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Maximizing oral intake tolerance in malignant gastric outlet obstruction – a Markov decision tree analysis comparing duodenal stenting, endoscopic ultrasound-guided gastroenterostomy and surgical gastrojejunostomy based on a meta-analysis of randomized controlled trials

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Introduction: Malignant gastric outlet obstruction (GOO) has a significant impact on quality of life. Endoscopic ultrasound-guided gastroenterostomy (EUS-GE) has shown promising results. Traditional isolated outcome measures do not sufficiently address critical considerations for end-of-life patients like oral intake tolerance. This study aimed to determine via a probabilistic approach, the optimal management strategy for GOO patients that maximizes their oral intake tolerance.

Methods: A Markov decision model was developed, with input variables based on a systematic review and meta-analysis of randomized controlled trials (RCT) comparing duodenal stenting (DS), EUS-GE and surgical gastrojejunostomy (GJ). A prospective cohort study with a comparator group was also included for EUS-GE model given the scarcity of RCTs. Model assumption was a patient with malignant GOO, with equal probabilities of being allocated to 1 of 3 treatment options. Each data point was evaluated using pooled probabilities from the meta-analysis of clinical outcomes. Primary outcome was successful oral intake tolerance at various time points of 1–6 months post-intervention.

Results: Fifteen studies were included into the Markov model. Based on 10 000 simulations in each arm, at a survival of 1-month, DS and EUS-GE had the highest likelihood of oral intake (81.2% and 80.4%) compared to GJ (75.5%). However, at a survival of 6-month, EUS-GE and GJ were better at palliating GOO, with likelihood of oral intake at 23.8% and 25.2%, compared to 21.3% for DS.

Conclusion: For patients with a prognosis of more than 1-month, a surgical GJ, or EUS-GE if technical expertise is available, is preferred for GOO palliation.

Keywords: endoscopic ultrasound, gastric outlet obstruction, gastrojejunostomy, palliation, stent

Introduction

Malignant gastric outlet obstruction (GOO) has a significant impact on quality of life[1]. Unfortunately, for a large proportion of patients, curative resection was not possible, either due to

HIGHLIGHTS

- A Markov decision tree analysis from a meta-analysis of randomized controlled trials between duodenal stenting (DS), endoscopic ultrasound-guided gastroenterostomy (EUS-GE) and surgical gastrojejunostomy (GJ)
- For patients with a life expectancy of 1-month, DS and EUS-GE were more likely to maximize oral intake for such patients
- However, for patients with a life expectancy of 5- or 6-month, surgical GJ, or EUS-GE if expertise were available, had significantly better oral intake tolerance than DS.

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advanced gastroduodenal[2] or pancreatobiliary malignancies[3]. Successful palliation of GOO is not only of paramount importance for improving quality of life, but may also have an impact on overall survival, as patients with persistent GOO are unlikely to be candidates for systemic chemotherapy. Currently, malignant GOO is commonly palliated via duodenal stenting (DS), surgical gastrojejunostomy bypass (GJ), and more recently, an endoscopic ultrasound-guided gastroenterostomy (EUS-GE)[1]. Previously, survival scores were used to help predict which patients were most likely to benefit from either DS or GJ[4]. However, the recently popularized EUS-GE procedure, has emerged as an alternative to either method, avoiding the surgical morbidities commonly associated with a GJ, while appearing to have a longer lasting stent patency than a DS[1].

However, while comparative studies and reviews have summarized the different clinical success rates or complications for each of these three interventions[1,5-9], all these outcomes were assessed individually. They do not sufficiently address oral intake tolerance, which is probably the most critical consideration for these groups of patients. Furthermore, as the outcomes were assessed individually, it did not account for differing life expectancies for these patients while balancing the recurrent obstruction rates with the adverse events associated with each procedure.

Thus, the aim of this study is to systematically review and meta-analyze the available literature on DS, EUS-GE and GJ in the palliation of malignant GOO. Subsequently, a probabilistic Markov decision tree model was constructed, to determine the optimal strategy that maximizes oral intake tolerance at different survival time points of 1-, 2-, 3-, 4-, 5-, and 6-month.

Methods

Search strategy

The systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. PUBMED/MEDLINE, EMBASE and Cochrane databases were searched for studies from inception to 30 September 2024. The search terms used were ((“gastric outlet obstruction” OR “GOO” OR “gastric obstruction”) AND (“gastric bypass” OR “gastrojejunostomy” OR “stent*” OR “gastroenterostomy) NOT “bariatric”) AND “trial”). Studies who reported malignant GOO in exclusively pancreatobiliary malignancies were excluded. Randomized controlled trials (RCT) which reported outcomes of any of the treatment arms (DS, EUS-GE, or GJ) with a comparator group were included. As there was only one RCT reporting outcomes on EUS-GE, a prospective cohort study was also included. In cases of duplicate studies from the same cohort, only the largest and most detailed study was included. Conference abstracts were excluded. The search was conducted by two independent authors, and any discrepancies resolved by a third author. The study protocol was registered in the PROSPERO database.

Data extraction

Following an initial title and abstract search, full text review of shortlisted articles was performed independently by two authors and data from each study was independently extracted. Data extracted included study information (author, year, centre, patient group, interventions, follow-up duration) as well as key outcome measures to be inputted as probabilistic datapoints for the Markov model. These outcome measures included the proportion of patients with periprocedural mortality, mortality and stent dysfunction/ gastrojejunostomy obstruction at 1-, 2-, 3-, 4-, 5-, and 6-months, technical and clinical success, reintervention and complications. For the analysis, 4-, 8-, 12-, 16-, 20-, and 24-weeks, and 30-, 60-, 90-, 120-, 150-, and 180-days were taken to be equivalent as 1-, 2-, 3-, 4-, 5-, and 6-months, respectively.

Assessment of study quality

Study quality was assessed independently by two authors and any conflicts resolved with consultation with a third author. The Cochrane Risk of Bias (ROB) 2.0 tool was used to assess the individual bias domains[10].

Synthesis of findings

For outcome variables reported by only one single study, the event rate reported was used as the input probability variable for the Markov model. For outcome variables reported by multiple studies, a pooled event rate was calculated based on the reported intention-to-treat outcome for each study and used for as the input probability variable. Statistical heterogeneity was assessed by the I^2 statistic[11]. Studies with $I^2 < 50\%$ were analyzed via the fixed effects model, but studies with $I^2 \geq 50\%$ were analyzed via the random effects model. Continuity correction was applied to all probabilities to account for zero event studies, and sensitivity analyses were performed. Results of the pooled event rate were presented on their Forest plots.

Markov model assumptions

The Markov decision tree was constructed by consensus from a team of six attending Gastroenterologists and Upper Gastrointestinal Surgeons from two institutions and academic medical centre. One of the surgeons (LWLO) had extensive experience in all three interventions of DS, EUS-GE and GJ. The model assumes a patient with malignant GOO from an unresectable malignancy, with equal likelihood of being treated with either a DS, EUS-GE or GJ. The model then follows with a decision tree of possible health states, with probability transitions specific to each strategy, based on previous input probability variables from the systematic review. The model exits with three outcomes, oral intake, no oral intake or crossover. Crossover is defined as crossing over from an initial management strategy (e.g., DS) to another strategy (e.g., EUS-GE or GJ). The model follows the patient up to 180-days, accounting for the predicted survival based on the disease process at each time point as well.

Markov modeling

The model is generated with 10 000 simulations each, with equal probability of undergoing DS, EUS-GE and GJ, and with equal probability of death from 1 to 6-month, based on pooled input probabilities synthesized from the systematic review. The outcome was to determine the optimal palliative strategy that maximizes oral intake at each time point.

Statistical analysis

Statistical analyses were performed via R version 4.2.2. (R Foundation for Statistical Computing, Vienna, Austria)[12],

using the "meta," "metafor, "ggplot2" packages. The pairwise probability test was performed to integroup differences in simulated outcomes at each time point. A *P* value of <0.05 was taken as statistically significant.

Results

Study characteristics

The PRISMA flow diagram for the study is represented in Fig. 1. A total of 275 studies were identified, for which 21 studies were selected for full text reviews, for which 15 studies were included for the analysis[13-27].

Of the 15 studies, there were 14 RCTs[13-26]. As there was only one RCT that investigated EUS-GE, hence the only prospective cohort study investigating EUS-GE with DS was also included for the analysis[27]. Eight trials investigated between different DS[13-20], one trial compared between different GJ techniques[21], four trials compared between GJ and DS[22-25]. One trial and one prospective cohort study compared EUS-GE and DS[26,27]. The study characteristics were summarized in Table 1.

Decision tree

The Markov decision tree for DS, EUS-GE and GJ were presented in Fig. 2. The likelihood probabilities at each step in the decision tree were represented by their probabilities (*P(1), P(2), P(3)…*), and the complement of the event as (*P(1'), P(2'), P(3') …)*. Given that a patient with a patent stent or GJ will still not be able to tolerate orally if he demises from the disease process, we estimated the expected life expectancy of an individual at the six time points. Complete 1 to 6-month survival data were available from three studies, that investigated between different DS[20], DS and GJ[23] and DS and EUS-GE[26]. Hence, the pooled probabilities of mortality at these points were used to derive the probability of mortality in the model at these time points, *P(Mortality)*. This will ensure that the baseline survival

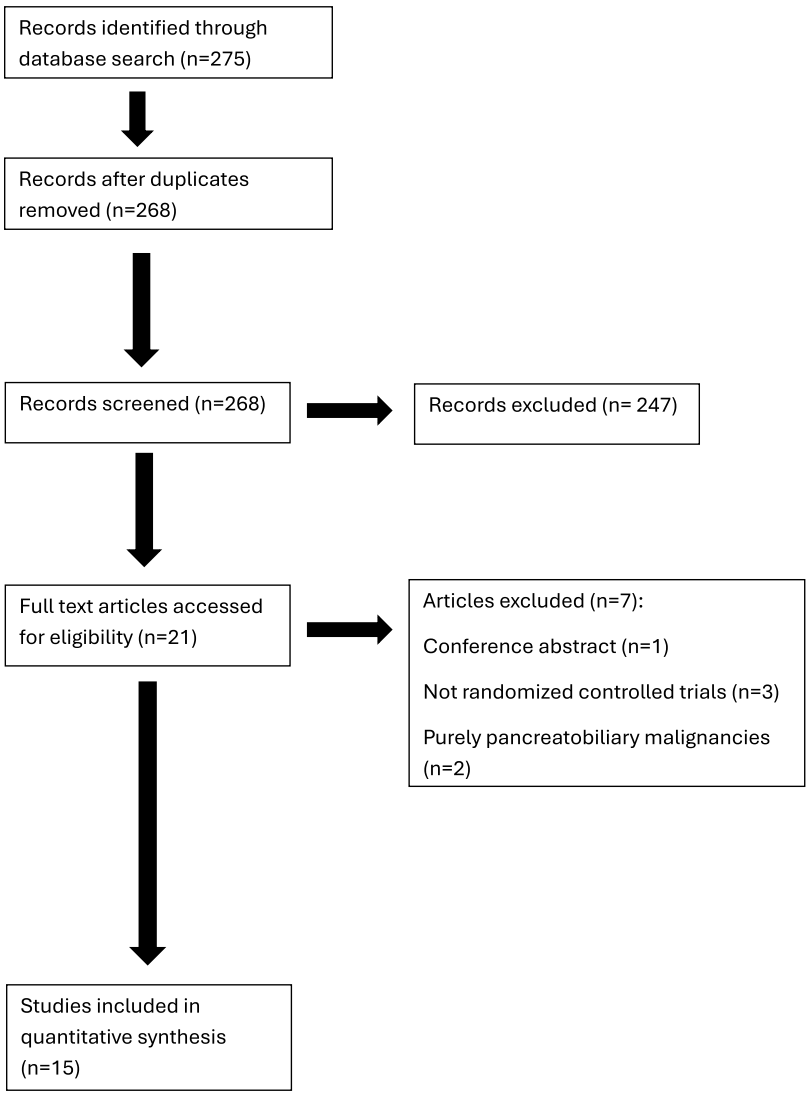

Figure 1. PRISMA flow diagram.

Table 1

Baseline characteristics of included studies

Author, year	Centre	Study	Intervention (I): Control (C):	Number (n) I	Number (n) C	Follow-up duration	Malignancy type	Mortality at different time intervals	Technical success	Clinical success	Dysfunction at different time intervals*	Re-intervention	Leak/ Perforation	Successful salvage/ resolved gastroparesis
Kim, 2010[13]	1 centre, South Korea	RCT	I: covered self-expandable metal stent C: uncovered self-expandable metal stent	40	40	8 weeks	Gastric (100.0%)	NA	I: 100% C: 100%	I: 95% C: 90%	60-day I: 38.7% C: 38.9%	NA	I: 0% C: 0%	NA
Lim, 2014[14]	4 centres in South Korea	RCT	I: covered self-expandable metal stent C: uncovered self-expandable metal stent	59	61	Till death	Gastric (84.2%) Pancreatic (7.5%) Duodenal (1.7%) Ampullary (1.7%) Bile duct (5%) Gallbladder (1.7%)	NA	I: 100% C: 100%	I: 100% C: 98.4%	Overall I: 22% C: 21.3%	I: 22.0% C: 21.3%	I: 0% C: 0%	NA
Maetani, 2014[15]	2 centres in Japan	RCT	I: triple layer covered self-expanding metal stent C: Uncovered self-expandable metal stent	31	31	Till death	Gastric (32.3%) Duodenum (56.5%) Anastomosis (11.3%)	NA	I: 100% C: 100%	I: 87.1% C: 93.5%	120-day I: 22.8% C: 23.3%	NA	I: 0% C: 3.2%	NA
Shi, 2014[16]	4 centres in China	RCT	I: individualized stent C: uncovered self-expandable metal stent	33	32	Till death	Gastric (100.0%)	NA	I: 96.9% C: 96.9%	I: 93.8% C: 93.5%:	Overall I: 12.1% C: 25.0%	I: 9.4% C: 22.5%	NA	NA
Lee, 2015[17]	Multi-centre, South Korea	RCT	I: covered metal stent with anti-migration device C: uncovered self-expandable metal stent	51	51	16 weeks	Gastric (100.0%)	30-day: I: 5.9% C: 5.9%	I: 98.0% C: 96.1%	I: 96.1% C: 90.2%	60-day I: 27.5% C: 37.3% 120-day I: 31.4% C: 58.8%	I: 14.3% C: 37.8%	I: 0% C: 0%	NA
Shi, 2018[18]	4 centres in China	RCT	I: individualized stent C: Funnel covered stent	44	44	Till death	Gastric (100%)	NA	I: 97.7% C: 97.7%	I: 97.7% C: 100%	Overall I: 6.9% C: 4.7%	I: 6.9% C: 4.7%	NA	NA
Yamao, 2020[19]	Multi-centre, Japan	RCT	I: covered self-expandable metal stent C: Uncovered self-expandable metal stent	182	184	3 months	Pancreatic (48.9%) Gastric (32.2%) Gallbladder (6.0%) Others (12.8%)	1-month I: 14.9% C: 14.2% 2-month I: 33.4% C: 35.5%	I: 100% C: 100%	I: 90.1% C: 91.3%	Overall I: 23.4% C: 35.2% 1-month I: 7.8% C: 16.7%	NA	I: 1.6% C: 1.6%	NA

(*Continues*)

Table 1
(Continued).

Author, year	Centre	Study	Intervention (I): Control (C):	Number (n)		Follow-up duration	Malignancy type	Mortality at different time intervals	Technical success	Clinical success	Dysfunction at different time intervals*	Re-intervention	Leak/ Perforation	Successful salvage/ resolved gastroparesis
				I	C			3-month I: 50.3% C: 51.6%			2-month I: 11.7% C: 24.4% 3-month I: 16.3% C: 30.9%			
Teoh, 2024[20]	International multi-centre	RCT	I: partially covered metal stent C: uncovered self-expandable metal stent	59	58	1 year	Gastric (40.0%) Pancreatic (40.0%) Duodenal (7.0%) Periampullary (4.3%) Cholangiocarcinoma (1.7%)	1-month I: 6.8% C: 5.2% 2-month I: 50.8% C: 51.8% 3-month I: 64.4% C: 60.7% 4-month I: 71.2% C: 67.9% 5-month I: 72.9% C: 73.2% 6-month I: 81.3% C: 75.0%	I: 100% C: 100%	I: 91.5% C: 98.2%	NA	I: 20.3% C: 25.0%	NA	NA
Navarra, 2006[21]	1 centre, Italy	RCT	I: Laparoscopic GJ C: Open GJ	12	12	2 months	Pancreatic (45.8%) Gastric (25.0%) Others (29.2%)	NA	I: 100% C: 100%	I: 100% C: 83.3%[a]	1-month I: 0% C: 0%	I: 0% C: 0%	I: 0% C: 0%	I: NA C: 100%
Mehta, 2006[22]	1 centre, UK	RCT	I: Laparoscopic GJ C: uncovered self-expandable metal stent	13	12	1 year	Pancreatic (55.6%) Gastric (14.8%)	2-month I: 0% C: 0% Peri-operative mortality I: 23.1%	I: 100% C: 83.3%	I: 76.9%[a] C: 100%	NA	NA	I: 0% C: 0%	I: 100% C: NA

(*Continues*)

Table 1
(Continued).

Author, year	Centre	Study	Intervention (I): Control (C):	Number (n) I	Number (n) C	Follow-up duration	Malignancy type	Mortality at different time intervals	Technical success	Clinical success	Dysfunction at different time intervals*	Re-intervention	Leak/ Perforation	Successful salvage/ resolved gastroparesis
							Disseminated metastases (14.8%) Cholangiocarcinoma (7.4%) Gallbladder (3.7%) Benign gastric ulcer (3.7%)	C: 16.7%						
Jeurnink, 2010[23]	Multi-centre, the Netherlands	RCT	I: Laparoscopic GJ C: uncovered self-expandable metal stent	18	21	180 days	Pancreas (71.8%) Duodenum (10.3%) Gastric (7.7%) Extrinsic (5.1%) Bile duct (2.6%) Ampullary (2.6%)	30-day I: 16.7% C: 23.8% 60-day I: 27.8% C: 57.1% 90-day I: 55.6% C: 71.4% 120-day I: 61.1% C: 76.2% 150-day I: 66.7% C: 76.2% 180-day I: 77.8% C: 85.7%	I: 94.1% C: 95.2%	I: 83.3% C: 80.0%[b]	30-day I: 5.5% C: 4.8% 60-day I: 5.5% C: 9.5% 90-day I: 5.5% C: 14.3% 120-day I: 5.5% C: 14.3% 150-day I: 5.5% C: 23.8% 180-day I: 5.5% C: 38.1%	I: 11.8% C: 47.6%	I: 5.9% C: 0%	I: 0.0% C: 80.0%
Fiori, 2013[24]	1 centre, Italy	RCT	I: Open GJ C: covered self-expandable metal stent	9	9	Till death	Gastric (100%)	Peri-operative mortality I: 0% C: 0%	I: 100% C: 100%	I: 66.7%[a] C: 88.9%	30-day I: 0% C: 11.1% 60-day I: 0% C: 22.2% 90-day I: 0%	I: 0% C: 33.3%	NA	I: 100% C: 100%

(*Continues*)

Table 1
(Continued).

Author, year	Centre	Study	Intervention (I): Control (C):	Number (n)		Follow-up duration	Malignancy type	Mortality at different time intervals	Technical success	Clinical success	Dysfunction at different time intervals*	Re-intervention	Leak/ Perforation	Successful salvage/ resolved gastroparesis
				I	C						C: 22.2% 120-day I: 0% C: 33.3% 150-day I: 0% C: 33.3% 180-day I: 0% C: 33.3%			
Fiori, 2021[25]	1 centre, Italy	RCT	I: self-expandable DS C: open partitioning GJ	13	14	6 months	Gastric (100%)	Peri-operative mortality I: 0% C: 0%	I: 100% C: 100%	I: 100% C: 92.9%[a]	4-month I: 46.2% C: 0%	I: 46.2% C: 0%	I: 0% C: 0%	I: 100% C: 100%
Teoh, 2023 [26]	International, multi-centre	RCT	I: EUS-GE C: uncovered self-expandable metal stent	48	49	6 months	Pancreatic (45.4%) Gastric (28.9%) Duodenal (11.3%) Periampullary (8.2%) Cholangiocarcinoma (3.1%) Gallbladder (3.1%)	1-month I: 20.8% C: 12.2% 2-month I: 29.2% C: 26.5% 3-month I: 33.3% C: 36.7% 4-month I: 39.6% C: 46.9% 5-month I: 45.8% C: 61.2% 6-month I: 50.0% C: 67.3%	I: 96.0% C: 100%	I: 100% C: 91.8%	1-month I: 2.6% C: 13.0% 2-month I: 2.9% C: 15.8% 3-month I: 3.1% C: 22.2% 4-month I: 3.6% C: 25.8% 5-month I: 7.4% C: 40.0% 6-month I: 8.0% C: 50.0%	I: 0% C: 32.7%	I: 0% C: 0%	

(*Continues*)

Table 1
(Continued).

Author, year	Centre	Study	Intervention (I): Control (C):	Number (n)		Follow-up duration	Malignancy type	Mortality at different time intervals	Technical success	Clinical success	Dysfunction at different time intervals*	Re-intervention	Leak/ Perforation	Successful salvage/ resolved gastroparesis
				I	C									
Vanella, 2023[27]	1 centre, Italy	Prospective cohort study	I: EUS-GE C: uncovered self-expandable metal stent	76	NA	6 months	Pancreatic (75.7%) Gastric (7.1%) Biliary (7.1%) Ampullary (5.7%) Others (4.3%	Peri-operative mortality I: 2.9%	I: 90.8%	I: 97.1%	1-month I: 1.4% 2-month I: 2.9% 3-month I: 4.3% 4-month I: 4.3% 5-month I: 4.3% 6-month I: 5.7%	I: 60.0%	I: 2.8%	

The columns represent the following: Column 1 (Author, year) – author and year of publication of the included studies; Column 2 (Centre) – the centres and country involved; Column 3 (Study) – type of study (RCT = randomized controlled trial); Column 4 (Intervention (I): Control (C)) – the interventional (I) and control (C) arms in the study; Column 5 (Number) – the number of patients in the I and C arms respectively; Column 6 (Follow-up duration) – the duration of follow-up for the study; Column 7 (Malignancy type) – the cause for gastric outlet obstruction in the study, represented by the proportion of patients with a particular type of malignancy represented as a percentage (%); Column 8 (Mortality at different time intervals) – the proportion of patients who demised at different time intervals reported in the study. Peri-operative mortality represents studies who reported only peri-operative mortality outcomes, while NA = not applicable. Studies who reported outcomes by different time intervals (i.e., 30-day/1-month) were reported as such. Column 9 (Technical success) – technical success of the intervention as reported by the studies; Column 10 (Clinical success) – defined as successful resolution of GOO following technical success as reported by the studies; Column 11 (Dysfunction at different time intervals) – represents the stent or LAMS dysfunction, or recurrence of GOO after GJ as reported by the studies at different time points. For studies that did not break down the dysfunction by time interval, the overall dysfunction rate was used. NA = Not applicable. Column 12 (Reintervention) – describes the reintervention rate following stent or LAMS dysfunction or recurrent GOO. NA = not applicable. Column 13 (Leak/ perforation) – describes the proportion of immediate periprocedural complications related to either intestinal perforation or leakage. NA = not applicable. Column 14 (successful salvage/ resolved gastroparesis) – successful salvage of stent dysfunction or resolution of GOO following GJ due to gastroparesis.

*Dysfunction represents either stent dysfunction for DS, lumen-apposing metal stent (LAMS) dysfunction for EUS-GE or recurrence of gastric outlet obstruction for GJ.

[a]Gastroparesis, which resolved after the 1st month after procedure.

[b]Total of 4 patients with clinical failure. 3 (15.0%) were due to persistent obstructive symptoms while 1 (5.0%) resolved after repeat endoscopy and further stenting.

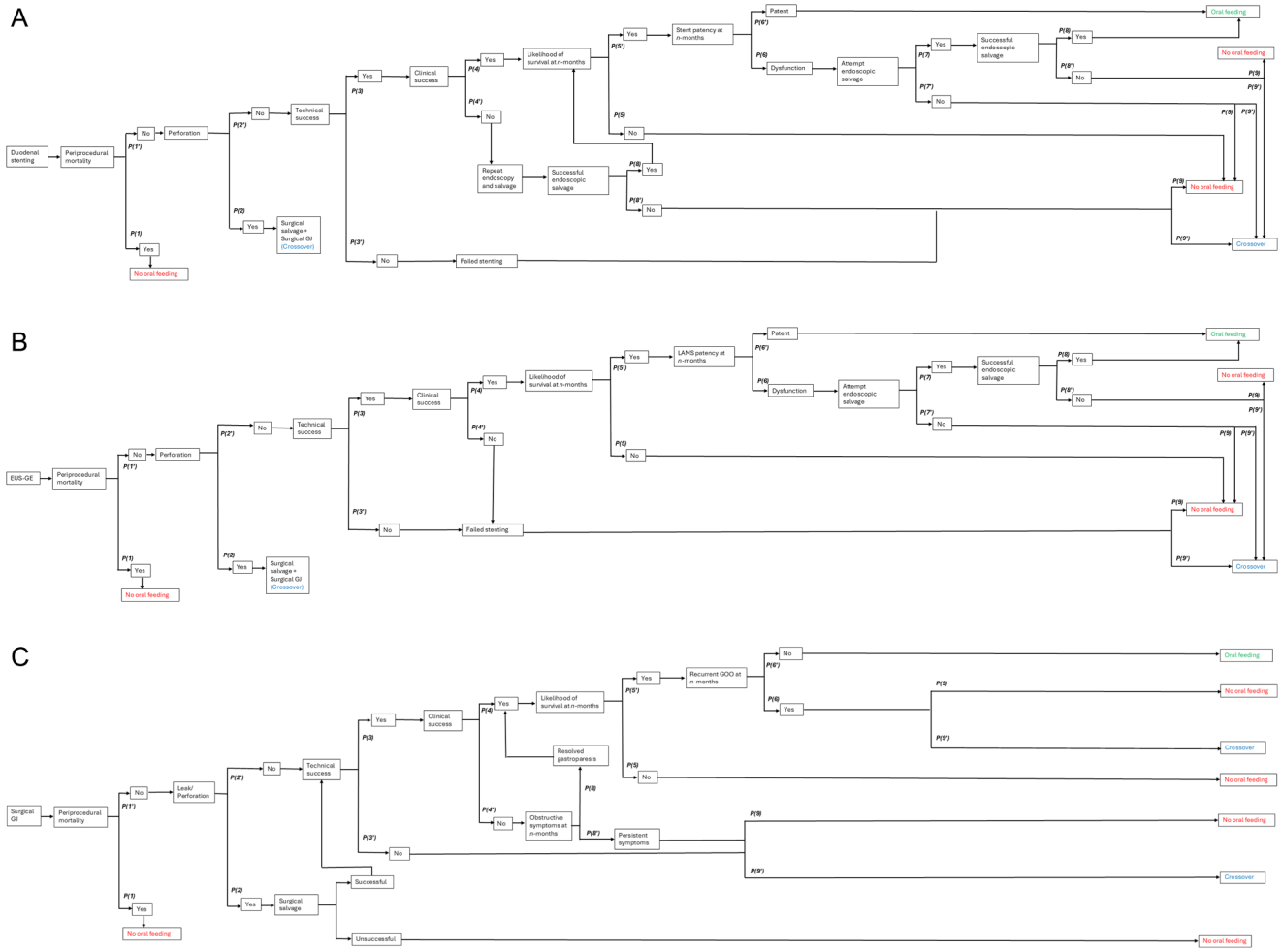

Figure 2. (A) Markov decision tree for DS. The input probabilities at each step of the decision tree was based on the pooled probabilities as reported in Table 2. (B) Markov decision tree for EUS-GE. The input probabilities at each step of the decision tree was based on the pooled probabilities as reported in Table 2. (C) Markov Decision Tree for GJ. The input probabilities at each step of the decision tree was based on the pooled probabilities as reported in Table 2.

probabilities of the model were the same across all three interventions. *P(Mortality)* was modified as a conditional probability, *P(5)* = *P(Mortality|1)*, based on the initial likelihood of periprocedural mortality after intervention, *P(1)* via the formula, *P(Mortality)–P(1)/P(1')*, to account for differing periprocedural mortality probabilities across all three interventions. Incidence of stent dysfunction or GOO recurrence were also pooled at different time points and were fitted into the model, *P(6)*.

Duodenal stenting

A 9-step decision tree was constructed for DS. Given there are multiple RCTs for DS, the control group for DS in the prospective cohort study[27] was not included in the meta-analysis. In individuals who failed all interventions and reinterventions, it was assumed that they will be equally likely to have either no oral intake or a crossover intervention to either GJ or EUS-GE, with an equal probability of 0.5 for each, *P(9)*.

Endoscopic ultrasound-guided gastroenterostomy

A similar 9-step decision tree was constructed for EUS-GE. However, as there were no reported successful salvages following technical, *P(3)* or clinical failure, *P(4)*, those patients will be assumed to be equally distributed at 0.5 probability to either no oral intake or crossover interventions to either DS or GJ, *P(9)*.

Surgical gastrojejunostomy

An 8-step decision tree was constructed for GJ. The likelihood of endoscopic salvage following recurrent obstruction was not included, *P(7)* in the decision tree, compared to DS or EUS-GE. This was because in recurrent obstructions of the GJ, there were no successful salvage interventions[23]. All leaks or perforations reported in the GJ cohort had successful surgical salvage performed[23]. Patients with failed interventions were assumed to be equally distributed at 0.5 probabilities to either no oral intake, or a crossover to DS, as it was themed theoretically not possible to perform a EUS-GE on an existing GJ.

Probabilistic outcomes

The selected input values and their ranges for the probabilistic analyses were summarized in Table 2. The forest plots for the meta-analyses of the pooled probability estimates were summarized in Supplementary Figures (available at:

Table 2

Input values and ranges for the probabilistic analysis for the markov decision tree analysis

	DS		EUS-GE		GJ	
Decision tree step	**Pooled probability (95% confidence interval)**	**Reference (s)**	**Pooled probability (95% confidence interval)**	**Reference (s)**	**Pooled probability (95% confidence interval)**	**Reference (s)**
P(1) = Probability of periprocedural mortality	0.08 (0.05-0.12)	[17,19,20,22-26]	0.11 (–0.07-0.29)	[26,27]	0.06 (–0.03-0.15)	[22-25]
P(2) = Probability of perforation/ leak	0.00 (0.00-0.01)	[13-15,17,19,22,23,25,26]	0.00 (–0.01-0.02)	[26,27]	0.01 (–0.01-0.03)	[21-23,25]
P(3) = Probability of technical success	1.00 (1.00-1.00)	[13-20,22-26]	0.93 (0.89-0.98)	[26,27]	0.99 (0.97-1.01)	[21-25]
P(4) = Probability of clinical success	0.95 (0.93-0.97)	[13-20,22-26]	1.00 (0.98-1.01)	[26,27]	0.88 (0.78-0.97)	[21-25]
P(Mortality) = Probability of mortality at *n*-months						
1-month	0.12 (0.06-0.18)	[20,23,26]	0.12 (0.06-0.18)	[20,23,26]	0.12 (0.06-0.18)	[20,23,26]
2-month	0.40 (0.29-0.51)		0.40 (0.29-0.51)		0.40 (0.29-0.51)	
3-month	0.53 (0.40-0.66)		0.53 (0.40-0.66)		0.53 (0.40-0.66)	
4-month	0.60 (0.48-0.72)		0.60 (0.48-0.72)		0.60 (0.48-0.72)	
5-month	0.66 (0.56-0.75)		0.66 (0.56-0.75)		0.66 (0.56-0.75)	
6-month	0.73 (0.63-0.83)		0.73 (0.63-0.83)		0.73 (0.63-0.83)	
P(5) = Conditional probability of mortality at *n*-months accounting for *P(1)*						
1-month	0.04 (0.01-0.07)	[17,19,20,22-26]	0.01 (–0.15-0.12)	[20,23,26,27]	0.06 (0.04-0.09)	[20,22-26]
2-month	0.35 (0.25-0.44)		0.33 (0.31-0.34)		0.36 (0.31-0.42)	
3-month	0.49 (0.37-0.61)		0.47 (0.44-0.52)		0.50 (0.42-0.60)	
4-month	0.57 (0.45-0.68)		0.55 (0.51-0.61)		0.57 (0.50-0.67)	
5-month	0.63 (0.54-0.72)		0.62 (0.59-0.65)		0.64 (0.57-0.71)	
6-month	0.71 (0.61-0.81)		0.70 (0.65-0.76)		0.71 (0.64-0.80)	
P(6) = Probability of stent/ LAMS[a]/ GJ dysfunction at *n*-months						
1-month	0.11 (0.06-0.16)	[19,23,24,26]	0.02 (–0.01-0.04)	[26,27]	0.01 (–0.02-0.04)	[21,23,24]
2-month	0.24 (0.17-0.32)	[13,17,19,23,24,26]	0.03 (0.00-0.05)	[26,27]	0.01 (–0.02-0.04)	[21,23,24]
3-month	0.22 (0.15-0.29)	[19,23,24,26]	0.03 (0.00-0.06)	[26,27]	0.02 (–0.03-0.08)	[23,24]
4-month	0.30 (0.19-0.41)	[15,17,23,24,26]	0.04 (0.01-0.08)	[26,27]	0.01 (–0.02-0.05)	[23-25]
5-month	0.35 (0.24-0.45)	[23,24,26]	0.05 (0.01-0.09)	[26,27]	0.02 (–0.03-0.08)	[23,24]
6-month	0.44 (0.33-0.55)	[23,24,26]	0.06 (0.02-0.11)	[26,27]	0.02 (–0.03-0.08)	[23,24]
P(7) = Probability of attempted salvage/ reinterventions	0.22 (0.15-0.28)	[14,16-18,20,23,24,26]	0.30 (–0.29-0.89)	[26,27]	0.01 (–0.01-0.04)[b]	[21,23-25]
P(8) = Probability of successful endoscopic salvage[c]	0.98 (0.94-1.02)	[23-25]	0.67 (0.01-1.32)	[26,27]	NA	NA
P(8) = Probability of resolved gastroparesis[d]	NA	NA	NA	NA		
1-month					0	[21-25]
2-6 months					0.79 (0.41-1.18)	[21-25]
P(9) = Probability of no oral intake or crossover[e]						
No oral intake	0.5		0.5		0.5	
Crossover	0.5		0.5		0.5	

The columns represent the following: Column 1 (Decision tree step) – represents the probabilities in each step of the Markov Decision Tree for Figure 2A, 2B, and 2C. Column 2 (DS), Column 3 (EUS-GE), Column 4 (GJ) – reports the pooled probabilities derived from the meta-analysis forest plot for each step in the Markov Decision Tree in Figure 2A, 2B, and 2C. The pooled probabilities and their 95% confidence intervals are reported. The references denote the studies used to derive the pooled probabilities for that step. Rows 2-11 – reports the probability of event (i.e., 1,2,3,…) corresponding to the step in the Markov Decision Tree. The pooled probabilities at each step based on the forest plot, was used as the input probability for the event in that step of the model. The complement of the event, (P(1′), P(2′), …) as seen in Figure 2A, 2B, and 2C were derived by the formula (P(1′) = 1-P(1), P(2′) = 1-P(2), …).

[a]LAMS = Lumen apposing metal stent.

[b]Not included in the Markov decision tree analysis.

[c]Assumed that endoscopic reinterventions performed at any time point for salvage carries the same success rate.

[d]Given that gastroparesis was transient, and all studies resolved by the 2nd month.

[e]Assumption that if an intervention failed, patient would have equal probability of being assigned to an alternative intervention (crossover), or will have inability to tolerate orally (no oral intake).

http://links.lww.com/JS9/D948) and used as input variables for Table 2, as well as in the decision tree.

Markov model

Based on 10 000 simulations, the optimal modality that maximizes oral intake tolerance at 1 to 6 months were summarized in Table 3 and Fig. 3. At 1-month, both DS and EUS-GE had a significantly higher likelihood of successful oral intake compared to GJ. The likelihood of DS declined significantly subsequently, with the lowest oral intake rates from 2- to 6-month. GJ GJ was significantly associated with higher oral intake rates at 2- and 4-month after intervention. EUS-GE and GJ were both

Table 3

Markov decision tree analysis based on 10000 simulations on DS, EUS-GE and GJ on 1- to 6-month oral intake tolerance

	DS	EUS-GE	GJ	*P*-value
1-month	8116*	8039*	7545	DS vs EUS-GE: 0.520 DS vs GJ: < 0.001 EUS-GE vs GJ: < 0.001
2-month	5047	5373	5701*	DS vs EUS-GE: < 0.001 DS vs GJ: < 0.001 EUS-GE vs GJ: < 0.001
3-month	4131	4340*	4423*	DS vs EUS-GE: 0.009 DS vs GJ: < 0.001 EUS-GE vs GJ: 0.728
4-month	3328	3591	3890*	DS vs EUS-GE: < 0.001 DS vs GJ: < 0.001 EUS-GE vs GJ: < 0.001
5-month	2834	3044*	3183*	DS vs EUS-GE: 0.004 DS vs GJ: < 0.001 EUS-GE vs GJ: 0.105
6-month	2129	2377*	2520*	DS vs EUS-GE: < 0.001 DS vs GJ: < 0.001 EUS-GE vs GJ: 0.059

The values represent the number of cases where patient achieves successful oral intake.
*Optimal modality that maximizes oral intake tolerance at that time point.

significantly associated with a higher likelihood of oral intake compared to DS at 3-, 5-, and 6-month from intervention.

Sensitivity analyses

Sensitivity analyses revealed that the DS and EUS-GE model were most sensitive to perturbations in probabilities for *P(2)*, or presence of perforation. However, this was unlikely to have any implications for the final model, as the pooled probability of *P(2)* was 0 in both groups for the model. No step in the clinical decision tree was particularly sensitive to perturbations for the GJ model.

Discussion

While a Markov decision tree analysis has been utilized in the past in other areas such as foregut[28] or hernia surgery[29], to our knowledge, this was the first Markov decision tree analysis that evaluated the various modalities of palliating malignant GOO and its impact on maximizing oral intake tolerance. Utilizing input probabilities pooled from a meta-analysis of available RCTs, we demonstrated that different management strategies can impact the likelihood of successful oral intake at different time points of survival for patients with malignant GOO.

From the model, for patients with an expected life expectancy of 1-month or less, DS or EUS-GE conferred significantly higher likelihood of oral intake compared to GJ. This was likely due to the increased likelihood of gastroparesis in the GJ group at 1-month. This finding was consistent with reported literature, which reported up to 10% gastroparesis rates following GJ, compared to <1% seen after DS or EUS-GE[30]. Postoperative gastroparesis or paralytic ileus is common after abdominal surgeries and has been postulated to be contributed by intestinal manipulation intraoperatively[31], neurohormonal responses to surgical stress[32], opioid use[33] and disruption of the interstitial cells of Cajal of the gastric pacemaker[34] in the gastric antrum and body. Unlike GJ, EUS-GE and almost all DS cases in the studies were performed under conscious sedation or monitored

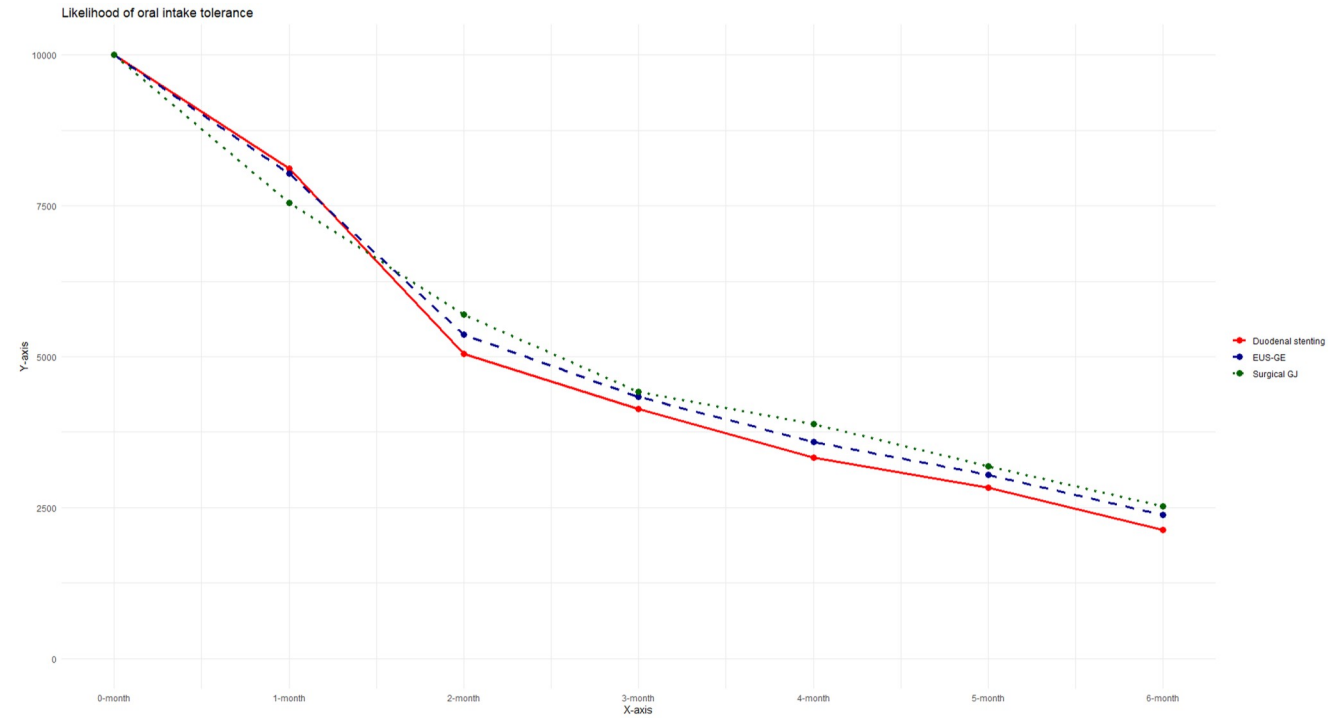

Figure 3. Line graph showing the likelihood of successful oral intake for DS, EUS-GE and GJ at 1 to 6 months after intervention. The x-axis represents the survival time points at 1 to 6-month. The y-axis represents the 10 000 simulated patients in the Markov model (n = 10 000) at each corresponding time point.

anesthesia care[13-20,22-27], which likely contributed to reduced opioid use. Coupled with the lack of intestinal manipulation, this likely accounted for the reduced gastroparesis incidence seen in DS and EUS-GE. In addition, we believe postoperative edema of the GJ anastomosis, likely also contributed to the higher gastroparesis rates seen in the 1st month. This was ameliorated in the DS and EUS-GE group, as the slowly expanding nature of the self-expanding metal stents, may result in reduced tissue trauma and edema after intervention.

For patients with a longer life expectancy at 5- or 6-month, DS was significantly inferior to EUS-GE and GJ in maximizing oral intake tolerance. This was not unexpected and was likely due to an increased incidence of DS dysfunction over time. While GJ exhibited the highest probability of oral intake tolerance at 5- or 6-month, this result was comparable to EUS-GE. In addition, EUS-GE had a better 1-month oral intake due to reduced incidence of gastroparesis. At 2- and 4-month follow-up, EUS-GE was shown in the model to have a lower likelihood of successful oral intake compared to GJ. The exact reason was unclear but given the consistent non-inferiority of EUS-GE compared to GJ seen at 3-, 5-, and 6-month, this might be a result of the slightly better pooled GJ patency rates seen at 2- and 4-months. This was probably contributed by the uncommon nature of GJ obstruction, hence under-estimating the probabilities of GJ obstruction at 2- and 4-months (see Table 2).

Based on the results of the model, we propose an algorithm to guide the management of patients with malignant GOO, based on the presence or absence of concomitant biliary obstruction, as well as the predicted likelihood of survival (Fig. 4). Prognostication can be estimated based on available prognostic scoring systems[35-37]. In the absence of biliary obstruction, we advocate a EUS-GE first approach for patients deemed to have an estimated survival of more than 1-month. Given the less invasive nature of EUS-GE, an attempted endoscopic ultrasound can be performed for all patients with malignant GOO without concomitant biliary obstruction. If technically feasible, an EUS-GE was preferable to a surgical GJ, given the equivalent outcome at up to 6-months with better early oral intake tolerance. If no suitable bowel loop can be identified, patients can then be transitioned to a surgical GJ. For patients with an estimated survival of 1-month or less, a DS first approach should be attempted. This is especially so if there was concomitant biliary obstruction, as an endoscopic retrograde cholangiopancreaticography (ERCP) can also be performed and biliary decompression performed following DS deployment. For patients with concomitant biliary obstruction with an expected life expectancy of more than 1-month, a surgical GJ first approach can be adopted, as a biliary-enteric anastomosis can be performed in the same setting, alleviating both biliary and GOO. We believe in the setting of biliary obstruction, there may not be any additional benefits of a EUS-GE, as the lumen apposing metal stent (LAMS) does not permit a straightforward access to the biliary tree.

One limitation of this model was that it did not account for other concomitant disorders commonly seen in this group of patients with malignant GOO, such as biliary obstruction, as discussed above. However, we adjusted for the impact of biliary sepsis on survival by pooling the probabilities of survival across all groups in the model (Table 2). This ensured that the baseline survival probabilities for all three groups were equivalent at each time point. It also gives a better estimate of successful oral intake tolerance, as stent or GJ patency will have no impact on oral intake tolerance if patients were unlikely to survive past that time point.

Another limitation of this model was that the survival time points were only modeled up to 6-months. This was limited by the paucity of follow-up data for EUS-GE after 6 months[26]. However, this model would still be adequate for most patients with metastatic gastric or pancreatic cancer with GOO, given that the median survival ranges from 3 to 7 months[38-40]. Longer term follow-up results for EUS-GE will be highly anticipated to help shed light on the long-term LAMS patency rates.

In addition, the model was constructed based on probabilities obtained from RCTs. As many of these procedures were performed in high volume centres by technical experts, the model most likely reflect the ideal situation, and may not be generalizable to the general population. As seen in the sensitivity analyses, for DS and EUS-GE, the model can be significantly altered by the rates of intraprocedural complications like perforation. The authors further advocate that to minimize other infective complications, prophylactic antibiotic therapy can be considered

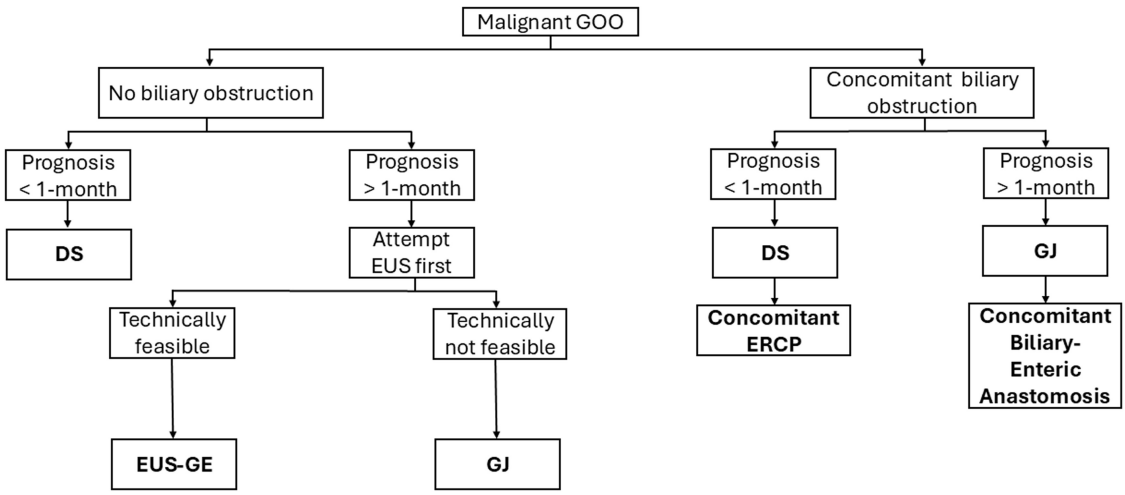

Figure 4. Proposed algorithm for the management of malignant GOO based on results of the Markov model.

prior to EUS-GE, like a surgical GJ[41]. The authors also propose that an EUS-GE first approach should be adopted for patients with an expected prognosis of more than 1 month, only in the setting where technical expertise are readily available.

Conclusion

Based on a Markov decision tree analysis from a meta-analysis of RCTs, for patients with malignant GOO with an expected prognosis of less than 1-month, DS or EUS-GE, if technical expertise is available, should be considered to maximize oral intake tolerance. For patients with a modest prognosis of up to 5- or 6-months, a surgical GJ, or an EUS-GE, if technical expertise is available, should be employed instead. A surgical GJ is probably most optimal for patients with a prognosis longer than 6-month, while awaiting long-term follow-up data for EUS-GE.

Ethical approval

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Consent

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Author contributions

C.K.M. conceived of the project idea. C.K.M., L.W.L.O., J.T.H.T., J.G.X.T., W.W.K., and B.P.M.Y. were involved in the construction of the Markov decision tree, together with input and expert opinion from B.R.D., M.P., and C.K.W.K. C.K.M. and B.R.D. performed the literature review and meta-analysis, with consultation with B.P.M.Y. for resolution of any conflicts. C.K.M. and B.R.D. extracted the probabilities required for the Markov decision tree. C.K.M. performed the Markov chain analysis and graphical plots. All authors contributed to the interpretation of results. C.K.M. took the lead in writing the manuscript. B.R.D., L.W.L.O., J.T.H.T., J.G.X.T., M.P., C.K.W.K., W.W.K., and B.P.M.Y. provided valuable input in the direction of the manuscript. All authors provided critical feedback and helped shape the research, analysis, and the final manuscript.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

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Data availability statement

Dataset and statistical code is available upon reasonable request.

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