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Total abdominal colectomy is cost-effective in treating colorectal cancer in patients with genetically diagnosed Lynch Syndrome

Boxiang Jiang [a], Asya Ofshteyn [a], Jay J. Idrees [a], Matthew Giglia [b], Carlos Gallego [c], Sharon L. Stein [a], Emily Steinhagen [a, *], on behalf of University Hospitals Research in Surgical Outcome & Effectiveness (UH-RISES)

[a] Department of Surgery, University Hospital Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH, 44106, USA
[b] Department of Surgery, Ochsner Medical Center, 17050 Medical Center Drive, Baton Rouge, LA, 70816, USA
[c] Department of Medical Genetics, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH, 44106, USA

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ABSTRACT

Background: Lynch syndrome (LS) has a 80% lifetime risk of developing colorectal cancer and metachronous cancer. No studies have examined the quality adjusted life expectancy after SEG or TAC for LS patients, which this study was aiming for. If TAC offers a higher quality adjusted life year (QALY) to SEG in LS patients, preoperative diagnosis of LS is critical as it alters the recommended surgical procedure.
Methods: A Markov decision tree was constructed using Treeage software to compare QALY of LS patients following SEG or TAC. Probabilities, cost, and utility were obtained from literature. Cost-effectiveness analyses were performed.
Results: TAC dominates SEG as both the life-saving and cost-saving strategy. TAC dominated SEG on QALY (17.80 vs 17.13 QALY) for a cohort of LS patients diagnosed at an average of 30 year old and followed every 2 years after initial surgery.
Conclusions: We conclude that TAC as the primary surgical option for LS patients diagnosed with Stage I-III colon cancer is cost-effective. Further cost-effectiveness study is recommended to include extracolonic malignancies in LS patients.

Introduction

Lynch Syndrome (LS) is an autosomal dominant hereditary colorectal cancer (CRC) syndrome caused by a mutation in one of the mismatch repair genes and accounts for approximately 2–5% of CRC.[1] The lifetime risk for colorectal cancer in individuals with LS ranges from 25 to 80%, a 10–20 fold increase over an individual of average risk.[2,3] Patients with LS are also significantly more likely to have metachronous CRC.[3] Current guidelines for CRC surveillance in LS patients include colonoscopy every one to two years beginning at age 20–25.[1]

Historically, most LS patients with CRC underwent segmental colectomy (SEG) similar to those patients with sporadic CRC, though many clinicians offered a more extensive total abdominal colectomy (TAC).[1] More recently, recognition of the risk of metachronous cancers has led to a change in guidelines, suggesting TAC is the preferred surgery.[1,3] However, the survival benefit of undergoing TAC has not been studied in LS patients, and there have been concerns about reduced quality of life in patients after TAC compared to SEG.[4,5]

Decision analysis modeling is an invaluable tool for evaluating the relative benefit and cost-effectiveness of treatments. It can also be used to analyze data from smaller studies to create more powerful evidence for a particular treatment strategy. For example, implementation of mammogram screening has been shown to save one quality adjusted life year (QALY) at a cost of $30,000 to $80,000.[6] While there are a number of small studies directly evaluating the outcomes of LS cohorts after SEG or TAC, there have been no larger studies or meta-analyses looking at this question in a genetically diagnosed cohort. We hypothesized that TAC is cost-effective than SEG in treating LS patients with CRC.

* Corresponding author. University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH, 44106, USA.
E-mail address: Emily.Steinhagen@UHhospitals.org (E. Steinhagen).

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Methods

Literature review

A systematic review of literature using PubMed, Ovid MedLine and Google Scholar was performed. Search terms included "Lynch syndrome", "cost-effectiveness", "metachronous cancer", "segmental resection", and "colectomy". Peer reviewed publications from 1950 to 2017 were identified. Manuscripts were reviewed to assess relevance, and bibliographies were reviewed to ensure other relevant publications were identified. Studies that included genetically diagnosed LS patients who underwent SEG or TAC and assessed postoperative survival, recurrence, and metachronous cancer were utilized. Studies that did not include definitive genetic diagnosis and only relied upon Amsterdam or other clinical criteria were excluded.

Decision analysis model

TreeAge Pro 2018© (Williamstown, MA) software was used to develop a decision tree analysis model to compare QALY and cost for LS patients following SEG and TAC (Fig. 1). For the purpose of the model, patients were assumed to be genetically diagnosed LS and CRC with a mean age of 30 years. Treatment strategies of SEG or TAC were compared. After the selected surgical intervention, patients were screened biannually for cancer recurrence by either colonoscopy (for SEG patients) or flexible sigmoidoscopy (for TAC patients). Markov cohorts were used to model the health outcomes of each group. In the Markov cohort, each patient was assumed to be in one of three health states: 1) alive and disease free, 2) alive with metachronous cancer, or 3) dead (either from disease or other causes). Recurrence could not be assessed as there was inadequate literature for this outcome in the LS population. The primary endpoint was patient survival free of CRC. All patients in the health state of disease-free survival were assumed to receive biannual surveillance. They could continue to be disease-free, found to have metachronous cancer, or die from other causes. Once they were found to have metachronous cancer, they were transitioned to the health state of metachronous cancer. In this state, they could either survive, which brought them back to disease-free survival, or they would die of colorectal cancer or other causes (Fig. 1). The termination conditions of the Markov cohort were reached when all subjects in the cohort either passed away or underwent 20 cycles of screening, or 60 years of screening. The endpoints of the decision analysis model were quality adjusted life year (QALY) and cost. The quality adjusted life year was defined as effectiveness. Finally, the incremental cost-effectiveness ratio (ICER) were calculated based on the formula below.

$$ICER = \frac{Cost_{TAC} - Cost_{SEG}}{Effectivness_{TAC} - Effectivness_{SEG}}$$

Variables for the decision analysis model

Data for the model was extracted from the literature as outlined above and is summarized in Table 1. Utility values ranged from 0 (death) to 1 (perfect health). A short-term utility reduction was accounted for in the immediate postoperative period. For the Markov model, 2% annual discount was applied to each cycle. The costs used in the model were adjusted based on inflation rate to the value of the dollar in 2018.

Base case analysis

The base case of the model uses variables defined in Table 1. The base case values represent the most likely values based on our literature review. A cost-effectiveness analysis was performed and the ICER was calculated. Dominance was defined as when one treatment arm was more effective and cost saving than the other treatment arm.

Sensitivity analysis and Monte Carlo simulation

After running the model using the base case variables, sensitivity analyses were performed to assess the effect of key variables on the model outcome. These variables included the rate of metachronous cancer and the utility after either surgery. A Monte Carlo simulation was performed to assess the overall variability of the model. Monte Carlo simulation, also known as probabilistic simulation, samples multiple variables from distributions to assess the effect of uncertainty on the model.

Results

Literature review results

Literature search identified 123 studies. Six studies with 1024 patients met the inclusion criteria and were utilized in the analysis. Of these, 762 patients (74.4%) underwent SEG and 262 (25.6%) underwent TAC. In the SEG cohort, 165 patients developed metachronous cancer (21.7%) while 12 patients in TAC developed metachronous cancer (4.6%). Overall mortalities in SEG and TAC groups were similar. However, TAC cohort has reduced metachronous cancer rate and reduced cancer specific mortality (Table 1).

Base case analysis

In the base case analysis, the TAC arm dominated the SEG arm. A single TAC saved 0.67 QALY (17.80 vs 17.13 QALY, TAC vs. SEG respectively) with a saving of $17,925 ($47,381 vs $65,306, TAC vs. SEG, respectively). This leads to an incremental cost-effectiveness ratio (ICER) of $-26,624/QALY for patients undergoing TAC. The ICER is negative because TAC is both the life-saving and cost-saving strategy.

Sensitivity analyses

The model was sensitive to the rate of metachronous cancer after SEG. When the annual rate of metachronous cancer after segmentectomy fell below 0.2%, the SEG arm became the cost-effective option (Fig. 2).

The model was also sensitive to the long-term utility of TAC. When the utility of post-TAC fell below 0.9, the SEG arm became the cost-effective option (Fig. 3).

Monte Carlo Simulation

After base case analysis, the variability of the model was tested using Monte Carlo Simulation (probabilistic analysis). Repeat sampling of critical variables (mortality rates after colectomies, annual rates of metachronous cancer after colectomies, cost of colonoscopy, cost of sigmoidoscopy, and cost of colectomy) generated a Monte Carlo cohort of 10,000 patients. The median effectiveness was 17.76 QALY and 16.98 QALY for TAC and SEG, respectively. The median cost was $49,893 and $69,353 for TAC and SEG, respectively. These concluded a median ICER ratio of $-24,862/QALY with 10th percentile and 90th percentile at $-36,400/QALY and $-13,781/

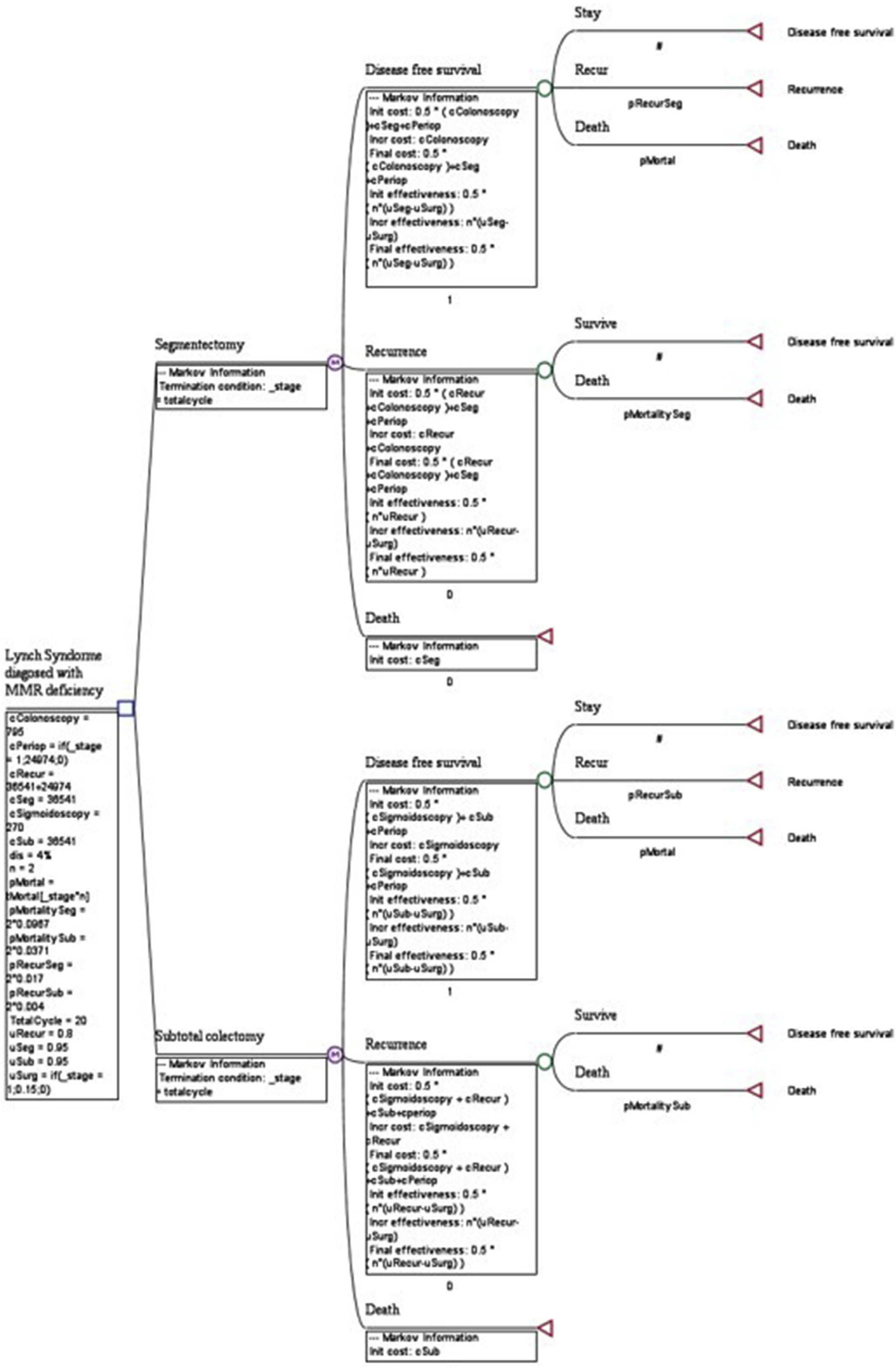

Fig. 1. Decision analysis tree model.

Table 1
Variables of the Decision analysis model.

Probabilities	Base Case	Range	References
5 year mortality rate after SEG	37%	14–59%	14–19
5 year mortality rate after TAC	14%	0–34%	14–19
5 year event free survival after SEG	63%	41–86%	14–19
5 year event free survival after TAC	86%	76–100%	14–19
10 year metachronous cancer rate after SEG	16%	10–30%	14–19
10 year metachronous cancer rate after TAC	4%	3.4–10%	14–19
Utilities	**Base Case**	**Range**	**References**
SEG	0.95	n/a	5,7,8
TAC	0.95	n/a	5,7,8
Metachronous cancer	0.80	n/a	5,7,8
Immediate post-operation period	0.85	n/a	
Cost ($)	**Base Case**	**Range**	**References**
Colectomies	36,541	9268–63,814	20–22
Perioperative care	24,974		20–22
Sigmoidoscopy	270	269–497	20–22
Colostomy	795	794–979	20–22
Treatment for metachronous cancer	61,515	34,242–88,788	20–22

QALY, respectively (Fig. 4). TAC arm dominated the SEG arm 100% of the time.

Discussion

This decision analysis demonstrates the benefit of more extensive surgery for LS patients with CRC, strengthening the quality of data in the existing literature. Moreover, it demonstrates the cost effectiveness of this strategy.

The most recent practice parameters from the American Society of Colon and Rectal Surgeons (ASCRS) recommends total colectomy for individuals with LS who are undergoing surgery for colon cancer.[1] However, the recommendation was based on multiple small retrospective studies that showed a reduction of metachronous cancer after TAC.[1] There are no prospective or randomized trials that compare these two surgical strategies, and such a trial would be logistically difficult. Therefore, studies like ours are important because they incorporate the best available data for analysis.[4,7] Furthermore, this study is the first to show TAC offers improved QALY in addition to the survival benefit for LS patients compared to SEG.

Our model showed TAC was both a life-saving and cost-saving method compared to SEG for LS patients with colorectal cancer, which is novel to this analysis. The ICER was $-26,624/QALY. Previous cost-effectiveness studies have attempted to determine survival benefit for LS patients.[4,7] This study confirms findings of other

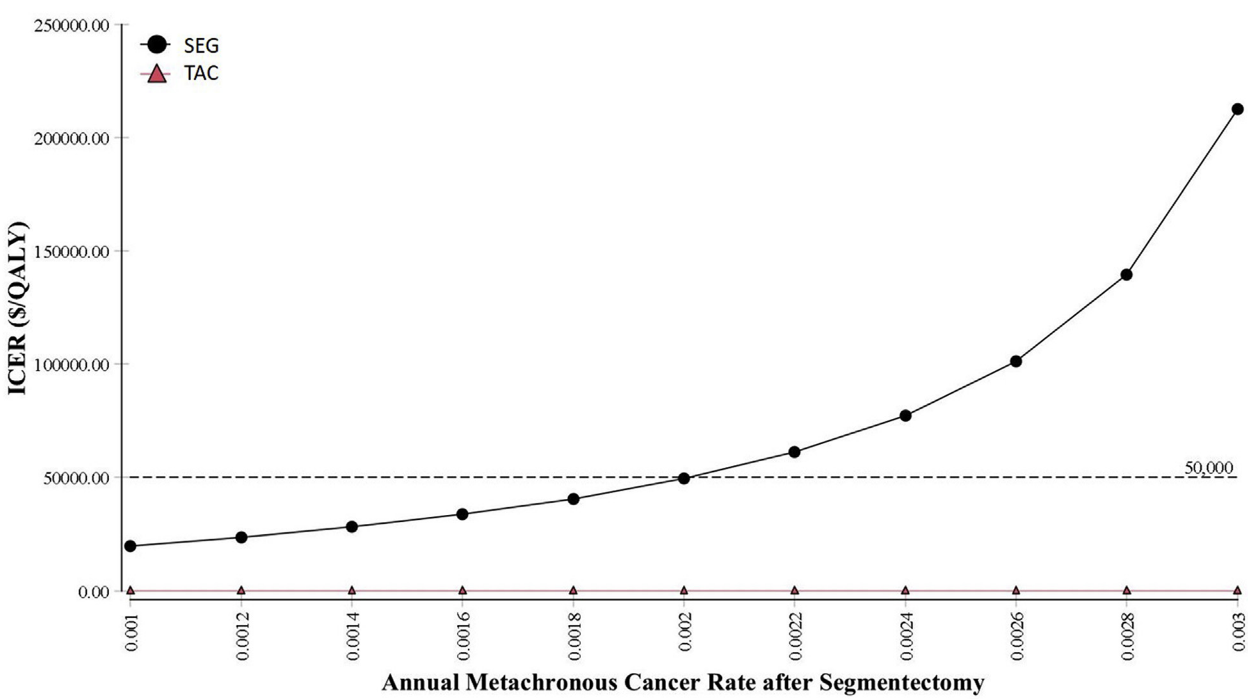

Fig. 2. Sensitivity analysis of ICER vs annual metachronous cancer rate after SEG. The dashed line shows the ICER value at $50,000/QALY. When the annual metachronous cancer rate goes above 0.2% after SEG, the SEG arm is no longer to be cost-effective.

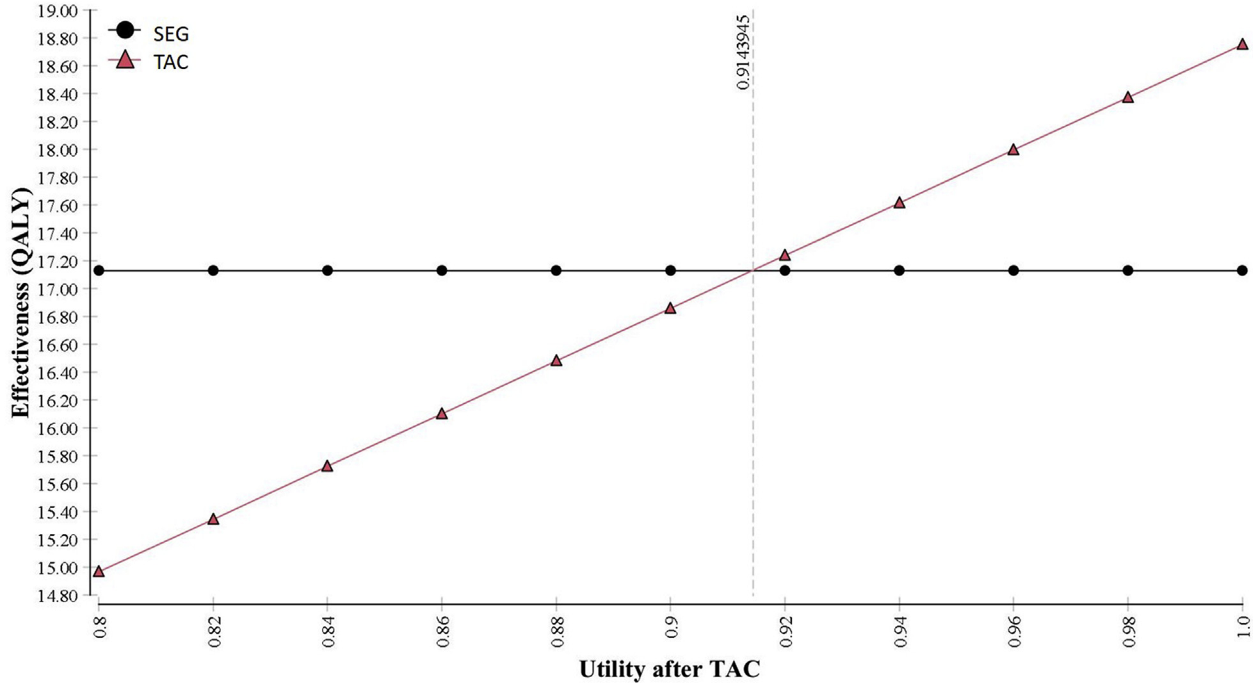

Fig. 3. Effectiveness vs Utility after TAC. The triangle markers showed the effectiveness of TAC and the sphere markers showed the effectiveness of SEG. When the utility after TAC falls below 0.91, TAC is no longer to be effective. In this plot, the utility of SEG is constant at 0.95.

analyses and extends the scope of the results.[4,7] A prior analysis suggested that TAC improved life expectancy compared to SEG in suspected Lynch patients but did not evaluate QALY or cost.[7] A previous model did not conclude there was a significant difference in the utility of the approaches; additionally it did not address cost issues.[4] Our study shows not only the improved life expectancy, but also cost-effectiveness of more extensive surgery.

Both patients and clinicians consider quality of life when considering extent of surgery and is a concern that may lead an individual to prefer one option over another. However, multiple studies have not shown significant differences in quality of life when comparing SEG and TAC.[5,8] Both a nationwide study in the Netherlands and one in Australia showed that quality of life was similar at long term follow-up despite TAC patients reporting lower

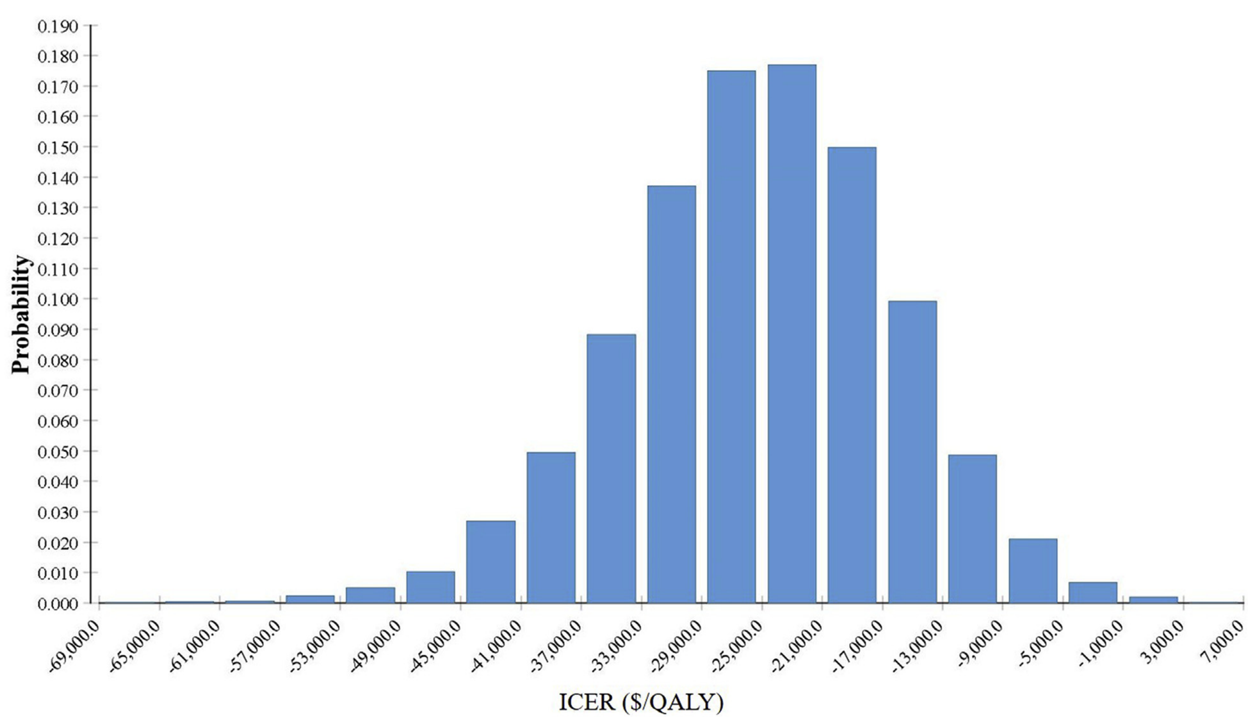

Fig. 4. Monte Carlo Simulation Probability histogram plot of 10,000 hypothetical patients. This plot shows the distribution of ICER (SEG vs TAC).

functional scores.[5,8] In their study, SEG patients reported a worse constipation score compared to the TAC patients.[5] We used an overall quality of life score rather than functional scores to determine post-operation utilities in our model, and therefore had different assumptions than previous models.[4,7] The post-operation utilities of TAC and SEG were the same in the base case of our model, which likely accounts for the difference in our findings.[4]

One important difference between our analysis and previous literature is that the current study was restricted to those who had a genetic diagnosis of LS. Previously, many studies examining outcomes for LS patients included those that met the Amsterdam II Criteria.[9] There are important differences between those patients that meet the Amsterdam II Criteria and those that have a germline mutation in a mismatch repair gene. The sensitivity and specificity of the Amsterdam II Criteria are approximately 40–80% and 50%, respectively[10,11] and using these criteria led to heterogeneous cohorts. Over the past few decades, testing for LS has become more widespread. Including only genetically diagnosed LS patients in our model improves precision over previous studies.[9]

Our results have important clinical implications. ASCRS currently accepts SEG as a viable alternative in treating patients with LS due to the concern of inferior functional outcomes after TAC, despite its superior benefit for preventing metachronous cancer.[1] Balancing the functional outcomes and risk of metachronous cancer can be difficult. This study analyzes existing data and quantifies the quality of life benefit of TAC compared to SEG. With this information, clinicians can counsel LS patients more precisely regarding surgical options when planning surgery for CRC.

Our study is subject to the limitations of the statistical method used. The outcome is only as good as the data used to populate the model. The data regarding these treatment strategies are limited, heterogeneous, and diverse in quality. In addition, colorectal cancer recurrence (rather than metachronous cancer) was not factored into the model due to a lack of existing data on recurrence rates in LS. Stage for stage, LS patients tend to have better survival[12] while having potentially decreased benefit from chemotherapy.[13] Therefore, estimates of recurrence from sporadic CRC might not be appropriate. In addition, our model does not include disease-free survival for other LS associated cancers. In terms of providing patients with good quality information to assist with informed decision making, an outcome of disease-free survival of all cancers would be more powerful than disease-free survival for CRC alone. Despite these issues, the feasibility of larger scale prospective studies on LS patients is limited, and analyses such as this one are therefore useful.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.03.011.

Conclusion

In this cost-effectiveness decision analysis, TAC was more cost-effective than SEG in treating LS patients with colon cancer. This is the first study to show this benefit. Further decision analyses should be performed to consider the effect of extra-colonic malignancy in LS patients.

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