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Cost-Utility Analysis Addition of Bevacizumab to Standard Chemotherapy in KRAS-mutation Colorectal Cancer

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ABSTRACT

There is a high incidence of colorectal cancer in Indonesia. Colorectal cancer was ranked fourth with an incidence of 8.6% and a colon cancer mortality rate of 4% while rectal cancer was 3.6% in Indonesia. The addition of Bevacizumab to Standard chemotherapy (FOLFOX/FOLFIRI/XELOX) in KRAS-mutation colorectal cancer patients has better clinical outcomes; however, it has a very high cost in terms of colorectal cancer treatment. The objective of this study was to determine the utility and economic impact of adding Bevacizumab as an adjunct therapy for KRAS-mutation colorectal cancer patients. A Markov model was developed to estimate the Cost-utility analysis (CUA) using a societal perspective. Humanistic outcomes are expressed in the form of QALY (Quality-adjusted life years) using an EQ-5D-5L instrument with an Indonesian value set. Medical expenses data were collected from both RSUP Dr. Sardjito and patients. Utility data were obtained from interviews with 30 patients undergoing chemotherapy at the hospital. This study compared the cost and utility of patients receiving Bevacizumab supplementation or patients receiving standard chemotherapy alone. The societal perspective resulted in a cost-effectiveness ratio (ICER) of US$3.098 per QALY. The addition of Bevacizumab to standard chemotherapy in KRAS-mutation colorectal cancer patients is considerably cost-effective from a societal perspective.

1. Introduction

Colorectal cancer is a disease with the third-highest incidence and second-highest mortality of all types of cancer in the world. The incidence of colorectal cancer is 10% and the death rate is 9.4% of all cancers in the world. Colorectal cancer increased rapidly with an incidence of 49.6% of colon cancer and 57.8% of rectal cancer in Asia. The percentage incidence rate of colon cancer in Southeast Asia is 56,065 cases, with a mortality rate of 30,510 cases, while the incidence of rectal cancer is 46,649 cases, along with a mortality rate of 25,499 cases (Ferlay et al., 2020). In Indonesia, colorectal cancer is ranked fourth with a percentage of 34,189 (8.6% of all cancers), and the colon cancer mortality rate is 9.444 cases (4% of all cancers), while rectal cancer has 8,322 cases (3.6% of all cancers) (Bray et al., 2018). Finally, colorectal cancer has the second-ranked incidence of all types of cancer at RSUP Dr. Sarjito, with the number of cases of 2,532 in 2008-2019.

Colorectal cancer cases not only cause a high clinical burden, but also an economic burden, particularly in Asia. The total cost of colorectal cancer treatment in Vietnam amounted to 132.9 million USD with indirect costs as much as 83.58% of the total expenses (Tran et al, 2020). The annual stage-spesific cost of treatment in Malaysia is 2045.1 USD for stage I, Stage II was 2434 USD, stage III was 2749.7 USD and Stage IV was 2699.4 USD (Azzani et al., 2016). In Korea, the economic burden of colorectal cancer amounted to 3 to 100 million USD with the highest cost of indirect cost (Byun et al., 2014). Furthermore, the economic burden of colorectal cancer amounted to 298148718 USD with 32,4% used for direct medical expenses in Iran (Vahdatimanesh et al., 2012). Finally in Indonesia, the direct medical costs of colorectal cancer paid by BPJS Kesehatan amounted to IDR 335,395,468,425 in 2018 (Andriani et al., 2021).

Inappropriate use of therapeutic options causes not only a high economic burden but also unpredictable clinical outcomes. In terms of cancer, several conditions, including advanced, metastatic or several types of mutations require targeted therapy. Based on cancer registry data Dr. Sardjito as many as 40.9% of patients were diagnosed at Stage 4 in 2008-2021, it's an increase compared to 2008-2019 of 41%. For example, the administration of capecitabine had a median overall survival (OS) of 16.8 months and a median progression-free survival (PFS) of 5.1 months (Cunningham et al., 2013). Whereas, the administration of FOLFOX4 chemotherapy gave a median OS for 10.8 months and a median FPS for 4.7 months (Giantonio et al., 2007).

In case of colorectal cancer, several clinical outcomes are worse due to genetic mutations. RAS mutations (KRAS/NRAS) caused worse PFS in patients who developed Ras mutants when receiving FOLFIRI plus cetuximab therapy compared to RAS mutants who received FOLFIRI plus Bevacizumab (6.1 vs. 12.2 months). Therapy with Bevacizumab provides a better response in populations with KRAS or NRAS mutants (Heinemann et al., 2014).

The addition of Bevacizumab to standard chemotherapy (FOLFOX/FOLFIRI/XELOX) has better clinical outcomes of treatment. Based on previous research, the cost-utility analysis from a societal perspective for colorectal cancer using the FOLFOX/FOLFIRI/XELOX regimen is approximately 42,789 USD or IDR 667,611,693/QALYs. Furthermore, the addition of Bevacizumab is about USD 67,774 or IDR 1,057,279,616 per QALY, and the ICER is USD 28,446 per QALY or IDR 443,759,789 per QALY. From the healthcare provider's perspective, the cost incurred on the FOLFOX/FOLFIRI/XELOX regimen was 359 million, and the cost of Bevacizumab therapy alone was

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108 million, with the ICER of 345 million/QALY (Kristin et al., 2021). Therefore, a pharmacoeconomic analysis is required to confirm whether the addition of Bevacizumab to standard therapy for populations with KRAS mutations is a cost-effective treatment.

2. Methods

Study design

This study combined real-world data from an observational study and modelling approaches from a societal perspective. The Markov model gives an overview of the course of colorectal cancer patients (Figure 1) (Tappenden et al., 2007). We hypothesised a cohort of 1000 KRAS-mutation colorectal cancer patients who received 12 cycles of standard chemotherapy (FOLFOX/FOLFIRI/XELOX) in the model, and they were followed until 70 years of age. An observational study was conducted to collect clinical data, which included examination of vital signs, allergic history, laboratory tests, anatomical pathology, radiological examinations, mutation tests, chemotherapy protocols, chemotherapy doses, types, and doses of premedication. Humanistic Data in the form of utility was measured using an EQ-5D-5L questionnaire with an Indonesian value set (Purba et al., 2017).

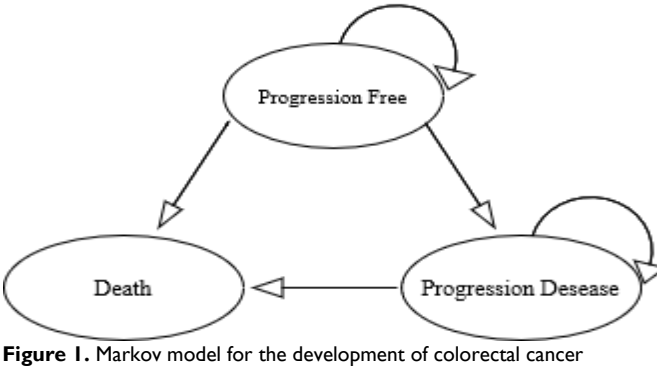

Figure 1. Markov model for the development of colorectal cancer

Population and samples

The population in this study was colorectal cancer patients who received standard chemotherapy and or Bevacizumab in addition to standard chemotherapy. The inclusion criteria were patients who were diagnosed with colorectal cancer in 2023 and 2024 at Dr Sardjito's Hospital, patients who received the FOLFOX/FOLFIRI/XELOX regimen, those who received the FOLFOX/FOLFIRI/XELOX regimen with the addition of Bevacizumab, 18 years and older, had complete clinical and financial data, and patients who received chemotherapy for at least two cycles.

Data collection

Utilities and cost

The costs were calculated from a societal perspective, and all costs were converted to 2023 US dollars. The price of Bevacizumab biosimilar at Dr Sardjito Hospital was US$116.60 116,6/100 mg vial. The cost for each health state in the model, including direct medical costs, was obtained from the billing department at Dr. Sardjito Hospital. The components of direct medical costs include surgical costs, radiotherapy, chemotherapy, medicine, health equipment, non-operative actions, accommodation, nursing services, specialist doctor consulting services, general practitioner services, transfusions, clinical pathology, anatomical pathology, and radiodiagnostics. Direct non-medical costs are taken from interviews with patients and/or caregivers. Components of direct non-medical costs include transportation costs such as online mobile, gasoline, and food costs. The indirect cost referred to is the cost due to the loss of patient and/or their companion productivity when the patient is undergoing surgery, chemotherapy, or radiotherapy. In this study, no patients received additional Bevacizumab; therefore, Bevacizumab is administered in cases of metastatic colorectal cancer with mutant KRAS at a dose of 5 mg/kg, given in combination with FOLFOX/FOLFIRI chemotherapy, and 7.5 mg/kg if given with the XELOX regimen (NCCN, 2023).

Transition probabilities

The transition probability value is calculated from the new incidence number of state progression-free and progression using the formula (Setiawan et al., 2017).

$$P=1-\exp(-rt)$$

With (P) as probability, (r) as instantaneous event rate, and (t) as time in year. To convert probability to rate, the formula is used:

$$R = -(\ln (1-p)/t$$

Data analysis

Cost-effectiveness analysis

The goal of this analysis is to examine the additional cost required for each one-unit change in effectiveness (QALYs) and to help determine which option is more cost-effective. The ICER calculation formula is as follows:

$$ICER = \frac{Cost\ (chemoterapy + bevacizumab) - Cost\ chemotherapy}{Outcome(chemoterapy + bevacizumab)\ -\ Outcome\ chemotherapy}$$

Bevacizumab was considered cost-effective when the ICER fell below the willingness-to-pay threshold of three times GDP per capita. The 2023 GDP per capita for Indonesia was US$4,630.28 (BPS, 2023).

Sensitivity analysis

Uncertainty analysis was done with deterministic sensitivity analysis. This analysis is done by changing the value of the input parameters one by one and then see how the change ICER. The process of replacing the ICER value is done manually and then the results are compared with the ICER value of basecase. The calculation value is the result of replacing each value of the input parameter displayed in the form of a tornado diagram. To understand which factors most affect the ICER value if an intervention is carried out in the form of a fluctuative from the original value (Setiawan et al., 2017).

3. Result and Discussion

Colorectal cancer patients with progression-free and progression conditions that meet the inclusion criteria, up to 30 patients, for data on medical direct costs, non-medical direct costs, indirect costs, and utilities derived from RSUP Dr. Sardjito. In cases of colorectal cancer, standard chemotherapy is given, including FOLFOX, FOLFIRI, or XELOX, and for patients with metastatic colorectal cancer with a KRAS mutation, additional Bevacizumab is given. The further provision of Bevacizumab is not covered by Indonesia's Health and Social Security Agency (BPJS Kesehatan), so the patient must pay the additional cost of Bevacizumab. Colorectal cancer patients with progression-free and progression conditions do not get additional Bevacizumab even though patients are in metastatic conditions, due to Bevacizumab being outside the National Guarantee of Health package, so they must be paid in general terms. In this study, ICER calculations were performed by comparing the cost difference when assuming the addition of Bevacizumab and standard chemotherapy, with the difference in utility resulting from adding Bevacizumab and standard chemotherapy. The utility value of Bevacizumab is based on previous research conducted in Indonesia, including studies at Dr Sardjito Hospital.

Clinical outcomes

FOLFOX/FOLFIRI/XELOX chemotherapy has a median survival value of 8.8 months (Kristin et al., 2021). Capecitabine chemotherapy has a median overall survival of 16.8 months and a median progression-free survival of 5.1 months (Cunningham et al., 2013). FOLFIRI chemotherapy has a median overall survival of 15.6 months and a median progression-free survival of 6.2 months (Tappenden et al., 2007).

Input parameters of the Markov model

Patient's characteristics

Colorectal cancer treatment typically involves a combination of surgery, chemotherapy, and radiotherapy (Kemenkes RI, 2017). Surgery is used in the early stages to cure, while chemotherapy is the leading choice in the severe stage for palliative treatment, and radiation therapy is the primary treatment for rectal cancer. A total of 30 patients were included in this study (Table I). The chemotherapy regimen commonly used among patients was FOLFOX, which was used by 40%, FOLFIRI by 23%, and XELOX by 37%. This research shows that colorectal cancer patients at Dr. Sardjito Hospital with health state progression are those at stage IV or metastasis, while progression-free are patients with stage I-III. From medical record data, 60% of patients are in a health state progression and 40% are progression-free. In Table I most of the patients were female, only in the FOLFIRI group the proportion of male sex was greater. After the Kruskal Wallis test, the P value of 0.810 > 0.05 was obtained, so that the sex between the three groups of standard chemotherapy FOLFOX/FOLFIRI/XELOX did not differ. The age range of the colorectal cancer patients in this study was from 22 years to 75 years with an average patient age of 51 years. Furthermore, statistical tests include a normality test with a P value >0.05, then the age data of colorectal cancer patients with normal distribution and a homogeneity test and obtained a significance value of 0.978>0.05, then it can be concluded that the age of the three groups of chemotherapy standard homogeneous and can be done a way ANOVA test. The results of statistical tests using Anova produced a significance value of 0.895>0.05 and concluded that the average age of patients in the three standard chemotherapy no difference.

Transition probabilities

In the base-case analysis, the annual transition probabilities for chemotherapy alone versus chemotherapy plus Bevacizumab for overall survival (OS) and progression-free survival (PFS) were derived from previous studies (Aparicio et al., 2018). This study utilised overall survival and progression-free survival data from health state progression-free (stages I-III) and progression (stages IV or metastasis).

Bevacizumab treatment was associated with an additional cost of US$ 4.207. Treatment Bevacizumab biosimilar resulted in an ICER US$ 3.098 to gain one additional QALY. The ICER Bevacizumab can be moved forward by the use of an effective biomarker to identify those patients who are more advantaged from treatment. For illustration, KRAS transformation testing recognises which patients with mCRC would benefit more from medicines such as cetuximab or panitumumab, increasing the cost-effectiveness of these interventions (Ungari et al., 2017).

The cost-effectiveness plane picture can include a comparison of costs and therapeutic output between FOLFOX/FOLFIRI/XELOX chemotherapy and the addition of Bevacizumab. The addition of Bevacizumab is found in quadrant (i) which means that the addition of Bevacizumab has better effectiveness and is more expensive than current standard chemotherapy. Therefore, it requires pharmacoeconomic studies to determine whether the addition of Bevacizumab will be accepted in health services in cases of colorectal cancer. Furthermore, the ICER value is compared to the WTP value in Indonesia. In principle, the addition of Bevacizumab will be accepted by the decision maker if the resulting ICER value, when compared to standard FOLFOX/FOLFIRI/XELOX chemotherapy is lower than the Indonesian WTP value.

Sensitivity analysis

The tornado diagram shows that the discount rate, including utility discounts and cost discounts, has a big influence on the ICER value obtained. So, if there is a change in the reduced rate value, it will result in a change in ICER value which is quite meaningful. The effect of this sensitivity analysis means that before the policy maker makes a decision related to whether it is necessary or not to add this Bevacizumab to be implemented in colorectal cancer cases in Indonesia, information related to the discount rate must be known with certainty so that the decisions taken also provide definite results (Setiawan et al., 2017).

We clarity be mindful that the majority of patients displayed to hospitals in Indonesia arrived in poor common conditions. In expansion, there were financial variables that likely influenced patients' compliance to chemotherapy strategies, i.e., chemotherapy recurrence, clinic get-to, transportation taking a toll, and caregiver's time.

Table I. Patient characteristics

Characteristics	FOLFOX (N = 12)		FOLFIRI (N = 7)		XELOX (N = 11)		TOTAL (N = 30)		P *value*
	N	%	N	%	N	%	N	%	
Gender									
Man	5	41,67	4	57,14	5	45,45	14	46,67	0,810
Woman	7	56,33	3	42,86	6	54,54	16	53,33	
Age (year)									
Mean	51		50		53		51		0,895
Median (min;max)	50 (26;68)		52 (22;66)		55 (34;75)		52 (22;75)		
Marital status									
Marriage	11	91,67	6	85,71	10	33,33	27	90,00	0,895
Divorce	0	0,00	0	0,00	1	3,33	1	3,33	
Single	1	8,33	1	14,29	0	0,00	2	6,67	
Education									
Elementary	8	66,67	7	100	4	13,33	19	63,33	0,116
Junior high school	1	8,33	0	0,00	4	13,33	5	16,77	
Senior high school	1	8,33	0	0,00	2	6,67	3	10,00	
Bachelor	2	16,67	0	0,00	1	3,33	3	10,00	
Job									
Civil servent	2	16,77	1	14,29	1	3,33	4	13,33	0,831
Privat employee	1	8,33	0	0,00	2	6,67	3	10,00	
Other informal jobs	3	25,00	4	57,14	2	2,00	9	30,00	
Jobless	6	50,00	2	28,57	6	20,00	14	46,67	

Table 2. Parameter input of the Markov model for colorectal cancer based on the clinical pathway

Parameter	Base-case value	Source
Transition probabilities (Tp) of chemotherapy alone		
Tp from progression-free to progression-free	0,8553	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression-free to progression	0,1198	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression-free to death	0,0247	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression to progression	0,0681	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression to death	0,3189	Calculated from OS and FPS (Aparicio et al., 2018)
Transition probabilities (Tp) of chemotherapy plus Bevacizumab		
Tp from progression-free to progression-free	0,9006	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression-free to progression	0,0794	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression-free to death	0,0198	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression to progression	0,8593	Calculated from OS and FPS (Aparicio et al., 2018)
Tp from progression to death	0,1406	Calculated from OS and FPS (Aparicio et al., 2018)
Cost (US$)		
Direct medical cost (DMC)		
DMC progression-free chemotherapy	4.808	Billing at Dr. Sardjito Hospital
DMC progression-free chemotherapy + Bevacizumab	9.221	Billing at Dr. Sardjito Hospital
DMC progression chemotherapy	7.059	Billing at Dr. Sardjito Hospital
DMC progression chemotherapy + Bevacizumab	11.130	Billing at Dr. Sardjito Hospital
Non–direct medical cost (NDMC)		
NDMC progression-free state chemotherapy	1.329	Interviews with patients
NDMC progression-free state chemotherapy + Bevacizumab	1.329	Interviews with patients
NDMC progression state chemotherapy	1.723	Interviews with patients
NDMC progression state chemotherapy + Bevacizumab	1.723	Interviews with patients
Indirect cost (IC)		
IC progression-free state chemotherapy	318	Interviews with patients
IC progression-free state chemotherapy + Bevacizumab	318	Interviews with patients
IC progression state chemotherapy	401	Interviews with patients
IC progression state chemotherapy + Bevacizumab	401	Interviews with patients
Utility		
Progression free state chemotherapy	0,639	Interviews with patients
Progression chemotherapy	0,588	Interviews with patients
Progression-free state chemotherapy + Bevacizumab	0,793	Kristin et al. (2021)
Progression-state chemotherapy + Bevacizumab	0,659	Kristin et al. (2021)
Discount Rate		
Cost	0,03	KPTK (2022)
Utility	0,03	KPTK (2022)

Table 3. Estimated cost (US$)

Parameters	FOLFOX		FOLFIRI		XELOX		All	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Direct medical cost	*6573*	*1477*	*5812*	*1311*	*3755*	*1227*	*5287*	*1895*
Direct medical cost surgery	*1611*	*1220*	*903*	*1220*	*1603*	*1142*	*1401*	*1126*
Room	116	54	55	36	101	67	95	62
Medicine	784	437	183	113	514	479	550	460
Transfusion	62	72	25	1	21	13	38	49
Laboratory	61	40	80	44	55	32	62	36
Radiology	56	39	31	2	51	24	50	28
Sterilization service	58	69	25	34	71	78	49	66
Medical gas services	13	6	15	1	16	8	14	8
Surgery	556	288	638	116	693	397	710	422
Anasthesi services	146	42	74	5	138	50	117	66
Consultant visit specialist	35	36	83	77	47	29	42	38
Nursing services	76	51	30	12	70	43	65	44
Radiodiagnostic services	53	0	135	50	169	32	100	81
Cost EKG	4	0	4	0	4	0	4	0
Non-operative services	4	3	26	42	3	3	8	19
Direct medical cost chemotherapy	*5097*	*804*	*5060*	*947*	*2152*	*349*	*3933*	*1780*
Room	653	199	697	218	27	0	412	354
Medicine	1381	254	1300	624	0	0	1494	703
Transfusion	748	381	371	401	113	311	683	449
Laboratory	362	153	433	116	324	128	366	138
Consultant visit specialist	352	186	330	80	89	0	245	176
Nursing services	286	68	262	71	0	0	331	251
Cost EKG	44	0	44	0	44	0	44	0
Chemotherapy	1137	0	1137	0	943	0	1059	97
Nutritional cost	42	0	21	23	7	16	42	0
Patient waiting rates	11	3	9	2	0	0	10	3
Other cost	90	46	54	42	48	63	96	36

Direct non-medical cost	*1799*	*1762*	*2742*	*4171*	*2033*	*2376*	*2079*	*2539*
Direct non-medical surgery	*483*	*438*	*706*	*1043*	*601*	*675*	*574*	*664*
Transportastion	391	441	622	1047	504	686	482	670
Parking	7	1	2	0	3	9	2	6
Meal	90	22	81	13	94	22	90	20
Direct non-medical cost of chemotherapy	*474*	*443*	*725*	*1045*	*549*	*692*	*554*	*673*
Transportastion	391	441	622	1047	504	686	482	670
Parking	0	0	0	0	0	0	0	0
Meal	82	37	100	15	42	14	70	30
Direct non-medical cost on the onpatient	842	882	1311	2084	883	1058	952	1226
Transportastion	782	881	1245	2095	839	1055	898	1212
Parking	2	1	2	3	2	4	1	3
Meal	59	22	64	24	42	14	52	21
Indirect cost	*402*	*205*	*420*	*163*	*314*	*190*	*373*	*199*
Indirect cost of surgery	*21*	*11*	*19*	*9*	*26*	*14*	*23*	*12*
Loss productivity patient	15	11	20	9	11	10	9	11
Loss productivity companion	16	8	13	12	16	11	14	10
Indirect cost of chemotherapy	*235*	*144*	*277*	*112*	*120*	*92*	*191*	*144*
Loss productivity patient	177	144	267	7	44	41	64	97
Loss productivity companion	229	81	286	176	96	56	141	129
Indirect cost on patient	146	92	124	50	187	101	159	82
Loss productivity patient	3	5	11	4	6	6	5	6
Loss productivity companion	117	53	88	79	149	35	99	70
Total cost	*9045*	*2284*	*8974*	*4757*	*6102*	*2795*	*6688*	*3939*

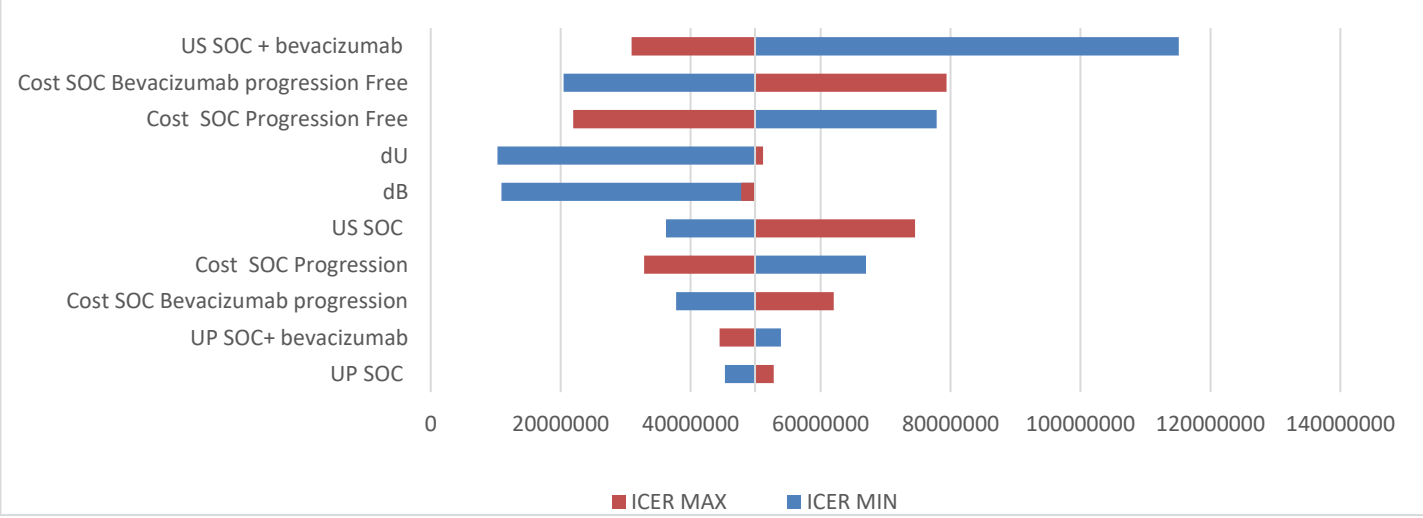

Figure 2. Tornado diagram

However, in this study, we did not investigate the potential impact of these variables on a patient's survival outcomes. In terms of cost-utility analysis, we note limitations associated with the methodology. The utility parameters of patients receiving Bevacizumab adjunctive therapy were not specific to mCRC. Cost and utility data were also obtained from only one hospital, which may not be enough to capture the variation in Indonesia. Understanding the uncertainty within this parameter, we evaluate by running univariate sensitivity analysis with 1,000 simulations.

4. Conclusions

The value of ICER for the addition of Bevacizumab to standard chemotherapy is US$ 3.098 per QALY. Considering this value is below the threshold of 3 times Indonesia's GDP per capita in 2022, which is US$ 13.890 the addition of Bevacizumab to standard chemotherapy is considered cost-effective for KRAS-mutant colorectal cancer patients in Indonesia.

5. Acknowledgement

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6. Statement of Ethics

The study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Gadjah Mada University, Sardjito General Hospital, Ref.No.:KE/FK/0218/EC/2024.

7. References

Andriani Y, Kristina SA, Wiedyaningsih C. 2021. Estimasi biaya pengobatan langsung penyakit kanker di Indonesia: Estimasi direct medical cost (DMC), *Majalah Farmasetik*, 17(3), 251-255.

Aparicio T, Bouch ´O, Taieb J. 2017. Bevacizumab + chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: A randomized phase II trial PRODIGE 20 study results, *Annals of Oncology*, 29(1), 133-138.

Azzani M, Roslani AC, Su TT. 2016. Financial burden of colorectal cancer treatment among patients and their families in a middle-income country, *Support Care Cancer*, 24(10),4423-4432.

BPS. 2023. Pertumbuhan Ekonomi Indonesia Triwulan IV-2022. Badan Pusat Statistik, Jakarta.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA: A Cancer Journal for Clinicians*, 68(6), 394-424.

Byun JY, Yoon SJ, Oh IH, Kim YA, Seo HY, Lee YH. 2014. Economic Burden of Colorectal Cancer in Korea, *Journal of Preventive Medicine and Public Health*, 47(2), 84–93.

Cunningham D, Lang I, Marcuello E. 2013. Bevacizumab plus capecitabine versus Capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): An open-label, randomised phase 3 trial, *Lancet Oncology*, 14(11), 1077-1085.

Ferlay J, Ervik M, Lam F, Colombet M. 2020. Cancer Today (powered by GLOBOCAN 2018). International Agency for Research on Cancer.

Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP. 2007. Bevacizumab in Combination with Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group study E3200, *Journal of Clinical Oncology*, 25(12), 1539-1544.

Heinemann V, von Weikersthal LF, Decker T. 2014. FOLFIRI plus cetuximab versus FOLFIRI plus Bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial, *Lancet Oncology*, 15, 1065-1075.

Kemenkes RI. 2017. Pedoman Nasional Pelayanan Kedokteran Tata Laksana Kanker Kolorektal. Kementerian Kesehatan Republik Indonesia, Jakarta.

KPTK. 2022. Pedoman Umum Penilaian Teknologi Kesehatan di Indonesia. Pusat Kebijakan Pembiayaan Dan Desentralisasi Kesehatan Badan Kebijakan Pembangunan Kesehatan Kementerian Kesehatan RI, Jakarta.

Kristin E, Khoe LC, Endarti D, Widayati K. 2021. Economic evaluation of adding Bevacizumab to chemotherapy for metastatic colorectal cancer (mCRC) patients in Indonesia, *Asian Pacific Journal of Cancer Prevention*, 22(6), 1921-1926.

NCCN. 2023. NCCN Clinical Practice Guidelines in Oncology Colon Cancer.

Purba FD, Hunfeld JAM, Iskandarsyah A. 2017. The Indonesian EQ-5D-5L value set, *PharmacoEconomics*, 35(11), 1153–1165.

Setiawan D, Endarti D, Suwantika A. 2017. *Farmakoekonomi Modeling*. UM Purwokerto Press, Purwokerto.

Tappenden P, Jones R, Paisley S, Carroll C. 2007. The cost-effectiveness of Bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales, European *Journal of Cancer*, 43(17), 2487-2494.

Tran BT, Choi KS, Nguyen TX. 2020. The direct and indirect costs of colorectal cancer in Vietnam: An economic analysis from a social perspective, *International Journal of Environmental Research and Public Health*, 18(1), 12.

Ungari AQ, Pereira LRL, Nunes AA, Peria FM. 2017. Cost-effectiveness analysis of XELOX versus XELOX plus Bevacizumab for metastatic colorectal cancer in a public hospital school, *BMC Cancer*, 17(1), 691.

Vahdatimanesh Z, Zendehdel K, Sari AA, Farhan F, Nahvijou A, Delavari A, Daroudi R. 2017. Economic burden of colorectal cancer in Iran in 2012, *Medical Journal of the Islamic Republic of Iran (MJIRI)*, 31, 115.