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Economic Evaluation

Cost-Effectiveness Analysis of Monoclonal Antibodies Associated With Chemotherapy in First-Line Treatment of Metastatic Colorectal Cancer

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ABSTRACT

Objectives: This study aimed to evaluate the cost-effectiveness of anti–epidermal growth factor receptor (cetuximab and panitumumab) or anti–vascular endothelial growth factor (bevacizumab) monoclonal antibodies associated with conventional chemotherapy (CT) (fluorouracil and leucovorin with irinotecan) as a first-line treatment for unresectable metastatic colorectal cancer.

Methods: A partitioned survival analysis model was adopted to simulate direct health costs and benefits comparing therapeutic options in a 10 years' time horizon. Model data were extracted from the literature and costs were obtained from Brazilian official government databases. The analysis considered the perspective of the Brazilian Public Health System; costs were measured in local currency (BRL) and benefits in quality-adjusted life-years (QALY). A 5% discount rate was applied to costs and benefits. Alternative willingness-to-pay scenarios, varying from 3 to 5 times the cost-effectiveness threshold established in Brazil, were estimated. The results were presented incremental cost-effectiveness ratio (ICER), and both deterministic and probabilistic sensitivity analyses were performed.

Results: The most cost-effective choice would be the association of CT with panitumumab, with an ICER of $58 330.15/QALY compared with isolated CT. The second-best option was CT with bevacizumab and panitumumab, with an ICER of $71 195.40/QALY compared with panitumumab alone. Although having higher costs, the second-best option was the most effective. Both strategies were cost-effective in part of the Monte Carlo iterations, considering the 3× threshold.

Conclusions: The therapeutic option CT + panitumumab + bevacizumab represents the most significant effectiveness gain in our study. It is the second-lowest cost-effectiveness, and this option includes monoclonal antibodies association for patients with and without KRAS mutation.

Keywords: antibodies, colorectal neoplasms, cost-effectiveness evaluation, health evaluation, monoclonal, neoplasm metastasis.

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Introduction

Colorectal cancer (CRC) is the second most lethal globally, with > 2 million individuals diagnosed and approximately 1 million deaths from this neoplasm in 2019. The age-adjusted incidence rate for that year was 33.1 and 21.2 per 100 000 men and women, respectively.[1]

In Brazil, CRC is the second most common malignant neoplasm in both sexes, not considering nonmelanoma skin tumors. The National Cancer Institute estimates an annual incidence of 41 010 cases in 2022, with a crude incidence rate of 19.64 and 19.03 new cases per 100 000 for men and women, respectively.[2] As observed in other countries, CRC has affected younger people, but its incidence has decreased in groups older than 50 years.[3,4] In 20% to 30% of newly diagnosed patients with CRC, metastasis will be detected before discovery of cancer, meaning an unresectable metastatic CRC (mCRC).[5] Patients' prognosis of untreated mCRC is quite unfavorable, with median survival ranging from 3 to 6 months.[6]

The mCRC treatment can be provided in various combinations with chemotherapy (CT) alone or with other cytotoxic agents, biological agents, or targeted therapies such as monoclonal antibodies. Systemic treatment can combine CT based on oxaliplatin, irinotecan, or fluorouracil (5FU). The most commonly used combinations are 5FU and leucovorin with oxaliplatin (FOLFOX) and 5FU and leucovorin with irinotecan (FOLFIRI). Concerning monoclonal antibodies, agents targeting the epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, and the vascular endothelial growth factor (VEGF) receptor, such as bevacizumab, stand out.[7-9]

The antibody binding to the VEGF receptor (anti-VEGF) and inhibits tumor-induced angiogenesis. In contrast, the EGFR (anti-

EGFR) binding blocks the cell proliferation chain linked to the KRAS proto-oncogene, both technologies inhibiting tumors from spreading.[10,11] Nevertheless, mutations in KRAS proto-oncogene can activate KRAS pathway regardless of antibody binding to the EGFR, characterizing an inherent resistance to EGFR inhibition. KRAS mutations were found in 30% to 50% of mCRC, predicting worse treatment responses with cetuximab and panitumumab.[6,12,13]

Therefore, clinical guidelines recommend cetuximab and panitumumab associated with CT only for patients with mCRC expressing EGFR without KRAS gene mutation (wild-type) or as single agents in patients who failed CT based on oxaliplatin and irinotecan or in patients intolerant to irinotecan. Because bevacizumab does not present this type of restriction, it is indicated in combination with CT for the treatment of patients with mCRC, regardless of the KRAS gene mutation.[14]

Oncological treatments have increasingly allocated public health resources. This study aimed to analyze the first-line treatment cost-effectiveness for unresectable mCRC with monoclonal antibodies anti-EGFR (cetuximab and panitumumab) or anti-VEGF (bevacizumab) associated with conventional CT from the perspective of the Brazilian Unified Health System (SUS).

Methods

Model Structure

This study compared the following treatment options: (1) CT alone for all subjects, (2) CT + bevacizumab for all subjects, (3) CT + cetuximab for 60% of subjects and CT alone for 40% of subjects, (4) CT + bevacizumab + cetuximab for 60% of subjects and CT + bevacizumab for 40% of subjects, (5) CT + panitumumab for 60% of subjects and CT alone for 40% of subjects, and (6) CT + bevacizumab + panitumumab for 60% of subjects and CT + bevacizumab for 40% of subjects, for conventional CT was considered the FOLFIRI regimen.

The analysis was performed from the SUS perspective using treatment strategies registered for mCRC and regarding KRAS gene mutations, occurrence of which comes close to 40% of individuals according to the literature.[6,12,13]

A partitioned survival analysis model was built in Microsoft Excel (Microsoft, Redmond, WA)spreadsheets for Office 365, comparing the 6 treatment strategies consisting of 3 mutually exclusive transition health states (partitions), as shown in Figure 1: (1) progression-free survival (PFS), (2) progression, and (3) death. After extracting the data from survival curves, area under the curve of each partition was estimated based on trapezoid rule.[15,16]

The main assumptions of the model were as follows: no return to the state progression-free state; the utility depends only on health state; and all patients on conventional therapy are in FOLFIRI regimen and progression are in FOLFOX regimen.

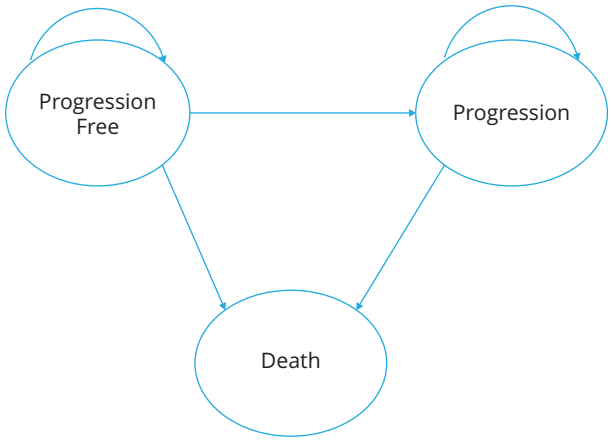
The model estimates were based on monthly costs and benefits with a horizon time of 10 years. This time is similar to the natural survival history of patients with mCRC, and it was considered sufficient to capture costs and consequences related to this population. Following the Brazilian methodological guidelines,[17] a discount rate of 5% has been applied for both costs and benefits.

Clinical Efficacy

Data from PFS and overall survival (OS) curves of patients using CT alone were adopted as references.[18] The curves were extracted using the WebPlotDigitizer tool.[19] Hazard ratio (HR) estimates for each treatment were extracted from 2 systematic reviews (SRs) with meta-analysis.[20] We extracted the randomized controlled trial (RCT)[21-23] data from adverse events grades 3 and 4 (diarrhea, hematotoxicity, and skin reactions) to use in the model (Table 1). We assessed the risk of bias in RCT studies with the RoB 2.0[24] tool and in SR studies with the AMSTAR tool.[25] The certainty of evidence assessed by GRADE[26] was considered moderate for most outcomes.

Based on extracted Kaplan-Meier curves, exponential, Weibull, lognormal, log-logistic, Gompertz, and generalized gamma models were fitted with R package flexsurv[27] to allow the extrapolation of clinical research data to a more extended horizon time model.[28] The choice of the best survival functions was considered the visual inspection of predicted survival and the goodness-of-fit criteria (Akaike information criterion/ Bayesian information criterion).[29] The relative comparison between each strategy considered the HR values from available published meta-analysis.

Figure 1. Markov states. Illustrate the disease development process of metastatic colon cancer.



Benefit Outcome

Benefits were estimated with the quality-adjusted life-years (QALYs). Due to the lack of Brazilian population data, the utility of progression-free and disease progression states was extracted from international literature. An SR of health status utilities for CRC was evaluated,[30] and the data published by Färkkilä et al[31] were the only ones that reported utility on metastatic status measured with the EQ5D, which is the most recommended tool in Brazil (Table 1).

Costs

Direct medical costs were KRAS mutation test, treatment regimens, resources for patient follow-up, and treatment of adverse events. To determine and measure health resources, we used data from scientific literature, information from drug leaflets, Clinical Practice Guidelines in Oncology from the Ministry of Health, and oncology specialists from the Brazilian National Cancer Institute. All costs were obtained by consulting data from the Brazilian National Cancer Institute central hospital pharmacy (for the last purchases values of medicines); the Table of Procedures, Medicines, Orthoses/Prostheses, and Special Materials of the SUS; Health Prices Database; and the SUS Department of Informatics. The value of the genetic test for KRAS identification was obtained through an average of 3 budget requests to private laboratories because it is not available in the SUS.

Table 1. Main model inputs and source of resources.

Parameters	Point estimate	95% CI		Distribution	Source
HR of progression-free survival (PFS)					
CT + bevacizumab	0.61	0.51	0.74	Beta	19
CT + cetuximab or CT + panitumumab	0.79	0.66	0.94	Beta	6
HR of overall survival					
CT + bevacizumab	0.86	0.75	0.98	Beta	19
CT + cetuximab or CT + panitumumab	0.87	0.75	1.02	Beta	6
Utility of progression-free survival	0.82	0.78	0.86	Beta	27
Utility of disease progression	0.64	0.55	0.75	Beta	
Parameters	Point estimate	Minimum	Maximum	Distribution	Source
KRAS and/or NRAS gene mutation investigation, $	327.34	261.87	392.81	Gamma	Private laboratories
Cost of the medication vial, $					
Bevacizumab	612.79	490.23	735.35	Gamma	INCA
Cetuximab	326.28	261.02	391.54	Gamma	INCA
Panitumumab	370.89	296.71	445.07	Gamma	INCA
Irinotecan	15.28	12.22	18.34	Gamma	INCA
Fluorouracil	2.02	1.62	2.42	Gamma	INCA
Leucovorin	40.60	32.05	48.07	Gamma	INCA
Oxaliplatin	36.17	28.94	43.40	Gamma	INCA
Costs of monitoring patients, $					
From 1st to 24th month	63.13	50.50	75.76	Gamma	SIGTAP
From the 25th to the 60th month (semester)	42.52	34.02	51.02	Gamma	SIGTAP
From the 61st to the 120th month (Annual)	21.04	16.83	25.25	Gamma	SIGTAP
Expenditures on main adverse events, $					
Diarrhea	80.67	64.54	77.44	Gamma	SIGTAP and BPS
Hematotoxicity	68.39	54.71	65.65	Gamma	SIGTAP
Skin reactions	7.45	5.96	7.15	Gamma	SIGTAP and BPS

BPS indicates Health Prices Database; CT, chemotherapy; HR, hazard ratio; INCA, Brazilian National Cancer Institute; PFS, progression-free survival; SIGTAP, Table of Procedures, Medicines, Orthoses/Prostheses, and Special Materials of the SUS; SUS, Brazilian Unified Health System.

The therapeutic regimens costs for the interventions were estimated using drugs dosages calculated for a 70-kg-average weight and 164-cm-average height adult (older than 18 years) obtained in the Brazilian Household Budget Survey.[32]

The model was elaborated with the unit treatment costs, considering drug bottle cost and therapeutic scheme in the first-line and second-line treatment, patient follow-up items (during and after treatment), and main adverse events grades 3 or 4. The Brazilian reimbursement payment is a package, including items such as vials, examinations, consultation, and adverse events treatment (Appendix Tables 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.04.003).

Treatments were considered as conducted until disease progression or death of the patient, for a maximum of 6 months (Table 1). Considering the formal cost-effectiveness threshold of R$40 000.00/QALY established in Brazil, analyses for monoclonal antibody prices were conducted to achieve 3 hypothetical threshold scenarios, considering 3 to 5 times the official threshold.[33] The incremental cost-effectiveness ratios (ICERs) and their dominance relationships with 3 strategies were estimated.[34] All items priced for 2021 were converted from Brazilian currency (real [R$]) to international dollar (purchasing power parity) at a ratio of 1:2.281.[35]

Sensitivity Analysis

A deterministic sensitivity analysis was conducted by varying the values of several relevant model variables, such as therapies cost, incidence rates, and utility values. A tornado diagram was built to visualize the impact of such variation's impact on the ICER. A probabilistic sensitivity analysis was conducted using 1000 Monte Carlo simulations. The most appropriate statistical distributions were defined according to the available methodological guidelines for each parameter considered in the model's sensitivity analysis.[17,36] Data were also presented with the cost-effectiveness plane scatterplot and acceptability curves to analyze the treatment option probability of being cost-effective compared with CT alone.

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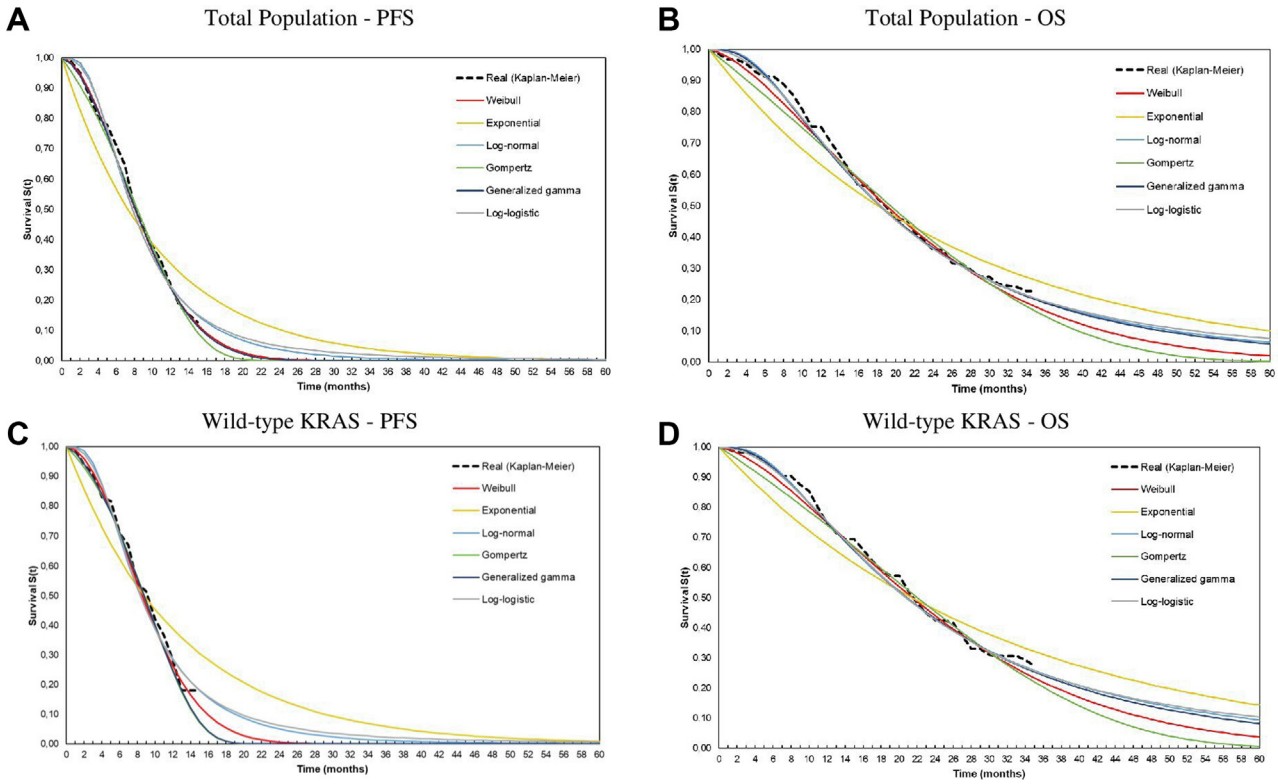
Results

The survival curves derived from the Weibull, log-logistic, and generalized gamma models did not differ significantly from the results of clinical trials. PFS and OS curves for all mCRC and mCRC wild-type KRAS patients are shown in Figure 2.

All strategies showed incremental gains compared with conventional CT. The therapeutic options CT + panitumumab + bevacizumab and CT + cetuximab + bevacizumab showed the best effectiveness results, both with 1.66 QALYs. CT + panitumumab was the most cost-effective strategy, with $58 330.15/QALY, followed by CT + panitumumab + bevacizumab with $71 195.40/QALY. Nondominated strategies included the incorporation of treatments with conventional CT + panitumumab or conventional CT + bevacizumab + panitumumab.

Figure 2. The survival curves derived from the exponential, Weibull, lognormal, log-logistic, Gompertz, and generalized gamma models of PFS and OS for total population and wild-type KRAS population.



OS indicates overall survival; PFS, progression-free survival.

The cost and effectiveness of all alternatives in the base case analysis are presented in Table 2. The therapeutic options CT + cetuximab, CT + bevacizumab, and CT + cetuximab + bevacizumab were dominated (higher costs without gains of effectiveness) by the other strategies under analysis. The results show that the best choices are the conventional CT associated with panitumumab with an ICER of $58 330.15/QALY regarding the conventional CT alone, followed by conventional CT associated with bevacizumab and panitumumab with an ICER of $96 998.15/QALY regarding conventional CT and panitumumab alone. Besides, the latter option presented the most significant gain.

Analysis of tornado diagrams indicates the risk of death, risk of progression, and monthly cost of treatment as the most impacting components in ICER, for all combinations of interventions compared with standard care (Fig. 3).

The result of 1000 Monte Carlo simulations with all therapeutic alternatives is presented in the scatter plot (Fig. 4). Despite some overlapping uncertainties, the most cost-effective treatment was conventional CT + panitumumab.

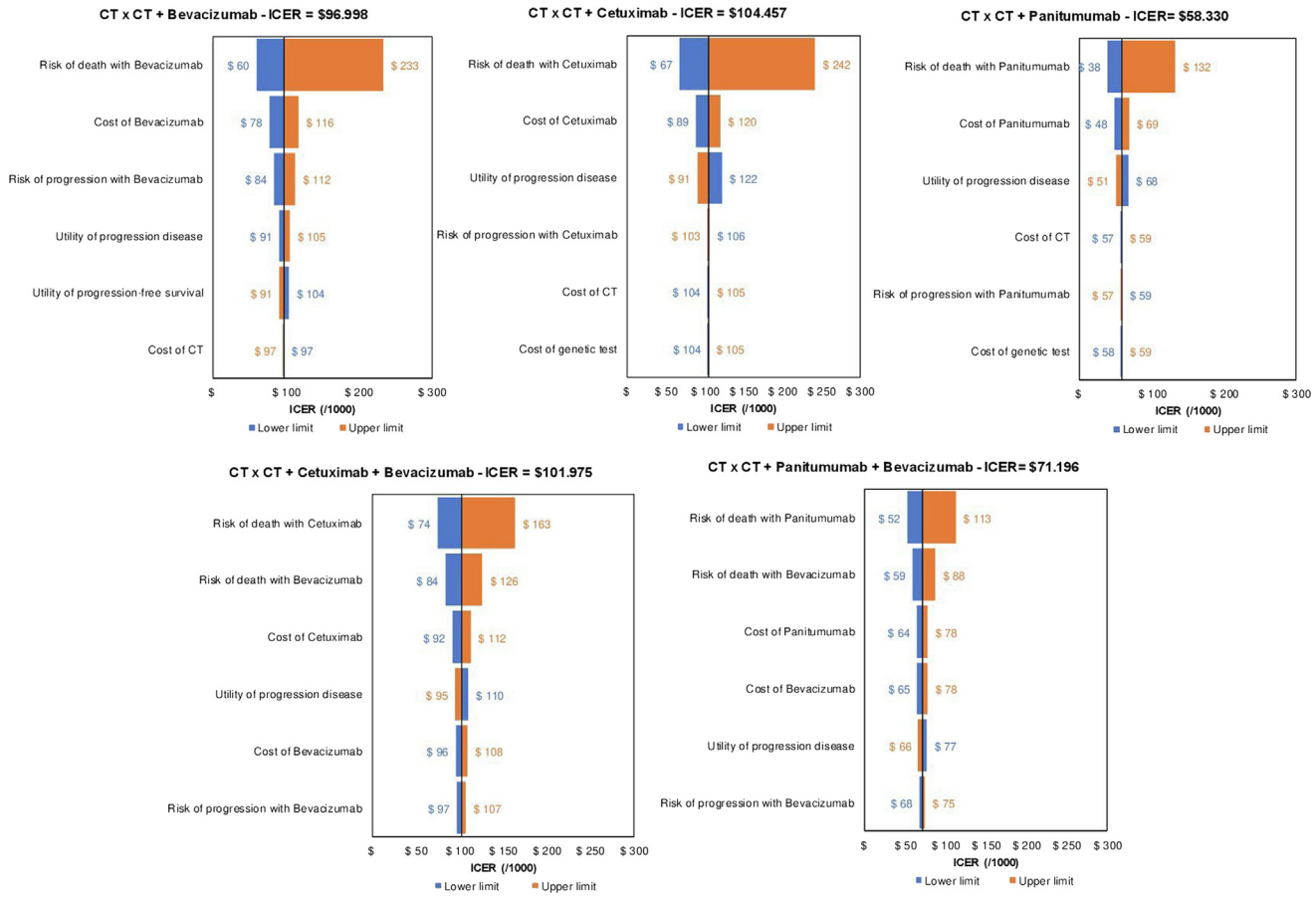
Regarding the hypothetical scenario analysis of cost-effectiveness thresholds, the alternatives CT + bevacizumab, CT + cetuximab, and CT + cetuximab + bevacizumab overcome the 5 times threshold scenario. The therapeutic option CT + bevacizumab + panitumumab is between 3 and 5 times the threshold, closer to 5 times the threshold, whereas the alternative CT + panitumumab is also between 3 and 5 times the threshold, but closer to 3 times.

Table 2. Cost and effectiveness for all alternatives in the base case analysis.

Therapeutic strategies	Costs ($)	Effectiveness (QALY)	Incremental effectiveness	Incremental Costs ($)	ICER* ($)
CT	6161.46	1.37			
CT + panitumumab	17 690.16	1.56	0.20	11 869.44	58 330.15
CT + cetuximab	26 806.94	1.56	-	9873.53	Dominated
CT + panitumumab + bevacizumab	27 248.95	1.66	0.10	9558.79	96 998.15
CT + bevacizumab	30 058.144	1.61	-	3439.87	Dominated
CT + cetuximab + bevacizumab	36 365.73	1.66	-	6433.67	Dominated

CT indicates chemotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
*Disregards dominated strategies and compares with the last most cost-effective strategy.

Figure 3. Tornado diagram for the one-way sensitivity analysis of each scenario.



CT indicates chemotherapy.

If 3 times the cost-effectiveness threshold were adopted, a reduction in the price would be necessary to make these options cost-effective, at an average of 61.7% for bevacizumab, 63.5% for cetuximab, and 30.2% for panitumumab (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.04.003). Besides the threshold analyses, the acceptability or willingness-to-pay curves of monoclonal antibody interventions compared with standard therapy are presented in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.04.003.

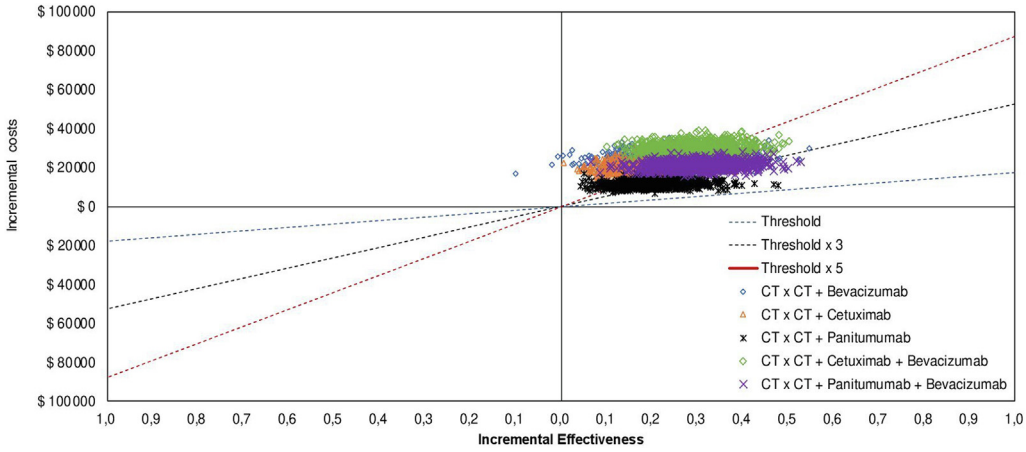
Discussion

Treatment for mCRC has evolved in recent years. Monoclonal antibodies (bevacizumab, cetuximab, panitumumab) associated with irinotecan-based cytotoxic agents, oxaliplatin, 5FU, and leucovorin (FOLFIRI/FOLFOX) have clinical benefits on PFS and OS.[37]

Nevertheless, decisions regarding treatments are usually driven by several factors, such as costs (medical, nonmedical, direct, and indirect), adverse events and toxicity, guidelines, and patient preferences, besides clinical practice.[38] We developed a partitioned survival analysis decision model to estimate the cost-effectiveness of monoclonal antibodies in first-line therapy for patients with unresectable mCRC in the SUS context. Our study demonstrated that the therapeutic options CT + cetuximab, CT + bevacizumab, and CT + cetuximab + bevacizumab were dominated (higher costs without gains of effectiveness). Thus, the analyzed scenarios indicate that the best option would be to include CT + panitumumab or CT + panitumumab + bevacizumab in the product basket, even though such options are above the reference of 1 gross domestic product per capita[33]. We highlight the CT + panitumumab + bevacizumab option that can be used by all patients with or without KRAS mutations.

The cost-effectiveness threshold helps to understand the relationship between the cost value and the health gain generated by technologies in the health system. The cost-effectiveness limit established for Brazil by the National Commission for the Incorporation of Technologies is R$40 000.00 per QALY. At the discretion of the National Commission for the Incorporation of Technologies, in some situations (positive modifiers), an alternative threshold may be used: rare diseases (affects up to 65 people in every 100 000 individuals) implying significant reduction in quality-adjusted survival, disease affecting children (younger than 18 years) and implying a significant reduction in quality-adjusted survival, severe disease (where mCRC could fit), and endemic disease in low-income populations with few therapeutic alternatives available. In these cases, a threshold of up to 3 times the reference value is acceptable.[39] The austerity policies limited public spending, and efficient allocation became essential for SUS resource sustainability. In that way, a threshold helps in choosing

Figure 4. The Monte Carlo probabilistic sensitivity analysis for all treatment groups.



CT indicates chemotherapy.

and electing priorities.[40,41] Several international studies have evaluated the cost-effectiveness of routine RAS proto-oncogene screening in patients with mCRC[42-44] using cetuximab or bevacizumab as first-line versus CT for mCRC.[45-47] A study conducted in the United States by Shankaran et al[45] showed that cetuximab has an ICER of US$107 630/QALY (US$86 487/life-year) compared with bevacizumab in wild-type KRAS patients. Studies conducted in Canada by Ewara et al[46] and Lawrence et al[47] compared 3 treatments: bevacizumab, cetuximab, or panitumumab plus CT in patients with wild-type KRAS mCRC; the results showed that bevacizumab associated with CT outperformed the 2 other first-line treatment strategies. In contrast, Han et al[38] developed a study in China to estimate the cost-effectiveness of cetuximab and bevacizumab, both associated with FOLFIRI in patients with left-sided wild-type RAS mCRC. Their results showed that FOLFIRI plus cetuximab treatment could improve health outcomes and efficiency using financial resources concerning FOLFIRI with bevacizumab.

Nevertheless, comparisons with our results are limited because no studies included all treatment alternatives, compared with CT alone, in both groups of patients: wild-type and mutant KRAS.

The present model has limitations inherited from systematic meta-analyses reviews in which we used to extract the HR values as no head-to-head comparisons of each treatment. Therefore, it was necessary to use a survival functions to infer consequences beyond the lifetime of the RCT. Nonetheless, both estimate sources were correctly included and treated in the sensitivity analyses. It is noteworthy that as an assumption and simplification of the model, only one conventional treatment option (FOLFIRI) and a single second-line treatment (FOLFOX) were used in the progression case, which may be different from clinical practice. Nevertheless, such simplification is based on the lack of evidence of the superiority of such conventional treatments, which would have little or no impact on the model results.

Additionally, the effectiveness data came from clinical studies conducted outside Brazil in different contexts, which may reflect some heterogeneity because of local standards of therapeutic care and differences in patient values and preferences. Our assumption of general age-specific mortality in the progression-free disease state may have excluded the risk of death from causes other than a progressive disease, such as fatal adverse events. Nevertheless, given the fact that, eventually, the entire cohort progresses to a cancer-specific risk of death, the OS estimates obtained are close to the observed in clinical practice.

In contrast, the model compares different drug alternatives for 2 types of KRAS status. The model seeks to represent an actual decision making of resource allocation decisions by comparing strategies and not isolated medicines. Using resources such as cost-effectiveness frontiers and threshold analyses could improve the decision. Despite some limitations in generalizing the effectiveness data, all cost data have been adjusted to the context and local currency. Regarding effectiveness, the present model adopts robust data extrapolation methods for the survival fitting with exponential, Weibull, log-logistic, generalized gamma, and Gompertz. The profile of the fitted functions were very close to what is observed in the advanced CRC clinical practice, being also used previous studies.[35] Following local and international economic evaluation guidelines, we appropriately treated all main uncertainties in the deterministic and probabilistic sensitivity analyses. To the best of our knowledge, this is the first study to assess the cost-effectiveness of monoclonal antibody therapies for mCRC within the SUS perspective. The results presented here can better guide local managers in their resource allocation decision.

Conclusion

By analyzing the value of a therapy, the cost-effectiveness assessment of treatments becomes important for both managers and physicians. The therapeutic option CT + panitumumab + bevacizumab represents the most significant effectiveness gain in our study. It is the second-lowest cost-effectiveness, and this option includes monoclonal antibodies association for patients with and without KRAS mutation. Although the use of monoclonal antibodies has had a positive effect on survival, the complexity of using several treatment options in different combinations and the high cost of these new therapeutic options justify the concern regarding the sustainability of treatment from a perspective of finite and blocked resources for 20 years, as in Brazil.[48,49]

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2023.04.003.

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Critical revision of the article for important intellectual content: Barufaldi, de Albuquerque, do Nascimento, Martins, Zimmermann, de Souza

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