# Cost-effectiveness of stereotactic body radiotherapy versus conventional radiotherapy for the treatment of surgically ineligible stage I non-small cell lung cancer in the Brazilian public health system

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## Summary

**Background** The Brazilian public health system does not pay for the use of Stereotactic body radiotherapy (SBRT) due to its costs and the absence of cost-effectiveness analysis showing its benefit. The present study aims to evaluate whether the SBRT is a more cost-effective strategy than the conventional fractionated radiotherapy (CFRT) for surgically ineligible stage I non-small cell lung cancer (NSCLC) in the Brazilian public health system.

**Methods** Adopting the perspective of the Brazilian Unified Healthcare System (SUS) as the payer, a Markov model with a lifetime horizon was built to delineate the health states for a cohort of 75-years-old men with medically inoperable NSCLC after treatment with SBRT or CFRT. Transition probabilities and health states utilities were adapted from the literature. Costs were based on the public health system reimbursement values and simulated in the private sector.

**Findings** The SBRT strategy results in more quality-adjusted life-year (QALYs) and costs with an incremental cost-effectiveness ratio (ICER) of R$ 164.86 (U$ 65.16) per QALY and R$ 105 (U$ 41.50) per life-year gained (LYG). This strategy was cost-effective, considering a willingness-to-pay of R$ 25,000 (U$ 9,881.42) per QALY. The net monetary benefit (NMB) was approximately twice higher. The outcomes were confirmed with 92% of accuracy in the probabilistic sensitivity analysis.

**Interpretation** Using a threshold of R$25,000 per QALY, SBRT was more cost-effective than CFRT for NSCLC in a public health system of an upper-middle-income country. SBRT generates higher NMB than CFRT, which could open the opportunity to incorporate new technologies.

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**Keywords:** Stereotactic body radiotherapy; Conventional fractionation; Surgically ineligible stage I non-small cell lung cancer; Radiotherapy; Cost-effectiveness

## Introduction

In Brazil, lung cancer is the second most incident cancer in men and the fourth in women. It is the leading cause of cancer-related deaths worldwide,[1] most related to tobacco.[2] In addition, the prevalence of non-small-cell lung cancer (NSCLC) in never-smoking is increasing.[3]

Surgical resection is the standard of care for early-stage NSCLC.[4] However, many patients have several comorbidities, and surgery is not indicated for them.[5,6] Radiotherapy (RT) is a convenient, safe, and potentially

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## Research in context

*Evidence before this study*

There are cost-effectiveness studies of Stereotactic body radiotherapy (SBRT) in the treatment of non-small cell lung cancer (NSCLC) providing evidence that SBRT is a cost-effective option compared to conventional radiotherapy, radiotherapy ablation and best supportive care for medically inoperable early-stage NSCLC. However, there are no studies evaluating the cost-effectiveness of SBRT versus conventional fractionated radiotherapy (CFRT) for NSCLC assessing quality-adjusted life-years (QALYs) as outcomes, the present study is the first one. Besides, the cost-effectiveness of SBRT versus CFRT for NSCLC has not been investigated in upper-middle-income countries. The Brazilian public health system does not pay for the use of SBRT due to its costs and the absence of a cost-effectiveness analysis showing its benefit.

*Added value of this study*

To the best of our knowledge, this is the first study to evaluate whether SBRT is cost-effective when compared to CFRT for treating medically inoperable early-NSCLC in an upper-middle-income country. Adopting the perspective of the Brazilian Unified Healthcare System (SUS) as the payer, a Markov model with a lifetime horizon was built to delineate the health states for a cohort of 75-years-old men with medically inoperable NSCLC after treatment with SBRT or CFRT.

*Implications of all the available evidence*

Like many other upper-middle-income countries, Brazil has a limited number of linear accelerators (LINAC) equipped with the technology to perform SBRT. In the country, public and private insurance do not cover or pay for the use of SBRT. The principal argument against the coverage and payment for the SBRT is the costs and the absence of cost-effectiveness analysis showing its benefit. The incremental cost-effectiveness ratio was below the willingness to pay threshold, which strongly supports the incorporation of the intervention. These results might be reproducible in other upper-middle-income countries.

curative option for these patients.[7,8] Traditionally, a long course of CFRT over 4–6 weeks (20 or more fractions) is delivered with a curative intention. However, the outcomes of disease control of CFRT for early-stage NSCLC are poor.[9]

Recent technological advances such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), gated radiotherapy, and tracking tumour movement have allowed safely employment of ablative radiation doses in lung lesions.[10] This technique, named stereotactic body radiotherapy (SBRT), is typically given as a hypofractionated course from one to five fractions over 1–2 weeks.[7,11] Since 2000, the use of SBRT for treating medically inoperable stage I NSCLC has increased rapidly.[12] In initial studies, SBRT shows a high local tumour control and good survival.[13,14] For instance, in the RTOG 0236, a prospective single-arm study, SBRT for early inoperable NSCLC patients, produced 90% of the primary tumour control in 3 years.[15] The impressive outcome obtained with SBRT drew attention to performing a randomized clinical trial comparing head-to-head SBRT with the conventional schedule. In the Chisel trial, patients with early NSCLC (T1-2aN0M0) unfit for surgery were randomized to receive SBRT with a dose of 48 Gy (4 fx) - 54 Gy (3fx) or CFRT with 50 Gy (20fx) or 66 Gy (33fx).[7] The SBRT arm significantly improved the 2-year local control (89% vs. 65%) and overall survival rates (77% vs. 59%).[7]

Like many other upper-middle-income countries, Brazil has a limited number of linear accelerators (LINAC) to attend to the demand of cancer patients in the country. Many of the available LINACs in Brazil are considered obsolete by the manufacturers. Moreover, only 24,2% of the operational LINACs are equipped with technology to perform SBRT. In the country, public and private insurance health do not cover or pay for the use of SBRT.[16] The principal argument against the coverage and payment for the SBRT is the costs and the absence of cost-effectiveness analysis showing its benefit. The economic ambivalence around the SBRT has directly two severe consequences: first, it affects many patients who do not have access to the technology and its oncological benefits; second, radiotherapy facilities are restricted to optimizing the number of patients treated per radiotherapy machine to improve treatment accessibility.

Based on this scenario, the present work was designed to answer the question: Is SBRT a cost-effective strategy compared with CFRT from the perspective of the SUS as the payer in an upper-middle-income country?

## Methods

We developed a Markov model to assess whether SBRT is a more cost-effective strategy than CFRT for patients with surgically ineligible stage I (T1–T2aN0M0) NSCLC. Using the TreeAge Pro software (TreeAge® Healthcare Version 2021), the model estimates the costs and benefits, the latter expressed as quality-adjusted life-years (QALYs) and life-years gained (LYG). The software calculates the incremental cost-effectiveness ratio (ICER) by dividing the difference in lifetime costs by the difference in lifetime effects (QALYs) between the two strategies as follows: (Cost of Strategy A – Cost of Strategy B) / (Effect of Strategy A– Effect of Strategy B). This study is reported according to the CHEERS checklist (Table S1 - *Supplementary Material*).[17] To reflect the long-term consequences of the treatment of early NSCLC, the model had a 1-year cycle length and time

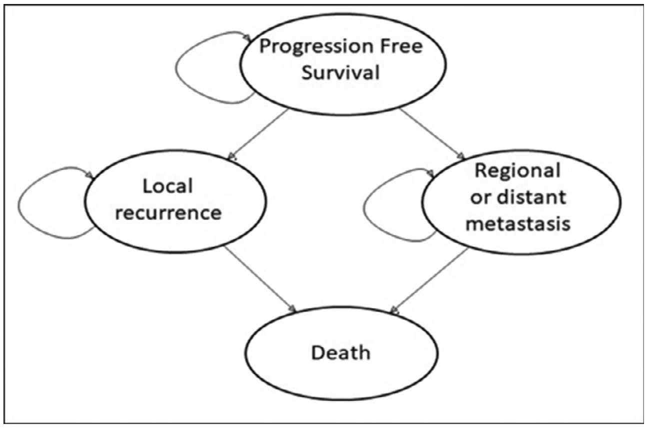


**Figure 1. Markov diagram**.

Markov diagram. We assumed that patients started in the state 'progression-free survival', i.e., with no evidence of disease or symptom like or similar to the radiation collateral effects. These patients could either stay there or move to the state 'local recurrence' or 'regional or distant metastasis'. In order to be more conservative, it was assumed that when patients had a local recurrence, they were salvaged with SBRT in both arms. Thus, patients in the 'local recurrence' state could either stay there or die (absorbing state). The patients that stayed in 'local recurrence state', were considered as patients that had a local recurrence but were treated, that is, they had the disease remission. Patients in "regional or distant metastasis' could either stay there or die. The transition probabilities from local recurrence or regional or distant metastasis to death were calculated based on published studies reporting patients' overall survival from these states.

horizon of 30 years (lifetime). The analysis was conducted from the perspective of the Brazilian Unified Healthcare System (SUS). In line with recommendations from the Brazilian guideline for economic evaluations, costs and effects were discounted at 5%.[18]

When entering the model, the target population was a cohort of 75-year-old men with surgically ineligible stage I NSCLC, representing the CHISEL trial's[7] cohort average age used as the bases for the transition probabilities calculation. According to Globocan, lung cancer in Brazil is most common in men older than 75 years.[19] Early-stage NSCLC currently represents a minority of all NSCLC diagnoses, but with ongoing improvement in treatment, it is a group with an increased likelihood of long-term disease control and survival.[20] Besides, elderly patients with early-stage NSCLC are a suitable population to evaluate SBRT cost-effectiveness once a significant proportion of this population is not optimal candidates for definitive surgical resection due to tumour characteristics, patient frailty, or comorbid status[20] being the use of SBRT considered an excellent alternative for these patients[21] including in Brazil.[22]

### Strategies for the comparison and model overview

The compared strategies were SBRT (54 Gy in three fractions of 18 Gy, or 48 Gy in four fractions of 12 Gy if the tumour was < 2 cm from the chest wall) and standard radiotherapy (66 Gy in 33 daily fractions of 2 Gy or 50 Gy in 20 daily fractions of 2.5 Gy, according to the institutional preference).[7]

The Markov model was chosen to be used as they are suitable for chronic diseases or situations where events are likely to recur over time.[23] The Markov model structure was based on interviews with two radiation oncologists and one oncologist. The Markov model structure comprises the states 'progression-free survival', 'local recurrence', 'regional or distant metastasis' and 'death' (absorbing state). We defined the Markov states based on health states that have similar costs and utilities. According to National Comprehensive Cancer Network (NCCN) guideline,[24] inoperable NSCLC patients with regional or distant recurrence that had prior radiotherapy should be treated with systemic therapy. Thus, we assumed that regional and distant metastasis could be grouped. The explanation regarding each health state is presented in Figure 1.

### Utilities

The utilities of 'Progression-free survival' and 'Local recurrence' were estimated using the study by Grutters et al.[25] which uses the EQ-5D to assess health-related quality of life (HRQoL) in survivors of non-small cell lung cancer (NSCLC). The utilities of 'Regional or distant metastasis' were estimated using the study by Chouaid et al.[26] which uses the EQ-5D to assess the utility in patients with advanced NSCLC (Table 1). An explanation of QALY and utility scores calculation is given in Methods 1 (*Supplementary material*).

### Costs

Cost data were expressed in Brazilian currency (Reais), as suggested by the Brazilian guideline for economic evaluations. The unit costs values for the

| Variable | Mean value | Source |
|---|---|---|
| *Probabilities* | | |
| SBRT | | |
| From PFS[a] to LR[b] | 0.17 | [7] |
| From PFS to RR[c] or DM[d] | 0.22 | [7] |
| CFRT | | |
| From PFS to LR | 0.43 | [7] |
| From PFS to RR or DM | 0.27 | [7] |
| SBRT or CFRT | | |
| From LR to Death | 0.61 | [29] |
| From RR or DM to Death | 0.81 | [30] |
| *Utility* | | |
| Progression-free survival | 0.77 | [25] |
| Local recurrence | 0.61 | [25] |
| Regional or Distant metastasis | 0.58 | [26] |
| *Costs (R$)* | | |
| SBRT_and_CFRT_initial_costs | 3563 | DATASUS Tabnet |
| Progression-free survival | 1566 | DATASUS Tabnet |
| Local recurrence | 2738 | DATASUS Tabnet |
| Regional or Distant metastasis | 8954 | DATASUS Tabnet |

***Table 1*: Inputs used in the Markov model and their sources: probabilities, utilities and costs.**

[a] PFS: Progression-free survival.
[b] RL: Local recurrence.
[c] RR: Regional recurrence.
[d] DM: Distant metastasis.

year 2021 were obtained from the official SUS database, namely the Table of Procedures, Medications and Ortheses, Prostheses, and Special Materials for the National Health System (DATASUS Tabnet). Resource use (e.g., the number of diagnostic exams and clinical procedures) was estimated based on recommendations from international guidelines, such as the NCCN guideline (NCCN, 2021), with minor adaptations for Brazilian reality made by two experienced radiation oncologists in the management of NSCLC. Annual costs were calculated for each Markov model health state. Tunnel states were implemented to attribute different annual costs per year per health state. The costs involved with each state are described as follows:

1. The 'Progression-free survival' health state includes costs of follow-up exams and consultations with doctors and paramedical staff (physiotherapists, i.e).
2. The 'Local recurrence' health state comprises the costs of the second course of radiotherapy, follow-up exams and consultations with doctors and paramedical staff.
3. The 'Regional or distant metastasis' health state includes costs of systemic therapy for lung cancer, follow-up exams and consultations with doctors and paramedical staff.

Table 1 summarizes the cost input data extracted from DATASUS Tabnet 2021.[27] To allow comparisons with other settings, conversion of the results presented in Brazilian real (R$) to United States dollar (US$) was performed by using a Purchasing Power Parities (PPP) rate, from OECD Data 2021.[28] Table S2 (*Supplementary Material*) provides detailed costs, contributing to understanding how the values of recurrences and rehabilitation were assessed.

## Probabilities

After a systematic search of the electronic databases, the study by Ball et al.[7] provides the transition probabilities from progression-free survival to local recurrence and progression-free survival to regional recurrence or distant metastasis. Ball et al.[7] was selected as it is the most recent and detailed phase III randomized clinical trial that compares SBRT and CFRT. Considering that SBRT has higher control rates, to be more conservative, we assumed that both arms had the local recurrence re-irradiated with SBRT. Thus, the probability of moving from local recurrence to death in both arms was estimated from a meta-analysis[29] which evaluates the SBRT in patients with local recurrence of lung cancer. We calculate the transition probabilities as time-dependent ones, considering the chance of changing from one health state to another depending on how long the patient stayed in the previous healthy state. Tunnel states were also used in these circumstances. The mean probabilities values are presented in Table 1. Table S3 (*Supplementary Material*) presents the probabilities values by year.

## Model validation and sensitivity analysis

To validate the model, we consulted experts on the adequacy of input data and the conceptual appropriateness of the model. For cross-model validation, we verified the extent to which other models for lung cancer came to different conclusions.[31] To characterize overall uncertainty in the outcome measures, we use Tornado as a deterministic sensitivity analysis.

To obtain low-cost values for the deterministic analyses, we reduced the base cost value by 40%. In Brazil, the private sector pays higher values than paid values in the public sector. Thus, we considered the values paid in the private sector as the high cost in the deterministic analysis. The values were extracted from a table used for the health insurance companies called the Brazilian Hierarchical Classification of Medical Procedures (CBHPM). Most of the values present in the CBHPM are more than 200% of the amounts paid by the public sector. Still, regarding the deterministic analyses, the probabilities and utilities varied by 15%, and the discount rate varied from 3,5% to 6%.

We also performed a probabilistic sensitivity analysis with Monte Carlo simulation with 10.000 simulations.

| Strategy | Cost (R$) | Incremental costs (R$) | QALYs | Incremental QALYs | LYG | Incremental LYG | ICER (R$) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Costs/QALY | Costs/LYG |
| CFRT | 12922.67 | | 2.00 | | 3.25 | | | |
| SBRT | 13020.26 | 97.58 | 2.59 | 0.59 | 4.17 | 0.92 | 164.86 | 105.94 |

***Table 2*: Base case results.**

We used a standard deviation of 15% for probabilities and 40% for utilities and costs. This method contributes to assessing how a simultaneous change of several variables affects the incremental cost-effectiveness ratio (ICER) values. Gamma distributions were used for cost parameters. Probabilities and utilities were considered to be beta-distributed.

### Role of the funding source

The funder did not have any role in the study design, data collection, data analysis, interpretation, or writing of the manuscript.

## Results

### Base-case analysis

The SBRT strategy costs R$ 13,020.26 (U$ 5,146.24) in the base-case scenario, resulting in an incremental cost of R$ 97.58 (U$ 38.33) compared with the CFRT strategy. Accordingly, men that were offered the SBRT strategy had an incremental gain of 0.59 QALYs and 0.92 LYG. The ICER for the base-case analysis was R$ 164.86 (U$ 65.16) per QALY and R$ 105 (U$ 41.50) per LYG. The baseline threshold for ICER for Brazil is yet to be defined, but following previous studies, we considered R$ 25,000 (U$ 9,881.42) per QALY.[32,33] Base-case results are described in Table 2 and Figure S1 (*Supplementary Material*).

### Sensitivity analysis

In the deterministic sensitivity analysis, the variables with the largest impact on the ICER were the cost of "local recurrence" treatment (which includes re-irradiation, follow-up exams and consultations), cost of "progression-free survival" (follow-up exams and consultations with doctors and other paramedical staff), cost of "regional or distant metastasis" and the probabilities of moving from regional or distant metastasis to death in SBRT and CFRT arms.

In a scenario where local recurrence treatment costs were based on CBHPM, the ICER decreased to R$ -10,107.23/QALY (U$ -3,994.95/QALY), once the probability of having a failure is higher for CFRT and, in this scenario, the cost to treat a failure would be more expensive. However, if the costs of progression-free survival were based on CBHPM, the ICER would also increase to R$ 7709.03/QALY (U$ 3,047.03/QALY), once it is expected that patients on the SBRT arm expend more time at this health state. Besides, if the costs of regional or distant failure increase to CBHPM values, the ICER would also increase to R$ 1937. 03 (U$ 765.61) per QALY.

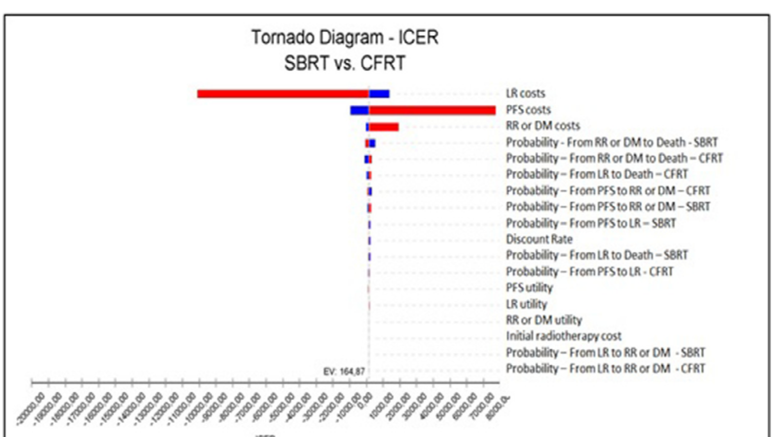


**Figure 2. Tornado Diagram of 1-Way Sensitivity Analysis**.

Blue: upper value; Red: lower value; LR: local recurrence; PFS: progression-free survival; RR: regional recurrence; DM: distant metastasis; X-axis: Incremental cost-effectiveness ratio (ICER): Cost (R$) per quality adjusted life year (QALY). Y-axis: Probability, cost and utility parameters in the model.

One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER for SBRT versus CFRT to the treatment of surgically ineligible stage I non-small cell lung cancer in the Brazilian public health system.

The cost-effectiveness ratio was also sensitive to the probabilities of moving from regional or distant metastasis to death in SBRT, if this probability were smaller, the ICER would decrease to R$-48,80 (U$ -18.97) per QALY, once it would improve the SBRT effectiveness. On the other hand, if the probability of moving from regional or distant metastasis to death in CFRT were higher, the ICER would increase to R$ 308,05 (U$ 121.73) per QALY because the CFRT strategy would be less expensive.

The Tornado diagram is presented in Figure 2 and indicates that for all intervals considered in the analysis the SBRT is considered cost-effective when compared to CFRT, considering a willingness to pay R$25,000 (U$ 9,881.42) per QALY. Table S4 (*Supplementary Material)* describes all the uncertainty intervals with the impact for each variable.

In the probabilistic sensitivity analysis, most of the 10.000 interactions are in the northeast quadrant, suggesting that the SBRT strategy is certainly more expensive and generates more QALYs (Figure 3). In addition, some interactions are in the southeast quadrant, indicating that SBRT might also be less costly and more effective.

The cost-effectiveness acceptability curve showed a probability of SBRT being cost-effective of 92,03% at a willingness to pay (WTP) of R$ 25,000/QALY (U$ 9,881.42/QALY) (Figure 4). Besides, it becomes cost-

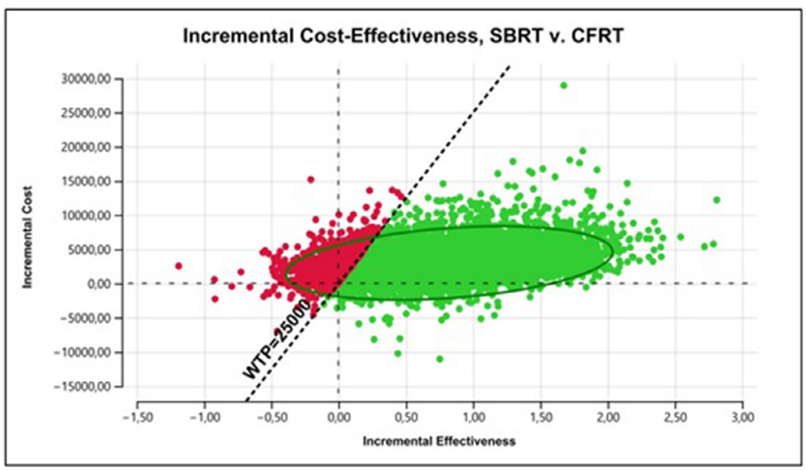


**Figure 3. Incremental cost-effectiveness plane from the probabilistic sensitivity analyses (PSA) 10000 interactions**.

The result of each iteration/simulation in the PSA is plotted on the cost-effectiveness (CE) plane. This graphic presents a "cloud" of possible outcomes. Each point on the scatter plot represents one simulation iteration. The points in the North East quadrant of the CE plane suggest that SBRT more effective. The dotted line represents the willingness to pay threshold, allowing the interpretation of the number of simulations which is above or below it. Incremental Costs (R$). Incremental effectiveness (QALY).

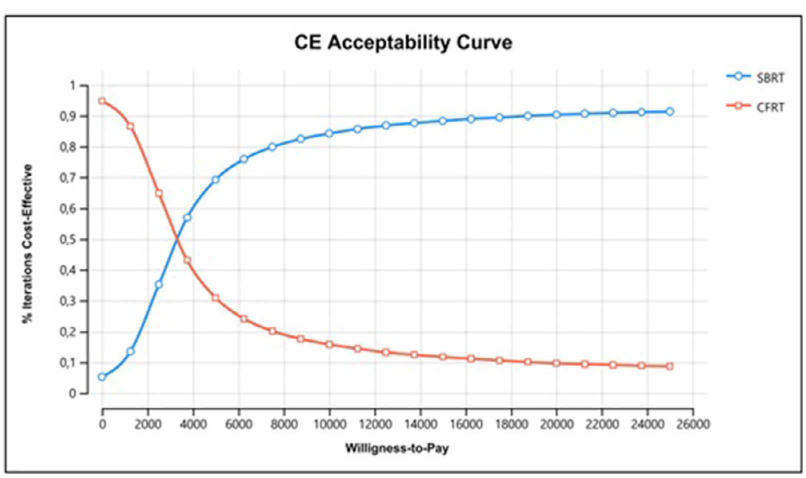


**Figure 4. Cost-effectiveness acceptability curve**.

Cost-effectiveness acceptability curve for SBRT versus CFRT provided to treatment of surgically ineligible stage I non-small cell lung cancer in the Brazilian public health system. Willingness-to-pay [cost (R$) per QALY]. QALY quality-adjusted life-years.

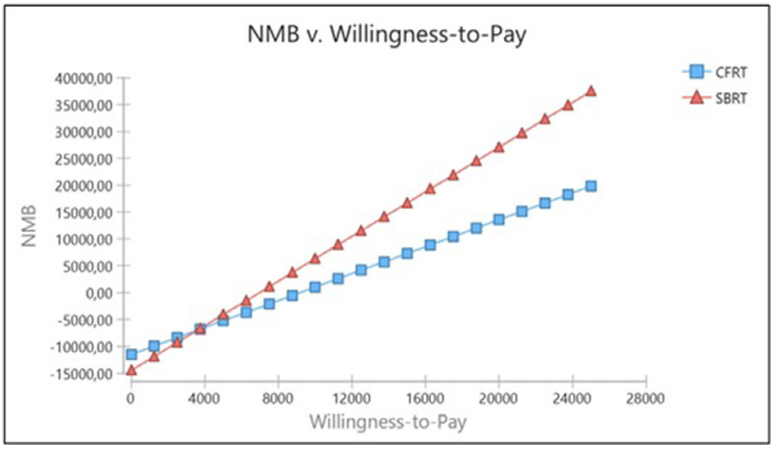


**Figure 5. NMB x Willingness-to-pay for both strategies**.
The Net Benefit approach calculates average net benefit for each option. SBRT has the positive NMB outcomes higher than CFRT. Net Monetary Benefit (NMB).

effective at a minimum threshold of R$ 3750/QALY (U$ 1482.21/QALY).

Finally, the probabilistic sensitivity analysis also provided the net monetary benefit (NMB) versus willingness-to-pay analysis indicating that with a willingness-to-pay of R$ 25.000/QALY (11563.37/QALY), the Net Monetary Benefit (NMB) is approximately twice higher for SBRT than for CFRT (Figure 5).

## Discussion

In the current study, SBRT was more cost-effective than CFRT to treat medically inoperable early NSCLC from the Brazilian public health system perspective. The SBRT strategy was more effective and more costly, resulting in a positive ICER of R$ 164.86 ($ 65.16) per QALY. The sensitivity analysis also revealed a superiority of SBRT even using the values generally adopted by the private sector, which are higher than the value reimbursed by the public sector (~200%). The NMB versus willingness-to-pay analysis indicates that a willingness-to-pay of 25.000/QALY was about twice higher than CFRT with an acceptability curve after a threshold of R $3.750 (U$ 1734.51) per QALY. The outcomes in favour of SBRT from our analysis are similar to the treatment effectiveness in other countries, with similar conclusions.[34,35] The recent study by Sun et al.[35] presents a systematic review on the cost-effectiveness of SBRT in the treatment of NSCLC, providing evidence that SBRT is a cost-effective option compared to conventional radiotherapy, radiofrequency ablation and best supportive care for medically inoperable, early-stage NSCLC. Besides, this literature review reinforces the argument that there are no studies evaluating the cost-effectiveness of SBRT versus CFRT for NSCLC in upper-middle-income countries; the present study is the first one.[35] The study by Mitera et al.[34] compares the cost-effectiveness of SBRT versus CFRT in patients with early-stage I NSCLC who either are ineligible for or refused surgery in Canada, their results also favour SBRT as a cost-effective treatment, but this study assesses only LYG and does not evaluate QALYS.[33]

It is worth mentioning that although it would be expected for the costs of SBRT to be lower than CFRT (as the staff and LINAC time should be shorter), the SBRT has a higher base cost than CFRT when analyzing public sector costs. The explanation for this result is a specific difference between public and private health in Brasil. In the public system, the number of treatments or fractions received by the patients is irrelevant from a costing perspective, i.e., the costs are calculated based on the entire course of treatment. In the private sector, treatment costs are directly related to the number of treatments or fractions received. Therefore, as the base costs were derived from the public sector, the initial costs of CFRT and SBRT were considered the same when a patient entered the Markov model. However, after going through all Markov model paths, the SBRT had a higher base cost than CFRT due to longer life expectancy, that is, a longer time within regional or metastatic recurrence health state for patients in the SBRT arm, which is associated with higher costs.

The public health system pays for about 80% of all radiation therapy courses in Brazil and the remaining 20% is paid by private insurance. The present study also allows us to compare the existent contrast between these two reimbursement models (public and private) in the same country. In the public system, the value paid for radiotherapy procedures has not been readjusted since 2010, resulting in a significant difference between the values paid for the public and private sectors.

Brazil has faced a profound LINAC shortage in the last decade, which has significantly impacted accessibility to adequate oncological treatment. In 2012, the Brazilian Federal Government purchased 80 linear accelerators to be installed throughout the country, contemplating all regions. Eight years later, only 35 installations have been carried out, which means a radiotherapy network of 244 machines in operation.[16] The world health organization preconizes one machine per 500,000 inhabitants, which means a deficit of at least 180 machines.[16] It is crucial to highlight that only 24% of the machines operating have SBRT capability, and most are from private units (RT2030). In this regard, the minimum threshold of R$ 3750/QALY (U$ 1482.21/QALY) identified in our analysis is a significant finding from a public payer perspective. First, because R$ 3750.00 (U$ 1482.21) is far below the WTP value (R$25,000), which means that these investment costs would be rapidly offset by the incremental benefits of incorporating SBRT in the public health system. Second, updating the current reimbursement lump sum would stimulate hospitals to invest in modern facilities and equipment. Besides, setting up new facilities benefits patients by increasing accessibility to contemporary radiotherapy techniques and reducing the waiting time.

The findings are strongly supported by the probabilistic analysis with Monte Carlo simulation that showed a model accuracy of 92,03% at a willingness to pay (WTP) of R$ 25,000/QALY. Additionally, the NMB produced by SBRT was about twice higher than CFRT. The higher NMB provided by SBRT, if incorporated by the health system, could also open the door to embody new LINACs and other therapeutic agents in the health care chain, such as immunotherapy[36,37] and target therapies for lung cancer, contributing to reducing the regional disparities in the accessibility to cancer treatment in Brazil.[38]

Although our analysis shows significant findings, it is crucial to highlight some limitations. First, the analysis was limited to patients with early-stage NSCLC who are ineligible for surgery and peripheral tumours. Thus, although these findings are valuable, they will not be immediately applicable to surgically eligible patients or central tumours. Second, our SBRT cost-effectiveness analysis was limited to only early NSCLC, limiting our findings to other tumours such as prostate, renal cell carcinoma, and hepatic metastases. Third, our estimations were performed with probabilities and utilities from other countries due to the absence of specific data on the Brazilian population. Fourth, the hospitalization costs were not assessed; if they were considered, the SBRT costs would be smaller because of reduced treatment sessions, staff time, and local recurrence probability. However, even with these limitations, the present study provides a Markov model that can be useful for designing further cost-effectiveness analyses for other cancer sites, radiotherapy modalities, and other developing countries. The literature about the theme from these countries is scarce but essential to incorporate new interventions in health systems with limited resources.

## Conclusion

Therefore, SBRT is cost-effective when compared to CFRT for treating medically inoperable early-NSCLC from the perspective of the SUS in Brazil. The incremental cost-effectiveness ratio was below the willingness to pay threshold, which strongly supports the incorporation of the intervention. Besides, the probabilistic sensitivity analysis of the outcomes resulted in excellent precision and reduced uncertainty, reinforcing that in Brazil, the government should strongly consider the SBRT the standard of care for early NSCLC. These results might be reproducible in other upper-middle-income countries.

### Contributors

GVA: Literature search, study design, writing, elaboration of discussion and conclusion

MTLR: Elaboration of methodology, data collection, data analysis and results

JHCO: Substantively revised the article

JSC-G: Substantively revised the article

AAJ: Study design, writing, substantively revised the article.

### Data sharing statement

The main data generated or analyzed during this study are included in this published article [and its *supplementary information files*]. A more detailed dataset used and/or analyzed during the current study is available from the corresponding author upon reasonable request.

### Declaration of interests

AAJ, GVA and MTLR received funding from Varian Medical Systems. AAJ received payment or honoraria for lectures, presentations, speakers bureaus or educational events from Varian Medical Systems and AstraZeneca. JSC-G and JHCO declare no conflict of interest.

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### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100329.

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