Cost-Effectiveness of Adjuvant FOLFOX and 5FU/LV Chemotherapy for Patients with Stage II Colon Cancer

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Purpose*. We evaluated the cost-effectiveness of adjuvant chemotherapy using 5-fluorouracil, leucovorin (5FU/LV), and oxaliplatin (FOLFOX) compared with 5FU/LV alone and 5FU/LV compared with observation alone for patients who had resected stage II colon cancer.* ***Methods****. We developed 2 Markov models to represent the adjuvant chemotherapy and follow-up periods and a single Markov model to represent the observation group. We used calibration to estimate the transition probabilities among different toxicity levels. The base case considered 60-year-old patients who had undergone an uncomplicated hemicolectomy for stage II colon cancer and were medically fit to receive 6 months of adjuvant chemotherapy. We measured health outcomes in quality-adjusted life-years (QALYs) and estimated costs using 2007 US dollars.* ***Results****. In the base case, adjuvant chemotherapy of the FOLFOX regimen had an incremental cost-effectiveness ratio (ICER) of $54,359/ QALY compared with the 5FU/LV regimen, and the 5FU/ LV regimen had an ICER of $14,584/QALY compared with the observation group from the third-party payer perspective. The ICER values were most sensitive to 5-year relapse probability, cost of adjuvant chemotherapy, and the discount rate for the FOLFOX arm, whereas the ICER value of 5FU/LV was most sensitive to the 5-year relapse probability, 5-year survival probability, and the relapse cost. The probabilistic sensitivity analysis indicates that the ICER of 5FU/LV is less than $50,000/QALY with a probability of 99.62%, and the ICER of FOLFOX as compared with 5FU/LV is less than $50,000/QALY and $100,000/QALY with a probability of 44.48% and 97.24%, respectively.* ***Conclusion****. Although adjuvant chemotherapy with 5FU/LV is cost-effective at all ages for patients who have undergone an uncomplicated hemicolectomy for stage II colon cancer, FOLFOX is not likely to be cost-effective as compared with 5FU/LV.* ***Key words:*** *colon cancer; stage II; cost-effectiveness; Markov model; calibration.* **(Med Decis Making 2013;33:521– 532)**

In 2012, 143,000 new cases of colorectal cancer were estimated.[1] Behind lung cancer, colorectal cancer is the second-leading cause of cancer death.[2,3] Survival rates over the past 2 decades have improved, primarily due to advances in screening, diagnosis, and treatment. For example, the introduction of 5-fluorouracil (5FU)–based adjuvant chemotherapy in the late 1980s reaped a 30% mortality reduction for stage III colon cancer.[2] Since 1990, 5FU-based adjuvant chemotherapy has been acknowledged as the standard of care for stage III colon cancer. The FOLFOX regimen (oxaliplatin, 5FU, and leucovorin) has been established as a widely accepted standard for adjuvant therapy in stage III colon cancer based on the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer

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(MOSAIC) trial since its publication in 2004.[4] The cost-effectiveness of adjuvant FOLFOX compared with 5FU/LV (5FU and leucovorin) in the stage III setting has been analyzed and described by Eggington and colleagues,[5] with an acceptable cost/quality-adjusted life year (QALY) of £2970 ($3800) for the addition of oxaliplatin.

The benefit of 5FU/LV-based adjuvant chemotherapy for unselected stage II colon cancer patients is uncertain. To address this uncertainty, several studies have focused on estimating the magnitude of the benefit. An earlier study included 1016 stage II patients and found that the 5-year survival was 80% for untreated patients and 82% for patients treated with FU + leucovorin, where the survival difference was not statistically significant.[6] The QUick and Simple And Reliable (QUASAR) study conducted a large-scale randomized trial on 3239 patients (91% with stage II disease) to explore the effectiveness of adjuvant chemotherapy for stage II colorectal cancer.[7] This study found that 5-year survival without and with adjuvant chemotherapy is 80% and 83.6%, respectively. A recent study demonstrated the potential utility of adjuvant chemotherapy in stage II colon cancer based on the data of 20,898 patients from 18 randomized trials. This study reported that 8-year survival of patients undergoing adjuvant chemotherapy improved from 66.8% to 72.2% ($P = 0.026$) when compared with observation alone.[8]

There is also uncertainty around the risk/benefit of adding oxaliplatin to 5FU for adjuvant treatment of stage II colon cancer, which has been considered in the MOSAIC study.[9] The MOSAIC study suggests an improvement from 84.3% to 87% of 3-year disease-free survival in stage II colon cancer patients with the addition of oxaliplatin to 5FU/LV treatment: a small, albeit consistent survival benefit. However, the benefit up to this point has been too small to merit the widespread use of adjuvant chemotherapy for stage II colon cancer.

Overall, although these studies found a small benefit in overall survival with adjuvant chemotherapy for both 5FU/LV and FOLFOX in stage II colon cancer,[10] it is still not clear whether this small gain outweighs the additional burden of this treatment due to cost and toxicity.[11] In the most recently updated data of the MOSAIC trial, the benefit of FOLFOX over 5FU/LV was small in stage II disease, and no comparison was made to observation alone.[12] Therefore, adjuvant chemotherapy using 5FU/LV may have a better incremental cost-effectiveness ratio (ICER) for stage II colon cancer since it has similar efficacy and is less costly than oxaliplatin-containing regimens. The purpose of this study is to investigate whether the use of FOLFOX as compared with 5FU/LV and 5FU/LV as compared with observation is cost-effective for patients who have had primary surgery for stage II colon cancer.

METHODS

We constructed 2 Markov models to estimate the incremental cost-effectiveness of treating postsurgery patients who had stage II colon cancer with adjuvant chemotherapy using FOLFOX compared with 5FU/LV and those using 5FU/LV compared with no treatment. We performed an analysis from the third-party payer perspective, which includes only the direct medical costs. We used QALYs to evaluate the effectiveness of the treatments. We considered 60-year-old patients with stage II colon cancer as our base case because of the median ages of the 2 important data sources in our research: QUASAR[7] and MOSAIC.[12] They had undergone a hemicolectomy for stage II colon cancer, recovered, and were medically fit to receive 6 months of adjuvant FOLFOX or 5FU/LV chemotherapy. We discounted costs and benefits by 3% per year.

Markov Models

We built 2 Markov models that represent the adjuvant chemotherapy period and follow-up period for patients who had stage II colon cancer, and the same Markov model applies to both regimens with different parameters. We individually simulated 5000 patients using the Markov models and implemented the simulation in the JAVA programming environment.

Adjuvant Chemotherapy Period Model. Our Markov model for the adjuvant chemotherapy period consists of the following 5 states (Figure 1A): well (state 1), minor toxicity (state 2), major toxicity (state 3), quitting adjuvant chemotherapy (state 4), and death due to adjuvant chemotherapy (state 5). We assumed that the transitions among those 5 states were Markovian. Following the Common Toxicity Criteria of the National Cancer Institute,[13] version 3, we used 3 levels (well, minor toxicity, and major toxicity) to represent the toxicity of adjuvant chemotherapy where ''well'' represents no toxicity (grade 0), ''minor toxicity'' represents mild or moderate adverse effects (grade 1 and 2), and ''major toxicity'' represents severe or life-threatening adverse effects (grade 3 and 4).[14] We set the cycle length of the Markov model as 1 month—that is, the transitions occur
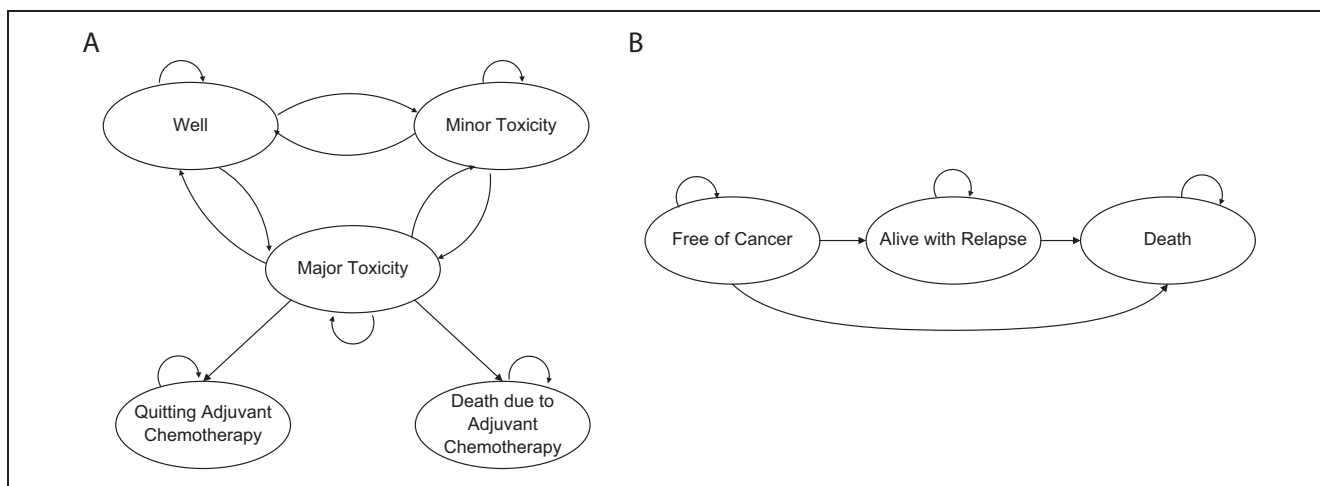
Figure 1. Adjuvant chemotherapy and follow-up period models. (A) Incremental cost-effectiveness ratio (ICER) of FOLFOX as compared with 5FU/LV. (B) ICER of 5FU/LV as compared with observation. 5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin.

on a monthly basis. The Markov model runs for 6 months. To have truly stage II disease, it would have to be established with surgery and pathologic analysis of the colon and lymph nodes. The surgery that is performed is a hemicolectomy. We initialize all patients to begin in state 1 (free of cancer) at the start of the adjuvant chemotherapy since we model the patients who had undergone an uncomplicated hemicolectomy for stage II colon cancer.

Follow-up Period Model. Patients without adjuvant chemotherapy (observation group) move directly to the follow-up period after the resection. Patients who receive adjuvant chemotherapy (chemotherapy groups) enter the follow-up period after the adjuvant chemotherapy, which lasts for 6 months. We modeled the follow-up period using the following 3 states (Figure 1B): free of cancer (state 1), alive with relapse (state 2), and death (state 3). The total follow-up time is 5 years. We set the cycle length as 1 year for the observation group. On the other hand, since the chemotherapy group undergoes treatment for 6 months, we set the follow-up period as 4.5 years, where the cycle length is 6 months for the first cycle and 1 year for the subsequent cycles. We apply annual transition probabilities for the initial 6-month cycle. Therefore, the overall duration for the chemotherapy group is also 5 years.

Assumptions

Patients endure different grades of toxicity during chemotherapy due to toxicity accumulation and

toxicity alleviation measures such as dose reduction, delay, and growth factor use, if necessary. To accurately evaluate the QALYs of the patients during the chemotherapy period, it is necessary to model toxicity dynamically instead of setting it constant during the 6 months. However, the lack of the intermediate toxicity data hinders such an attempt. To overcome this problem, we used *calibration*, a commonly used method in cancer simulation models,[15–17] to estimate the intermediate toxicity parameters using final toxicity values (i.e., overall percentages of well (P_w)/ minor toxicity (P_{mi})/major toxicity (P_{ma})/quitting adjuvant chemotherapy (P_q)/death due to adjuvant chemotherapy (P_d)),[18] which is described in more detail in the next subsection. During months 1 to 6, we modeled the toxicity progression using the Markov model representing the adjuvant chemotherapy period and assumed that no patients relapse. This is justified because relapse is unlikely at this point.

For the follow-up period model, we ignored the differences between the relapse probability of the patients in the chemotherapy groups and that of the patients in the observation group after 5 years due to limited data. More specifically, we assumed that the relapse rate after year 5 is zero, and we calculated the life expectancy of the patients without relapse at the end of the follow-up period using US Life Tables.[19] However, the patients who have relapsed and are alive at the beginning of the sixth year continue to be simulated in the follow-up model using respective mortality probabilities until they reach the death state. Note that each patient has been simulated individually in the Markov simulation model.

Table 1 Parameters Used for Calibration

Parameters	Value, %		Data Source
	FOLFOX	5FU/LV	
Overall toxicity after adjuvant chemotherapy			
Percentage of major toxicity P_{ma}	50.9	6.6	André and others, 2004[4]
Percentage of minor toxicity P_{mi}	41.1	60.3	
Percentage of well P_w	8.0	33.1	
Percentage of death due to adjuvant chemotherapy P_d	0.5	0.5	de Gramont and others, 2007[36]
Percentage of quitting adjuvant chemotherapy P_q	25.3	13.5	André and others, 2009[12]

5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin.

Calibration Process

We denoted the transition probabilities of the adjuvant chemotherapy model by $P_{w\text{-}w}$, $P_{w\text{-}mi}$, $P_{w\text{-}ma}$, $P_{mi\text{-}w}$, $P_{mi\text{-}mi}$, $P_{mi\text{-}ma}$, $P_{ma\text{-}w}$, $P_{ma\text{-}mi}$, $P_{ma\text{-}ma}$, $P_{ma\text{-}q}$, and $P_{ma\text{-}d}$, where subscript w represents the well state, mi represents the minor toxicity state, ma represents the major toxicity state, q represents quitting the adjuvant chemotherapy state, and d represents death due to the adjuvant chemotherapy state. For example, $P_{w\text{-}mi}$ represents the probability that a patient who is in the well state in the current month will move to the minor toxicity state in the next month. Among these probabilities, we calculated $P_{w\text{-}w}$ as 0.66 directly using the following equation: $P_w = (P_{w\text{-}w})$,[6] where P_w is shown in Table 1. We derived some other probabilities ($P_{w\text{-}mi}$, $P_{mi\text{-}ma}$, and $P_{ma\text{-}mi}$) directly as well—for example, $P_{w\text{-}mi} = 1 - P_{w\text{-}w} - P_{w\text{-}ma}$. To estimate the remaining parameters, we used a calibration method,[16] which proceeds as follows:

Step 1: We defined a plausible value range and a step size for each probability parameter based on expert opinion. For example, we set $P_{w\text{-}ma}$ in [0.01, 0.1] and $P_{ma\text{-}d}$ in [0, 0.04] with a step size of 0.01, $P_{mi\text{-}w}$ in [0.30, 0.80], $P_{mi\text{-}mi}$ in [0.20, 0.50], $P_{ma\text{-}w}$ in [0, 0.30], $P_{ma\text{-}ma}$ in [0, 0.30], and $P_{ma\text{-}q}$ in [0, 0.20] with a step size of 0.02.

Step 2: Using each combination of these parameters, we simulated the toxicity transition trajectories for a cohort of 5000 patients. We classified each patient according to his or her most advanced toxicity level. For example, after 6 months, if the patient experienced well, minor toxicity, and major toxicity, we classified her or him as a patient with major toxicity. Then, for each parameter combination, we calculated the corresponding values from the output statistics—that is, overall percentages of well (P'_w), minor toxicity (P'_{mi}), major toxicity (P'_{ma}), quitting adjuvant chemotherapy (P'_q), and death due to adjuvant chemotherapy (P'_d), which are presented in Table 1.

Step 3: For each combination of these parameters, we compared the values of the corresponding output statistics (P'_{ma}, P'_{mi}, P'_w, P'_d, and P'_q) with the actual data (P_{ma}, P_{mi}, P_w, P_d, and P_q; Table 1) by calculating the total square error (TSE).[14] We then selected the parameter combination with the minimum TSE.

$$TSE = (P_{ma} - P'_{ma})^2 + (P_{mi} - P'_{mi})^2 + (P_w - P'_w)^2 + (P_d - P'_d)^2 + (P_q - P'_q)^2.$$

Our calibration process has generated the following parameter values that are used in the adjuvant chemotherapy period model: $P_{w\text{-}ma} = 0.03$, $P_{mi\text{-}w} = 0.36$, $P_{mi\text{-}mi} = 0.32$, $P_{ma\text{-}w} = 0.1$, $P_{ma\text{-}ma} = 0.3$, $P_{ma\text{-}q} = 0.2$, and $P_{ma\text{-}d} = 0.01$ for the FOLFOX regimen and $P_{w\text{-}ma} = 0.03$, $P_{mi\text{-}w} = 0.36$, $P_{mi\text{-}mi} = 0.32$, $P_{ma\text{-}w} = 0.1$, $P_{ma\text{-}ma} = 0.3$, $P_{ma\text{-}q} = 0.2$, and $P_{ma\text{-}d} = 0.01$ for the 5FU/LV regimen.

Base-Case Parameters

All parameters used in the base-case analysis, including probabilities, utilities, and costs, are listed in Tables 1 to 5.

Several clinical studies report on the incidence of toxic effects due to 5FU/LV or FOLFOX.[4,12,20] We use the toxicity values reported in the MOSAIC trial for both treatment arms, where we define the highest incidence of toxicity events with a grade 3 or higher grade as ''major toxicity,'' the remaining patients with the incidence of any toxicities as ''minor toxicity,'' and the patients with no gradable toxicity as ''well.'' Although the data used for estimation come from a mixed cohort of stage II and stage III patients, which may amplify the toxicity values for stage II patients, overestimation of toxicity is preferable to underestimation in this analysis in favor of conservative and reliable conclusions.

Table 2 Probability Parameters

Toxicity after Adjuvant Chemotherapy Period	Value, %			Data Source
6 months after chemotherapy				
Percentage of minor toxicity	39.7			
Percentage of major toxicity	1.3			André and others,
18 months after chemotherapy				2004[4]
Percentage of minor toxicity	23.2			
Percentage of major toxicity	0.5			

Follow-up Period	FOLFOX	5FU/LV	Observation	Data Source
Relapse and survival data				
5-year relapse probability, %	*16.3 ± 20	*20 ± 20	†24 ± 20	
1-year relapse probability, %	*2	*4	†5.5	†QUASAR
2-year relapse probability, %	*9	*11	†13	Collaborative Group,
3-year relapse probability, %	*11.5	*14	†19	2007[7]
4-year relapse probability, %	*14	*18	†21	*André and others,
5-year relapse probability, %	*16.3	*20	†24	2006[10]
5-year survival probability, %	*87 (82–90)	*87 (82–90)	‡80 (75–82)	‡IMPACT B2
				Investigators, 1999[6];
				O'Connell and others,
				2004[30]
Transition probability				
State 1 (free of cancer) to state 2				
(alive with relapse)				
State 1 to state 2 in year 1	0.02	0.04	0.055	
State 1 to state 2 in year 2	0.0714	0.0729	0.0794	Calculated from annual
State 1 to state 2 in year 3	0.0275	0.0337	0.0690	relapse probability
State 1 to state 2 in year 4	0.0282	0.0465	0.0247	from year 1 to year 5
State 1 to state 2 in year 5	0.0267	0.0244	0.0380	
State 1 to state 2 > year 5	0	0	0	Assumed
State 2 (alive with	0.2978	0.2252	0.2935	Calculated from annual
relapse) to state 3 (death)	(0.2–0.5075)	(0.1554–0.3676)	(0.2423–0.4217)	relapse probability
				from year 1 to year 5
				and 5-year survival
				probability
State 1 (free of cancer) to state 3 (death)				
State 1 to state 3 in year 1		0.009493		
State 1 to state 3 in year 2		0.010449		
State 1 to state 3 in year 3		0.011447		Arias, 2007[19]
State 1 to state 3 in year 4		0.012428		
State 1 to state 3 in year 5		0.013408		
Expectation of life at age 65 years		18.7		
Discount rate, %		3 (0–5)		

5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin.

In the follow-up period, as the cancer relapse probabilities were time dependent,[21] we used an annual transition probability from state 1 (free of cancer) to state 2 (alive with relapse) instead of the stationary transition probability for those 5 years. First, we estimated the 1-year to 5-year relapse probabilities of the observation group and chemotherapy groups with FOLFOX and 5FU/LV using the Kaplan-Meier relapse curve of the QUASAR trial[7] and the Kaplan-Meier disease-free survival (DFS) curve of the MOSAIC trial,[12] respectively. We assumed that "1 − DFS" was equal to the relapse probability, which was a conservative estimation for the impact of FOLFOX because it was slightly higher than the actual relapse probability. We obtained the 5-year survival probability of the observation group from the

Table 3 Calculation of Transition Probabilities from State 2 to 3

	FOLFOX	5FU/LV	Observation
Death in year 1	$0.02x$	$0.04y$	$0.055z$
Death in year 2	$(0.09 - 0.02x)x$	$(0.11 - 0.04y)y$	$(0.13 - 0.055z)z$
Death in year 3	$(0.115 - 0.09x + 0.02x^2)x$	$(0.14 - 0.11x + 0.04y^2)y$	$(0.19 - 0.13z + 0.055z^2)z$
Death in year 4	$(0.14 - 0.115x$ $+ 0.09x^2 - 0.02x^3)x$	$(0.18 - 0.14y$ $+ 0.11y^2 - 0.04y^{3>})y$	$(0.21 - 0.19z + 0.13z^2$ $- 0.055z^3)z$
Death in year 5	$(0.163 - 0.14x + 0.115x^2$ $- 0.09x^3 + 0.02x^4)x$	$(0.2 - 0.18y + 0.14y^2$ $- 0.11y^3 + 0.04y^4)y$	$(0.24 - 0.21z + 0.19z^2$ $- 0.13z^3 + 0.055z^4)z$
5-year death probability	0.13	0.13	0.20
Transition probability from state 2 to 3[a]	$x = 0.2978$	$y = 0.2252$	$z = 0.2935$

5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin.
[a]Transition probability from relapse to death of all causes (disease-related and overall mortality).

Table 4 Costs and Ratio Parameters

	FOLFOX	5FU/LV	Observation	Data Source
Adjuvant chemotherapy period (±20%)	$29,000	$6500	0	Aballéa and others, 2007[23]
Adjuvant chemotherapy induced toxicity cost and ratio				
Grades 3–4 neutropenia	$132 ($118–$156)	$132 ($118–$156)	0	Tumeh and others, 2009[3]
Percentage of grade 3–4 neutropenia	41.1	4.7	0	André and others, 2004[4]
Febrile neutropenia (hospitalization)	$3522 ($1879–$8291)	$3522 ($1879–$8291)	0	Tumeh and others, 2009[3]
Percentage of febrile neutropenia	*1.8 †(0–2.4)	*0.2 †(0–0.9)	0	*André and others, 2004[4] †Kuebler and others, 2007[37]
Grade 3–4 diarrhea	$117 ($97–$137)	$117 ($97–$137)	0	Tumeh and others, 2009[3]
Percentage of grade 3–4 diarrhea	*10.8 †(0–30)	*6.6 †(0–15)	0	*André and others, 2004[4] †Viele, 2003[38]
Relapse cost (±20%)	$58,800	$61,200	$61,200	Aballéa and others, 2007[23]

5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin.

QUASAR trial[7] and the 5-year survival probability of the chemotherapy groups from the 6-year survival probability of the MOSAIC trial.[12] Second, using those data, we derived the annual transition probabilities from state 1 to state 2 accordingly.[22]

For example, the 1-year and 2-year relapse probabilities are 2% and 9%, respectively, for the FOLFOX chemotherapy group. Then, the transition probability from state 1 to 2 in year 1 under FOLFOX therapy (P_1^{1-2}) is easily computed as 0.02. The transition probability from state 1 to 2 in year 2 under FOLFOX therapy is calculated as follows: $(1 - 0.02) * P_2^{1-2} + 0.02 = 0.09$, then $P_2^{1-2} = 0.0714$. Similar calculations hold for the 5FU/LV therapy using respective parameters. The transition probabilities from state 1 (free of cancer) to state 3 (death) are obtained using US Life Tables.[19] The calculation of the transition probabilities

from state 2 (alive with relapse) to state 3 (death) proceeds as follows. Let x, y, and z represent the transition probabilities from state 2 (alive with relapse) to state 3 (death) for the FOLFOX, 5FU/LV, and observation groups, respectively. We assume that x, y, and z are constant from years 1 to 5. Table 3 presents the computations to find x, y, and z. In Table 2, the 5-year death probability is taken as 13% for the chemotherapy groups since the 5-year survival probability is 87%, as shown in Table 2. Similarly, the 5-year death probability for the observation group is 20%. Table 3 uses the fact that summation of deaths through years 1 to 5 is equal to the 5-year death probability to calculate x, y, and z.

We expressed all costs in 2007 US dollars. Two separate studies reported the cost of FOLFOX and 5FU/LV as $29,000 and $6500 in 2007[23] and

Table 5 Utility Parameters

Adjuvant chemotherapy period		
Well	0.84	Ramsey and Andersen, 2000[26]
Minor toxicity	0.73 (0.6–0.84)	Best and others, 2010[39]
Major toxicity	0.59 (0.49–0.68)	
Alive with relapse (±20%)	0.47	Camilleri-Brennan and Steele, 2001[40]
Follow-up period		
Sixth to 12th month for chemotherapy group	0.84	Ramsey and Andersen, 2000[26]
First year for observation group	0.84	
Second year	0.85	
Third year	0.87	
Fourth year	0.79	
Fifth year	0.79	
65–74 years old	0.84	Fryback and others, 1993[41]
≥75 years old	0.82	Fryback and Lawrence, 1997[25]
≥65 years old	0.83	(0.84 + 0.82)/2

$34,628 and $765 in 2004,[24] respectively. We chose the most recent cost report for our base-case analysis. Despite the fact that these cost figures are from 2007, Medicare billing rates have been flat for these regimens for the past 5 years and therefore are applicable for the cost-effectiveness calculations. Note that we included the most costly adverse effects in our analysis and used the corresponding incidence rates for cost calculations.

We use several studies to estimate the utility of adjuvant chemotherapy for patients. An important component for utilities is the utility of patients without adjuvant chemotherapy. Considering the surgery before chemotherapy, we applied a slightly lower utility than a healthy individual[25] to the "well" state based on a study by Ramsey and Andersen,[26] who showed that patients without adjuvant chemotherapy had a utility of 0.84. We used the same study to estimate the utilities from year 2 through year 5. For minor toxicity, we calculated the utility by computing the mean of the utilities of the patients with mild (0.785) and moderate neuropathy (0.679) in those receiving adjuvant chemotherapy. For major toxicity, we used the average utility of patients with severe neuropathy (0.585). On the other hand, we set the utility of patients who are well between the 6th and 12th month of the chemotherapy group and the first year of the observation group to 0.84, which is the utility for the patients who are well during chemotherapy.

Sensitivity Analysis

We also conducted an extensive sensitivity analysis, in which we tested the effect of uncertainty in clinically important parameters. We found the ranges for the sensitivity analysis using available published data, and otherwise we varied them within 20% of the mean estimates, as shown in Tables 2, 4, and 5. When the 5-year relapse probability varied, we adjusted the 1-year to 5-year relapse probability using the same distribution as shown in the base case. Afterwards, we updated the transition probabilities from state 1 (free from cancer) to 2 (alive with relapse) and state 2 (alive with relapse) to 3 (death) accordingly.

We ran our model for patients at different ages between 50 and 80 years. We calculated age-based ICER values assuming all parameters except the mortality rates are kept constant. In addition to the above analysis, we recalculated the ICER when nonmedical costs, such as costs due to the workdays lost caused by adjuvant chemotherapy, are included in the analysis. This is especially important for patients younger than or equal to 65 years. Furthermore, we conducted a probabilistic sensitivity analysis to address the uncertainty around some of the parameters. Because the available data for the uncertain parameters were in the form a range with a midpoint or a most likely value obtained from a large clinical study, we assumed a triangular distribution around the uncertain parameter values. We defined the base-case value as the mode, the minimum value reported in the literature (or the lower bound) as the lower limit, and the maximum value reported in the literature (or the upper bound) as the upper limit of the triangular distribution, as shown in Tables 2, 4, and 5. We obtained probabilities of cost-effectiveness by using common random numbers when comparing the alternatives. Although there is no absolute cost-effectiveness threshold value, we used $50,000/QALY as a reference value in this research. Note that the costs as mentioned

Table 6 Cost-Effectiveness Analysis of the Base Case (Discounting at 3%)

Base Case		QALYs	ICER
Chemotherapy group (FOLFOX)	$35,271	11.65	$54,359/QALY
Chemotherapy group (5FU/LV)	$15,158	11.28	$14,584/QALY
Observation group	$9616	10.9	
Without Adjustment for Quality of Life		**LYs**	**ICER**
Chemotherapy group (FOLFOX)	$35,271	14.28	$52,929/LY
Chemotherapy group (5FU/LV)	$15,158	13.90	$9896/LY
Observation group	$9616	13.34	

5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

in this study correspond to the prices, and therefore the third-party payer's perspective is taken.

RESULTS

In the base-case analysis, the patient receiving adjuvant chemotherapy with the 5FU/LV regimen gained 0.38 QALYs at a cost of $5542 as compared with observation, and the patient receiving adjuvant chemotherapy with the FOLFOX regimen gained 0.37 QALYs at a cost of $20,113 as compared with the 5FU/LV regimen (Table 6). Consequently, the ICER of adjuvant chemotherapy with FOLFOX was 54,359/QALY, and adjuvant chemotherapy with 5FU/LV was 14,584/QALY. In an analysis of life years (LYs) saved, without quality weights, the adjuvant chemotherapy with FOLFOX yielded 14.28 LYs, 5FU/LV yielded 13.90 LYs, and the observation group yielded 13.34 LYs. Therefore, the ICER of adjuvant chemotherapy with FOLFOX and 5FU/LV was $52,929/LY and $9896/LY, respectively.

Figure 2 presents the tornado diagrams that summarize the results of the 1-way sensitivity analysis for parameters that significantly change the ICER values, where the vertical solid line represents the ICER values under base case. The ICER values of FOLFOX are most sensitive to the 5-year relapse probability, cost of adjuvant chemotherapy, and the discount rate, whereas the ICER values of 5FU/LV are most sensitive to the 5-year relapse probability, 5-year survival probability, and the relapse cost. The results are least sensitive (not shown in the tornado diagram) to the percentage of chemotherapy-induced toxicity and its cost (grade 3–4 neutropenia, grade 3–4 febrile neutropenia [hospitalization], and grade 3–4 diarrhea).

Figure 3 displays the results of the sensitivity analysis for various ages, which shows that the ICER of the adjuvant chemotherapy with FOLFOX as compared with 5FU/LV increases exponentially with age, especially when the patient is older than 65 years. The ICER of the adjuvant chemotherapy with 5FU/LV as compared with observation also increases by age, but rather at a much smaller rate when compared with the ICER of FOLFOX.

Next, we conducted a sensitivity analysis on cost perspective such that the costs due to the workdays lost caused by adjuvant chemotherapy are considered. Restricted by the limited data on the financial impact of the toxicity of adjuvant chemotherapy, we made a compromising assumption that all unretired patients younger than or equal to 65 years did not work during the full 6 months of adjuvant chemotherapy at all. As the annual US average wage in 2003 was $40,405[27] and approximately 52.8%[28] patients were labor force participations when they were 60 years old, the ICER increased to $42,655/QALY for 5FU/LV. For patients who were 50 years old, 80.4%[28] of them were not retired, so the ICER increased from $11,560/QALY to $45,399/QALY for 5FU/LV. The unretired percentage of patients shrank sharply to 16%[28] for people age 65 years or older, so the ICER of 65-year-old patients increased from $17,234/QALY to $27,336/QALY for 5FU/LV.

We also performed a probabilistic sensitivity analysis for the uncertain parameters (Figure 4). The probability of the cost-effectiveness of 5FU/LV as compared with observation was 99.62% with a $50,000/QALY threshold and 99.98% with a $100,000/QALY threshold. On the other hand, the probability of the cost-effectiveness of FOLFOX as compared with the 5FU/LV was 44.48% with a $50,000/QALY threshold and 97.24% with a $100,000/QALY threshold. The mean of the ICERs was $55,697/QALY and $16,136/QALY for FOLFOX and 5FU/LV, respectively.

A - ICER of FOLFOX as compared to 5FU/LV

5-year relapse probability (13%-19.6%)

Cost of FOLFOX ($23,200-$34,800)

Discount rate (0%-5%)

5-year survival probability (82%-90%)

Relapse cost ($47,040-$70,560)

Utility of major toxicity (0.49-0.68)

Utility of minor toxicity (0.6-0.84)

Utility of alive with relapse (0.38-0.56)

ICER ($/QALY); base case $54,359/QALY

B - ICER of 5FU/LV as compared to Observation

5-year relapse probability (16%-24%)

5-year survival probability (82%-90%)

Relapse cost ($48,960-$73,440)

Discount rate (0%-5%)

Cost of 5FU/LV ($5,200-$7,800)

Utility of minor toxicity (0.6-0.84)

Utility of alive with relapse (0.38-0.56)

Utility of major toxicity (0.49-0.68)

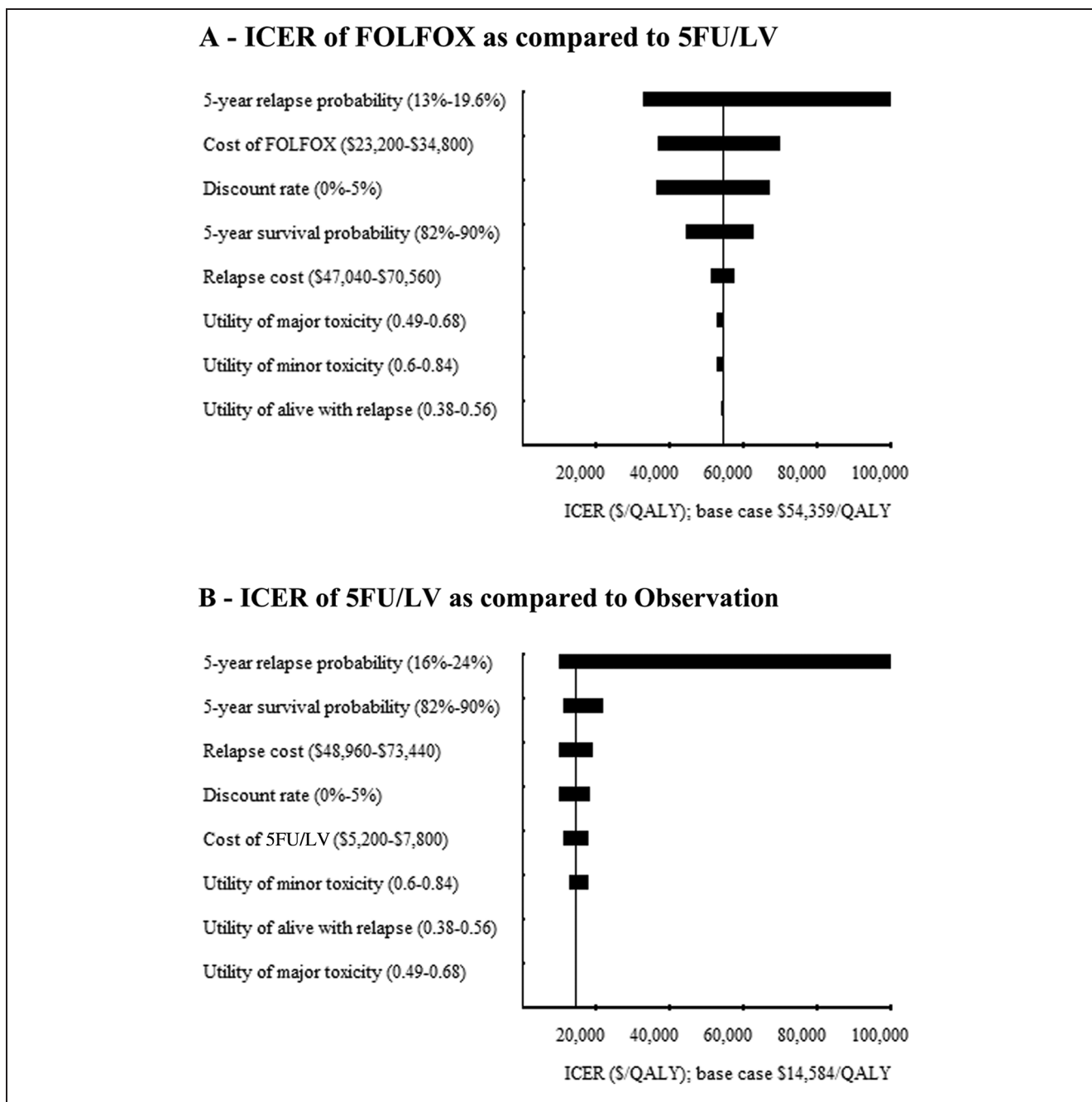ICER ($/QALY); base case $14,584/QALY

Figure 2. Tornado diagram summarizing the results of the 1-way sensitivity analysis. 5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin; QALY, quality-adjusted life year.

DISCUSSION

Compared with no postoperative treatment, adjuvant chemotherapy with 5FU/LV for stage II colon cancer achieves an ICER of $14,584/QALY, which is cost-effective with respect to the benchmark of $50,000/QALY. However, adjuvant chemotherapy with FOLFOX for stage II colon cancer as compared with 5FU/LV is less likely to be cost-effective, with a base-case ICER of $54,359/QALY. It is also
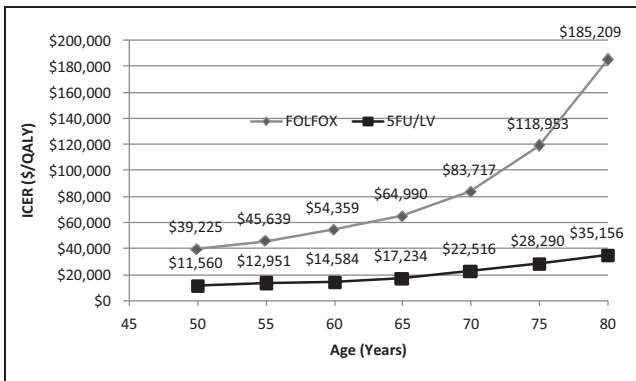
Figure 3. Sensitivity analysis over age. 5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
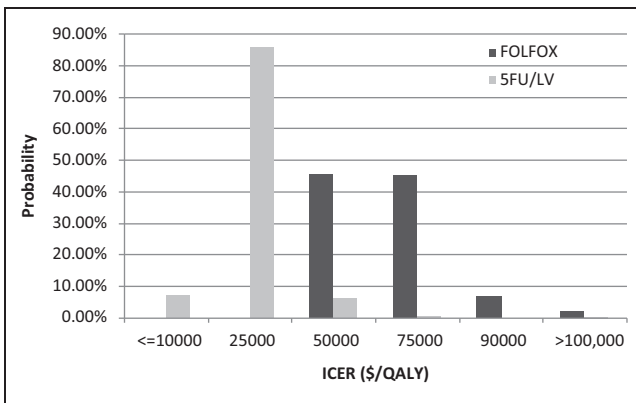

Figure 4. Probabilistic sensitivity analysis. 5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5FU, leucovorin, and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

reasonable to conclude that no matter whether the costs due to lost workdays are considered, 5FU/LV is cost-effective for people at all ages, whereas FOLFOX is cost-effective for patients younger than or equal to 55 years only when the costs due to lost workdays are not considered. The cost-effectiveness ratio is most sensitive to 5-year relapse probability. Because of the uncertainty around some of the parameters used in our models, we conducted a probabilistic sensitivity analysis of these parameters. We found that the ICER of 5FU/LV is less than $50,000/QALY almost surely, and the ICER of FOLFOX as compared with 5FU/LV is less than $50,000/QALY with 44.48% probability and less than $100,000/QALY with 97.24% probability.

Because the data on the clinical utility of adjuvant chemotherapy for stage II colon cancer continue to

evolve,[29] a comparative cost-effectiveness analysis of various adjuvant chemotherapy regimens may appear to be premature. In fact, most studies focus on trials comparing the effects of adjuvant chemotherapy with observation instead of conducting a cost-effectiveness analysis. Our analysis is important to resolve whether the probable significant benefit due to chemotherapy in stage II patients[11] is justified in terms of cost and toxicity. Previous studies noted that there was probably a small benefit for adjuvant treatment of stage II colon cancer, so the most important question is whether this small benefit might prove to be clinically significant for recommendation as standard therapy. As a decision support tool, cost-effectiveness provides a useful methodology to pursue the answer.

It is well known that not all stage II patients are likely to benefit equally from the adjuvant chemotherapy.[10] Patients with inadequate nodal sampling, nearly or completely obstructing tumors, lymphovascular invasion, or elevated carcinoembryonic antigen are thought to be at higher risk of relapse. O'Connell and others[30] stated that according to the American Joint Committee on Cancer staging guidelines (sixth edition), the 5-year stage-specific survival is as follows: I (93.2%), IIa (84.7%), IIb (72.2%), IIIa (83.4%), IIIb (64.1%), IIIc (44.3%), and IV (8.1%). They argued that the 5-year survival of IIIa patients is significantly higher than that of stage IIb patients, which may be explained by current clinical practice that stage III patients normally receive adjuvant chemotherapy, but stage II patients generally do not. No matter whether this conjecture is valid or not, those data suggest that it is preferable to study IIa and IIb separately. However, restricted by the limited data for differentiating outcomes between stage IIa and IIb and the effect of chemotherapy from the literature, we did not stratify stage II colon cancer further.

Going forward, advances in understanding risk stratification for stage II colon cancer may aid the selection of who should receive adjuvant chemotherapy. Genes predictive of varying risk of recurrence, as well as sensitivity to 5FU-based chemotherapy (microsatellite instability, chromosome 18q loss of heterozygosity), have been identified and are in the process of being more fully validated. The difference in relapse-free survival between high- and low-risk groups within stage II was about 15% to 18%. Assessing risk at diagnosis would help in making the decision to undertake chemotherapy, as well as what kind, more straightforward. Data presented at the 2009 and 2010 American Society of Clinical Oncology Annual Meeting gave a window into risk stratification beyond T stage and nodal sampling using modern

DNA sequencing technologies exploring genes that reflect tumor invasiveness and chemosensitivity.[31–33] Using these tools may help risk stratify and gauge clinical efficacy further, allowing for a more complete discussion of risk/benefit of chemotherapy.

Similarly, as more patients reach retirement age, it is worth noting that the ICER of FOLFOX increases dramatically with age, as other medical comorbidity and death from noncancer causes factor into the model. This cost-effectiveness analysis may help decision making to restrict multiagent chemotherapy to those patients who are most fit to receive chemotherapy and most likely to have expectations of noncancer survival that extend beyond 10 years.

As we await the results of intergroup trials (ECOG 5202) looking to answer the question of feasibility/applicability of molecular markers in risk stratification, the cost-effectiveness of adjuvant chemotherapy can only be improved. Other trials under way look to lessen the amount of chemotherapy delivered from 6 months to 3 months and perhaps decrease some of the cumulative toxicity of oxaliplatin as well as the cost of the drug by half.

Other regimens, including capecitabine, an oral formulation of 5FU, have been developed over the past decade. Capecitabine has the advantage of easier delivery and less cost for administration but increased cost of the drug. As we do not have the same kind of direct comparison of efficacy between capecitabine and FOLFOX in stage II disease, we did not include it specifically in this analysis. There is a body of literature to suggest that the efficacy is at least noninferior in stage III colon cancer,[34] and the cost differential is minimal when including clinic time and administration costs.[35]

Our conclusions are that it is likely to be cost-effective to consider 5FU/LV-based chemotherapy for stage II colon cancer. The addition of a more toxic and costly, but slightly more efficacious, chemotherapy is less likely to be cost-effective. Examining comparative cost-effectiveness in an area where there is continued clinical exploration and debate hopes to make the discussion more focused on the clinical efficacy than the concern for economic impact. Future trials dedicated to stratifying risk and quantifying benefit will be beneficial in future decision making regarding adjuvant chemotherapy.

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