

## Economic evaluation of monoclonal antibody in the management of colorectal cancer

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### Abstract

**Objective:** This study aims to determine the cost of colorectal cancer (CRC) management and compare the cost effectiveness of cetuximab and bevacizumab in the management of CRC. **Method:** This economic evaluation study from a societal perspective involves collecting resource utilization data based on the clinical pathway of colorectal cancer management. The cost calculated includes drugs, human resources, administrative, investigations as well as capital cost. Patient's cost was also calculated based on an interview with colorectal cancer patients. Effectiveness estimates for monoclonal antibody (cetuximab and bevacizumab) treatment were modeled from study respondents based on references from other studies. **Results:** Cost of treating a case of colorectal cancer in stage I is RM13,623 (RM12,467-RM14,777), stage II RM19,753 (RM16,734-RM23,520), stage III RM24,972 (RM20,291-RM29,654) and stage IV RM27,163 (RM23,192-RM31,133). Cost of CRC management increase with the increasing stage of the disease (Kruskal Wallis,  $X^2=106$ ,  $p<0.001$ ). Based on estimates of 2671 new cases of CRC, the incremental cost of cetuximab is RM20,556,480 and bevacizumab is RM7,557,953 at 50% stage III and IV as compared to the conventional chemotherapy. The incremental cost per quality adjusted life years gained for cetuximab is RM38,869 and RM14,290 for bevacizumab. Although both types of monoclonal antibody are considered cost effective (based on WHO guidelines of less than three times of GDP), bevacizumab is considered more cost effective than cetuximab. Cost effectiveness was sensitive to the percentage of late stages of CRC. **Conclusions:** Cost of treating late stage of CRC is high and bevacizumab are more cost effective compared to cetuximab in the management of the late stage of CRC.

**Keywords:** economic evaluation; cost effectiveness; colorectal cancer; monoclonal antibody

### Introduction

Colorectal cancer incidence is rapidly increasing in many Asian countries including Malaysia. It is the most common cancer in Malaysian males and the second most common in females after breast cancer. In the year 1998, the incidence rate of colorectal cancer in Malaysia is 11 per 100,000 population and it has increased to 14.5 per 100,000 population in 2006 [1]. Apart from the increasing incidence, the majority of patients presented at the late stage with poor prognosis [2-3]. First National Colorectal Cancer Patients Report showed that in 2008 only 2% of CRC patients were diagnosed at stage I and 3% at stage II. A study in 2005, showed that 53.9% of respondents presented at stage III and IV [3]. This is mainly due to the changes in population's lifestyle such as increase prevalence of smoking, unhealthy diet, lack of exercise [4] and also low level of population's awareness towards health, particularly colorectal cancer as well as absence of population based screening for colorectal cancer in Malaysia [5].

For many years, chemotherapy regimens use in Malaysia has been those with the active 5 fluorouracil (5-FU) and also levamisole. However, since the past few years the new third generation platinum compound, oxaliplatin and a semisynthetic topoisomerase inhibitor, irinotecan have been used for advanced staged colorectal cancer treatment. Introduction of a biologic agent, monoclonal

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antibody such as cetuximab and bevacizumab into the therapeutic landscape of metastatic CRC in which it has been used in conjunction with a chemotherapy regimen for example FOLFOX or FOLFIRI has been proven to be more effective, tailored and better tolerated treatment for advanced stage colorectal cancer in many countries. Cetuximab blocks the epidermal growth factor receptor (EGFR) and bevacizumab binds to vascular endothelial growth factor (VEGF) will suppress the cancer growth. In 60–80% of colorectal cancer cases, there is up regulation or over expression of EGFR gene and this is relevant for cetuximab. However 30–50% of these EGFR are mutated at KRAS gene and they are not responding to cetuximab. Therefore, the use of cetuximab is only for those with KRAS wild type and not mutated KRAS. Cetuximab improves median time to progression from 1.5 months to 4.1 months as well as median survival time from 6.9 months to 8.6 months as compared to conventional chemotherapy [6]. Cetuximab also offers important quality of life benefit in which less deterioration of quality of life scores as compared to conventional treatment and improvement in global health status at 8 weeks post treatment [7].

The addition of bevacizumab to FOLFOX4 has also been proven to improve survival duration from 10.8 months to 12.8 months for patients previously treated with fluoropyrimidine and irinotecan [8], 15.6 months to 20.3 months in combination with irinotecan, Fluorouracil and leucovorin (IFL) as compared to IFL and placebo while adverse effects related to the use of monoclonal antibody are manageable [9]. Monoclonal antibody has been approved to be used in the treatment of advanced colorectal cancer in many developed countries within Asia like Japan, Korea and Singapore [10]. In Malaysia, although it has been registered with National Pharmaceutical Control Bureau Ministry of Health, it is not yet listed in the Ministry of Health Drug Formulary due to the inadequacy of its evidence in effectiveness as well as cost effectiveness within the local settings. Therefore, it cannot be used in the public hospitals. In a scenario where the health care cost is rapidly escalating, evaluation of economic burden related to colorectal cancer treatment and a proper economic evaluation of this new mode of treatment in a local setting is crucial. This study aims to determine the cost of colorectal cancer management from a societal perspective and the cost effectiveness of cetuximab and bevacizumab in conjunction with conventional chemotherapy for the treatment of colorectal cancer.

## Methods

A cross sectional study was done from June to December 2011 in four public tertiary hospitals in the central region of Malaysia which provide surgical and oncology services. Confirmed colorectal cancer patients from out-patient clinic, wards and day care centers were universally selected regardless the stage of the disease or chemotherapy regime. The selection was based on criteria, age more than 18, confirmed diagnosis of colorectal cancer for at least six months, agree to participate and no mental illness.

The first part of the study was to establish a clinical pathway in colorectal cancer management. This is done through a focus group discussions conducted among expert involved in managing colorectal cancer patients such as surgeons, oncologist, pathologist, radiologist and nursing staff. As Malaysia may not have a standard protocol in CRC management, the pathway helped in reducing variation in clinical practice. Subsequently, based on clinical pathways which was developed, resources used were identified and provider's cost was calculated based on activity based costing which includes cost of human resources, chemotherapy drugs which includes related investigations such as KRAS testing, procedures, administrative and radiological as well as hematological testing. Respondents' sociodemographic and financial data were collected through face to face interview and review of medical records. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C-30 was used to evaluate patient's quality of life. In costing analysis, few assumptions were made such as 60% of all CRC in Malaysia are KRAS wild type, MAB were only used for 2nd and 3rd line of treatment, no adverse effect of MAB, and life years saved on bevacizumab and cetuximab were the same.

Effectiveness estimates for monoclonal antibody were modeled from study respondents based on references from studies [7, 11–12]. Modeling was necessary due to the absence of local clinical trial data. The primary health outcome for economic analysis in this study is Life Years Saved. Therefore, the primary health economic outcome is the incremental cost per life years saved of cetuximab and bevacizumab vs conventional chemotherapy. Secondary analysis was performed using quality adjusted life years (QALYs) based on utility values which used physical function scores directly observed from study respondents and life years saved.

## Effectiveness estimates

### *Life expectancy*

Estimation of life expectancy in the conventional chemotherapy group was derived from age specific mortality rate of CRC patients [13] based on life table generated. Estimation of life expectancy in the monoclonal antibody treatment group was calculated based on a study [11], in which survival benefit in cetuximab/ irinotecan is estimated to be 0.18 years. Imputation of this value to the life expectancy of study respondents resulted in life expectancy of CRC patients on both cetuximab and bevacizumab.

### *Life Years Saved (LYS)*

The life expectancy of CRC on conservative chemotherapy are compared to the life expectancy of the normal population to get the life years saved in conservative chemotherapy group, while comparison on life expectancy in both types of treatment (conservative and monoclonal antibody) give rise to life years saved in monoclonal antibody group.

**QALYs**

Based on a formula  $QALYs = LYS \times \text{utility value}$  and physical function score from the EORTC QLQ C-30 represent the utility value for respondents in this study which is on conventional chemotherapy alone and imputation of 8.5% increase in physical function score in combination MAB with conventional chemotherapy group based on study [7], QALYs of both treatment options was calculated and compared to get the QALYs saved of each treatment option.

**Resource utilization and cost data**

Provider’s cost such as drug cost, procedure cost and investigations were calculated based on the clinical pathway of CRC management while overhead cost, administrative cost was included in in-patient hospitalization and out-patient consultation cost based on University Kebangsaan Malaysia Medical Centre (UKMMC) clinical cost modeling software output which is RM922 per in-patient per day and RM283 per outpatient clinic visit. For in-patient cost, the median duration of hospitalization for each stage based on the study respondents were multiplied by RM922 and for out-patient cost, RM283 was multiplied by the average number of clinic visits for each stage based on clinical pathways. Patient’s costs included are hospital/clinic fee, cost of medications includes complementary and traditional medicines and other indirect costs such as transportation cost, food and caregiver’s cost. Median patient cost of RM661 was used to calculate the total cost of CRC management. The total cost of CRC management of each stage of the disease was the sum cost of provider’s cost (from clinical pathways, in-patient cost, out-patient cost) and patient’s cost.

**Sensitivity analysis**

One way sensitivity analysis were undertaken to capture the uncertainties in the percentage of patients with stage III and IV in which monoclonal antibody should be given.

**Results**

**Sociodemographic profiles of respondents**

A total of 160 respondents involved in the study. The majority came from Hospital Tuanku Jaafar (33.8%), Hospital Kuala Lumpur (29.4%), UKMMC (29.3%) and Hospital Selayang (7.5%). Male accounted for 57.5% of all respondents and female another 42.5%. The mean age of respondent is  $58.47 \pm 12.04$  years and the majority are in the younger old age group which is 55–64 years (36.3%) while only 9.3% age >75 years old. The mean age by stage is stage II  $66.50 \pm 9.84$  years, stage III  $57.76 \pm 11.78$  years and stage IV  $57.63 \pm 12.29$  years. Statistical analysis using ANOVA test shows that there is a significant difference in the mean age of respondents of different stages and post hoc analysis showed these differences occurred between stage II and stage III as well as stage II and stage IV in which mean age is younger in stage III and stage IV as compared to stage II. Majority is in the late stage of CRC (stage III and IV) 91.2% and 8.8% in stage II. According to

ethnicity Malays are 60.6% followed by Chinese 28.8%, Indian 10.0% and Sikh 0.6%. Most of them educated up to secondary school (49.4%), only 6.9% never attend formal school. Most of the respondents were no longer working (65.6%) in which 45.7% had to give up working due to their disease, 24.8% pensioner, 14.3% full time housewife, 8.6% never had any job, 5.8% only work when their health permits and 1% student at a university. As expected 55.6% of respondent did not have monthly income which gives median income of the respondents RM0 but for another 44.4% who have monthly income, the median income is RM1700 (IQR2300). However, a majority (56.3%) has an income between RM0-RM499, 5.6% between RM500-RM999, 8.8% between RM1000-RM1499, 8.1% between RM1500-RM1999, 3.8% between RM2000 RM2499, 3.8% between RM2500-RM2999 and 13.8% have an income of more than RM3000 per month.

**Cost estimates**

The societal cost of CRC management of different strategies is presented in Table 1. The mean cost of treating stage I CRC is RM13622, stage II RM19752, stage III RM24972 and stage IV RM27377. This cost is higher when combination chemotherapy which combines conventional chemo and monoclonal antibody is going to be used. The mean cost of CRC management using cetuximab for stage III is RM53962 and RM37734 if bevacizumab is going to be used. For stage IV the cost is RM62124 with cetuximab and RM45896 with bevacizumab.

**Table 1** Cost of CRC management by different strategies

Stage	Mean cost (RM)		
	Conventional chemotherapy	Combination chemotherapy with monoclonal antibody	
		Cetuximab	Bevacizumab
I	13622	-	-
II	19752	-	-
III	24972	53962	37734
IV	27163	62124	45896
Mean	21377	58043	41815

**Economic burden of CRC management**

Based on the CRC incidence rate of 14.5 per 100,000 populations [1] and the number of at risk population in Malaysia are 18,423,700, the estimated new cases of CRC a year is 2671 cases. Therefore, by using the percentage of cases for each stage of a study [2] whereby 2.8 % stage I, 35.5% stage II, 40.2% stage III, 21.5% stage IV

The economic burden of CRC management of new cases alone is estimated at RM62, 134,641 per year using conventional chemotherapy. Based on the estimated number of CRC new cases per year, estimated CRC with KRAS wild type at 60% and the percentage of CRC in stage

III and IV between 50–90%, the economic burden of CRC management using monoclonal antibodies (cetuximab) is RM82, 691,021 at 50%, RM97, 990,155 at 70% and RM113, 231,246 at 90% stage III and IV. The cost of using bevacizumab at 50% stage III and IV is RM69, 692,473, RM79, 782,451 at 70% and RM89, 830,614 at 90%.

*Effectiveness estimates*

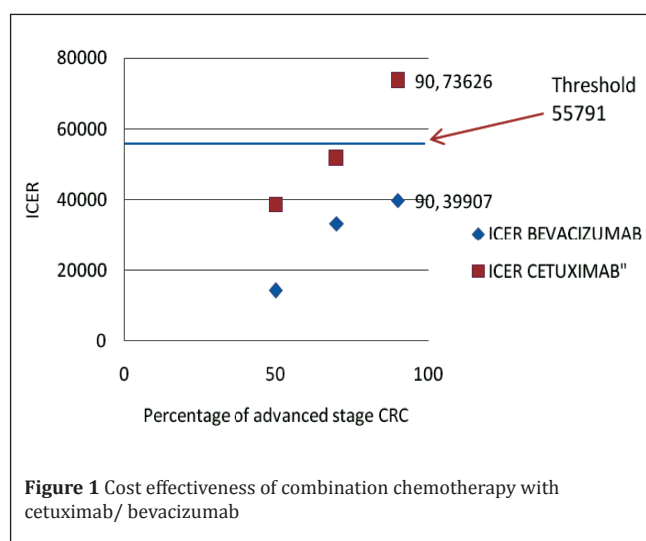
Based on median life expectancy, mean life years saved of respondents in this study are  $3.34 \pm 1.30$  years and with a survival benefit of 0.18 years on monoclonal antibody [11], the mean life years saved in patients on combination chemotherapy and monoclonal antibody are  $3.46 \pm 3.10$  years. Therefore, secondary analysis which calculates the QALYs saved for each treatment option showed that median QALYs saved for conventional chemotherapy is  $0.057 \pm 0.01$  and  $0.255 \pm 0.25$  in combination with monoclonal antibody.

*Cost effectiveness analysis*

Cost effectiveness analysis compared the three different treatment options which are conventional chemotherapy, combination chemotherapy with cetuximab and combination chemotherapy with bevacizumab. The costs considered are the total cost of managing new cases of CRC a year. The effectiveness estimates are life years saved and QALYs. One way sensitivity analysis was done at scenarios where different percentages of stage III and IV of CRC which are 50%, 70% and 90% were considered. Table 2 showed that compared to the conventional chemotherapy, combination chemotherapy with bevacizumab at 50% of stage III and IV of CRC has the lowest cost per life years saved (LYS) as well as cost per QALYs (RM7541 and RM8179). Cost per LYS and cost per QALYs is higher when the percentage of stage III and IV CRC increase.

*Incremental cost effectiveness*

Based on the total cost of CRC management for new cases, analysis showed that with the additional cost of RM7, 557,951 to treat a total number of new cases of CRC with combination chemotherapy with bevacizumab at 50% of stage III and IV CRC and a total of 528.86 QALYs saved as compared to the conventional chemotherapy, the incremental cost per QALYs saved (ICER) is RM14, 290. One way sensitivity analysis involving a proxy of cost variances revealed that cost effectiveness is sensitive to the percentage of stage III and IV of CRC. Threshold analysis showed cost effectiveness of combination chemotherapy with bevacizumab remains below the prespecified threshold (3 times gross domestic product per capita) only if percentage of advanced stage of CRC is between 50–90 percent but in combination with cetuximab is between 50–70 percent (Table 3) (Figure 1).



**Figure 1** Cost effectiveness of combination chemotherapy with cetuximab/ bevacizumab

**Table 2** CEA of three treatment strategies of CRC and sensitivity analysis

Strategies	Total cost ( RM)	Total life years saved (LYS)	Cost/LYS (RM)	Total QALYs	Cos/QALYs (RM)
Conventional	62,134,541.65	8,921.00	6,964.97	7,826.03	7,939.47
Cetuximab 50%	82,691,021.4	9,241.66	8,947.64	8,520.49	9,704.96
Cetuximab 70%	97,990,155.36	9,241.66	10,603.09	8,520.49	11,500.53
Cetuximab 90%	113,231,246.10	9,241.66	12,252.26	8,520.49	13,289.29
Bevacizumab 50%	69,692,473.50	9,241.66	7,541.12	8,520.49	8,179.40
Bevacizumab 70%	79,782,451.56	9,241.66	8,632.91	8,520.49	9,363.59
Bevacizumab 90%	89,830,614.26	9,241.66	9,720.18	8,520.49	10,542.89



**Table 3** Incremental cost effectiveness ratio estimated from the model

<i>Strategies</i>	<i>Total cost (RM)</i>	<i>Incremental cost (RM)</i>	<i>Total QALYs saved</i>	<i>Incremental QALYs saved</i>	<i>ICER</i>
Conventional	62,134,541.65	-	152.25	-	-
Cetuximab 50%	82,691,021.4	20,556,479.75	681.11	528.86	38,869.42
Bevacizumab 50%	69,692,473.50	7,557,931.85	681.11	528.86	14,290.99
Bevacizumab 70%	79,782,451.56	17,647,909.91	681.11	528.86	33,369.72

**Discussion**

Combination of monoclonal antibodies with the conventional chemotherapy such as fluorouracil, oxaliplatin or irinotecan has been proven to be an effective therapeutic intervention in CRC patients who have progressed after conventional chemotherapy. Therefore, the combination of monoclonal antibodies with conventional chemotherapy is appropriate to be used as a second or third line setting. However, to introduce this new strategy for CRC treatment in Malaysian scenario requires proper clinical and cost effectiveness evidence in a local setting.

In this analysis, modeling was necessary due to the absence of local data on survival of CRC patients treated with monoclonal antibody for a direct comparison. Therefore, imputation of survival benefit of 0.18 years [11] to the respondent’s data is necessary. Although this poses some drawbacks in the result this is unavoidable because new treatment in oncology offer particular methodological problem for economic analysis as a standard comparator is absent or highly variable across treatment centers and new agent usually add new elements in the treatment pathways. Other important findings are the advanced stage of CRC are significantly higher in a younger age population (ANOVA, F=3.53, p=0.032) which reflects the lack of awareness and risky behavior among this group of population which should be addressed in health promotion activities by the authority.

The societal cost of CRC management of conventional chemotherapy in this study ranges between RM13, 622 to RM27, 163 with an average of RM21, 377. This is lower than an average cost to manage a case of lung cancer per year in Malaysia which is RM44, 725 [14]. Early stage of CRC which is stage I and II, most of the cases they only need surgical intervention whereas in lung cancer most of the cases need chemotherapy that incur a very high cost. In cervical cancer, the average cost of treatment is RM25, 623 per case per year [15].

Cost effectiveness analysis showed that the incremental cost effectiveness ratio per LYS and Incremental cost effectiveness ratio per QALY saved are higher in the

combination chemotherapy with either cetuximab or bevacizumab as compared to the use of conventional chemotherapy suggesting that in general treating CRC with conventional chemotherapy is still cost effective compared to combination with monoclonal antibody. This finding is almost similar to other studies done in developed countries [12] and they conclude that the incremental cost effectiveness ratio of cetuximab over best supportive care alone is high. In Japan study also found that ICER for cetuximab plus fluorouracil/ leucovorin combination treatment was also high compared to other chemotherapies for metastatic CRC [16]. However, when we compare the six treatment option scenarios of adding a monoclonal antibody to the conventional chemotherapy alone in which the scenarios vary in the percentage of stage III and IV showed that the most cost effective option among them is the combination treatment with bevacizumab at 50% stage III and IV. This is because in Malaysia the cost of bevacizumab per cycle of treatment is lower compared to cetuximab and percentage of stage III and IV is one of the cost effectiveness drivers. Higher percentage of late stages will lower the cost effectiveness of the combination treatment (Table 2).

The incremental cost per life years saved of RM23, 569 for bevacizumab in treating CRC in this study is lower compared to other studies done in developed countries. In a UK study showed that the incremental cost per life years gained for cetuximab is about £42,975 and since their acceptable threshold is between £25,000 - £30,000, cetuximab is not considered a cost effective treatment for metastatic CRC in UK [17]. In Malaysia, since there is no threshold set as yet, therefore three times per capita gross domestic product (GDP) can be used as a guide [18]. In 2007, Malaysian per capita GDP is RM18, 597 and three times per capita GDP is RM55, 791. Based on that, combination chemotherapy with bevacizumab is a cost effective treatment provided that stage III and IV CRC are below 70% of the total cases. However, cetuximab is only cost effective when stage III and IV CRC are below 50% of the total cases. This result is not in line with other studies done in developed countries because the population sample in this study includes all stages of CRC and this caused the total cost to be lower than expected while other studies mainly done in the advanced stage CRC.

## Conclusion

Incremental costs associated with the combination of chemotherapy with monoclonal antibody in treating CRC is high compared to the current conventional chemotherapy. Combination chemotherapy with bevacizumab is very cost effective when advanced stage CRC is below 70% and combination chemotherapy with cetuximab is cost effective only when advanced stage less than 50% of the total number of CRC patients.

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## Conflict of interest

The authors wish to express that they have no conflict of interest.

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