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The price is right: Routine fluorescent cholangiography during laparoscopic cholecystectomy

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ABSTRACT

Background: Early experience with indocyanine green–based fluorescent cholangiography during laparoscopic cholecystectomy suggests the potential to improve outcomes. However, the cost-effectiveness of routine use has not been studied. Our objective was to evaluate the cost-effectiveness of fluorescent cholangiography versus standard bright light laparoscopic cholecystectomy for noncancerous gallbladder disease.

Methods: A Markov model decision analysis was performed comparing fluorescent cholangiography versus standard bright light laparoscopic cholecystectomy alone. Probabilities of outcomes, survival, toxicities, quality-adjusted life-years, and associated costs were determined from literature review and pooled analysis of currently available studies on fluorescent cholangiography ($n = 37$). Uncertainty in the model parameters was evaluated with 1-way and probabilistic sensitivity analyses, varying parameters up to 40% of their means. Cost-effectiveness was measured with an incremental cost-effectiveness ratio expressed as the dollar amount per quality-adjusted life-year.

Results: The model predicted that fluorescent cholangiography reduces lifetime costs by $1,235 per patient and improves effectiveness by 0.09 quality-adjusted life-years compared to standard bright light laparoscopic cholecystectomy. Reduced costs were due to a decreased operative duration (21.20 minutes, $P < .0001$) and rate of conversion to open (1.62% vs 6.70%, $P < .0001$) associated with fluorescent cholangiography. The model was not influenced by the rate of bile duct injury. Probabilistic sensitivity analysis found that fluorescent cholangiography was both more effective and less costly in 98.83% of model iterations at a willingness-to-pay threshold of $100,000/quality-adjusted life year.

Conclusion: The current evidence favors routine use of fluorescent cholangiography during laparoscopic cholecystectomy as a cost-effective surgical strategy. Our model predicts that fluorescent cholangiography reduces costs while improving health outcomes, suggesting fluorescence imaging may be considered standard surgical management for noncancerous gallbladder disease. Further study with prospective trials should be considered to verify findings of this predictive model.

Introduction

Laparoscopic cholecystectomy is among the most commonly performed operations, with close to 1 million cases performed annually in the United States.[1] The minimally invasive technique has decades worth of experience demonstrating feasibility, safety, and efficacy and is the gold standard for surgical management of gallstone disease. Despite advances in laparoscopic techniques and

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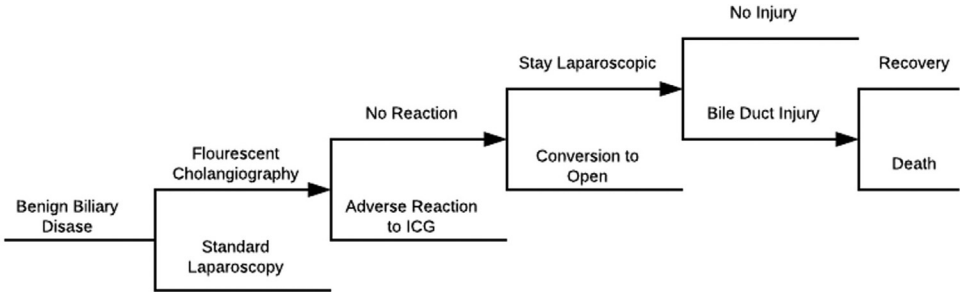

Fig 1. Branch of model decision tree. Each patient enters the model and undergoes either fluorescent cholangiography or standard bright light laparoscopy. The arrows represent chance events with varying probabilities of each outcome occurring. At the end of the tree, patients enter 1 of 3 chronic health states: (1) normal recovery; (2) bile duct injury with recovery; and (3) death.

equipment, iatrogenic injury to the common bile duct (CBDI) still occurs at a rate of 0.08% to 1.5%.[2–4] Furthermore, conversion to open occurs at a rate between 3% and 15%.[5] Both CBDI and conversions significantly increase morbidity and mortality, adversely affect quality of life (QOL), and are associated with substantial costs to the patient, the healthcare system, and society as a whole.[6,7]

Recently, the development of indocyanine green (ICG)–based near-infrared (NIR) fluorescent cholangiography during laparoscopic cholecystectomy (herein referred to as FC) provides an innovative surgical adjunct, permitting visualization of biliary anatomy to be used with the "critical view of safety" technique.[8,9] ICG is a water-soluble dye with peak spectral absorption at 800 nm. When administered intravenously, ICG binds to plasma proteins and is rapidly metabolized by hepatic parenchymal cells, with subsequent secretion into bile.[10] Using high-resolution, dynamic NIR fluorescent imaging, surgeons can achieve improved visualization of extrahepatic biliary anatomy, at times before commencing dissection of Calot's triangle.[11] Performance of FC is simple, requires minimal training, facilitates identification of biliary structures, and offers the potential to decrease complications with minimal added risk.[12,13] Still unproven, some surgeons have advocated for FC to become the standard of care in laparoscopic cholecystectomy.[13]

The objective of our study is to perform a cost-effectiveness analysis of routine FC versus standard bright light laparoscopic cholecystectomy (LC) in patients with noncancerous biliary disease. We incorporate probabilities of pertinent surgical outcomes, associated quality of life measures, and direct costs for each index operation into a model created to predict average lifetime costs per quality-adjusted life-year (QALY) for patients undergoing this common procedure.

Materials and methods

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines to describe this analysis.

Decision model

The cost-effectiveness of 2 strategies for laparoscopic cholecystectomy in patients with noncancerous gallbladder disease was compared: (1) FC: use of fluorescent cholangiography to visualize the biliary tree during laparoscopic cholecystectomy; (2) LC: standard bright light laparoscopic cholecystectomy. A decision analysis tree was constructed using the Markov model, which involves estimating continuous risk over time and assumes a finite number of chronic health states.[14] In the model, patients were given a probability of requiring conversion to an open approach, sustaining CBDI, and/or death (Fig 1). Patients in the FC arm had the additional chance of adverse reaction to ICG in the form of anaphylaxis, which could result in death. After cholecystectomy, patients entered 1 of 3 chronic health states: successful cholecystectomy without CBDI (either laparoscopic or open), CBDI, or death. Outcomes excluded from the model included minor adverse reaction to ICG, morbidity or mortality unrelated to CBDI, and long-term sequelae of conversion to open such as incisional hernia.

All events of interest are modeled as transitions from one state to another. They are assigned health utility scores ranging from 0 (death) to 1 (perfect health) and serve as estimates of QOL. Patients began with health utility scores of 1 and deductions were incurred for each complication. Patients entering the chronic health state of CBDI had deductions extended over the entirety of a patient's lifetime. All health utility scores were obtained by searching the Tufts Medical Center Cost-Effectiveness Analysis Registry.[15–18] The specific values for health utility scores and deductions as well as the literature sources used in the model are present in Table I.

The base-case model simulates outcomes for a 45-year-old female with noncancerous gallstone disease. The model was run using a 1-year cycle length over a 35-year time horizon to capture the long-term impact of patient outcomes. The risk of mortality due to other causes was estimated from the Social Security Administration Actuarial Life Table.[19] TreeAge Pro 2019 (TreeAge Software, Williamston, MA) was used to build the model.

Model probabilities

The probability of events at each node were estimated from a review of the literature. All parameters used for the base-case analysis are listed in Table I. Internal validation was performed by directly comparing the proportion of patients in each health state at different model timepoints to the expected values reported in the literature.

Outcome probabilities following standard laparoscopy (LC)

For LC, we preferentially reviewed systematic reviews, meta-analyses, and retrospective studies of large-scale databases managed by surgical society or public health agencies. Historically, the reported rate of CBDI ranged between 0.3% and 1.5%.[2,20,21] In 2003, Flum et al reported a rate of 0.5% among 1,570,361 Medicare claims for laparoscopic cholecystectomy.[2] More recent studies suggest the rate may have decreased over time due to increased experience and improved technology, with rates reported as low as 0.08%.[22,23] We selected a rate of 0.20% based on 2 recent large-scale database analyses in the United States: Mangieri et al reported a rate of 0.19% after reviewing 217,774 cases from the National Surgical Quality Improvement Program (NSQIP) registry, and Fong et al reported a rate of 0.22% after reviewing 711,454 cases from the California Office of Statewide Health Planning and Development

Table I
Parameters for cost-effectiveness model

Parameter	Base case						Distribution for PSA	First author
	Both†		Standard laparoscopy		Fluorescent cholangiography			
	Value	95% CI	Value	95% CI	Value	95% CI		
Transition Probabilities*								
Bile duct injury			0.20	0.052–0.71	0.10	0.004–0.173	Beta	Fong[24]; Mangieri[4] N/A‡
Conversion to open			6.2	5.37–11.90	1.62	0.90–3.2	Beta	Pucher[5] N/A§
Adverse reaction to ICG					0.05	0.032–0.072	Beta	Hope-Ross[28]
Mortality of adverse reaction to ICG					0.51	0.30–0.80	Beta	Caro[29]
Mortality of CBDI over initial year	4.5	2.9–6.45					Beta	Dolan[25]
HR of mortality due to CBDI long-term	2.79	2.71–2.88					Beta	Flum[2]
Costs ($)								
Standard Laparoscopy	1,408	394–1,879					Gamma	UCSD
Fluorescent Cholangiography	741	481–1,060					Gamma	UCSD
Bile Duct Injury	60,331	39,450–86,173					Gamma	Savader[7]
Conversion to Open	7,728	4,990–10,939					Gamma	Lengyei[6]
Adverse Reaction to ICG (Anaphylaxis)	26,074	11,044–37,432					Gamma	HCUPnet National Inpatient Sample Database[30]
Health Utilities								
Cholecystectomy	0.912	0.896–0.928					Beta	Rystedt[15]
Bile Duct Injury (Initial Year)	−0.20	−0.28 to −0.12					Beta	Teerawattananon[16]
Bile Duct Injury (Long Term)	−0.126	−0.18 to −0.5					Beta	Rystedt[15]
Conversion to Open	−0.19	−0.27 to −0.12					Beta	Morris[17]
Adverse Reaction to ICG	-0.0008	−0.0012 to −0.00051					Beta	Ward[18]

CI, confidence interval; *PSA*, probabilistic sensitivity analysis; *CBDI*, common bile duct injury; *HCUP*, Healthcare Cost and Utilization Project; *ICG*, indocyanine green; *UCSD*, University of California, San Diego Medical Center Business Office.

* Shown as percentages rather than true probabilities for simpler visualization. For example, the probability of CBDI is 0.0020; however, it is reported in this table as a rate of 0.20%.

† Both in this instance refers to values that pertain to standard laparoscopy and fluorescent cholangiography

‡ Given no reported instances of CBDI in the literature during 3,331 reported cases of FC, a nonzero value of 0.10% was chosen as base case. This rate was varied from 0.00% to 0.30% in the model during the sensitivity analysis.

§ Pooled analysis of 20 studies reporting conversion to open rates: 24 conversions reported in 1,485 cases of FC.

database (Supplementary Table S1).[4,24] We selected a probability for conversion to open of 6.2% based on a 2018 meta-analysis of 347,803 patients by Pucher et al that pooled 130 studies reporting conversion rates.[5] Patients incurring CBDI were given a 4.5% probability of mortality in the initial postoperative period.[25] For those who survived the initial year postprocedure, a hazard ratio of 2.7 was used to model the lifelong risk of mortality due to CBDI.[2] A list of alternative outcome probabilities is available in Supplementary Table S1.

Outcome probabilities following fluorescent cholangiography

We performed a literature review of studies published through October 2020 and identified 40 studies detailing experience with FC for either laparoscopic ($n = 37$) or robotic-assisted laparoscopic cholecystectomy ($n = 3$) with a pooled total of 3,316 patients, with details listed in Table II. Reported indications for FC included biliary colic, gallbladder polyp, acute cholecystitis, chronic cholecystitis, acute pancreatitis, choledocholithiasis, and acute pancreatitis. There were no reported instances of CBDI in the literature. Due to the likelihood that this rate was a function of small sample size, we used a nonzero probability of 0.10% for the base-case rate of CBDI during FC. We subsequently performed a sensitivity analysis by varying this probability from 0.0% to 0.30% (which overlaps with rate from LC) as detailed below to allow crossover with the rate assigned for LC and account for the possibility that the true rates of CBDI are equivalent.

A 2017 systematic review of FC reported a rate of conversion to open of 0.5% (1/197 patients).[26] Broderick et al (2020) published the largest individual series of FC to date with 400 cases; the conversion rate was 1.5% compared to 8.5% among 989 cases of LC ($P < .0001$).[27] The pooled rate of conversion among studies reporting this outcome was 1.62% (24/1,486) for FC ($n = 20$) compared with 6.70% (94/1,699) for LC ($n = 8$) (Table II). We performed a 2 independent sample z-test to determine statistical significance of this difference in proportions. Given a resultant P value of $< .0001$, we selected the rate of 1.62% for our base-case analysis.

Adverse reaction to ICG

Severe adverse reactions to ICG in the form of anaphylaxis are infrequent and are reported at a rate of 0.05%.[28] Minor reactions to ICG were excluded from the model. No literature attributing mortality from an anaphylactic reaction to administration of ICG is published. We therefore used the mortality rate following adverse reaction to iodine contrast agents as a surrogate (0.51%).[29]

Costs

Cost analysis included expenditure for the index operation, complications of CBDI, conversion to open, and adverse reaction to ICG. The lifetime costs of managing CBDI and conversions to open were estimated from primary literature.[6,7] The cost of a severe adverse reaction to ICG was estimated from a Healthcare Cost and Utilization Database, National Inpatient Sample online query for the inpatient diagnosis of anaphylaxis.[30] Cost of index operation was estimated from the perspective of the hospital as the cost to third-party payers is typically equivalent between index operations; this included surgical equipment, ICG administration, and

Table II
Studies reporting experience with fluorescent cholangiography during laparoscopic cholecystectomy

First Author, Year	Sample size		Reported outcomes		Comparison of conversion rate					Comparison of operative duration			
	FC Cases (n)	LC Cases (n)	Bile duct injuries (FC)	Adverse reactions (FC)	Conversions w/ FC (incidence)	Conversion rate w/ FC (%)	Conversions w/ LC (incidence)	Conversion rate w/ LC (%)	P value	Operative duration (FC)	Operative duration (LC)	Difference in minutes	P value
Ishizawa, 2010	52	-	0	0	-	-	-	-	-	-	-	-	-
Tagaya, 2010	7	-	0	0	-	-	-	-	-	-	-	-	-
Ishizawa, 2011	7	-	0	0	-	-	-	-	-	-	-	-	-
Schols, 2013*	15	-	0	0	-	-	-	-	-	-	-	-	-
Schols, 2013	30	-	0	0	1	3.33	-	-	N/A	-	-	-	-
Tagaya, 2013	15	-	0	0	-	-	-	-	-	-	-	-	-
Dip, 2014	43	-	0	0	-	-	-	-	-	-	-	-	-
Boni, 2015	52	-	0	0	-	-	-	-	-	-	-	-	-
Dip, 2015	45	-	0	0	-	-	-	-	-	-	-	-	-
Kono, 2015	108	-	-	-	-	-	-	-	-	-	-	-	-
Osayi, 2015	82	-	0	0	-	-	-	-	-	-	-	-	-
van Dam, 2015	37	-	0	0	-	-	-	-	-	-	-	-	-
Dip, 2016	71	-	0	0	0	0.00	-	-	N/A	-	-	-	-
Igami, 2016	21	-	0	0	-	-	-	-	-	-	-	-	-
Tagaya, 2016	25	-	0	0	0	0.00	-	-	N/A	-	-	-	-
Zroback, 2016	12	-	0	0	-	-	-	-	-	-	-	-	-
Ankersmit, 2017	18	-	0	0	-	-	-	-	-	-	-	-	-
Koirala, 2017	12	-	0	0	-	-	-	-	-	-	-	-	-
Hiwatashi, 2018†	65	-	-	0	7	10.77	-	-	*	-	-	-	-
Pesce, 2018	50	-	0	0	4	8.00	-	-	N/A	-	-	-	-
Tsutsui, 2018	72	-	-	0	2	2.78	-	-	N/A	-	-	-	-
Ambe, 2019	29	49	0	0	0	0.00	1	2.40	Not reported	53	54	−1	$P = .4$
Calabro, 2019	29	-	0	0	-	-	-	-	-	-	-	-	-
Dip, 2019	318	321	0	0	1	0.31	4	1.25	Not reported	-	-	-	-
Bleszynski, 2019	108	-	0	0	0	0.00	-	-	N/A	70	80	−10	Not reported
Quaresima, 2019	44	44	0	0	0	0.00	-	-	N/A	86.9	117.9	−31	P=.0006
Pesce, 2019	26	-	0	0	0	0.00	-	-	-	-	-	-	-
Agnus, 2019	314	-	0	1	-	-	-	-	-	-	-	-	-
Yoshiya, 2019	39	91	0	0	1	2.56	20	22.00	P=.0017	129	150	−21	P=.0455
Keeratibharat, 2019	20	20	0	0	0	0.00	-	-	Not reported	-	-	-	-
Esposito, 2019	15	-	0	0	0	0.00	-	-	N/A	52	69	−17	Not reported
Broderick, 2020	400	989	0	-	6	1.50	84	8.50	P<.0001	72.53	99	−26.47	P<.0001
Calabro, 2020	31	68	0	-	0	0.00	-	-	N/A	105	121	−16	Not reported
Matsumara, 2020	20	-	0	-	0	0.00	-	0.00	N/A	-	-	-	-
Di Maggio, 2020	33	24	0	0	0	0.00	1	4.17	NS	104	134	−30	$P = .0001$
Lehrskov, 2020	60	60	0	-	0	0.00	1	1.67	Not reported	-	-	-	-
Koong, 2020	30	33	0	-	2	6.67	3	9.09	Not reported	-	-	-	-
Total	2340		0	1									
Studies Reporting Conversions ($n = 20$)	1,486	1,699			24	1.62	114	6.70	P < .0000‡				
Studies Reporting Operative Duration ($n = 7$)	858	1,265										−21.70	P < .001

A search of the PubMed/Medline and Google Scholar databases was performed through October 2020 by combining the terms "cholecystectomy," "laparoscopic cholecystectomy" with "fluorescent cholangiography," "indocyanine-green," "ICG," "near-infrared fluorescent cholangiography," "fluorescence guided surgery." All titles and abstracts from English language studies were reviewed for inclusion. Any study identified that reported use of fluorescence cholangiography during laparoscopic cholecystectomy was included in the table above. This report excludes studies on robotic-assisted laparoscopic cholecystectomy, single-incision laparoscopic cholecystectomy, and systematic reviews. References for the identified studies are provided in Supplementary Data.

A dash (-) signifies that the occurrence of interest was not mentioned.

FC, fluorescent cholangiography; *LC*, standard laparoscopy; *n*, sample size; *N/A*, not applicable; *NS*, nonsignificant.

* Excluded due to probable overlap in patient sample with Schols - 2013 (30) published same year, same authorship group.

† Did not compare FC to LC. However, among FC patients, conversion was 3/51 for patients whose cystic duct was identified with FC and 4/7 for those whose cystic duct was not identified, $P = .003$.

‡ Two independent sample z-test performed comparing pooled proportions of conversions among FC and LC.

Table III
Determinants of cost to hospital for laparoscopic cholecystectomy

Standard Laparoscopy	Cost total ($)	Cost per case ($)*
Laparoscopic Tower (100% depreciation at 5 y)	89,661.00	358.64
Fiberoptic Cable (100% depreciation at 2 y)	297.24	2.97
HD Laparoscope (100% depreciation at 2 y)	3,656.16	36.56
Laparoscopic Equipment Monthly Service Agreement	900.00	216.00
Additional Operating Room Minutes (21.71 min at $36.14/min)†	N/A	794.59
Total	94,514.40	1,408.77
Total (excluding OR min)	94,514.40	614.18
Fluorescent Cholangiography		
Laparoscopic Tower (100% depreciation at 5 y)	89,661.00	358.64
AIM Safelight Fiberoptic Cable (100% depreciation at 2 y)‡	566.89	5.67
Precision Ideal Eyes HD Laparoscope (100% depreciation at 2 y)‡	5,707.05	57.07
Laparoscopic Equipment Monthly Service Agreement	900.00	216.00
Indocyanine Green (1 dose)‡	N/A	103.41
Total	96,834.94	740.79

* Assumes an operating room volume of 50 laparoscopic cholecystectomies per year.
† Based on review of literature that FC decreases operating room time by 21.71 min.
‡ Additional requirements to perform fluorescent cholangiography during laparoscopic cholecystectomy.

the financial impact of operative duration. A third-party payer perspective was used for all other parameters.

FC capability requires 2 devices for NIR imaging, in addition to standard laparoscopic equipment: a specialized fiberoptic cable and high-definition laparoscope. A standard laparoscopic tower can be used for both FC and LC. We gathered price data from the University of California, San Diego Medical Center Business Office on laparoscopic towers, light cables, laparoscopes, and ongoing service agreements with the medical technology firm, Stryker Corporation (Kalamazoo, MI) (Table III). We included a 100% depreciation at 5 years for the tower and at 2 years for the specialized equipment based on standard corporate estimates. A baseline volume of 50 LCs performed per year was used to determine cost per case. Cost of a single dose of ICG was determined from the wholesale drug price (cost reported in the literature ranges from $17 to $130).[31] Use of additional instruments and disposable supplies was considered independent and equivalent to LC.

The final component of cost was operative duration. Broderick et al reported a 26.47-minute decrease in operative duration with FC, $P < .001$, controlled for primary surgeon.[27] A pooled analysis of 8 studies reporting operative duration weighted for volume showed a decrease in case duration of 21.71 minutes for FC compared to LC ($P < .001$; Table II). This difference was incorporated in cost estimates. A 2018 cross-sectional, longitudinal analysis of 302 short-term and specialty care hospitals in California reported the mean cost of 1 minute of operating room (OR) time as $37.45 (standard deviation $16.04) in the inpatient setting and $36.14 (standard deviation $19.53) in an ambulatory setting.[32] We used $36.14 per OR to determine the cost impact of operative duration. We estimated a mean cost per case for LC of $1,408.77 and $740.79 for FC (Table III). An additional analysis was performed to exclude the impact of OR duration on cost and a third to exclude equipment costs for LC to account for surgery centers with outdated equipment that would need to purchase a new laparoscopic tower to perform FC.

All costs were adjusted to 2020 US dollars using the Consumer Price Index. All costs and health utilities were discounted at 3% per year.

Analysis

Quality-adjusted life-years (QALYs) were used to measure the effectiveness of each arm. QALYs are determined by the product of a patient's health utility over time. The cost-effectiveness of FC versus LC was measured by determining the incremental cost-effectiveness ratio, or the incremental cost required to gain an additional QALY as detailed in prior cost-effectiveness studies.[33,34] A surgical strategy was considered cost-effective if the incremental cost-effectiveness ratio was below a willingness-to-pay threshold of $100,000/QALY.[34] A surgical strategy was considered dominant (or to have dominated) if it was predicted to be both less costly and more effective (produced more QALYs). One-way deterministic sensitivity analyses were performed on each model parameter to determine the impact of varying the model inputs on the overall results. Additionally, a probabilistic sensitivity analysis was performed to assess the influence of uncertainty in each of our model estimates. The analysis included 100,000 iterations of the model in which the costs, probabilities of outcomes, and health utilities were all varied simultaneously. A probability distribution was created for each variable based on the mean and 95% confidence interval (CI).[35] The distributions and parameters for each variable are listed in Table I.

Results

Base-case analysis

The base-case cost-effectiveness analysis predicted that the average lifetime cost per patient was $939 for FC compared to $2,174 for LC (Table IV). The projected effectiveness of each surgical strategy was similar, as FC yielded 28.83 QALYs over 35 years, while LC yielded 28.74. Overall, FC dominated LC as it was predicted to gain 0.09 additional QALYs and be $1,235 less costly per patient. FC dominated LC regardless of cost estimate used for LC, including no-cost for LC equipment.

One-way sensitivity analysis

The cost-effectiveness model was not sensitive to any of the model parameters. The most sensitive variable was the cost of FC. The model demonstrated that FC dominated LC at a cost ranging from $0 to $2,250 and would be cost-effective until the cost exceeded $3,663 (nearly 5 times greater than our base-case estimate [Fig 2, *B*]). The second most sensitive variable was the conversion to open rate during FC. Assuming a rate between 0.0 and 9.5%, FC was predicted to dominate LC, at a rate between 9.5% and 12.5% FC would be considered cost-effective but not dominant, and if the rate exceeded 12.5% (double the rate of 6.2% for LC), FC would no longer be considered cost-effective (Fig 2, *A*).

Table IV
Cost-effectiveness of fluorescent cholangiography versus standard laparoscopy during cholecystectomy

	Cost ($)	QALYs
Fluorescent cholangiography*	$939.36	28.83
Standard laparoscopy assuming equipment cost of $614*	$2,173.98	28.74
Standard laparoscopy assuming equipment cost of $0	$1,560.16	28.74
Standard laparoscopy assuming no difference in operative duration	$1,379.21	28.74

This table shows the predicted lifetime cost and QALYs for each model arm. Also shown are the results when varying the cost of standard laparoscopy to include or exclude equipment and impact of operative duration.
US, Unites States; *QALYs*, quality-adjusted life-years.
* Represents base-case model predictions.

The model was insensitive to the rate of CBDI during FC, which did not have an impact on the overall cost-effectiveness of FC during routine laparoscopic cholecystectomy (Fig 2, *C*). The remaining cost, outcome, and utility variables did not have a significant impact on the cost-effectiveness of FC.

Probabilistic sensitivity analysis

At a willingness-to-pay threshold of $100,000/QALY, FC dominated LC in 98.83% of the iterations and was cost-effective in 99.9%. Figure 3 shows a cost-effectiveness acceptability curve demonstrating the results of the PSA for various willingness-to-pay thresholds.

Discussion

The current cost-effectiveness study predicts that FC is both more effective (28.83 versus 28.74 QALYs) and less costly ($939 versus $2,174) per case than LC over the 35-year span of the model. This finding is driven by a few key factors. While routine FC adds a relatively small upfront investment for equipment, it may ultimately result in cost reduction. Current experience suggests FC decreases operative duration and the rate of conversion to open during laparoscopic cholecystectomy.[13,27,36,37] Decreased duration and conversions substantially reduce cost of the index operation, while the latter also improves quality of life.[3,38–40] Additionally, FC has a negligible toxicity profile, as the rate of severe allergic reaction to ICG is rare and avoidable.[28] Widespread adoption of this technology could prove useful as a value-enhancing surgical adjunct to the developed “critical view of safety” technique.

With a small sample size and no randomized prospective trials comparing outcomes between surgical strategies, we are unable to draw definitive conclusions about the effectiveness of FC. However, a marked reduction in the conversion rate with FC compared to LC was seen in the largest series published to date (1.5 % vs 8.5%).[27] A recent metanalysis by Dip et al also found a statistically and clinically significant reduction in conversion rates with FC (32 vs 255/10,000).[37] Finally, our pooled analysis found a significantly reduced rate of conversion (1.62% vs 6.70%; $P < .00001$), suggesting that FC can decrease the incidence of this outcome. Dip et al performed a randomized trial of FC versus LC and found a roughly 3-fold (OR 2.3 [95% CI 1.6−3.2] to 3.6 [1.6−9.3]) increase in the ability to visualize extra-hepatic biliary structures.[13] The improved delineation of critical biliary anatomy is a plausible explanation for the observed decrease in conversion rates. Conversion to open results in prolonged hospital length of stay for an otherwise often ambulatory operation increasing the cost of cholecystectomy by up to $8,500.[6,41] Furthermore, larger incisions increase postoperative pain and risk of long-term postoperative complications, both of which reduce QOL.[42,43] Notably, complications following conversion to open such as incisional hernia were not included in the current model given the lack of high-level evidence that FC lowers conversion rate. However, doing so would have skewed the results of the model in favor of FC.

Contrary to popular belief, FC likely decreases the index cost of cholecystectomy. FC requires an upfront cost of ~$125 per case to account for specialized equipment capable of NIR imaging and a single dose of ICG. This estimate does not account for use of NIR-capable equipment in other operations, which lowers the capital cost to the hospital. Regardless, data suggest this cost is offset by an approximately 20-minute reduction in operative duration, likely due to earlier visualization of important surgical landmarks.[27,36,44,45] Reduced operative time will vary substantially by institution and surgeon but can create $650 of cost savings per case or $65,000 over the depreciating lifetime of newly purchased FC equipment with an annual volume of 50 cases. More importantly, this creates potential to improve OR utilization. Depending on local OR efficiency, a 20-minute reduction in case duration over 3 to 4 cases may allow for an additional case to be performed during the day. Increased throughput would ultimately be the greatest financial benefit of FC.

Routine use of FC is the subject of ongoing debate. Proponents argue that FC is a safe, simple addition to aid in visualization of the biliary tree, with the potential to decrease the rate of CBDI.[46] Currently, no high-quality data exist to suggest FC effectively reduces the rate of CBDI. Although the published literature addressing FC is growing, a prospective trial powered to detect a statistically significant difference in this outcome between the 2 surgical strategies would require a multi-institutional study with upwards of 100,000 patients.[13] However, cost-effectiveness decision analyses are able to estimate the societal impact of a given medical intervention even if pertinent outcomes are infrequent. As such, we were able to evaluate routine use of FC during laparoscopic cholecystectomy for noncancerous gallbladder disease.

An important finding of our sensitivity analysis was that the probability of CBDI during FC did not impact the cost-effectiveness of its use. The base-case rate of CBDI during FC was varied from 0.00% to 0.30%, greater than the rate chosen for standard laparoscopy (0.20%). The findings of our analysis did not change (Fig 2). This is likely due to the relative infrequency of CBDI and minimal upfront cost of ICG, in stark contrast to the potential downstream cost of conversion or managing CBDI (~$7,000 to ~$65,000). These findings suggest that even if the use of ICG-based fluorescent cholangiography had no benefit on CBDI, standardization of this surgical technique is still cost-effective.

We did not compare FC to other modalities for intraoperative imaging of biliary anatomy, namely intraoperative cholangiogram (IOC). The routine use of IOC never achieved widespread adoption despite multiple studies suggesting the cost-effectiveness of IOC versus LC alone.[15,47] Relative to IOC, FC is easier to teach, learn, and supervise, does not require an incision of the biliary tree, has fewer operative steps amounting to less operative time, does not require radiation, and can be repeated an unlimited number of times throughout the operation.[12,48,49] Furthermore, it is significantly less costly.[31]

There are several limitations to this study that on around the quality of inputs used as parameters for the Markov model. The gold standard for model inputs include prospective, randomized trials for outcome probabilities, and well-designed, prospective assessments of health utility and cost. Only 14 of the 40 studies detailing experience with FC compared data with LC, and the study populations were heterogenous in nature. A total of 2,340 patients undergoing FC were identified in our search of the literature, limiting the ability to draw conclusions about clinical outcomes.

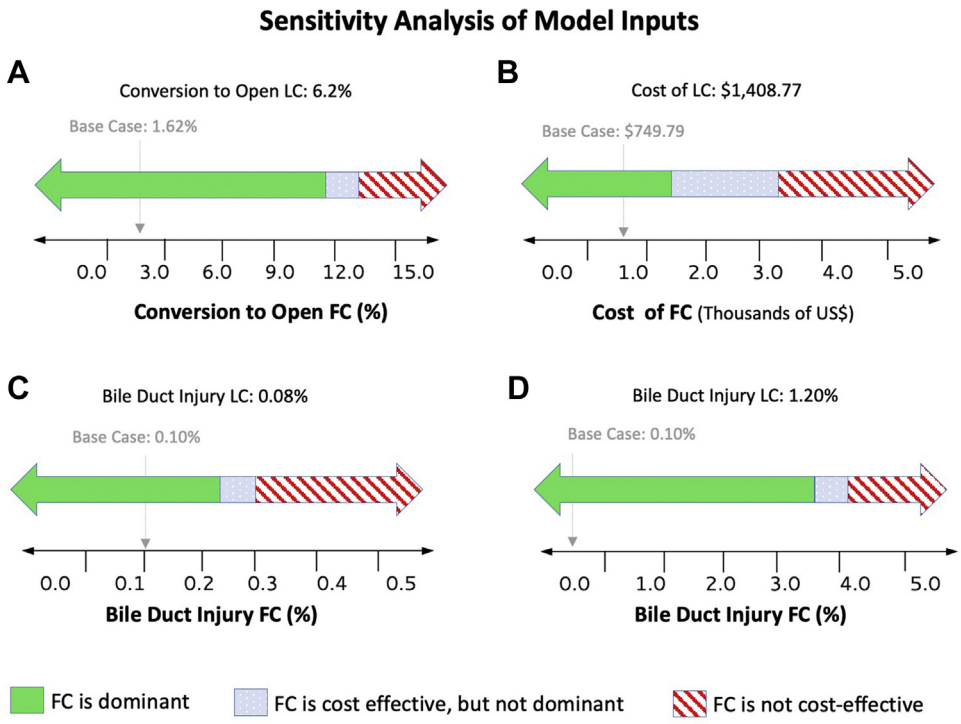

Fig 2. One-way sensitivity analyses. This graphic demonstrates the impact of varying the model inputs on the cost-effectiveness of routine ICG-based fluorescent cholangiography (FC) versus standard laparoscopy (LC) during cholecystectomy. A surgical strategy is considered dominant (or to dominate) if it is both less costly and more effective (produces more quality-adjusted life-years [QALYs]). A strategy is cost-effective if the incremental cost-effectiveness ratio is less than $100,000 per QALY. Example: Panel 2C. We assume a bile duct injury rate of 0.08% for LC. If the true rate of bile duct injury with FC lies between 0 and 0.23%, then FC dominates LC. If the true rate is 0.23 to 0.30%, FC is cost-effective but not dominant. At a rate higher than 0.30%, FC is no longer cost-effective. This figure demonstrates that the model is not sensitive to the probability of conversion to open or bile duct injury during fluorescent cholangiography, as the results do not change over a wide range of outcome probabilities.

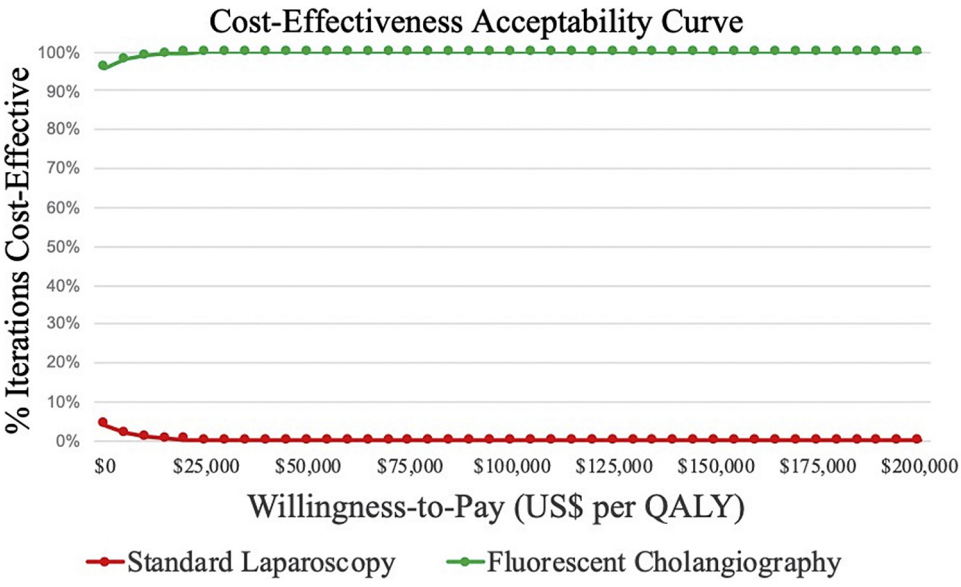

Fig 3. Probabilistic sensitivity analysis acceptability curve. A probabilistic sensitivity analysis runs 100,000 iterations of the model varying all probabilities, costs, and utilities simultaneously within the 95% confidence interval of each model parameter. This graph shows the percentage of individual iterations of the probabilistic sensitivity analysis that are cost-effective for fluorescent cholangiography versus standard laparoscopy as treatment options for benign gallbladder disease at varying levels of willingness-to-pay. The green line represents fluorescent cholangiography (FC) and the red line represents standard laparoscopy (LC). As the green line approaches 100%, 100,000 out of 100,000 iterations were cost-effective for FC versus LC.

Despite tens of millions of reported cases of LC over more than 3 decades, precise outcome probabilities in this well-studied population remain heterogenous. Similarly, studies on health utility and QOL following complications of cholecystectomy are variable. Thus, selecting model parameters for LC proved challenging. Cost data for the index operations came primarily from our single institution contract agreements. The true cost to other hospitals will vary based on contracts with device and pharmaceutical companies,

operative volume, and operative experience with each technique. The cost of downstream components of the model also came from a range of sources and is liable to variability. Regarding the study design, this is not a prospective, randomized trial comparing costs and outcomes, but rather a predictive model designed with the best available retrospectively collected data. As such, there are inherent limitations to the generalizability of the model estimations. Finally, we did not differentiate outcomes between cholecystectomy performed for biliary colic and inflammatory conditions such as acute cholecystitis or acute pancreatitis.

Despite these limitations, the results of our probabilistic sensitivity analysis, in which all model parameters were simultaneously varied up to 40% of their means, demonstrated that our model is insensitive to variation in these parameters. The same conclusion was predicted in 98.83% of iterations (Fig 3). As such, our base-case estimates would have to be severely inaccurate to change our results and subsequent conclusions of this study.

In conclusion, the current evidence favors routine use of fluorescent cholangiography during laparoscopic cholecystectomy as a cost-effective surgical strategy. FC enables reduced costs while improving health outcomes, suggesting fluorescence imaging may be considered standard for the management of benign biliary disease. Further study with prospective trials should be considered to verify findings of this predictive model.

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Conflicts of interest/Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2021.09.027].

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