


Laparoscopic versus open subtotal gastrectomy for gastric adenocarcinoma: cost-effectiveness analysis

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Background: Laparoscopic subtotal gastrectomy (LSG) for cancer is associated with good perioperative outcomes and superior quality of life compared with the open approach, albeit at higher cost. An economic evaluation was conducted to compare the two approaches.

Methods: A cost-effectiveness analysis between LSG and open subtotal gastrectomy (OSG) for gastric cancer was performed using a decision-tree cohort model with a healthcare system perspective and a 12-month time horizon. Model inputs were informed by a meta-analysis of relevant literature, with costs represented in 2016 Canadian dollars (CAD) and outcomes measured in quality-adjusted life-years (QALYs). A secondary analysis was conducted using inputs extracted solely from European and North American studies. Deterministic (DSA) and probabilistic (PSA) sensitivity analyses were performed.

Results: In the base-case model, costs of LSG were \$935 (€565) greater than those of OSG, with an incremental gain of 0.050 QALYs, resulting in an incremental cost-effectiveness ratio of \$18 846 (€11 398) per additional QALY gained from LSG. In the DSA, results were most sensitive to changes in postoperative utility, operating theatre and equipment costs, as well as duration of surgery and hospital stay. PSA showed that the likelihood of LSG being cost-effective at willingness-to-pay thresholds of \$50 000 (€30 240) per QALY and \$100 000 (€60 480) per QALY was 64 and 68 per cent respectively. Secondary analysis using European and North American clinical inputs resulted in LSG being dominant (cheaper and more effective) over OSG, largely due to reduced length of stay after LSG.

Conclusion: In this decision analysis model, LSG was cost-effective compared with OSG for gastric cancer.

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Introduction

Despite a decrease in global incidence over the past two decades, gastric cancer remains the third most common cause of cancer-related mortality worldwide, leading to over 723 000 deaths annually¹. Surgical resection is currently the only curative treatment. The advent of minimally invasive surgery has seen laparoscopic gastrectomy performed with increasing frequency. The safety and efficacy of minimally invasive subtotal gastrectomy is

supported by over a dozen RCTs, with many reporting a decreased incidence of postoperative complications compared with open surgery^{2–15}, as well as similar long-term oncological outcomes for both early and locally advanced tumours^{3,7,8,15–20}. Postoperative health-related quality of life (HRQoL) has also been found to be superior among patients who had laparoscopic (LSG) rather than open (OSG) subtotal gastrectomy^{6,21}. Although encouraging, these results should be considered alongside reports of the higher operative costs of laparoscopic gastrectomy^{22–24}.

In the context of limited healthcare resources, where providing one item of care often means having to forego another, determining the cost-effectiveness of new interventions before widespread adoption is an important undertaking. Although similar analyses have been conducted previously for other cancer operations, such as colectomy and oesophagectomy, there are no published economic evaluations of these surgical approaches for gastric adenocarcinoma^{25,26}.

The purpose of this study was to perform a cost-effectiveness analysis of LSG versus OSG for gastric adenocarcinoma from the perspective of Canada's publicly funded healthcare system. It was hypothesized that minimally invasive gastrectomy would be cost-effective compared with laparotomy in this patient population.

Methods

The target population was adults with non-metastatic gastric adenocarcinoma (UICC/TNM stage I–III). OSG was compared with minimally invasive subtotal gastrectomy, including both laparoscopically assisted and totally laparoscopic techniques. Both limited (D1) and extensive (D2) lymphadenectomy were included. In line with health technology assessment (HTA) guidelines, this study was conducted from the perspective of a publicly funded healthcare system^{27,28}. Given that prospective studies have reported a return to baseline quality-of-life values by 12 months after surgery, and that long-term oncological outcomes appear comparable between operative approaches, a 1-year time horizon was selected for analysis^{29–31}. No discounting of cost or QALYs was performed, given this 1-year time horizon.

Decision analysis model

This economic evaluation was conducted using a cohort-type decision analysis model. Such models use the best available evidence to determine the likelihood, costs and consequences of each outcome that can result from the interventions compared, quantifying the average patient experience to help guide policy decisions³². The specific type of model chosen for this study was the decision tree, which has been used previously in studies assessing minimally invasive procedures^{25,26}. Use of this model type was justified by the fact that most complications, expenses and quality-of-life changes are known to occur in the early postoperative period and can therefore be captured with a single 1-year cycle²⁷.

The decision tree is shown in *Fig. 1*. Patients with resectable gastric cancer enter the model at the time of

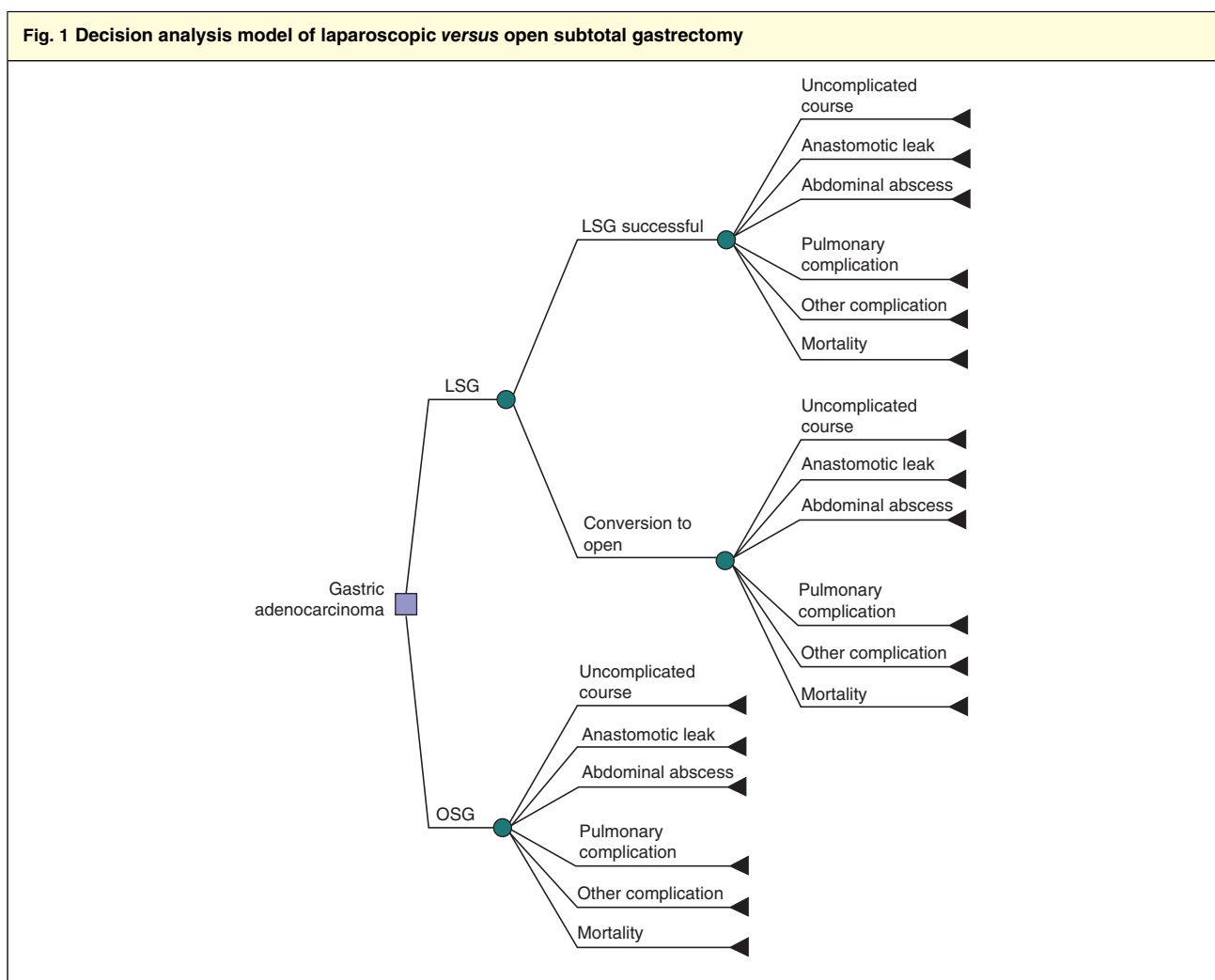
surgery, when they undergo either LSG or OSG. For every patient undergoing LSG, there is a probability that conversion to the open approach will be required. After surgery, patients may have an uncomplicated course or suffer from a postoperative complication (pulmonary, abdominal abscess, anastomotic leak, death or other morbidity). Every postoperative outcome modelled is assigned a specific probability, cost and health value, informed by the best available evidence. By multiplying the expense and the health value associated with each outcome by the probability of it occurring, the expected cost and utility of each treatment option is obtained. The incremental cost-effectiveness ratio (ICER) is then calculated by dividing the cost difference between two interventions by the difference in health units gained: $ICER = \text{Cost of LSG} - \text{Cost of OSG} / \text{QALYs for LSG} - \text{QALYs for OSG}$.

Model assumptions

This decision analysis model assumed that postoperative outcomes were mutually exclusive. Patients for whom minimally invasive gastrectomy required conversion to laparotomy were assigned operative costs and duration of the laparoscopic approach, while incurring postoperative outcomes, costs and utilities of open gastrectomy. Postoperative mortality was assigned the cost of an anastomotic leak and of 5 days spent in the ICU, as in a previous study²⁶. The study also assumed that utility losses were the same across all perioperative complications, except for death, which was valued at zero.

Literature review and meta-analysis of clinical outcomes

A review of MEDLINE, Embase, Web of Science, Cochrane Library and EconLit databases was conducted to identify the highest-quality evidence published between 2002 and 2017 with which to inform model parameter values. All relevant articles were collected, and their bibliographies screened for appropriate references. Trials comparing LSG with OSG for gastric adenocarcinoma were included. The decision-tree model was then populated with transition probabilities derived from meta-analysis of each perioperative outcome. HRQoL outcomes were obtained from Kim *et al.*⁶, whose study administered the cancer-specific European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire to both treatment arms before surgery and for up to 90 days afterwards, and disutility of postoperative complications was obtained from Avery *et al.*³³. A previously validated algorithm^{34–36} was used to map these scores to the generic



LSG, laparoscopic subtotal gastrectomy; OSG, open subtotal gastrectomy.

EQ-5D™ (EuroQol Group, Rotterdam, the Netherlands) instrument required to populate economic analysis models.

Costs

In contrast to clinical outcome data, there were few costing studies for laparoscopic and open gastric resection, with none providing information on the cost of postgastrectomy complications^{22,23}. For this reason, institutional costs from McGill University Health Centre were used to derive costs of operating room time, operative equipment, and daily hospital ward and intensive care use. In addition, following institutional ethical approval, 79 consecutive elective subtotal gastrectomies performed for gastric adenocarcinoma between 2012 and 2016 were reviewed. Direct medical costs (comprised of physician billing, costs

of equipment, medications, laboratory and radiology tests, nurse and support staff salary, and overhead costs) were compiled for every patient, calculating the individual costs of each of the postoperative complications modelled. Costs were then adjusted to 2016 Canadian dollars using the real healthcare inflation rate specific to Canada's health services and population growth rate³⁷. Canadian dollars were subsequently converted to euros by using the 2016 purchasing power parity (PPP) index of both currencies³⁸.

Secondary analysis using European and North American clinical outcomes

To assess whether regional variations in patient presentation, technical expertise and postoperative care patterns lead to differences in the cost-effectiveness of minimally

Table 1 Characteristics of studies included in the primary analysis

Reference	Country	Trial design	No. of patients		Stage	Type of node dissection	Type of anastomosis
			OSG	LSG			
CLASS-01 ²	China	Multicentre RCT	520	519	I: 303	D2	Billroth I: 565
					II: 215		Billroth II: 339
					III: 440		Roux-en-Y: 92
KLASS-01 ⁵	Korea	Multicentre RCT	698	686	I: 1240	D1+: 549 D2: 832	Billroth I: 935
					II: 92		Billroth II: 395
					III: 40	Roux-en-Y: 55	
JCOG 0912 ⁴	Japan	Multicentre RCT	455	457	I: 823	D1, D1+: 676 D2, D2+: 236	Billroth I: 432
					II: 69		Roux-en-Y: 240
					III: 19	Gastro-gastro: 236	
JLSSG 0901 ¹⁵	Japan	Multicentre RCT	234	226	I, II, III	D2	n.s.
COACT 1001 ⁸	China	Multicentre RCT	96	100	I: 78	D2	n.s.
					II: 62		
					III: 51		
COACT 0301 ⁷	China	Single-centre RCT	82	82	I: 158	D2	Billroth I: 155
					II: 5		Billroth II: 8
Chen Hu <i>et al.</i> ⁹	China	Single-centre RCT	41	41	I: 4	n.s.	Billroth I: 57
					II: 34		Billroth II: 25
					III: 40		
Hayashi <i>et al.</i> ¹³	Japan	Single-centre RCT	14	14	I: 28	D2	Billroth I Circular stapler
Huscher <i>et al.</i> ³	Italy	Single-centre RCT	29	30	I: 22	D1: 18 D2: 41	Billroth II: 12
					II: 9		Roux-en-Y: 47
					III: 19		
Kitano <i>et al.</i> ¹⁰	Japan	Single-centre RCT	14	14	I: 27	n.s.	Billroth I
					II: 1		Handsewn
Lee <i>et al.</i> ¹¹	Korea	Single-centre RCT	23	24	I: 46	D2	Billroth I
					III: 1		Circular stapler
Sakuramoto <i>et al.</i> ¹²	Japan	Single-centre RCT	32	31	I: 61	D2	Billroth I
					II: 1		Circular stapler
					III: 1		
Takiguchi <i>et al.</i> ¹⁴	Japan	Single-centre RCT	20	20	I: 38	D1: 38 D2: 2	Billroth I
					II: 2		Circular stapler

OSG, open subtotal gastrectomy; LSG, laparoscopic subtotal gastrectomy; n.s., not specified.

invasive gastrectomy, a secondary analysis was performed using model parameters derived exclusively from clinical outcomes described in European and North American studies. As above, a literature review and meta-analysis of seven studies^{3,16,17,39–42} was conducted. Studies featuring both total and subtotal gastrectomies were excluded if they provided combined outcomes without subgroup analyses of subtotal gastrectomy⁴³.

Sensitivity analysis

Uncertainty surrounding the parameters populating the model was assessed by conducting deterministic (DSA) and probabilistic (PSA) sensitivity analyses. DSA was

performed by varying the values of each parameter around its confidence interval one at a time, holding other parameters constant. PSA was conducted by running 10 000 Monte Carlo simulation trials that simultaneously varied all model parameters, assigning values drawn randomly from distributions fitted around each variable. ICERs from all 10 000 simulations were then plotted on a cost-effectiveness plane and compared with the base model. Finally, a cost-effectiveness acceptability curve was created to illustrate the likelihood of the laparoscopic intervention being cost-effective at various willingness-to-pay (WTP) thresholds. These thresholds represent the maximum amount that decision-makers are willing to spend per additional QALY gained. They vary across countries; some

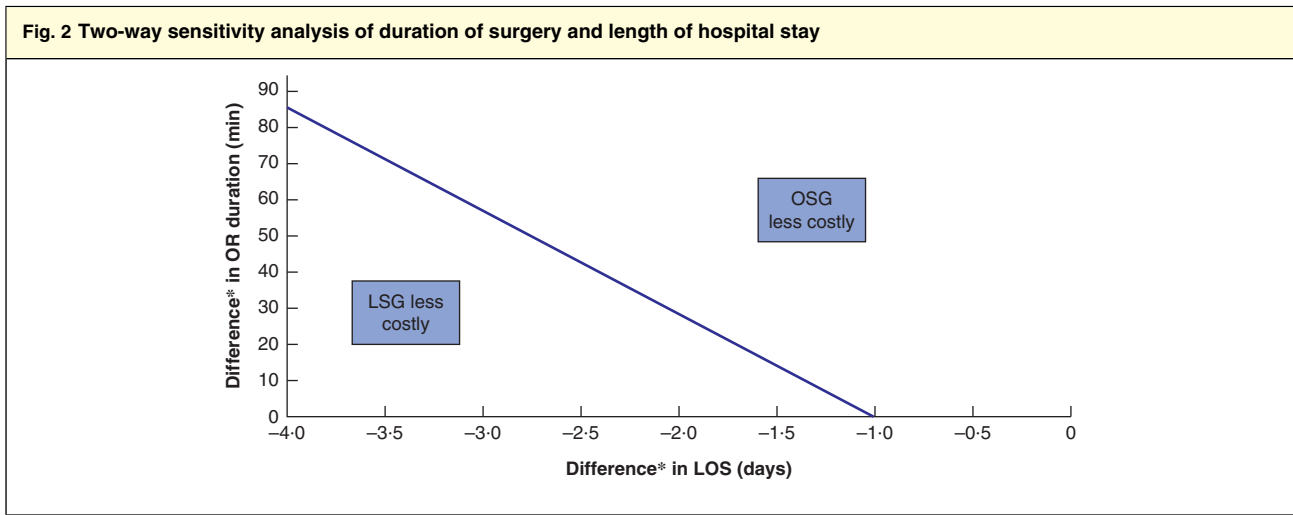
Table 2 Parameter values and distribution for the primary analysis			
	Value (DSA)*	Distribution (PSA)†	References
Probability of uncomplicated course		Beta	2,3,5,7–14
OSG	0.802 (0.782–0.822)	$\alpha = 1258, \beta = 311$	
LSG	0.839 (0.821–0.857)	$\alpha = 1310, \beta = 251$	
Probability of anastomotic leak		Beta	2,3,5,10–14
OSG	0.010 (0.004–0.015)	$\alpha = 13, \beta = 1337$	
LSG	0.011 (0.006–0.017)	$\alpha = 15, \beta = 1323$	
Probability of intra-abdominal abscess		Beta	2,3,5,10–14
OSG	0.013 (0.007–0.019)	$\alpha = 17, \beta = 1333$	
LSG	0.011 (0.006–0.017)	$\alpha = 15, \beta = 1323$	
Probability of pulmonary complication		Beta	2,3,5,10–14
OSG	0.042 (0.031–0.052)	$\alpha = 56, \beta = 1294$	
LSG	0.033 (0.023–0.042)	$\alpha = 44, \beta = 1294$	
Probability of mortality		Beta	2–5,7–15
OSG	0.003 (0.001–0.005)	$\alpha = 6, \beta = 2252$	
LSG	0.004 (0.001–0.006)	$\alpha = 8, \beta = 2236$	
Probability of conversion from LSG to OSG	0.015 (0.011–0.018)	Beta	2–5,7,8,10–14
		$\alpha = 58, \beta = 3902$	
Increased OR time with LSG (h)	0.918 (0.868–0.967)	Normal	2–5,7–14
		$\mu = 0.918, \sigma = 0.025$	
Increased LOS with OSG (days)	0.980 (0.730–1.230)	Normal	2–5,7–14
		$\mu = 0.980, \sigma = 0.128$	
Cost per OR hour (CAD)	1001.10 (412–1590)	Gamma	26
		$\alpha = 11.11, \beta = 90.10$	
Additional cost for laparoscopic equipment (CAD)	924.13 (381–1468)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 83.17$	
Cost per patient-day spent in hospital ward (CAD)	485.65 (200–771)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 43.71$	
Cost per patient-day spent in ICU (CAD)	1785.24 (736–2835)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 160.67$	
Additional cost of anastomotic leak (CAD)	21 240.67 (8751–33 730)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 1911.66$	
Additional cost of intra-abdominal abscess (CAD)	15 033.97 (6182–23 826)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 1350.36$	
Additional cost of pulmonary complication (CAD)	9347.61 (3851–14 844)	Gamma	Empirical‡
		$\alpha = 11.11, \beta = 841.28$	
Utility of uncomplicated course		Beta	6,34–36
OSG	0.803 (0.671–0.936)	$\alpha = 22.84, \beta = 3.98$	
LSG	0.852 (0.720–0.984)	$\alpha = 27.13, \beta = 6.64$	
Disutility from postoperative complication	–0.081 (0.00 to –0.052)	Beta	33,35
		$\alpha = 1.23, \beta = 14.08$	

*Values in parentheses are ranges used in deterministic sensitivity analysis (DSA). †Distribution used in probabilistic sensitivity analysis (PSA). ‡Values obtained from institutional costs at McGill University Health Centre. OSG, open subtotal gastrectomy; LSG, laparoscopic subtotal gastrectomy; OR, operating room; LOS, length of hospital stay; CAD, Canadian dollars.

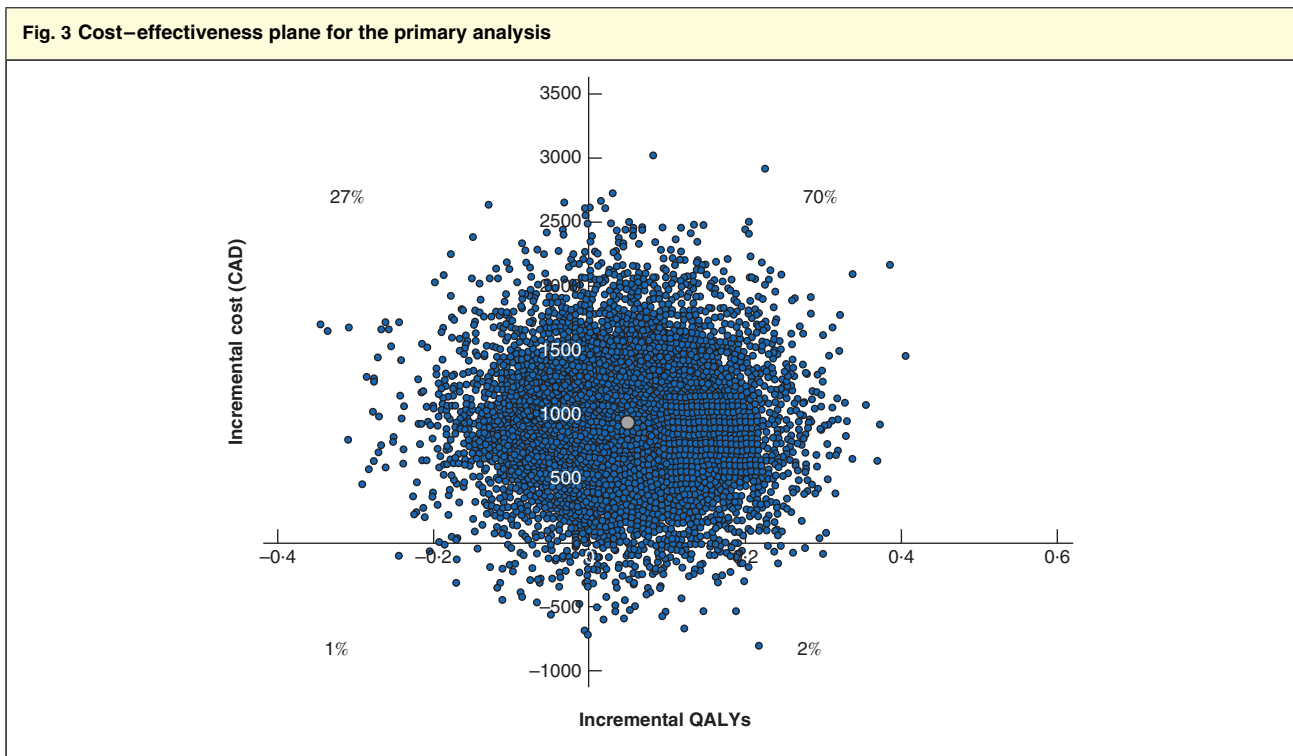
organizations, such as the National Institute for Health and Care Excellence in the UK, set explicit limits (£30 000 per QALY), whereas others, such as the Canadian Expert Drug Advisory Committee, do not explicitly state universal boundaries, with thresholds varying from \$20 000 to \$100 000 (€12 096 to €60 480) per QALY^{44,45}.

Results

The literature review identified 13 RCTs^{2–5,7–15} comparing OSG with LSG for gastric adenocarcinoma with details of each study shown in *Table 1*. Values for each model parameter derived from the meta-analysis are found in *Table 2*.



*Laparoscopic subtotal gastrectomy (LSG) minus open subtotal gastrectomy (OSG).



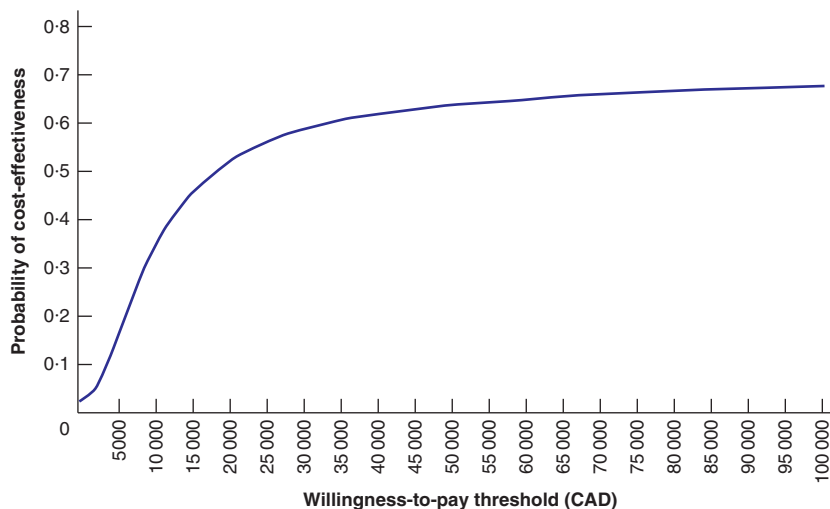
Results of the probabilistic sensitivity analysis, with each point representing one of the 10 000 Monte Carlo simulations performed. For each simulation, the difference in quality-adjusted life-years (QALYs) gained after laparoscopic compared with open subtotal gastrectomy is plotted on the x-axis, with cost difference on the y-axis. The percentage of points in each quadrant is indicated. The central pale dot represents the average result. CAD, Canadian dollars.

With a 12-month time horizon, LSG was associated with an additional 0.050 QALYs compared with the open procedure, at an additional cost of \$935 (€565), for a resulting ICER of \$18 846 (€11 398) per additional QALY gained.

One-way DSA showed the model to be most sensitive to changes in postoperative utility values, in operating

room and equipment costs, and in duration of surgery and length of hospital stay (LOS). *Fig. 2* shows a two-way DSA in which the difference in operative duration was varied simultaneously with the difference in postoperative LOS, highlighting the values for which either approach is cost-minimizing.

Fig. 4 Cost–effectiveness acceptability curve for the primary analysis



Using the results of the 10 000 Monte Carlo simulations, this graph illustrates the likelihood of laparoscopic subtotal gastrectomy being cost-effective compared with open subtotal gastrectomy at various cost–effectiveness threshold values. CAD, Canadian dollars.

Results of the 10 000 Monte Carlo simulation trials conducted for the PSA yielded a mean ICER of \$18 219 (€11 019) per additional QALY. ICER values for each simulated trial were plotted on the cost–effectiveness plane found in *Fig. 3*. *Fig. 4* shows the cost–effectiveness acceptability curve drawn from the Monte Carlo simulations, illustrating the probability of laparoscopic gastrectomy being cost-effective compared with open surgery for a range of WTP thresholds. LSG had a probability of cost-effectiveness over laparotomy of 52, 64 and 68 per cent at WTP thresholds of \$20 000 (€12 096) per QALY, \$50 000 (€30 240) per QALY and \$100 000 (€60 480) per QALY respectively.

Results of the secondary analysis

The literature review of North American and European studies identified seven studies^{3,16,17,39–42}, including one RCT. Study details and parameter values derived from meta-analysis of these studies are supplied in *Tables S1* and *S2* (supporting information).

Using model parameter inputs derived from clinical outcomes, LSG was associated with a 0.066 QALY gain and a \$1140 (€690) cost reduction, thus being dominant (more effective and less costly) over OSG. These results were due largely to greater reductions in postoperative LOS after LSG in these studies (1-day reduction in the base case *versus* 3.2-day reduction in the secondary analysis). Results remained robust after PSA, with 69 per cent of Monte Carlo simulations resulting in LSG being more effective

and less costly than OSG, compared with 3 per cent of simulations where LSG was less effective and more costly. The cost–effectiveness plane plotting for each simulation is shown in *Fig. S1* (supporting information).

Discussion

This cost–effectiveness analysis comparing LSG with OSG for gastric adenocarcinoma, using pooled data from high-quality clinical evidence to populate a decision analysis model, resulted in a base-case ICER of \$18 846 (€11 398) per QALY. This is well below the conservative and most frequently used Canadian WTP threshold of \$50 000 (€30 240) per QALY^{44,45}. PSAs showed the model to be relatively robust, with a cost–effectiveness likelihood of 64 per cent at this threshold value. A secondary analysis resulted in LSG being dominant in terms of both cost-effectiveness and HRQoL outcomes over OSG when considered in the context of patient care trajectories used in Europe and North America.

The DSAs conducted in this study can help guide clinicians and decision-makers towards practices that enhance the cost-effectiveness of both surgical approaches. Decreases in postoperative LOS led to significant cost reductions in the model. There were sizeable geographical differences in LOS, with the earlier post-LSG discharges of North American and European studies being an important factor in the minimally invasive approach becoming both more effective and cost-saving in this setting. The adoption of enhanced recovery after surgery protocols,

which have consistently been shown to reduce postoperative LOS^{46–48}, should therefore be considered for their financial and clinical benefits.

In selected patients with early-stage gastric cancer and low risk of nodal metastases, endoscopic mucosal resection or submucosal dissection should be considered as alternatives to surgery. Clinical evidence for these procedures has been encouraging, with consistent reports of reduced LOS, cost and morbidity, equivalent oncological outcomes, and superior post-procedure quality of life when compared with open or laparoscopic resection^{22,49–51}. In institutions where technical expertise is available, these techniques are likely to be cost-effective substitutes to gastrectomy in eligible patients.

This study has a number of limitations. Although built on the best available evidence, decision analysis models must rely on assumptions that approximate reality. Postoperative complications were modelled as mutually exclusive, which may have led to an underestimation of the costs and disutilities associated with open surgery, for which postoperative morbidity was greater. In addition, as HRQoL values were obtained from a single randomized trial with a focus on early gastric cancer, results may not be fully generalizable across different patient populations. Cost figures were derived from the experience of one Canadian tertiary care centre, and may differ from those of other healthcare systems. Although PSAs help to account for the parameter uncertainties surrounding HRQoL and costs, results should be interpreted with some caution. Finally, most studies comparing cancer-specific outcomes between laparoscopic and open gastrectomy focused on early disease. This study assumed oncological equivalency between open and laparoscopic operations; however, individual judgement must still play a role in choosing operative approach, especially for bulky or advanced cancers and those involving adjacent organ invasion, necessitating multivisceral resection.

Unlike the base case, which was informed by 13 randomized trials, the secondary analysis of Western data drew mostly from observational studies, with their inherent selection biases, potentially overestimating the benefits of LSG. The present study also adopted a health service perspective, which does not account for productivity loss of patients and caregivers. Although this perspective is recommended by HTA guidelines for publicly funded healthcare systems such as that in Canada²⁸, it may have underestimated the cost-effectiveness of laparoscopic surgery, which has been linked to earlier return to work²⁶. Given that long-term oncological outcomes have been found previously^{3,7,8,18–20} to be similar for laparoscopic and open gastrectomy, systemic therapy was not modelled into this

cost-effectiveness analysis. It is possible that the lower complication rates seen with the laparoscopic approach led to earlier access to chemotherapy, with subsequent differences in cost and HRQoL when compared with open gastrectomy. Finally, as clinical outcomes were obtained from clinical trials taking place in tertiary centres, findings may not be generalizable to peripheral, low-volume institutions. As suggested in many studies, oncological gastrectomy is likely to benefit from centralization of care^{52–54}.

LSG can be cost-effective and associated with improved HRQoL compared with OSG for gastric adenocarcinoma, with increased benefits seen in European and North American care contexts.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.