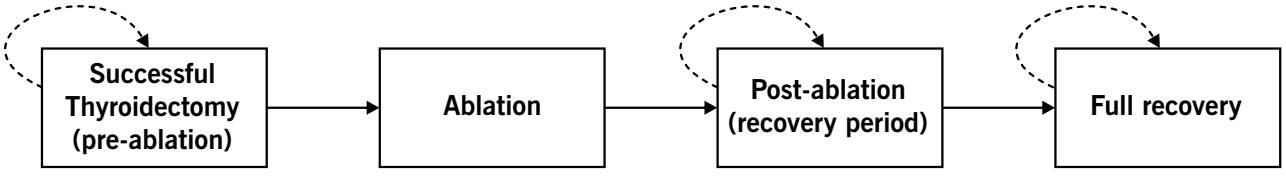
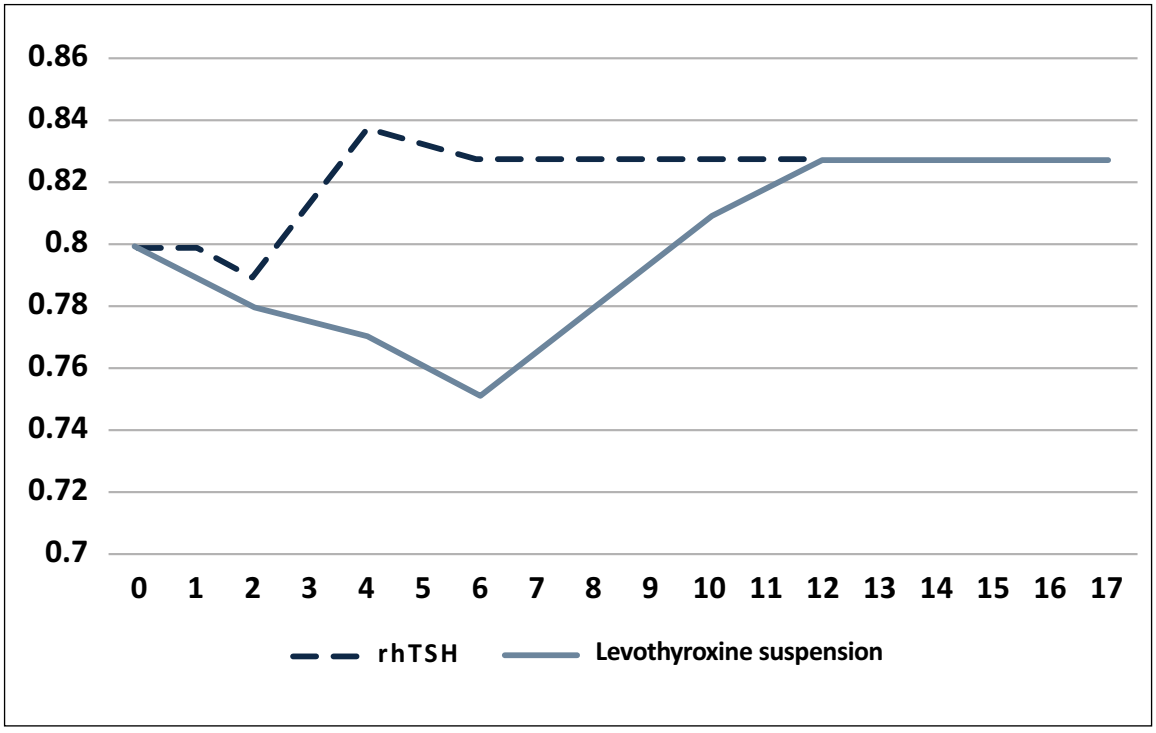


**Figure 2.** Utility values used in the model.




Source: Adapted from *National Institute for Health and Care Excellence* (NICE) [23].

### *Sensitivity analysis*

Probabilistic sensitivity (PSA) and univariate deterministic (tornado diagram) analyses were performed). In the PSA, 1,000 simulations were conducted, simultaneously varying all parameters according to statistical functions widely accepted in the literature: beta distribution for variables with values between 0 and 1 (such as proportion, utility parameters) and gamma distribution for variables with values from 0 to infinity (such as costs, days of lost work). The results were presented in scatter plots in incremental cost-effectiveness plans and in cost-effectiveness acceptability curves (CEAC), accompanied by descriptive analysis. Univariate deterministic analysis was presented by tornado diagram, in which the variation of each parameter was defined based on data available in the literature; in the absence of these, a standard variation of ±20% was applied. For costs based on the table of the Management System of the Table of Procedures, Medicines - SIGTAP, the values were multiplied by the correction factor of 2.8.[30]

### *Assumptions and limitations*

Some premises and limitations inherent to the construction of the economic model should be highlighted. First, due to the scarcity of national data, some parameters were obtained from international studies, which may not fully reflect the reality of Brazil, introducing uncertainties to the model. To minimize the impact of this limitation, adjustments were performed when possible and sensitivity analyses were performed to assess the robustness of the results in the face of variations in these data.

The length of stay in each stage of the model was defined based on the means reported in the studies used. Direct costs were defined based on the PCDT for DTC, but do not necessarily reflect the way clinical management is conducted in daily practice, and there may be variations in reality. While these approaches standardize the model, it is recognized that they may not capture individual patient variability; therefore, sensitivity analyses were conducted to explore the effect of different durations on the results.

**Table 1.** Direct and indirect costs included in the economic analysis

| Resource | Amount used* (in R$) | Quantity rhTSH | Quantity - Induction of endogenous hypothyroidism (i.e., LT suspension) | Variation (minimum -maximum) | Source |
|---|---|---|---|---|---|
| | **Pre-Ablation** | | | | |
| Total thyroidectomy | 451.37 | 1 | 1 | R$ 451.37- R$ 1,263.85 | SIGTAP/DATASUS (04.02.01.004-3) |
| Thyrostimulating hormone (TSH) dosage | 8.96 | 1 | 1 | R$ 8.96- R$ 25.09 | SIGTAP/DATASUS (02.02.06.025-0) |
| Free Thyroxine Dosage (T4 Free) | 11.60 | 1 | 1 | R$ 11.60 - R$ 32.48 | SIGTAP/DATASUS (02.02.06.038-1) |
| Thyroglobulin Antibody Dosage | 17.16 | 1 | 1 | R$ 17.16- R$ 48,05 | SIGTAP/DATASUS (02.02.03.062-8) |
| Conventional consultation | 10.00 | 1 | 1 + Consultations related to the management of manifestations of hypothyroidism[1] | R$ 10.00- R$ 28.00 | SIGTAP/DATASUS (03.01.01.007-2) |
| hrTSH administration | 0.00 | 2[2] | ---- | ----- | SIGTAP/DATASUS (03.01.10-020-9) |
| rhTSH - Alphathyrotropin | 1,821.95 | 2[2] | ---- | R$ 1,366.46- R$ 2,277.44 | BPS - Lowest Price |
| | **Ablation** | | | | |
| T4 therapy - Levothyroxine per day | R$ 0.07[3] | 1 100 mg/day tablet | ---- | 0.05-0.08 | BPS - Lowest Price |
| DTC iodotherapy (30 mCi) - Ambulatory | R$ 443.79 | Proportion of patients who used: 15.3% [4] | Proportion of patients who used: 15.3% [4] | R$ 443.79- R$ 1,242.61 | SIGTAP/DATASUS - SIA (03.04.09.005-0) |
| CDT iodine therapy (50 mCi) - Outpatient | R$ 614.70 | Proportion of patients who used: 18.9%[4] | Proportion of patients who used: 18.9%[4] | R$ 614.70- R$ 1,721.16 | SIGTAP/DATASUS - SIA (03.04.09.006-9) |
| CDT Iodine Therapy (100 mCi) - Hospital | R$ 1,071.90 | Proportion of patients who used: 65,9%[4] | Proportion of patients who used: 65,9%[4] | R$ 1,071.90- R$ 3,001.32 | SIGTAP/DATASUS - SIH (03.04.09.002-6) |
| Hospital admission for administration of CDT iodine therapy (100 mCi) | R$ 976.62 | Average daily rates: 1.11 | Average daily rates: 1,11 | R$ 976.62- 1,220.77 | DATASUS - SIH |
| Whole field scanning with radioiodine | R$ 338.70 | 1 | 1 | R$ 338.70- R$ 948.36 | SIGTAP/DATASUS (02.08.03.004-2) |
| Thyrostimulating hormone (TSH) dosage | 8.96 | 1 | 1 | R$ 8.96- R$ 25.09 | SIGTAP/DATASUS (02.02.06.025-0) |
| Free Thyroxine Dosage (T4 Free) | 11.60 | 1 | 1 | R$ 11.60 - R$ 32.48 | SIGTAP/DATASUS (02.02.06.038-1) - |
| Conventional consultation | R$ 10.00 | 1 | 1 | R$ 10.00-R$ 28.00 | SIGTAP/DATASUS (03.01.01.007-2) |
| | **Post-Ablation** | | | | |
| T4 therapy - Levothyroxine per day | R$ 0.07[3] | 1 tablet of 100 mg/day | Dose of 2.6 μg/kg/day for 7 days[5] and then the maintenance dose (100mg/ day) was considered | R$ 0.05- R$ 0.08 | BPS - weighted average |
| Whole field scanning with radioiodine | R$ 338.70 | 1 | 1 | R$ 338.70- R$ 948.36 | SIGTAP/DATASUS (02.08.03.004-2) |
| Thyrostimulating hormone (TSH) dosage | 34.11 | 1 | 1 | R$ 8.96- R$ 25.09 | SIGTAP/DATASUS (02.02.06.025-0) |

| Resource | Amount used* (in R$) | Quantity rhTSH | Quantity - Induction of endogenous hypothyroidism (i.e., LT suspension) | Variation (minimum -maximum) | Source |
|---|---|---|---|---|---|
| Free Thyroxine Dosage (T4 Free) | R$ 11.60 | 1 | 1 | R$ 11.60 - R$ 32.48 | SIGTAP/DATASUS (02.02.06.038-1) |
| Conventional consultation | R$ 10.00 | 1 | 1 | R$ 10.00- R$ 28.00 | SIGTAP/DATASUS (03.01.01.007-2) |
| | **Recovered** | | | | |
| T4 therapy - Levothyroxine per day | 0.05-0.08 | 1 tablet of 100 mg/day | 1 tablet of 100 mg/day | R$ 0.05- R$ 0.08 | BPS - Weighted average |
| | **Overhead** | | | | |
| Days of work - Absenteeism | R$ 144.95 | 3.1 ± 11.5 days [6] | 11.2 ± 19.1 [6] | R$ 130.46- R$ 159.45 | Usual real income (March, April and May 2023)/working days of the month - Borget et al, 2007 [31]. |

**Legend**: BPS: Health Price Bank; DTC: differentiated thyroid carcinoma; CMED: Chamber of Regulation of the Drug Market; DATASUS: Department of Informatics of the Unified Health System (DATASUS); PMVG: Maximum Sale Price to the Government, SIA: Outpatient Health Information System; SIH: Hospital Information System.

**Note:** *Accessed on February 14, 2024.

[1] It was assumed that in addition to the conventional consultation, additional consultations were carried out due to the absence of levothyroxine treatment, that is, due to the appearance of manifestations related to hypothyroidism. The proportion of additional consultations was established according to the NICE material (2022)[23]: 18% required an additional consultation, and 20% required 2 additional consultations.

[2] The recommended dosage of thyrotropin alfa is two doses of 0.9 mg administered at 24-hour intervals by intramuscular injection into the gluteal region (0.9 mg IM every 24 hours, for 2 days).[9]

[3] Value per day established by the lowest price found for the presentations of 25, 50, 75, 88, 100, 112, 125, 175, 200 mg and considering 100 mg the daily maintenance dose of the drug (range recommended in the package insert from 75 mg to 125 mg).[36]

[4] Established according to the proportion that each of the procedures found in SIH-DATASUS - 2022 and according to the study conducted by Schwengber et al, 2020.[37]

[5] A dose of 2.6 $\mu$g/kg/day for 7 days was considered, as recommended in the package insert.[36] In addition, the average weight of 74.1 kg was assumed for the calculation, according to the average weight for the age group of 40 to 59 years [38,39] (age group most affected by DTC).

As for indirect costs, the model considered only absenteeism, due to the scarcity of information on other economic impacts, such as informal care costs or loss of additional productivity. The inclusion of these costs without robust evidence could alter the results and potentially weaken the model if inadequately estimated.

Finally, the utility values initially reported in the studies were measured by the SF-36 and later recalibrated to the EQ-5D-3L, allowing the incorporation of these data into the model. Although this conversion is a recognized practice and similar to that adopted by NICE, it represents a possible limitation, since it may introduce small discrepancies in the final estimate of QALYs.

## Results

Treatment with rhTSH was associated with a higher clinical benefit and a higher total cost compared to the induction of endogenous hypothyroidism (i.e., levothyroxine suspension). The incremental cost-effectiveness ratio (RCEI) was R$ 73,661.68 per QALY gained, from the perspective of society, as shown in Table 2.

In addition, it was observed an agreement between the results of the probabilistic sensitivity analysis with the results of the base scenario, since the results of the simulations are in their entirety in the upper right quadrant, confirming that rhTSH has greater clinical benefit and incremental cost (Figure 3). Regarding the acceptability curve, a willingness to pay of R$ 40 thousand/QALY earned, there is a 0% probability that rhTSH is the most cost-effective option, whereas for a threshold of R$ 120 thousand/QALY gained, there is a 100% probability that rhTSH is the most cost-effective option (Figure 4).

Additionally, the deterministic sensitivity analysis demonstrated that the price of the technology and lost working days are the parameters that most impact the economic model, as shown in Figure 5.

**Table 2.** Costs, outcomes, and RCEI per patient for the cost-utility analysis.

| Strategy | Effectiveness (QALY) | Cost (R$) | RCUI |
|---|---|---|---|
| rhTSH | 0,2687 | R$ 4.761,98 | **R$ 73.661,68** |
| Induction of endogenous hypothyroidism (i.e., levothyroxine suspension) | 0,2602 | R$ 4.135,48 | |
| Difference | 0,0085 | R$ 626,50 | |

**Legend**: QALY, life year adjusted by quality; RCEI, incremental cost-utility ratio.

**Figure 3**. Scatter plot of probabilistic sensitivity analysis (outcome: quality-adjusted life years - QALY) from a societal perspective.

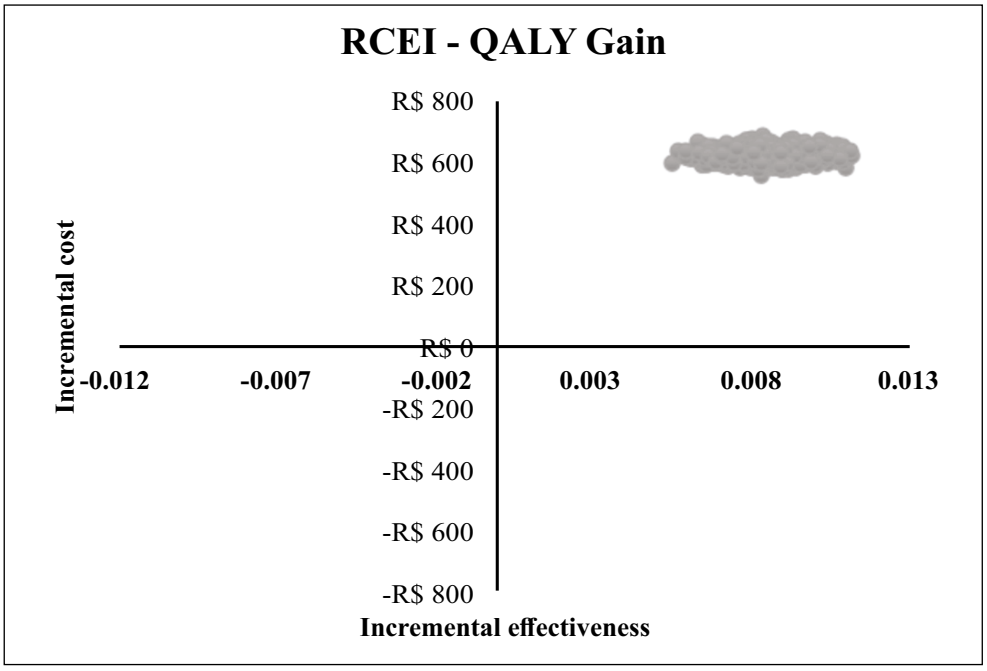



**Figure 4**. Cost-effectiveness acceptability curve (outcome: quality-adjusted life years - QALY) from the societal perspective.

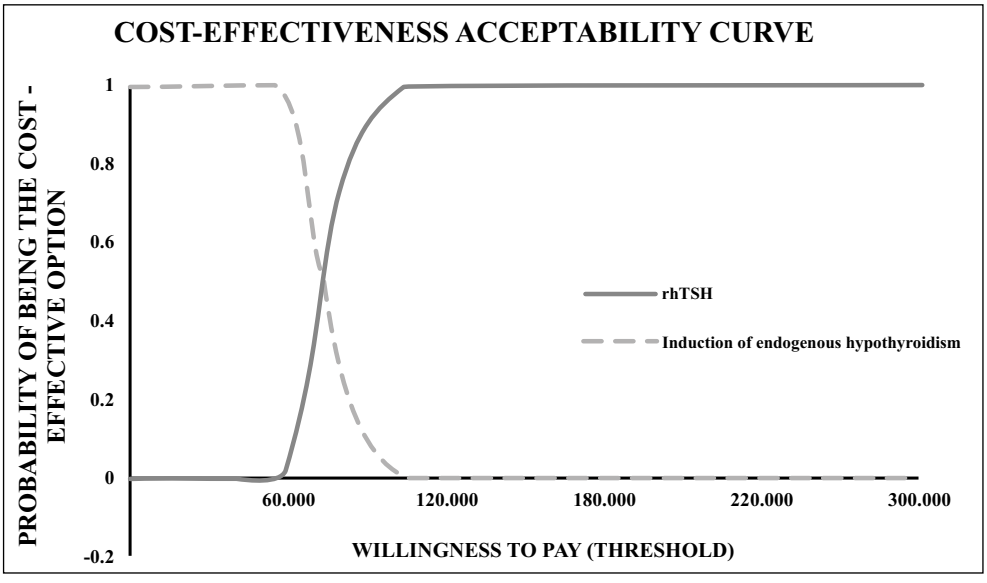
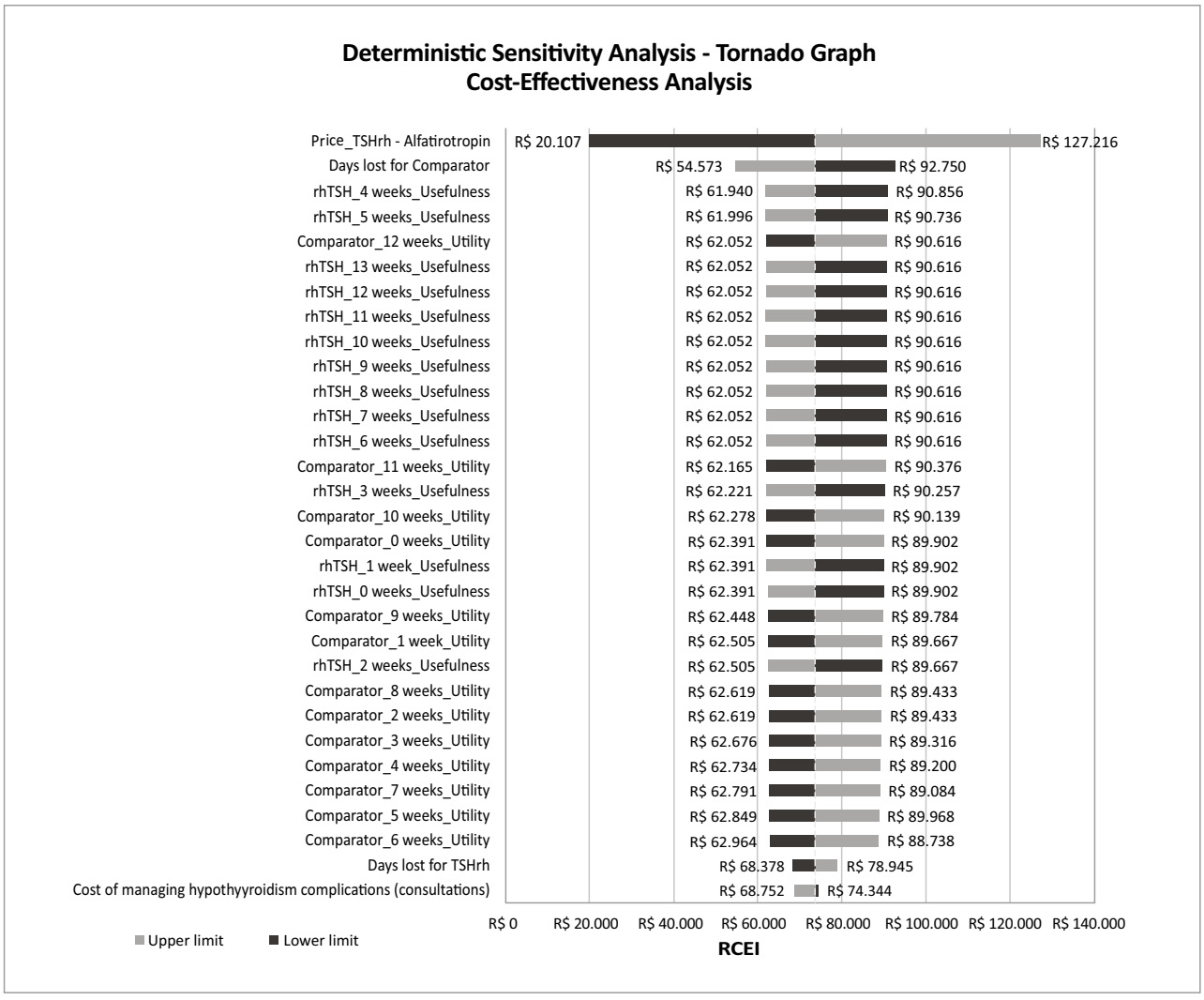


**Figure 5.** Tornado diagram (outcome: QALY gain) from the perspective of society.




## Discussion

Initial treatment with thyroidectomy, followed or not by radioiodine, has high rates of therapeutic success and disease control. Radioiodine ablation aims to destroy remaining thyroid tissues, reducing the risk of recurrence. However, the induction of endogenous hypothyroidism, resulting from levothyroxine suspension, is associated with a significant decrease in the quality of life of patients. In this context, rhTSH emerges as an effective alternative, allowing the optimization of radioiodine uptake without the need to induce symptoms of hypothyroidism. The economic analysis based on a Markov model revealed that, with an incremental cost to society of R$ 626.50, the use of rhTSH provides additional health benefits, represented by an incremental gain of 0.0085 QALY in preparation for radioiodine ablation.

In addition to health gains, there are significant social and economic benefits related to productivity. Studies with paired data from patients submitted to the two stimulation methods pointed to statistically significant differences in absenteeism between the groups. For example, 15.6% of patients who developed hypothyroidism reported a marked reduction in the ability to perform normal activities, compared to 8.6% in the group that used rhTSH.[31] This difference supported the application of a 50% differential in the data of Luster et al [32] and in the current model.

These findings are in line with international studies that evaluated interventions from the perspective of society in Canada[33] ($13,391 per QALY earned), United States of America ($52,554 per QALY earned)[24] and Korea (₩26,697,361 per QALY earned).[21] Also, in certain contexts there was a dominance of rhTSH, such as in Spanish hospitals (savings of -£614.16 and 0.048 QALY gained)[22] and in Germany.[32]

A strong point of this study is the adoption of the societal perspective, which allows you to consider both direct and indirect costs, offering a broader view of the economic impact of interventions. This approach is still little explored in national research, reinforcing the relevance of the study to support public health decisions. However, there are limits associated with the application of this perspective in the national scenario, especially, due to the absence of an official cost-effectiveness threshold outside the SUS, which makes it difficult to interpret the results in contexts other than the public health system. As a reference, NICE, an agency equivalent to Conitec, recommends the incorporation of indirect costs in the analyses and does not have different thresholds depending on the presence of these costs. Considering the same rationale, the threshold defined for the Unified Health System (SUS) for severe conditions such as cancer (i.e., R$ 120,000/QALY earned) and, therefore, this treatment would be considered cost-effective.[34] In addition, incorporating rhTSH may be more advantageous for specific subgroups, such as patients with cardiovascular comorbidities or clinical conditions that contraindicate the induction of hypothyroidism.[35]

As is inherent to economic models, some assumptions were adopted, which may limit the external validity of the analysis. The time of absenteeism used in the model was derived from an observational study conducted in France, which may limit its applicability to the Brazilian context. The absence of specific national data on DTCs resulted in the use of international estimates adjusted to the Brazilian reality, an accepted practice, but which adds uncertainties to the model. In addition, the indirect costs considered were restricted to absenteeism, without including other potential economic impacts, such as informal care costs, which were not sufficiently evidenced in the literature.

To strengthen the evidence base, future studies should focus on measuring the impact of absenteeism in Brazil, considering the specificities of the local labor and health system. Prospective research with representative samples is essential to provide more robust data that support economic models and guide public health decisions in the country.

## Conclusion

The study contributes to a better understanding of the cost-benefit relationship of using rhTSH in the treatment of DTC, highlighting its potential as a cost-effective alternative (depending on the threshold adopted), especially for patients who have a contraindication to the induction of endogenous hypothyroidism. The adoption of this technology can bring significant benefits in terms of quality of life and productivity, being especially relevant for perspectives seeking to balance clinical benefits with financial sustainability. However, further studies are still needed to confirm the validity and expand the applicability of the results in different population and economic contexts.

**Authors' contributions:**
MMF, HAO, RCL: Conceptualization. MMF, AFB: Data curation, formal analysis, research, methodology. MMF, LAO, RCL, HAO: Administration and planning. RCL, HAO: Oversight and validation. MMF, AFB, LAO: Redaction. HAO, RCL: Proofreading and editing.

**Conflict of interest**
The authors declare no conflicts of interest.

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**Declaration and availability of data**
The contents underlying the research text are contained in the manuscript.

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