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Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

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ABSTRACT

Objective: The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy has not been evaluated in China. The analysis aimed to compare the cost-effectiveness between FLOT and ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine) in patients with locally advanced resectable tumors.

Design: We developed a Markov model to compare the health and economic outcomes of FLOT and ECF/ECX in resectable gastric or gastroesophageal junction adenocarcinoma. The cost was estimated from the perspective of Chinese healthcare system. The clinical and utility inputs were derived from the FLOT4 phase II/III clinical trial or published literature. Sensitivity analyses were employed to assess the robustness of our result. The annual discount rate for costs and health outcomes was set at 5%.

Outcome measures: The primary outcome of incremental cost-effectiveness ratios (ICERs) was calculated as the cost per quality-adjusted life years(QALYs).

Results: The base-case analysis showed that compared with ECF/ECX, the use of FLOT chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of $851/QALY. The probabilistic sensitivity analysis demonstrated that FLOT was more likely to be cost-effective compared with ECF/ECX at a willingness-to-pay WTP value of $31,513/QALY. Sensitivity analysis results suggested that the hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) had the greatest impact on the ICER.

Conclusions: For patients with locally advanced resectable tumors, the FLOT chemotherapy is a cost-effective treatment option comparing with ECF/ECX in China.

Trial registration number: NCT01216644.

Keywords: Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy, FLOT, ECF/ECX , Cost-effectiveness.

Strengths and limitations of this study

- Perioperative FLOT improved overall survival compared with perioperative

ECF/ECX in patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma. However, the cost-effectiveness of perioperative FLOT in treating these patients remains unknown.

- To our knowledge, this is the first cost-effectiveness analysis comparing FLOT with ECF/ECX for patients with resectable gastric or gastroesophageal junction adenocarcinoma.
- The use of data in clinical trials may not represent the data in real clinical practice, because clinical trials have certain time constraints. For example, we used Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the trial.

SUBHEADLING: Economic evaluation of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

INTRUDOCTION

According to the latest global cancer burden data in 2020 released by the international agency for research on cancer (IARC) of the World Health Organization, China ranked first in the cancer-related deaths with approximately 480,000 cases recorded. Gastric cancer is the third most prevalent malignant tumor in the world and the third leading cause of cancer-related death in China[1].

Although significant progress has been made in early detection, the prognosis of patients with resectable gastric and gastroesophageal junction adenocarcinoma is still poor[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy were demonstrated they have significantly improved overall survival (OS) in patients with this cancer as compared with a simple surgery[3-6]. Based on this, perioperative chemotherapy is recommended as the preferred treatment for locally resectable diseases[3,7-9]. Postoperative chemoradiotherapy is the preferred treatment for patients with less surgical scope than D2 lymph node dissection[6,10,11]. Other treatment strategies, such as postoperative chemotherapy, are suitable for patients who have experienced primary lymph node dissection[12-14]. In Asian

countries, accumulating research evidence has shown that adjuvant chemotherapy after a D2 surgery significantly improves the tumor remission rate and R0 resection rate compared with D2 gastrectomy alone , and is associated with a favorable safety profile[15,16].

The Medical Research Council adjuvant gastric infusion chemotherapy (MAGIC) trial was the first and largest clinical trial that confirmed the survival benefits of perioperative chemotherapy[3]. In this trial, 503 patients with locally advanced resectable gastric and gastroesophageal junction adenocarcinoma were enrolled and were assigned to either the three cycles of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy or the surgery alone. The survival rate in the chemotherapy group was significantly higher compared to the simple surgery group (5-year survival, 36% vs 23%). The FNCLCC/FFCD II/III trial also found that perioperative chemotherapy for gastric cancer provided greater survival benefits than the surgery alone[3]. According to the trial evidence, the National Comprehensive Cancer Network Clinical (NCCN) Guidelines recommended perioperative chemotherapy as a routine regimen for advanced gastric cancer (class I evidence) in 2010, and a standard model of adjuvant chemotherapy for gastroesophageal adenocarcinoma[17]. Subsequently, the Chinese Society of Clinical Oncology (CSCO) Guidelines[18] recommended several chemotherapy regimens as preferred schemes. This includes cisplatin combined with fluorouracil (PF)[4], improved ECF scheme[19], oxaliplatin combined with capecitabine (XELOX)[20], oxaliplatin combined with fluorouracil (FLOFOX)[21], and oxaliplatin combined with S-1 (SOX)[22]. Although the great progression had been made on chemotherapies, the clinical prognosis of patients with advanced gastric or gastroesophageal junction cancer is still unsatisfactory, especially those with advanced cancers. In view of this, there is a pressing need for any novel chemotherapy regimen with a greater effectiveness than the existing ones.

In the phase II/III clinical trials of FLOT4, the researchers compared the perioperative chemotherapy FLOT (docetaxel, oxaliplatin, leucovorin, fluorouracil) with the standard chemotherapy ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine)[23,24]. Fluoropyrimidine and platinum combined with or without

anthracycline are the most used chemotherapeutic regimen. In a large prospective phase II/III randomized controlled trial of FLOT4, docetaxel was added to triple-drug regimen (FLOT regimen) and showed to improved survivals among patients with resectable gastric or gastroesophageal junction cancer with clinical stage CT2 or higher and lymph node positive (CN+) as compared with ECF/ECX regimen (50 months vs35 months; HR = 0.77; 95% confidence interval, 0.63-0.94). In this phase II/III trial, the proportion of patients with complete regression of pathology was significantly higher in the FLOT group than that in the ECF/ECX group. In addition, compared with the ECF/ECX group, patients in the FLOT group had a lower incidence of grade 3-4 adverse events (AEs), including neutropenia, leucopenia, nausea, infection, fatigue and vomiting (25% vs 40%), but had the same incidence of serious chemotherapy-related AEs (27% in both groups).

Based on the clinical trial evidence, FLOT chemotherapy is recommended for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA) by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition). However, its financial impact has not been studied yet from the perspective of Chinese healthcare system. Considering the high incidence and prevalence of gastric or gastroesophageal junction cancer, and limited health resources in China, the therapeutical benefits of FLOT chemotherapy must be weighed against the economic burden that it has imposed. This study aimed to evaluate whether the perioperative chemotherapy FLOT is cost-effective compared with ECF/ECX among patients with gastric and gastroesophageal junction adenocarcinoma from the perspective of Chinese medical system, based on the clinical result of the FLOT4 trial.

METHODS

Patients and regimens

The patient population analyzed in this study mirrored the patient enrolled in the FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and

ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction adenocarcinoma. In this study, a total of 716 patients were randomly assigned to receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group received three 3-week cycles preoperative chemotherapy and three 3-week cycles postoperative chemotherapy. Each 3-week cycle included epirubicin 50mg/m^2 on day 1, cisplatin 60mg/m^2 on day 1, and continuous intravenous infusion of fluorouracil 200mg/m^2 or oral capecitabine 1250mg/m^2 on days 1 to 21 at the discretion of investigators. Patients in the FLOT group received four 2-week cycles preoperative chemotherapy and four 2-week cycles postoperative chemotherapy, each of which included docetaxel 50mg/m^2 on day 1, oxaliplatin 85mg/m^2 on day 1, calcium folinate 200mg/m^2 on day 1 and 5-FU 2600mg/m^2 as 24-h infusion on day 1.

The operation was scheduled 4 weeks after the last preoperative chemotherapy. The interval between the two groups was 4 weeks (28 days). As per this clinical trial, patients may discontinue treatment due to unacceptable toxicity, disease progression, death, or patient requirements. When patients experienced disease progression, they would receive second-line treatment, including irinotecan, calcium folinate and fluorouracil[25].

Patient and public involvement

There was patient representation in the FLOT4 trial. However, patients or the public were not involved in this cost-effectiveness analysis.

Analytic Model

Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro 2018 software to estimate the clinical and outcomes of two perioperative chemotherapy regimens (FLOT and ECF/ECX) for patients with gastric and gastroesophageal junction adenocarcinoma in China(Figure 1).

The model included three mutually exclusive health states: progression-free survival (PFS), progression survival (PS) and death. The Markov cycle length was set as 2-week to fit the treatment schedule of the two groups. At the beginning of the

model, the whole cohort was in PFS state, and the transitions between health states in the model may occur during each Markov cycle. From the perspective of Chinese medical system, we used a lifetime horizon and a half-cycle correction to estimate the total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the annual discount rate for costs and health outcomes was set at 5% [26]. All costs used in the model were adjusted based on the consumer price index provided by the the People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar = 6.88 Chinese Yuan)[27]. According to the recommendation of World Health Organization (WHO), we used 3 times per capita GDP as the WTP threshold[28]. Given that China's per capita GDP was $10,504 in 2020, the WTP threshold used in the model was $31,513[29].

PFS and OS data were obtained from the Kaplan Meier survival curve in the trial. First, we used GetDataGraph Digitizer software version 2.24 to extract datapoints from published PFS and OS curves in the publications (http://getdata-graph-digitizer.com). These extracted point data were used to fit different parametric survival models (including Exponential, Weibull, Lognormal and Log-logistic). According to the result of statistical goodness-of-fit test using Akaike information standard (AIC) and Bayesian information criterion (BIC), the Log-logistic distribution was selected to fit these data points. The two parameters of Log-logistic distribution, scale parameters（θ）and shape parameters（κ）are shown in Table 1. Then, we used the parameters to calculate survival rate, which is $S(t) = \left\{1 + e^{\theta} t^{\kappa}\right\}^{-1}$, where t is time. Figure 2 shows the fitted Log-logistic survival curves for the FLOT and ECF/ECX regimens.

TABLE1 Input parameters for the model

Parameters	Values
Log-Logistic survival model of PFS	
ECF/ECX	θ=0.05168663 κ=1.004703
FLOT	θ=0.03274242 κ=0.9957772
Log-Logistic survival model of OS	
ECF/ECX	θ=0.02849954 κ=1.369613
FLOT	θ=0.022184 κ=1.279334
θ: scale; κ: shape; ECF/ECX: docetaxel, oxaliplatin, leucovorin, fluorouracil; FLOT: epirubicin, cisplatin, fluorouracil or capecitabine.	

Utility

According to the data reported in the FLOT4 trial, the baseline characteristics of patients in the FLOT and ECF/ECX groups were similar. Since the quality of life data were not published along with the results of this trial, the utility related to gastric cancer was taken from the literature[30,31]. Gockel et al used the Gastrointestinal Life Quality Index (GLQI) of 338 patients with gastrectomy to evaluate the quality of life, and then estimated the utility of patients with PFS health state as 0.81[30]. In addition, Sakamaki et al used the Time Trade-Off (TTO) to evaluate the utility of hospitalized patients with gastric cancer[31]. In their study, the utilities of patients receiving intravenous chemotherapy and advanced care were 0.68 and 0.50, respectively in their study. In the current model, we assumed that the utilities of the three health states were identical in both groups. Therefore, 0.68 (1-5 years) and 0.81 (5-10 years) were used as the utilities of patients with PFS health state in both groups. In addition, the utility of patients in PS health state was set to 0.5 and the utility of patients who survived for more than 10 years was set to 1.0[32]. The disutility of adverse events (AEs) was calculated by multiplying the utility decrement due to AEs by the incidence of AEs[33,34]. We assumed that all AEs occurred in the first cycle.

Cost

From the perspective of Chinese medical system, we evaluated the direct

healthcare expenditure costs in the model, including drug and administration costs, AE management costs, follow-up examination costs, second-line treatment costs, supportive treatment costs and surgery treatment costs. Data of drug and administration costs, follow-up examination costs and drug price were extracted from the local health system [35]. To calculate the dosage of chemotherapeutic drug, we assumed that a baseline patient has a weight of 65kg and a body surface area of 1.72 square meters[36].

Based on the data reported in the FLOT4 trial, after disease progressed, 25% of the patients in both groups who would receive second-line treatment and the second-line chemotherapy regimen was selected from the FLOT4 trial[37]. When patient experienced a further progression, they would receive supportive treatments until death[38]. The second-line chemotherapy regimen included intravenous injection of irinotecan 180mg/m^2 on days 1, calcium folinate 400 mg/m^2 on days 1, fluorouracil 400mg/m^2 on day 1, continuous intravenous injection of fluorouracil 1200mg/m^2 for more than 24 hours on day 1 and 2, and circulation every 14 days[25,39,40]. Data of the costs for drug administration，supportive and surgery treatments were extracted from published literature[41-43]. The follow-up examination included CT or MRI every three months until disease progression, recurrence or death. The price of CT or MRI came from the local health system[35]. According to expert suggestions and clinical practice, we correlated the grade 3-4 adverse events with a significant difference (P>0.05) between the two groups with the total cost. Therefore, according to the data provided by FLOT4 trial, the following AEs were included in the model: vomiting, nausea, neutropenia, anaemia, infections, diarrhoea. The costs of AE management were estimated by multiplying the management cost per event by the incidence of each AE. The incidence of AE was obtained from the FLOT4 trial and the unit cost was based on the published literature[32,41,44]. Table 2 lists all direct costs in the experiment.

Table 2. Baseline costs, risks, and utility values with ECF/ECX and FLOT perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma in China.

Parameters	Median	Range	Distribution	Reference
Costs, $				
Epirubicin per 10mg	12.1425	9.714-14.571	Lognormal	35
Cisplatin per 10mg	1.1607	0.92856-1.3928	Lognormal	35
Fluorouracil per 250mg	7.36	5.888-8.832	Lognormal	35
Capecitabine per 500mg	4.2167	3.37336-5.0600	Lognormal	35
Docetaxel per 20mg	46.3683	37.09464-55.6420	Lognormal	35
Oxaliplatin per 100mg	19.4627	15.57016-23.3552	Lognormal	35
Leucovorin per 100mg	3.8395	3.0716-4.6074	Lognormal	35
Irinotecan per 100mg	271.8785	217.5028-326.2542	Lognormal	35
CT per 3months[a]	60.2	30.1-90.3	Gamma	35
MRI per 3months[a]	123.3	61.7-185	Gamma	35
Administration per episode	12.33	9.87-14.8	Lognormal	41
Supportive care per episode	943.6	681.87-1347.66	Lognormal	42
Surgery	13638.2	10910.56-16365.84	Lognormal	43
Expenditures on main adverse events(Grade 3 or 4), $				
Nausea and vomiting per episode	39.6	17.9-76.5	Lognormal	32
Neutropenia per episode	530.8	198.5-863.1	Lognormal	32
Anaemia per episode	531.7	478.5-584.9	Lognormal	41
Diarrhoea per episode	44.3	28.5-54.6	Lognormal	32
Infections per episode	2853.93	2283.144-3424.716	Lognormal	44
Risk for main adverse events in ECF/ECX arm (Grade 3 or 4)[b]				
Nausea and vomiting	0.24	0.192-0.288	Beta	24
Neutropenia	0.39	0.312-0.468	Beta	24
Anaemia	0.06	0.048-0.072	Beta	24
Diarrhoea	0.04	0.032-0.048	Beta	24
Infections	0.09	0.072-0.108	Beta	24
Risk for main adverse events in FLOT arm (Grade 3 or 4)[b]				
Nausea and vomiting	0.09	0.072-0.108	Beta	24
Neutropenia	0.51	0.408-0.612	Beta	24
Anaemia	0.03	0.024-0.036	Beta	24
Diarrhoea	0.1	0.08-0.12	Beta	24
Infections	0.18	0.144-0.216	Beta	24
Risk for requiring second-linechemotherapy[b]	0.25	0.2-0.3	Beta	37
Utility[b]				
1-5 years in PFS for ECF/ECX arm	0.68	0.56-0.76	Beta	31
5-10 years in PFS for ECF/ECX arm	0.81	0.648-0.972	Beta	30
1-5 years in PFS for FLOT arm	0.68	0.56-0.76	Beta	31
5-10 years in PFS for FLOT arm	0.81	0.648-0.972	Beta	30

Beyond 10 years for 2 arms	1	-	-	32
PS in two arms	0.5	0.4-0.6	Beta	31
MRI = magnetic resonance imaging; CT = computed tomography; PFS =Progression-free survival; PS = Progression survival.				
[a]The range was assumed to be varied ± 50%.				
[b] The range was assumed to be varied ± 20%				

Sensitivity Analyses

One-way sensitivity analysis was performed to investigate the impact of individual changes in model parameters on our main model results, the results are shown as a tornado diagram. The median, distribution and range of model input parameters are shown in Table 2, and the ranges corresponding to the model parameters were derived from the published literature or within a reasonable range(± 20% or ± 50% of the base-case value). In accordance with Chinese Guidelines for Pharmacoeconomic Evaluations, the discount rate in this analysis was assumed to be between 0% and 8%[26]. We also performed a 10,000 repeated Monte Carlo probabilistic sensitivity analyses to evaluate the impact of simultaneous changes in parameters on the model results. In this probabilistic sensitivity analyses, each variable was randomly sampled from the appropriate distribution. A lognormal distribution was applied for the cost data and a beta distribution was applied for the utility value, probability or proportion. The result of PSA was depicted by a cost-effectiveness acceptability curve (CEAC).

RESULT

The economic and health results calculated by the model are displayed in Table 3. The QALYs associated with the FLOT (4.08QALYs) chemotherapy was longer than that with ECF/ECX (3.0QALYs), and the FLOT achieved an increase of 1.08QALYs over the course of disease. Compared with the cost of ECF/ECX regimen of $45,311.91, the direct medical costs of FLOT regimen was increased by $921.51 （$46,233.42 vs $45,311.91）. The corresponding ICER of the FLOT regimen was

$850.68 per QALY.

Table 3.The base-case model results for two treatments

Model outcome	Treatment strategy	
	ECF/ECX	FLOT
Costs in PFS($)	16,250.09	16,060.58
Costs in PS($)	29,061.82	30,172.84
Costs of total($)	45,311.91	46,233.42
QALYs in PFS(QALY)	2.44	3.5
QALYs in PS(QALY)	0.56	0.58
QALYs of total(QALY)	3	4.08
CER($/QALY)	15,103.97	11,331.72059
ICER for FLOT ($/QALY)	-	850.68

Tornado diagram (Figure 3) revealed that the HR of OS was the most influential parameter in our model. When the HR of OS was increased from 0.63 to 0.94, the ICERs ranged from $3,868.18 per QALY to $-16,856.98 per QALY. Other influential parameters included the HR of PFS, the proportion of surgery patients in the ECF/ECX chemotherapy group and the discount rate. Parameters that have a minor influence on the model included the proportion of AEs, such as nausea, diarrhoea and vomiting (grade 3 or 4). In generally, the ICERs remained below the WTP $31513 (three times of China's per capita GDP) within the fluctuation of all parameters.

The ICER scatter plot (Figure 4) shows the results of the probabilistic sensitivity analyses, including a set of points representing the incremental cost and benefit value pairs in Monte Carlo simulation (10,000 repetitions). The slash is the WTP threshold line, and 95% confidence interval of the estimates are surrounded by the ellipse. It can be seen from Figure 4 that ICER is mostly distributed in the first and fourth quadrants and below the threshold line. The plot below the threshold line accounted for 99.5% of all scatter plots, indicating that the possibility of FLOT chemotherapy regimen being cost-effective compared with the ECF/ECX treatment was 99.5%.

The CEAC (Figure 5) shows the cost-effectiveness probabilities of the FLOT chemotherapy generated by Markov Model simulation at different cost-effectiveness thresholds. The cost-effectiveness probability of the FLOT chemotherapy was

increased with the increasing WTP thresholds. When the WTP threshold was greater than $699.2/QALY, the probability of the FLOT chemotherapy being cost-effective was nearly 50% for patients with resectable gastric or gastroesophageal junction cancer. When the threshold exceeded $17,090/QALY, the cost-effectiveness possibility of the FLOT chemotherapy reached 99%.

Discussion

In the past decade, ECF and ECX were recommended as a class I regimen for patients with resectable gastric or gastroesophageal junction adenocarcinoma. After 2018, the FLOT chemotherapy regimen was included into the CSCO guidelines in China and the National Comprehensive Cancer Network (NCCN) in the United States[17,18]. According to the NCCN guidelines, combined therapy (surgery+chemotherapy) has been proved to significantly improve the survival rate of gastric cancer patients with local regional diseases and perioperative chemotherapy is recommended as preferred approach for the treating locally resectable diseases. The CSCO in China pointed out that the standard treatment for resectable advanced gastric cancer was D2 surgical resection combined with postoperative adjuvant chemotherapy. For patients with late stage (clinical stage III or above), the perioperative chemotherapy mode was selected. Moreover, this standard treatment has been fully recognized and recommended by East Asian countries. Although this treatment regimen has been proved to be effective in improving the overall survival of patients with advanced gastric cancer after resection, the survival states of patients with late stage (stage III B and III C) are still suboptimal. Therefore, a large number of clinical studies have been carried out in order to figure out how to further optimize the perioperative treatment of gastric cancer.

With the continuing development of chemotherapeutic drugs for gastric cancer, anthracycline drugs and platinum drugs have been introduced into the perioperative treatment of resectable gastric cancer. Docetaxel and oxaliplatin have been introduced

into FLOT chemotherapy scheme. In the PRODIGY study from Korea in East Asia, 468 cases of advanced gastric cancer were studied[45]. The intervention group received preoperative DOS regimen (docetaxel, oxaliplatin, S-1) chemotherapy for 3 cycles, and the control group received postoperative S-1 orally for 1 year. In the JACCRO G-07 study conducted in Japan, 915 cases of pathological stage III gastric cancer undergoing D2 operation were enrolled[46]. The intervention group was treated with DS regimen (docetaxel combined with S-1) for 6 cycles, followed by S-1 single drug until 1 year after operation, and the control group was treated with S-1 orally until 1 year after operation. The above two trials showed that the combining the docetaxel with other chemotherapeutic drugs conferred a greater efficacy than the docetaxel monotherapy. Not only docetaxel was added to the FLOT chemotherapy strategy, but also oxaliplatin was used instead of cisplatin. Oxaliplatin has a lower toxicity to gastrointestinal tract, liver, kidney and bone marrow than cisplatin and carboplatin and is more well tolerated. It also showed a superiority over many other chemotherapy regimens. The ARTIST-Ⅱ study conducted in Korea compared 8 cycles of postoperative SOX regimen (oxaliplatin combined with S-1) with oral S-1 for 1 year. The survival data showed that combined chemotherapy was better than single drug [47]. In the multi center phase III trial in Japan and South Korea, 711 patients with advanced gastric cancer were enrolled[48]. The intervention group was assigned to oxaliplatin plus folic acid and S-1, and the control group was assigned to S-1 plus cisplatin. Oxaliplatin plus folic acid and S-1 showed a clinically significant beneficial effect. Therefore, at present, FLOT scheme is considered to be one of the preferred schemes of perioperative chemotherapy combined with surgery, including three chemotherapeutic drugs, which is mainly suitable for patients with good performance status. However, for patients with good to moderate performance status and patients who cannot tolerate the combination regimen of these three drugs, the two drug combination regimen can be considered to lower the risk of drug toxicity. In China, the increasing incidence rate and mortality rate of gastric cancer have imposed considerable physical, psychological and economic burdens on the society, patients and their families, especially for the developing countries. Therefore, it is very crucial

to study the economic significance of this chemotherapy strategy in the field of medicine and policy.

In the FLOT4 trial, compared with the control group, the QALYs in the intervention group was increased by 1.08QALY and the cost per patient was increased by $921.51, resulting in an ICER of $850.68/QALY. Based on the current threshold of WTP, the FLOT strategy is more cost-effective. The univariate sensitivity analysis showed that the most influential parameter on the model results was the hazard ratio of overall survival, which could improve the ICER of FLOT strategy by reducing HR. This was followed by the hazard ratio of progression-free survival, the proportion of patients with ECF/ECX who underwent surgery, and the discount rate. The change of HR for overall survival made ICER fluctuate the most, but the ICER was still less than $10,504/QALY ($6,330.47/QALY). Moreover, when other number sensitive parameters changed within the specified range, ICER was also lower than WTP. Therefore, we can conclude that the parameters in the intervention have little impact on ICER results. However, there were significant differences in per capita GDP among 32 provinces in mainland China. The maximum difference was $18,731 (in 2020, the highest was Beijing's per capita GDP of $23,968, and the lowest was Gansu's per capita GDP of $5,238)[49]. For all provinces, the per capita GDP was $10,504, and three times the per capita GDP was $31,513. Therefore, the ICERs of the FLOT strategy were much lower than that of China's per capita GDP in 2020 and less than that of Gansu Province. This suggests that the FLOT perioperative chemotherapy regimen is much more cost-effective than ECF/ECX in the treatment of locally advanced resectable gastric or gastroesophageal junction adenocarcinoma in China. To our best knowledge, this study is the first cost-effectiveness analysis of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma.

There are some limitations in the current study. Firstly, we used Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the trial. However,

our model used AIC and BIC to estimate that the Log-logistic distribution had good goodness of fit, and Figure 2 showed that the Log-logistic survival model we selected satisfactorily matched the survival curve of the intevention. Both of them supported the validity of our model. Secondly, only direct medical costs were included in the model, and indirect costs were excluded, such as the additional burden imposed on families and caregivers, which may increase the total cost for treating patients with resectable gastric or gastroesophageal junction adenocarcinoma. Another limitation of the current economic analysis lied that other treatment strategies for advanced resectable gastric cancer have not been fully explored. With the success of targeted therapy and immunotherapy in the clinical practice of advanced gastric cancer, the pattern of perioperative treatment of resectable gastric cancer is moving closer towards this trend. For example, the research on treatment of HER-2 positive gastric cancer has attracted considerable attentions in recent years. Meanwhile, combining the perioperative chemotherapy with targeted treatment, was found to increase the pathological complete remission rate and improve overall survival benefit, while the safety is acceptable[50,51]. Therefore, we can expect that receiving higher cost targeted therapy can increase more cost-effectiveness.

Author affliations

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Contributors

Study design and supervision were contributed by H.Q. Zeng and X.H. Zeng; data analysis and interpretation were contributed by H.Q. Zeng, X.H. Zeng and Li-Ying Song; data collection was contributed by H.Q. Zeng, Chunjiang Wang; manuscript

writing was contributed by H.Q. Zeng, X.H. Zeng , Su-Jie Jia and Q. Liu; final approval of the manuscript was contributed by all of the authors.

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Data sharing statement No additional data available

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Research Ethics Approval This study does not involve human participants or animal subjects.

Competing interests The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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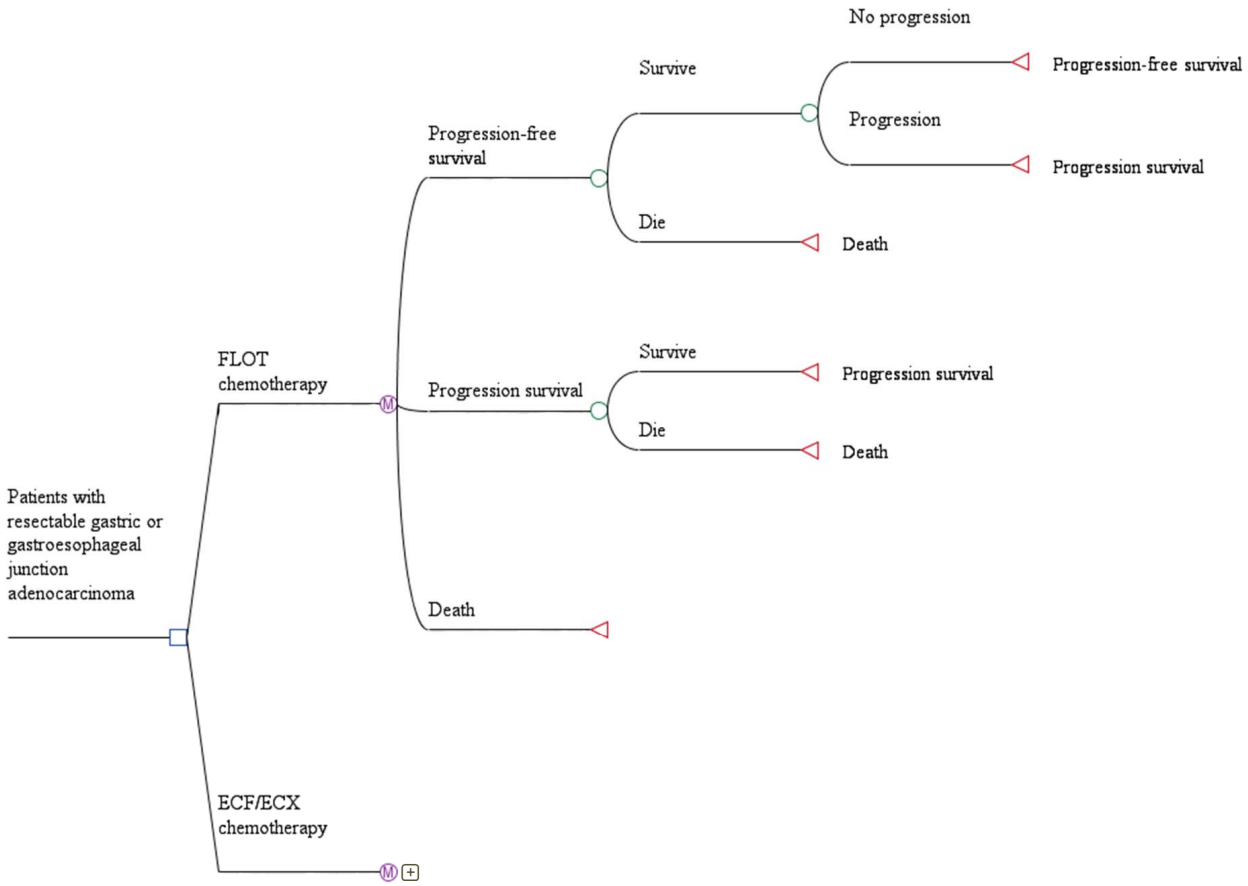
Figure 1. Markov model structure of FLOT and ECF/ECX strategies for the treatment of patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma

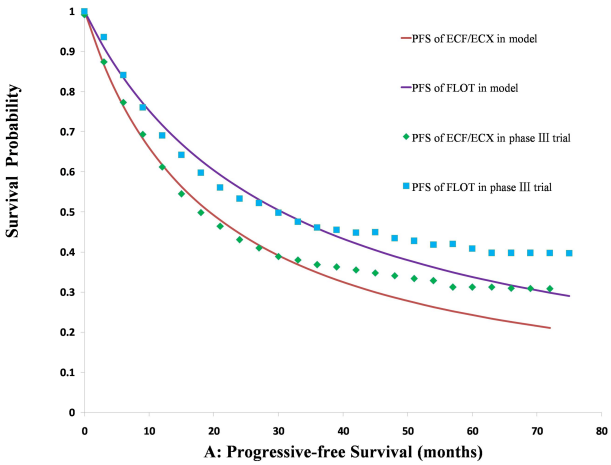
Figure 2. The Log-Logistic curves of (A) disease-free survival and (B) overall survival.

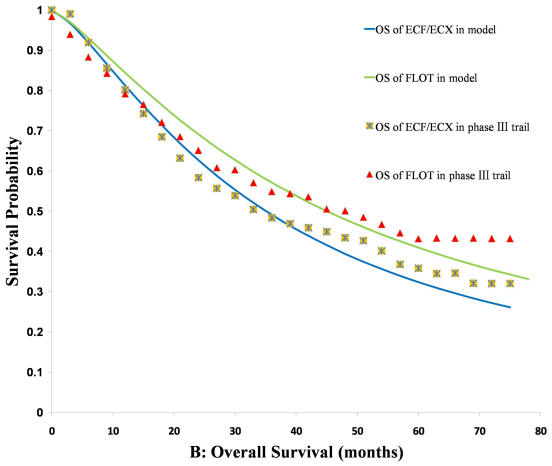
Figure 3. Tornado diagram for univariable sensitivity analyses. The grey dotted line represents the ICER of $850.6842 per QALY from the base-case results. ICER incremental cost-efectiveness ratio, QALY quality-adjusted life-year.

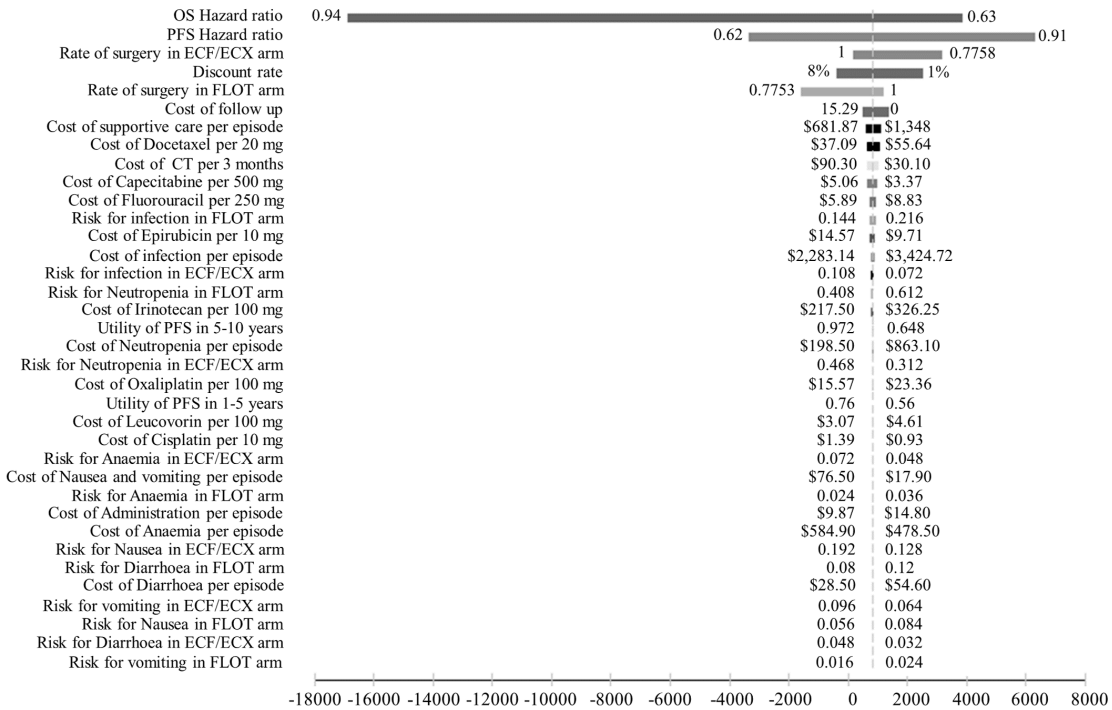
Figure 4. The results of Monte Carlo probabilistic sensitivity analysis for the strategies of FLOT VS ECF/ECX in scatter plots. The solid lines indicate the $31,513 threshold. The estimates of 95% were surrounded in the ellipses.

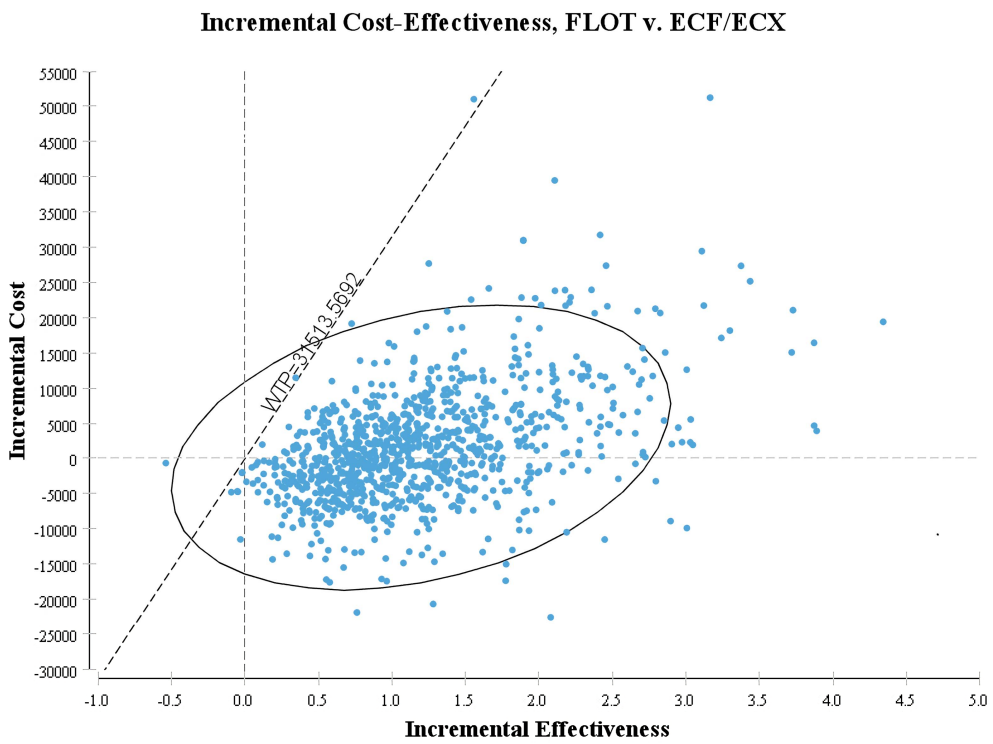
Figure 5. Acceptability curves for the two strategies at willingness-to-pay (WTP) thresholds in locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma patients. The vertical dashed line represent the threshold that the cost-effectiveness probability of FLOT chemotherapy reached 99%, and the solid line represent the WTP threshold of $10504 (the per capita GDP in China).

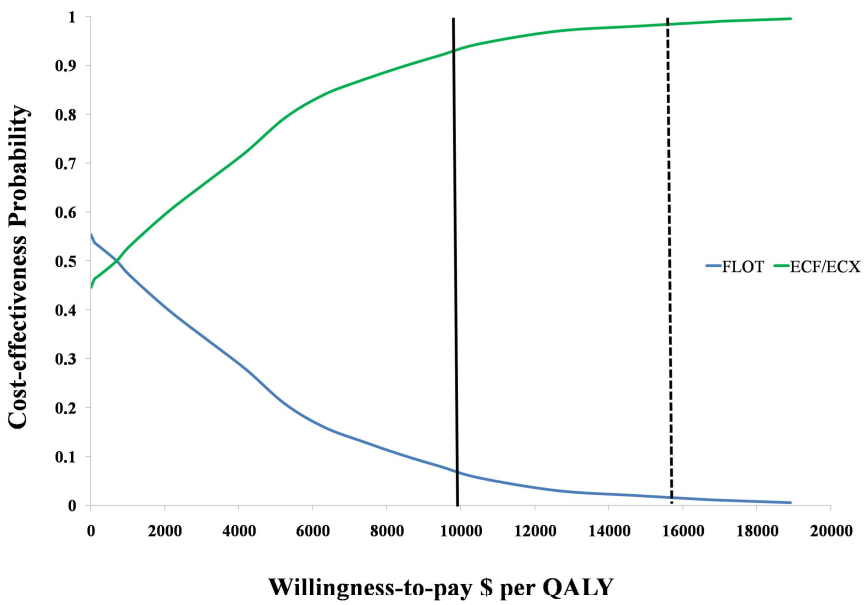

Patients with resectable gastric or gastroesophageal junction adenocarcinoma
FLOT chemotherapy
ECF/ECX chemotherapy
Progression-free survival
Progression survival
Death
Survive
Die
No progression
Progression
Progression-free survival
Progression survival
Death
Survive
Die
Progression survival
Death






OS Hazard ratio 0.94 0.63
PFS Hazard ratio 0.62 0.91
Rate of surgery in ECF/ECX arm 1 0.7758
Discount rate 8% 1%
Rate of surgery in FLOT arm 0.7753 1
Cost of follow up 15.29 0
Cost of supportive care per episode $681.87 $1,348
Cost of Docetaxel per 20 mg $37.09 $55.64
Cost of CT per 3 months $90.30 $30.10
Cost of Capecitabine per 500 mg $5.06 $3.37
Cost of Fluorouracil per 250 mg $5.89 $8.83
Risk for infection in FLOT arm 0.144 0.216
Cost of Epirubicin per 10 mg $14.57 $9.71
Cost of infection per episode $2,283.14 $3,424.72
Risk for infection in ECF/ECX arm 0.108 0.072
Risk for Neutropenia in FLOT arm 0.408 0.612
Cost of Irinotecan per 100 mg $217.50 $326.25
Utility of PFS in 5-10 years 0.972 0.648
Cost of Neutropenia per episode $198.50 $863.10
Risk for Neutropenia in ECF/ECX arm 0.468 0.312
Cost of Oxaliplatin per 100 mg $15.57 $23.36
Utility of PFS in 1-5 years 0.76 0.56
Cost of Leucovorin per 100 mg $3.07 $4.61
Cost of Cisplatin per 10 mg $1.39 $0.93
Risk for Anaemia in ECF/ECX arm 0.072 0.048
Cost of Nausea and vomiting per episode $76.50 $17.90
Risk for Anaemia in FLOT arm 0.024 0.036
Cost of Administration per episode $9.87 $14.80
Cost of Anaemia per episode $584.90 $478.50
Risk for Nausea in ECF/ECX arm 0.192 0.128
Risk for Diarrhoea in FLOT arm 0.08 0.12
Cost of Diarrhoea per episode $28.50 $54.60
Risk for vomiting in ECF/ECX arm 0.096 0.064
Risk for Nausea in FLOT arm 0.056 0.084
Risk for Diarrhoea in ECF/ECX arm 0.048 0.032
Risk for vomiting in FLOT arm 0.016 0.024
-18000 -16000 -14000 -12000 -10000 -8000 -6000 -4000 -2000 0 2000 4000 6000 8000


Incremental Cost-Effectiveness, FLOT v. ECF/ECX
Incremental Cost
Incremental Effectiveness
WTP=31513.5692
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
-25000
-30000
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0


Cost-effectiveness Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
FLOT
ECF/ECX
Willingness-to-pay $ per QALY

Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	2
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	3
Methods			

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	7
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	6
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	6-7
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	n/a
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	'n/a'
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	9

Methods

Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	6
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	6
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	10
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	12
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	12

Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	'n/a'
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	'n/a'
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-16
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	17
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	17

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Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

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Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

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ABSTRACT

Objective: The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin plus docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy in China remains unclear. The analysis aimed to compare the cost-effectiveness of FLOT versus ECF/ECX (epirubicin, cisplatin plus fluorouracil or capecitabine) in patients with locally advanced resectable tumors.

Design: We developed a Markov model to compare the healthcare and economic outcomes of FLOT and ECF/ECX in patients with resectable gastric or gastroesophageal junction

adenocarcinoma. Costs were estimated from the perspective of Chinese healthcare system. Clinical and utility inputs were derived from the FLOT4 phase II/III clinical trial and published literature. Sensitivity analyses were employed to assess the robustness of our result. The annual discount rate for costs and health outcomes was set at 5%.

Outcome measures: The primary outcome of incremental cost-effectiveness ratios (ICERs) was calculated as the cost per quality-adjusted life years (QALYs).

Results: The base-case analysis found that compared with ECF/ECX, the use of FLOT chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of $851/QALY. One-way sensitivity analysis results suggested that the hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) had the greatest impact on the ICER. Probabilistic sensitivity analysis demonstrated that FLOT was more likely to be cost-effective compared with ECF/ECX at a willingness-to-pay (WTP) threshold of $31,513/QALY.

Conclusions: For patients with locally advanced resectable tumors, the FLOT chemotherapy is a cost-effective treatment option compared with ECF/ECX in China.

Trial registration number: NCT01216644.

Keywords: Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy, FLOT, ECF/ECX , Cost-effectiveness.

Strengths and limitations of this study

- Perioperative FLOT significantly improved overall survival compared with perioperative ECF/ECX in patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma. However, the cost-effectiveness of perioperative FLOT among Chinese patients remains unknown.
- To our knowledge, this is the first cost-effectiveness analysis comparing FLOT with ECF/ECX for patients with resectable gastric or gastroesophageal junction adenocarcinoma in China.
- The use of data in clinical trials may not represent the data in real clinical practice, because clinical trials have certain time constraints. For example, we used

Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the trial.

SUBHEADLING: Economic evaluation of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

INTRUDOCTION

According to the latest global cancer burden data in 2020 released by the international agency for research on cancer (IARC) of the World Health Organization, China ranked first in the cancer-related deaths with approximately 480,000 cases recorded. Gastric cancer is the third most prevalent malignant tumor in the world and the third leading cause of cancer-related death in China[1].

Although significant progress has been made in early detection, the prognosis of patients with resectable gastric and gastroesophageal junction adenocarcinoma is still poor[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy had demonstrated their superior survival benefit in patients with this disease when compared with a simple surgery[3-6]. Based on this, perioperative chemotherapy is recommended as the preferred treatment for locally resectable diseases[3,7-9]. For patients whose surgical scope is less than D2 lymph node dissection, postoperative chemoradiotherapy is the preferred treatment [6,10,11]. Other treatment strategies, such as postoperative chemotherapy, are applicable patients who have udergone primary lymph node dissection[12-14]. In Asian countries, accumulating clinical evidence has shown that, compared with D2 gastrectomy alone , adjuvant chemotherapy after a D2 surgery significantly improves the tumor remission rate and R0 resection rate is associated with a favorable safety profile[15,16].

The Medical Research Council adjuvant gastric infusion chemotherapy (MAGIC) trial was the first clinical trial to confirm the survival benefits of perioperative chemotherapy[3]. In this trial, 503 patients with locally advanced resectable gastric and gastroesophageal junction adenocarcinoma were enrolled and were randomly assigned to receive three cycles of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy or

surgery alone. The survival rate in the chemotherapy group was significantly higher than the simple surgery group (5-year survival rate, 36% vs 23%). The FNCLCC/FFCD II/III trial also found that perioperative chemotherapy for gastric cancer provided greater survival benefits than the surgery alone[3]. According to the trial evidence, the National Comprehensive Cancer Network Clinical (NCCN) Guidelines recommended perioperative chemotherapy as a routine regimen for advanced gastric cancer (class I evidence) in 2022, and a standard adjuvant chemotherapy for gastroesophageal adenocarcinoma[17]. Subsequently, the Chinese Society of Clinical Oncology (CSCO) Guidelines[18] recommended several chemotherapy regimens as preferred schemes, including cisplatin combined with fluorouracil (PF)[4], improved ECF scheme[19], oxaliplatin combined with capecitabine (XELOX)[20], oxaliplatin combined with fluorouracil (FOLFOX)[21], and oxaliplatin combined with S-1 (SOX)[22]. Although the great progress had been made on chemotherapies, the clinical prognosis of patients with advanced gastric or gastroesophageal junction cancer is still unsatisfactory, especially those with advanced cancers. In view of this, there is a pressing need for any novel chemotherapy regimen with a greater effectiveness than the existing ones.

In the phase II/III clinical trials of FLOT4, the researchers compared the perioperative chemotherapy FLOT (fluorouracil, leucovorin, oxaliplatin plus docetaxel) with the standard chemotherapy ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine)[23,24]. Fluoropyrimidine and platinum combined with or without anthracycline are the most used chemotherapeutic regimen. In the FLOT4 trial, adding docetaxel to triple-drug regimen (FLOT regimen) was associated with improved survivals among patients with resectable gastric or gastroesophageal junction cancer with clinical stage CT2 or higher and lymph node positive (CN+) when compared with ECF/ECX regimen (50 months vs35 months; HR = 0.77; 95% confidence interval, 0.63-0.94). In this phase II/III trial, the proportion of patients with complete regression of pathology was significantly higher in the FLOT group than that in the ECF/ECX group. In addition, compared with the ECF/ECX group, patients in the FLOT group had a lower incidence of grade 3-4 adverse events (AEs),

including neutropenia, leucopenia, nausea, infection, fatigue and vomiting (25% vs 40%), but had the same incidence of serious chemotherapy-related AEs (27% in both groups).

In response to the positive results from FLOT4 trial, FLOT chemotherapy is recommended for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA) by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition). However, its financial impact has not been studied yet from the perspective of Chinese healthcare system. Considering the high prevalence of gastric or gastroesophageal junction cancer, and limited health resources in China, the therapeutical benefits of FLOT chemotherapy must be weighed against the economic burden that it has imposed. This study aimed to evaluate whether the perioperative chemotherapy FLOT is cost-effective compared with ECF/ECX among patients with gastric and gastroesophageal junction adenocarcinoma from the perspective of Chinese medical system.

METHODS

Patients and regimens

The patient population analyzed in this study mirrored the patient enrolled in the FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction adenocarcinoma. In this study, a total of 716 patients were randomly assigned to receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group received three 3-week cycles preoperative chemotherapy and three 3-week cycles postoperative chemotherapy. The chemotherapy regimen for each 3-week cycle was epirubicin 50mg/m^2 on the first day, cisplatin 60mg/m^2 on the first day, and continuous intravenous infusion of fluorouracil 200mg/m^2 or oral capecitabine 1250mg/m^2 from the first to the 21st days at the discretion of investigators. Patients in the FLOT group received four 2-week cycles preoperative chemotherapy and four 2-week cycles postoperative chemotherapy, which were docetaxel 50mg/m^2 on the

first day, oxaliplatin 85mg/m^2 on the first day, calcium folinate 200mg/m^2 on the first day and 5-FU 2600mg/m^2 as 24-h infusion the first day.

The operation was scheduled 4 weeks after the last preoperative chemotherapy. The interval between the two groups was 4 weeks (28 days). As per this clinical trial, patients may discontinue treatment due to unacceptable toxicity, disease progression, death, or patient requirements. When patients experienced disease progression, they would receive second-line treatment, including irinotecan, calcium folinate and fluorouracil[25].

Patient and public involvement

There was patient representation in the FLOT4 trial. However, this cost-effectiveness analysis does not involve human participants.

Analytic Model

Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro 2018 software to estimate the clinical outcomes of two perioperative chemotherapy regimens (FLOT and ECF/ECX) for patients with gastric and gastroesophageal junction adenocarcinoma in China(Figure 1).

The model comprised three mutually exclusive health states: progression-free survival (PFS), progressed survival (PS) and death. The Markov cycle length was set as 2-week to fit the treatment schedule of the two groups. At the beginning of the model, the whole cohort was in PFS state, and the transitions between health states in the model may occur during each Markov cycle. From the perspective of Chinese medical system, we used a lifetime horizon and a half-cycle correction to estimate the total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the annual discount rate for both costs and health outcomes was set at 5% [26]. All costs used in the model were adjusted based on the consumer price index provided by the the People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar = 6.88 Chinese Yuan)[27]. According to the recommendation of World Health

Organization (WHO), we used 3 times per capita GDP as the WTP threshold[26]. Given that China's per capita GDP was $10,504 in 2020, the WTP threshold used in the model was $31,513[28].

PFS and OS data were derived from the Kaplan Meier survival curve in the trial. First, we used GetDataGraph Digitizer software version 2.24 to extract datapoints from published PFS and OS curves in the publications (http://getdata-graph-digitizer.com).Then, these extracted point data was fitted with different parametric survival models (including Exponential, Weibull, Lognormal and Log-logistic). According to the result of statistical goodness-of-fit test using Akaike information standard (AIC) and Bayesian information criterion (BIC), the Log-logistic distribution was selected for survival fitting. The two parameters of Log-logistic distribution, scale parameters（θ）and shape parameters（κ）are shown in Table 1. Finally, we used the parameters to calculate survival rate, which is $S(t)=\left\{1+e^{\theta}t^{\kappa}\right\}^{-1}$, where t is time. Figure 2 shows the Log-logistic parameters estimated for the FLOT and ECF/ECX regimens.

Table 1. Log-logistic parameters

Parameters	**Values**
Log-Logistic survival model of PFS	
ECF/ECX	θ=0.05168663 κ=1.004703
FLOT	θ=0.03274242 κ=0.9957772
Log-Logistic survival model of OS	
ECF/ECX	θ=0.02849954 κ=1.369613
FLOT	θ=0.022184 κ=1.279334
θ: scale; κ: shape; ECF/ECX: docetaxel, oxaliplatin, leucovorin, fluorouracil; FLOT: epirubicin, cisplatin, fluorouracil or capecitabine.	

Utility

Since the quality of life data were not published along with the results of the

FLOT4 trial, the utility related to gastric cancer was taken from the literatures[20,29]. Gockel et al used the Gastrointestinal Life Quality Index (GLQI) to evaluate the quality of life of 338 patients with gastrectomy, and then estimated the utility of patients with PFS health state as 0.81[30]. In addition, Sakamaki et al used the Time Trade-Off (TTO) to evaluate the utility of hospitalized patients with gastric cancer[29]. In their study, the utilities of patients receiving intravenous chemotherapy and advanced care were 0.68 and 0.50, respectively. In the current model, we assumed that the utilities of the three health states were identical in both groups. Therefore, 0.68 (1-5 years) and 0.81 (5-10 years) were used as the utilities of patients with PFS health state in both groups. In addition, the utility of patients in PS health state was set to 0.5 and the utility of patients who survived for more than 10 years was set to 1.0[31]. The disutility of adverse events (AEs) was calculated by multiplying the utility decrement due to AEs by the incidence of AEs[32,33]. We assumed that all AEs occurred in the first cycle.

Cost

From the perspective of Chinese medical system, we considered the direct healthcare expenditure costs in the model, including drug and administration costs, AE management costs, follow-up examination costs, second-line treatment costs, supportive treatment costs and surgery treatment costs. Drug and administration costs, follow-up examination costs and drug price were extracted from the local health system [34]. To calculate the dosage of chemotherapeutic drug, we assumed that a baseline patient's weight was 65kg and body surface area was 1.72 square meters[35].

After disease progressed, 25% of the patients in both groups who would receive second-line treatment and the second-line chemotherapy regimen was selected from the FLOT4 trial[36]. When patient experienced further disease progression, they would receive supportive treatments until death[37]. The second-line chemotherapy regimen included intravenous injection of irinotecan 180mg/m^2 on days 1, calcium folinate 400 mg/m^2 on days 1, fluorouracil 400mg/m^2 on day 1, continuous intravenous injection of fluorouracil 1200mg/m^2 for more than 24 hours on day 1 and 2, and

circulation every 14 days[25,38,39]. Data of the costs for drug administration，supportive and surgery treatments were extracted from published literature[40-42]. The follow-up examination included CT or MRI every three months until disease progression, recurrence or death. The price of CT or MRI came from the local health system[34]. According to expert suggestions and clinical practice, we calculated the grade 3-4 adverse events with a significant difference (P>0.05) between the two groups. Therefore, according to the data available in the FLOT4 trial, the following AEs were included in the model: vomiting （F/E:2％/8％）, nausea （F/E:7％/16％）, neutropenia（F/E:51％/39％）, anaemia（F/E:3％/6％）, infections（F/E:18％/9％）, diarrhoea（F/E:10％/4％）. Costs for treating AEs were estimated by multiplying the cost per event by the incidence of each AE. The incidences of AEs were obtained from the FLOT4 trial and the unit cost were from the published literature[31,40,43]. Table 2 lists all direct costs used in the model.

Table 2. Baseline costs with ECF/ECX and FLOT perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma in China

Parameters	Median	Range	Distribution	Reference
Costs, $				
Drug of FLOT per episode	352.1896	286.03-429.04	Lognormal	35
Drug of ECF/ECX per episode	270.8938	220.00-330.00	Lognormal	35
CT per 3months[a]	60.2	30.1-90.3	Gamma	35
MRI per 3months[a]	123.3	61.7-185	Gamma	35
Administration per episode	12.33	9.87-14.8	Lognormal	41
Supportive care per episode	943.6	681.87-1347.66	Lognormal	42
Surgery	13638.2	10910.56-16365.84	Lognormal	43
Expenditures on main adverse events(Grade 3 or 4), $				
FLOT	808.36	424.81-1303.83	Lognormal	32,41
ECF/ECX	507.04	253.64-840.57	Lognormal	32,41
MRI = magnetic resonance imaging; CT = computed tomography.				
[a]The range was assumed to be varied ± 50%.				

Sensitivity Analyses

One-way sensitivity analysis was performed to investigate the impact of individual changes in model parameters on our model results, the results are shown as

a tornado diagram. The median, distribution and range of model input parameters are shown in Table 2 and 3, and the ranges corresponding to the model parameters were derived from the published literature or within a reasonable range(±20% or ±50% of the base-case value). In accordance with Chinese Guidelines for Pharmacoeconomic Evaluations, the discount rate in this analysis was assumed to vary between 0% and 8%[26]. We also performed a 10,000 repeated Monte Carlo probabilistic sensitivity analyses to evaluate the impact of simultaneous changes in parameters on the model results. In this probabilistic sensitivity analyses, each variable was randomly sampled from the appropriate distribution. A lognormal distribution was applied for the cost data and a beta distribution was applied for the utility value, probability or proportion. The result of PSA was depicted by a cost-effectiveness acceptability curve (CEAC).

Table 3. Baseline risks and utility values with ECF/ECX and FLOT perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma in China

Parameters	Median	Range	Distribution	Reference
Risk for main adverse events in ECF/ECX arm (Grade 3 or 4)[b]				
Nausea and vomiting	0.24	0.192-0.288	Beta	24
Neutropenia	0.39	0.312-0.468	Beta	24
Anaemia	0.06	0.048-0.072	Beta	24
Diarrhoea	0.04	0.032-0.048	Beta	24
Infections	0.09	0.072-0.108	Beta	24
Risk for requiring second-linechemotherapy[b]	0.25	0.2-0.3	Beta	37
Utility[b]				
1-5 years in PFS for ECF/ECX arm	0.68	0.56-0.76	Beta	31
5-10 years in PFS for ECF/ECX arm	0.81	0.648-0.972	Beta	30
1-5 years in PFS for FLOT arm	0.68	0.56-0.76	Beta	31
5-10 years in PFS for FLOT arm	0.81	0.648-0.972	Beta	30
Beyond 10 years for 2 arms	1	-	-	32
PS in two arms	0.5	0.4-0.6	Beta	31
PFS =Progression-free survival; PS = Progression survival.				

[b] The range was assumed to be varied ± 20%

RESULT

The economic and health results calculated by the model are displayed in Table 4. The QALYs associated with the FLOT (4.08QALYs) chemotherapy was longer than that with ECF/ECX (3.0QALYs), and the FLOT achieved an increase of 1.08QALYs over the course of disease. Compared with the cost of ECF/ECX regimen of $45,311.91, the direct medical costs of FLOT regimen was increased by $921.51 （$46,233.42 vs $45,311.91）. The corresponding ICER of the FLOT regimen was $850.68 per QALY. A detailed analysis of cost breakdown (Table 5), shows that FlOT increased the Second lines of treatment and suppotive treatment costs in $1080.41, plus $473.34 in drug costs, but allows to save $1264.89 in the management of the patient. Other cost groups were similar between treatments.

Table 4.The base-case model results for two treatments

Model outcome	Treatment strategy	
	ECF/ECX	FLOT
Costs in PFS($)	16,250.09	16,060.58
Costs in PS($)	29,061.82	30,172.84
Costs of total($)	45,311.91	46,233.42
QALYs in PFS(QALY)	2.44	3.5
QALYs in PS(QALY)	0.56	0.58
QALYs of total(QALY)	3	4.08
CER($/QALY)	15,103.97	11,331.72059
ICER for FLOT ($/QALY)	-	850.68

Table 5. Cost Breakdown Base-case Results

Cost breakdown($)	FLOT	ECF/ECX	Incremental
Cost of administration	380.28	336.72	43.56
Cost of management	493.33	1758.22	-1264.89
Second lines of treatment & suppotive treatment	29341.43	28261.02	1080.41
Cost of adverse events	748.36	453.18	295.18
Cost of surgery	13019.22	12725.29	293.93
Drug costs	2250.81	1777.47	473.34

Tornado diagram (Figure 3) revealed that the HR of OS was the most influential

parameter in our model. When the HR of OS was increased from 0.63 to 0.94, the ICERs ranged from $3,868.18 per QALY to $-16,856.98 per QALY. Other influential parameters included the HR of PFS, the proportion of surgery patients in the ECF/ECX chemotherapy group and the discount rate. Parameters that have a minor influence on the model included the proportion of AEs, such as nausea, diarrhoea and vomiting (grade 3 or 4). In generally, the ICERs remained below the WTP $31513 (three times of China's per capita GDP) within the fluctuation of all parameters.

The ICER scatter plot (Figure 4) shows the results of the probabilistic sensitivity analyses, including a set of points representing the incremental cost and benefit value pairs in Monte Carlo simulation (10,000 repetitions). The slash is the WTP threshold line, and 95% confidence intervals of the estimates are surrounded by the ellipse. It can be seen from Figure 4 that ICER is mostly distributed in the first and fourth quadrants and below the threshold line. The plot below the threshold line accounted for 99.5% of all scatter plots, indicating that the possibility of FLOT chemotherapy regimen being cost-effective compared with the ECF/ECX treatment was 99.5%.

The CEAC (Figure 5) shows the cost-effectiveness probabilities of the FLOT chemotherapy generated by Markov Model simulation at different cost-effectiveness thresholds. The cost-effectiveness probability of the FLOT chemotherapy was increased with the increasing WTP thresholds. When the WTP threshold was greater than $699.2/QALY, the probability of the FLOT chemotherapy being cost-effective was nearly 50% for patients with resectable gastric or gastroesophageal junction cancer. When the threshold exceeded $17,090/QALY, the cost-effectiveness possibility of the FLOT chemotherapy reached 99%.

Discussion

Since 2018, the FLOT chemotherapy regimen has occupied an important position in the CSCO guidelines in China and the National Comprehensive Cancer Network (NCCN) in the United States[17,18]. Although previous chemotherapy has proved to be effective in improving the overall survival of patients with advanced gastric cancer after resection, the prognosis of later-stage patients (stage III B and III

C) are still suboptimal. Therefore, further clinical studies are needed to find more effective perioperative treatment for gastric cancer.

In recent years, the use of anthracycline and platinum drugs has sprouted in the field of perioperative treatment of resectable gastric cancer. Two published phase III studies have demonstrated the clinical efficacy of docetaxel in the treatment of advanced gastric cancer, involving DOS (docetaxel, oxaliplatin, S-1) and DS (docetaxel combined with S-1) [44,45]. Moreover, oxaliplatin has showed favorable safety in the treatment gastrointestinal tract, liver, kidney, and bone marrow than cisplatin and carboplatin. Therefore, oxaliplatin has gradually replaced cisplatin in the current commonly used chemotherapy regimens. In the ARTIST- Ⅱ trail, the SOX regimen (oxaliplatin combined with S-1) showed superiority over single drug (S-1) in prolonging patient's survival[46]. Two pivotal phase III trial from Japan and South Korea also found that oxaliplatin combined with folic acid and S-1was associated with a clinically significant improvement among patients with advanced gastric cancer, when compared with S-1 plus cisplatin[47]. Based on these positive results, docetaxel and oxaliplatin have been introduced into FLOT chemotherapy regimen. At present, FLOT regimen is considered as a preferred strategy for perioperative chemotherapy combined with surgery, including three chemotherapeutic drugs that suitable for patients with good performance status. Notably, for patients with good to moderate performance status and patients who is not able to tolerate the combination regimen of these three drugs, the two drug combination regimen is recommended.

In China, the climbing incidence and mortality of gastric cancer have imposed considerable physical, psychological and economic burdens on the society, patients and their families. Therefore, it is very crucial to study the economic significance of this chemotherapy strategy in the field of medicine and policy. In this economic evaluation that compared with the ECF/ECX, the use of FLOT in patients with gastric and gastroesophageal junction adenocarcinoma achieved additional 1.08QALY at an incremental cost of $921.51, resulting in an ICER of $850.68/QALY. Based on the WTP threshold set for this analysis, the FLOT strategy was considered to be cost-effective. However, due to the extreme imbalance of economic development in

Chinese Mainland, the per capita GDP of the 32 provincial-level administrative regions varies greatly. The highest per capita GDP was reported in Beijing's per capita GDP ($23,968), and the lowest was reported in Gansu's ($5,238)[48]. For the whole Chinese Mainland the per capita GDP was $10,504, and three times the per capita GDP was $31,513. Because the ICERs of the FLOT strategy were much lower than three times the per capita GDP in Gansu Province ($15,714). This suggests that the FLOT perioperative chemotherapy regimen is more cost-effective than ECF/ECX in the treatment of locally advanced resectable gastric or gastroesophageal junction adenocarcinoma in all provincial-level administrative regions in Chinese Mainland.

The one-way sensitivity analysis showed that the most influential parameter on the model results was the hazard ratio (HR) of overall survival. Specifically, when the HR decreased from 0.94 to 0.63, the ICER of FLOT strategy versus ECF/ECX strategy ranged from $-16,856.98 per QALY to $3,868.18 per QALY. The other sensitive parameters included the hazard ratio of progression-free survival, the proportion of patients with ECF/ECX who underwent surgery, and the discount rate. The change of HR for overall survival made ICER fluctuate the most, but the ICER was still less than WTP ($10,504/QALY). Moreover, the ICER of FLOT strategy versus ECF/ECX strategy was always much lower than WTP regardless of the large fluctuation of model parameters. Consequently, we can conclude the uncertainty of parameters will not affect the robustness of our results.

It should be noted that, docetaxel prices played a more important role than the prices of other drugs in our model. From the perspective of cancer patients, the use of high-priced new drugs might impose a heavy financial burden on the both social and patients, which likely leads to delay, abandonment, and discontinuation of treatment[49]. In recent years, the Chinese government has conducted a series of price negotiation with many pharmaceutical enterprises with the aim of reducing the price of oncology drugs. Fortunately, docetaxel passed the price negotiation and the consistency evaluation of generic drugs successfully in March 2021[50]. This means that the market price of docetaxel will drop, which will make docetaxel less costly and more widely used in China. Since the implementation of the national drug

centralized procurement policy and the generic drug consistency evaluation, we can expect that cancer patients may benefit from these policies in China. To our best knowledge, this study is the first cost-effectiveness analysis of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma.

There are some limitations in the current study. Firstly, there is uncertainty regarding the outcomes of patients with gastric and gastroesophageal junction adenocarcinoma beyond the trial period, despite the use of validated extrapolation techniques. Secondly, some potential bias lied in only direct medical costs were incorporated in the model, however, our sensitive analysis found that our results were almost unaffected by changes in costs. Thirdly, another limitation of the current economic analysis was that other treatment strategies for advanced resectable gastric cancer have not been fully explored. With the successful application of targeted therapy and immunotherapy for advanced gastric cancer clinically, the pattern of perioperative treatment of resectable gastric cancer have been refreshed. For example, the research on treatment of HER-2 positive gastric cancer has attracted considerable attentions in recent years. Meanwhile, combining the perioperative chemotherapy with targeted treatment, was found to increase the pathological complete remission rate and improve overall survival benefit, while the safety is acceptable[51,52]. Therefore, we can expect that receiving higher cost targeted therapy can increase more cost-effectiveness.

Author affliations

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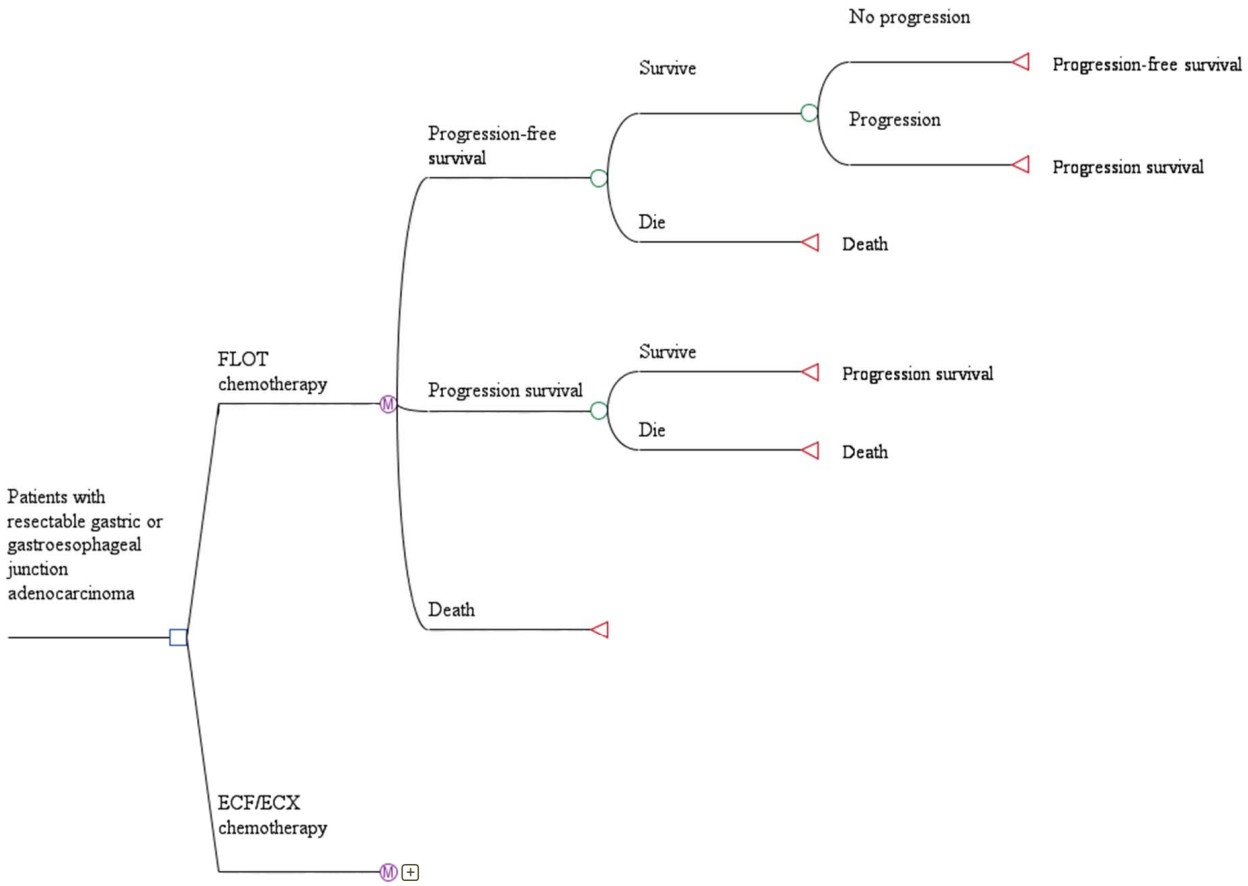
Figure 1. Markov model structure of FLOT and ECF/ECX strategies for the treatment of patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma

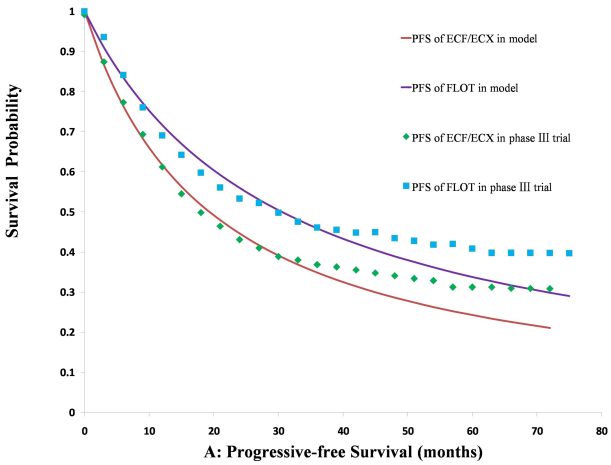
Figure 2. The Log-Logistic curves of (A) disease-free survival and (B) overall survival.

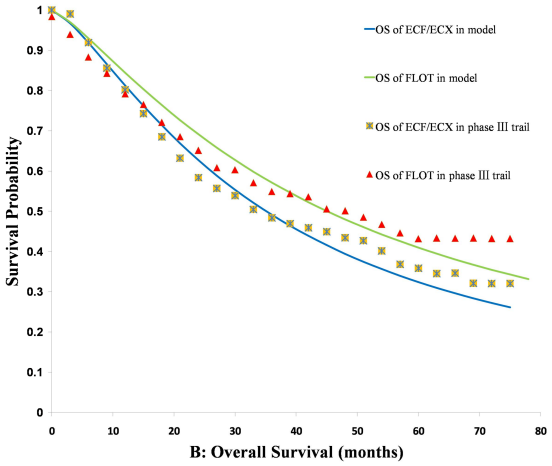
Figure 3. Tornado diagram for univariable sensitivity analyses. The grey dotted line represents the ICER of $850.6842 per QALY from the base-case results. ICER incremental cost-efectiveness ratio, QALY quality-adjusted life-year.

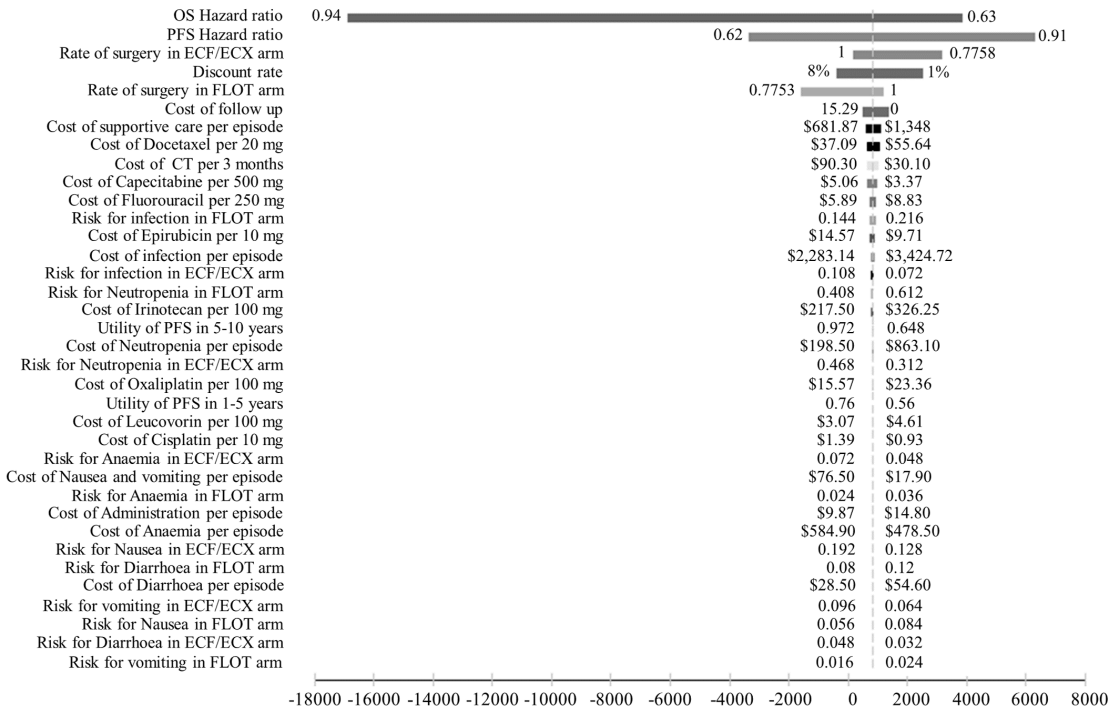
Figure 4. The results of Monte Carlo probabilistic sensitivity analysis for the strategies of FLOT VS ECF/ECX in scatter plots. The solid lines indicate the $31,513 threshold. The estimates of 95% were surrounded in the ellipses.

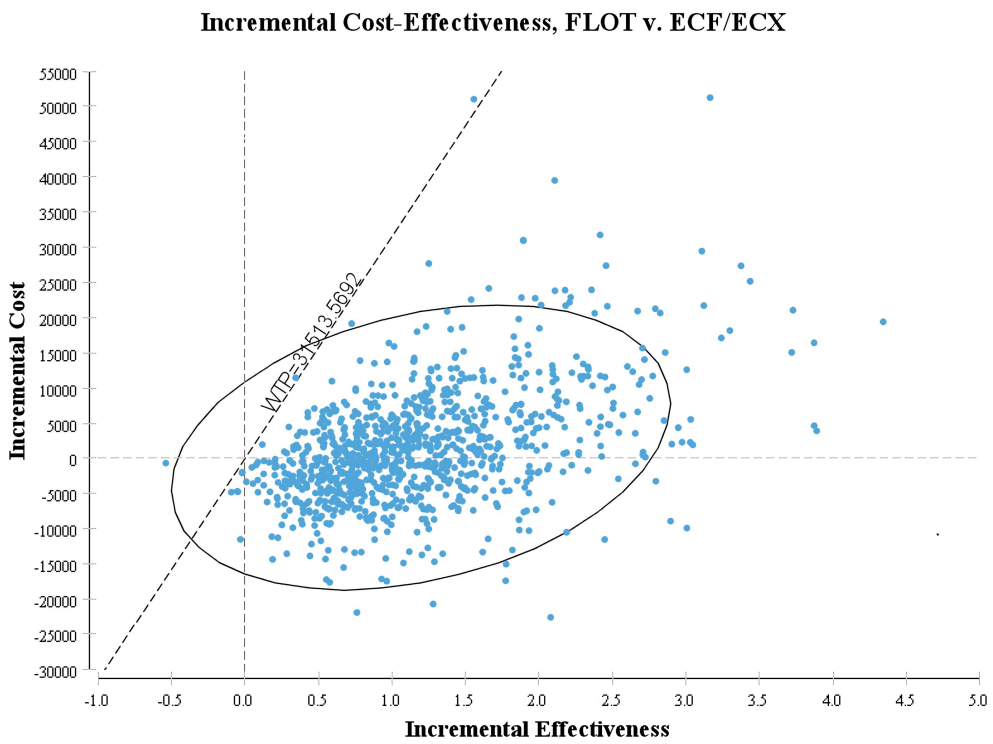
Figure 5. Acceptability curves for the two strategies at willingness-to-pay (WTP) thresholds in locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma patients. The vertical dashed line represent the threshold that the cost-effectiveness probability of FLOT chemotherapy reached 99%, and the solid line represent the WTP threshold of $10504 (the per capita GDP in China).

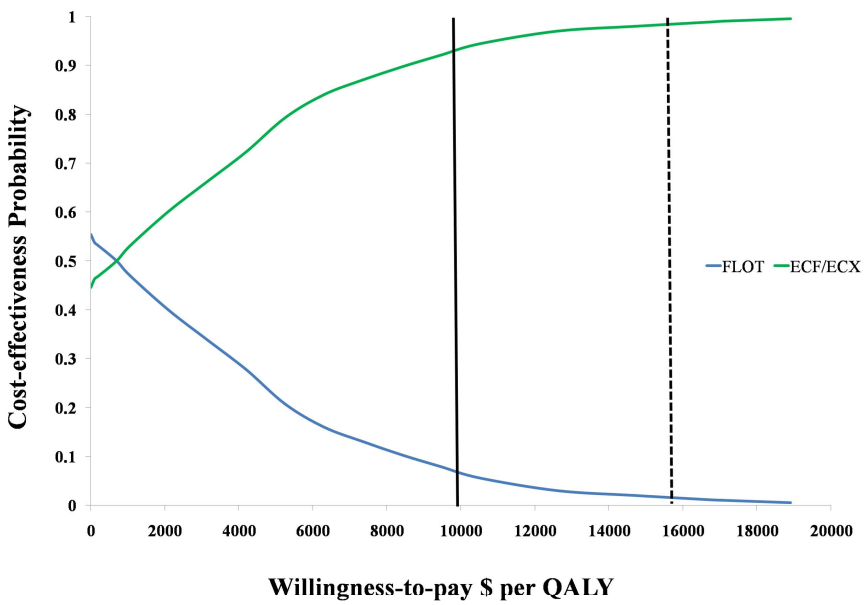

Patients with resectable gastric or gastroesophageal junction adenocarcinoma
FLOT chemotherapy
ECF/ECX chemotherapy
Progression-free survival
Progression survival
Death
Survive
Die
No progression
Progression
Progression-free survival
Progression survival
Death
Survive
Die
Progression survival
Death






OS Hazard ratio 0.94 0.63
PFS Hazard ratio 0.62 0.91
Rate of surgery in ECF/ECX arm 1 0.7758
Discount rate 8% 1%
Rate of surgery in FLOT arm 0.7753 1
Cost of follow up 15.29 0
Cost of supportive care per episode $681.87 $1,348
Cost of Docetaxel per 20 mg $37.09 $55.64
Cost of CT per 3 months $90.30 $30.10
Cost of Capecitabine per 500 mg $5.06 $3.37
Cost of Fluorouracil per 250 mg $5.89 $8.83
Risk for infection in FLOT arm 0.144 0.216
Cost of Epirubicin per 10 mg $14.57 $9.71
Cost of infection per episode $2,283.14 $3,424.72
Risk for infection in ECF/ECX arm 0.108 0.072
Risk for Neutropenia in FLOT arm 0.408 0.612
Cost of Irinotecan per 100 mg $217.50 $326.25
Utility of PFS in 5-10 years 0.972 0.648
Cost of Neutropenia per episode $198.50 $863.10
Risk for Neutropenia in ECF/ECX arm 0.468 0.312
Cost of Oxaliplatin per 100 mg $15.57 $23.36
Utility of PFS in 1-5 years 0.76 0.56
Cost of Leucovorin per 100 mg $3.07 $4.61
Cost of Cisplatin per 10 mg $1.39 $0.93
Risk for Anaemia in ECF/ECX arm 0.072 0.048
Cost of Nausea and vomiting per episode $76.50 $17.90
Risk for Anaemia in FLOT arm 0.024 0.036
Cost of Administration per episode $9.87 $14.80
Cost of Anaemia per episode $584.90 $478.50
Risk for Nausea in ECF/ECX arm 0.192 0.128
Risk for Diarrhoea in FLOT arm 0.08 0.12
Cost of Diarrhoea per episode $28.50 $54.60
Risk for vomiting in ECF/ECX arm 0.096 0.064
Risk for Nausea in FLOT arm 0.056 0.084
Risk for Diarrhoea in ECF/ECX arm 0.048 0.032
Risk for vomiting in FLOT arm 0.016 0.024
-18000 -16000 -14000 -12000 -10000 -8000 -6000 -4000 -2000 0 2000 4000 6000 8000


Incremental Cost-Effectiveness, FLOT v. ECF/ECX
Incremental Cost
Incremental Effectiveness
WTP=31513.5692
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
-25000
-30000
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0


Cost-effectiveness Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
Willingness-to-pay $ per QALY
FLOT
ECF/ECX

Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	2
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	3
Methods			

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	7
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	6
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	6-7
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	n/a
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	'n/a'
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	9

Methods

Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	6
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	6
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	10
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	12
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	12

Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	'n/a'
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	'n/a'
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-16
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	17
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	17

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Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

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Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

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ABSTRACT

Objective: The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin plus docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy in China remains unclear. The analysis aimed to compare the cost-effectiveness of FLOT versus ECF/ECX (epirubicin, cisplatin plus fluorouracil or capecitabine) in patients with locally advanced resectable tumors.

Design: We developed a Markov model to compare the healthcare and economic outcomes of FLOT and ECF/ECX in patients with resectable gastric or gastroesophageal junction

adenocarcinoma. Costs were estimated from the perspective of Chinese healthcare system. Clinical and utility inputs were derived from the FLOT4 phase II/III clinical trial and published literature. Sensitivity analyses were employed to assess the robustness of our result. The annual discount rate for costs and health outcomes was set at 5%.

Outcome measures: The primary outcome of incremental cost-effectiveness ratios (ICERs) was calculated as the cost per quality-adjusted life years (QALYs).

Results: The base-case analysis found that compared with ECF/ECX, the use of FLOT chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of $851/QALY. One-way sensitivity analysis results suggested that the hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) had the greatest impact on the ICER. Probabilistic sensitivity analysis demonstrated that FLOT was more likely to be cost-effective compared with ECF/ECX at a willingness-to-pay (WTP) threshold of $31,513/QALY.

Conclusions: For patients with locally advanced resectable tumors, the FLOT chemotherapy is a cost-effective treatment option compared with ECF/ECX in China.

Trial registration number: NCT01216644.

Keywords: Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy, FLOT, ECF/ECX , Cost-effectiveness.

Strengths and limitations of this study

- Perioperative FLOT significantly improved overall survival compared with perioperative ECF/ECX in patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma. However, the cost-effectiveness of perioperative FLOT among Chinese patients remains unknown.
- To our knowledge, this is the first cost-effectiveness analysis comparing FLOT with ECF/ECX for patients with resectable gastric or gastroesophageal junction adenocarcinoma in China.
- The use of data in clinical trials may not represent the data in real clinical practice, because clinical trials have certain time constraints. For example, we used

Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the trial.

SUBHEADLING: Economic evaluation of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma

INTRUDOCTION

According to the latest global cancer burden data in 2020 released by the international agency for research on cancer (IARC) of the World Health Organization, China ranked first in the cancer-related deaths with approximately 480,000 cases recorded. Gastric cancer is the third most prevalent malignant tumor in the world and the third leading cause of cancer-related death in China[1].

Although significant progress has been made in early detection, the prognosis of patients with resectable gastric and gastroesophageal junction adenocarcinoma is still poor[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy had demonstrated their superior survival benefit in patients with this disease when compared with a simple surgery[3-6]. Based on this, perioperative chemotherapy is recommended as the preferred treatment for locally resectable diseases[3,7-9]. For patients whose surgical scope is less than D2 lymph node dissection, postoperative chemoradiotherapy is the preferred treatment [6,10,11]. Other treatment strategies, such as postoperative chemotherapy, are applicable patients who have udergone primary lymph node dissection[12-14]. In Asian countries, accumulating clinical evidence has shown that, compared with D2 gastrectomy alone , adjuvant chemotherapy after a D2 surgery significantly improves the tumor remission rate and R0 resection rate is associated with a favorable safety profile[15,16].

The Medical Research Council adjuvant gastric infusion chemotherapy (MAGIC) trial was the first clinical trial to confirm the survival benefits of perioperative chemotherapy[3]. In this trial, 503 patients with locally advanced resectable gastric and gastroesophageal junction adenocarcinoma were enrolled and were randomly assigned to receive three cycles of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy or

surgery alone. The survival rate in the chemotherapy group was significantly higher than the simple surgery group (5-year survival rate, 36% vs 23%). The FNCLCC/FFCD II/III trial also found that perioperative chemotherapy for gastric cancer provided greater survival benefits than the surgery alone[3]. According to the trial evidence, the National Comprehensive Cancer Network Clinical (NCCN) Guidelines recommended perioperative chemotherapy as a routine regimen for advanced gastric cancer (class I evidence) in 2022, and a standard adjuvant chemotherapy for gastroesophageal adenocarcinoma[17]. Subsequently, the Chinese Society of Clinical Oncology (CSCO) Guidelines[18] recommended several chemotherapy regimens as preferred schemes, including cisplatin combined with fluorouracil (PF)[4], improved ECF scheme[19], oxaliplatin combined with capecitabine (XELOX)[20], oxaliplatin combined with fluorouracil (FOLFOX)[21], and oxaliplatin combined with S-1 (SOX)[22]. Although the great progress had been made on chemotherapies, the clinical prognosis of patients with advanced gastric or gastroesophageal junction cancer is still unsatisfactory, especially those with advanced cancers. In view of this, there is a pressing need for any novel chemotherapy regimen with a greater effectiveness than the existing ones.

In the phase II/III clinical trials of FLOT4, the researchers compared the perioperative chemotherapy FLOT (fluorouracil, leucovorin, oxaliplatin plus docetaxel) with the standard chemotherapy ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine)[23,24]. Fluoropyrimidine and platinum combined with or without anthracycline are the most used chemotherapeutic regimen. In the FLOT4 trial, adding docetaxel to triple-drug regimen (FLOT regimen) was associated with improved survivals among patients with resectable gastric or gastroesophageal junction cancer with clinical stage CT2 or higher and lymph node positive (CN+) when compared with ECF/ECX regimen (50 months vs35 months; HR = 0.77; 95% confidence interval, 0.63-0.94). In this phase II/III trial, the proportion of patients with complete regression of pathology was significantly higher in the FLOT group than that in the ECF/ECX group. In addition, compared with the ECF/ECX group, patients in the FLOT group had a lower incidence of grade 3-4 adverse events (AEs),

including neutropenia, leucopenia, nausea, infection, fatigue and vomiting (25% vs 40%), but had the same incidence of serious chemotherapy-related AEs (27% in both groups).

In response to the positive results from FLOT4 trial, FLOT chemotherapy is recommended for patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class IIA) by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer (2018 Edition). However, its financial impact has not been studied yet from the perspective of Chinese healthcare system. Considering the high prevalence of gastric or gastroesophageal junction cancer, and limited health resources in China, the therapeutical benefits of FLOT chemotherapy must be weighed against the economic burden that it has imposed. This study aimed to evaluate whether the perioperative chemotherapy FLOT is cost-effective compared with ECF/ECX among patients with gastric and gastroesophageal junction adenocarcinoma from the perspective of Chinese medical system.

METHODS

Patients and regimens

The patient population analyzed in this study mirrored the patient enrolled in the FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction adenocarcinoma. In this study, a total of 716 patients were randomly assigned to receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group received three 3-week cycles preoperative chemotherapy and three 3-week cycles postoperative chemotherapy. The chemotherapy regimen for each 3-week cycle was epirubicin 50mg/m^2 on the first day, cisplatin 60mg/m^2 on the first day, and continuous intravenous infusion of fluorouracil 200mg/m^2 or oral capecitabine 1250mg/m^2 from the first to the 21st days at the discretion of investigators. Patients in the FLOT group received four 2-week cycles preoperative chemotherapy and four 2-week cycles postoperative chemotherapy, which were docetaxel 50mg/m^2 on the

first day, oxaliplatin 85mg/m^2 on the first day, calcium folinate 200mg/m^2 on the first day and 5-FU 2600mg/m^2 as 24-h infusion the first day.

The operation was scheduled 4 weeks after the last preoperative chemotherapy. The interval between the two groups was 4 weeks (28 days). As per this clinical trial, patients may discontinue treatment due to unacceptable toxicity, disease progression, death, or patient requirements. When patients experienced disease progression, they would receive second-line treatment, including irinotecan, calcium folinate and fluorouracil[25].

Patient and public involvement

There was patient representation in the FLOT4 trial. However, this cost-effectiveness analysis does not involve human participants.

Analytic Model

Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro 2018 software to estimate the clinical outcomes of two perioperative chemotherapy regimens (FLOT and ECF/ECX) for patients with gastric and gastroesophageal junction adenocarcinoma in China(Figure 1).

The model comprised three mutually exclusive health states: progression-free survival (PFS), progressed survival (PS) and death. The Markov cycle length was set as 2-week to fit the treatment schedule of the two groups. At the beginning of the model, the whole cohort was in PFS state, and the transitions between health states in the model may occur during each Markov cycle. From the perspective of Chinese medical system, we used a lifetime horizon and a half-cycle correction to estimate the total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the annual discount rate for both costs and health outcomes was set at 5% [26]. All costs used in the model were adjusted based on the consumer price index provided by the the People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar = 6.88 Chinese Yuan) [27]. A WTP threshold of $31,513 was used in the current analysis.

This is based on the WHO recommendation based on which a health intervention should be considered as cost-effective if the ICER is between one to three times the GDP per capita of that country[26]. At this point, it should be mentioned that this WTP threshold has been widely used in cost-effectiveness studies within global health [28-30]. The GDP per capita in China was estimated at $10,504 in 2020[31].

PFS and OS data were derived from the Kaplan Meier survival curve in the trial. First, we used GetDataGraph Digitizer software version 2.24 to extract datapoints from published PFS and OS curves in the publications (http://getdata-graph-digitizer.com).Then, these extracted point data was fitted with different parametric survival models (including Exponential, Weibull, Lognormal and Log-logistic). According to the result of statistical goodness-of-fit test using Akaike information standard (AIC) and Bayesian information criterion (BIC), the Log-logistic distribution was selected for survival fitting. The two parameters of Log-logistic distribution, scale parameters（θ）and shape parameters（κ）are shown in Table 1. Finally, we used the parameters to calculate survival rate, which is $S(t)=\left\{1+e^{\theta}t^{\kappa}\right\}^{-1}$, where t is time. Figure 2 shows the Log-logistic parameters estimated for the FLOT and ECF/ECX regimens.

Table 1. Log-logistic parameters

Parameters	**Values**	
Log-Logistic survival model of PFS		
ECF/ECX	θ=0.05168663	κ=1.004703
FLOT	θ=0.03274242	κ=0.9957772
Log-Logistic survival model of OS		
ECF/ECX	θ=0.02849954	κ=1.369613
FLOT	θ=0.022184	κ=1.279334
θ: scale; κ: shape; ECF/ECX: docetaxel, oxaliplatin, leucovorin, fluorouracil; FLOT: epirubicin, cisplatin, fluorouracil or capecitabine.		

Utility

Since the quality of life data were not published along with the results of the FLOT4 trial, the utility related to gastric cancer was taken from the literatures[20,32]. Gockel et al used the Gastrointestinal Life Quality Index (GLQI) to evaluate the quality of life of 338 patients with gastrectomy, and then estimated the utility of patients with PFS health state as 0.81[33]. In addition, Sakamaki et al used the Time Trade-Off (TTO) to evaluate the utility of hospitalized patients with gastric cancer [32]. In their study, the utilities of patients receiving intravenous chemotherapy and advanced care were 0.68 and 0.50, respectively. In the current model, we assumed that the utilities of the three health states were identical in both groups. Therefore, 0.68 (1-5 years) and 0.81 (5-10 years) were used as the utilities of patients with PFS health state in both groups. In addition, the utility of patients in PS health state was set to 0.5 and the utility of patients who survived for more than 10 years was set to 1.0[34]. The disutility of adverse events (AEs) was calculated by multiplying the utility decrement due to AEs by the incidence of AEs[35,36]. We assumed that all AEs occurred in the first cycle.

Cost

From the perspective of Chinese medical system, we considered the direct healthcare expenditure costs in the model, including drug and administration costs, AE management costs, follow-up examination costs, second-line treatment costs, supportive treatment costs and surgery treatment costs. Drug and administration costs, follow-up examination costs and drug price were extracted from the local health system[37]. To calculate the dosage of chemotherapeutic drug, we assumed that a baseline patient's weight was 65kg and body surface area was 1.72 square meters[38].

After disease progressed, 25% of the patients in both groups who would receive second-line treatment and the second-line chemotherapy regimen was selected from the FLOT4 trial[39]. When patient experienced further disease progression, they would

receive supportive treatments until death[40]. The second-line chemotherapy regimen included intravenous injection of irinotecan 180mg/m^2 on days 1, calcium folinate 400 mg/m^2 on days 1, fluorouracil 400mg/m^2 on day 1, continuous intravenous injection of fluorouracil 1200mg/m^2 for more than 24 hours on day 1 and 2, and circulation every 14 days[25,41,42]. Data of the costs for drug administration，supportive and surgery treatments were extracted from published literature[43-45]. The follow-up examination included CT or MRI every three months until disease progression, recurrence or death. The price of CT or MRI came from the local health system[37]. According to expert suggestions and clinical practice, we calculated the grade 3-4 adverse events with a significant difference (P>0.05) between the two groups. Therefore, according to the data available in the FLOT4 trial, the following AEs were included in the model: vomiting （F/E:2％/8％）, nausea （F/E:7％/16％）, neutropenia （F/E:51％/39％）, anaemia （F/E:3％/6％）, infections （F/E:18％/9％）, diarrhoea （F/E:10％/4％）. Costs for treating AEs were estimated by multiplying the cost per event by the incidence of each AE. The incidences of AEs were obtained from the FLOT4 trial and the unit cost were from the published literature[34,43,46]. Table 2 lists all direct costs used in the model.

Table 2. Baseline costs with ECF/ECX and FLOT perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma in China

Parameters	Median	Range	Distribution	Reference
Costs, $				
Drug of FLOT per episode	352.1896	286.03-429.04	Lognormal	38
Drug of ECF/ECX per episode	270.8938	220.00-330.00	Lognormal	38
CT per 3months[a]	60.2	30.1-90.3	Gamma	38
MRI per 3months[a]	123.3	61.7-185	Gamma	38
Administration per episode	12.33	9.87-14.8	Lognormal	44
Supportive care per episode	943.6	681.87-1347.66	Lognormal	45
Surgery	13638.2	10910.56-16365.84	Lognormal	46
Expenditures on main adverse events(Grade 3 or 4), $				
FLOT	808.36	424.81-1303.83	Lognormal	35,44
ECF/ECX	507.04	253.64-840.57	Lognormal	35,44
MRI = magnetic resonance imaging; CT = computed tomography.				
[a]The range was assumed to be varied ± 50%.				

Sensitivity Analyses

One-way sensitivity analysis was performed to investigate the impact of individual changes in model parameters on our model results, the results are shown as a tornado diagram. The median, distribution and range of model input parameters are shown in Table 2 and 3, and the ranges corresponding to the model parameters were derived from the published literature or within a reasonable range(±20% or ±50% of the base-case value). In accordance with Chinese Guidelines for Pharmacoeconomic Evaluations, the discount rate in this analysis was assumed to vary between 0% and 8%[26]. We also performed a 10,000 repeated Monte Carlo probabilistic sensitivity analyses to evaluate the impact of simultaneous changes in parameters on the model results. In this probabilistic sensitivity analyses, each variable was randomly sampled from the appropriate distribution. A lognormal distribution was applied for the cost data and a beta distribution was applied for the utility value, probability or proportion. The result of PSA was depicted by a cost-effectiveness acceptability curve (CEAC).

Table 3. Baseline risks and utility values with ECF/ECX and FLOT perioperative chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma in China

Parameters	Median	Range	Distribution	Reference
Risk for main adverse events in ECF/ECX arm (Grade 3 or 4)[b]				
Nausea and vomiting	0.24	0.192-0.288	Beta	24
Neutropenia	0.39	0.312-0.468	Beta	24
Anaemia	0.06	0.048-0.072	Beta	24
Diarrhoea	0.04	0.032-0.048	Beta	24
Infections	0.09	0.072-0.108	Beta	24
Risk for requiring second-linechemotherapy[b]	0.25	0.2-0.3	Beta	40
Utility[b]				
1-5 years in PFS for ECF/ECX arm	0.68	0.56-0.76	Beta	34
5-10 years in PFS for ECF/ECX	0.81	0.648-0.972	Beta	33

arm				
1-5 years in PFS for FLOT arm	0.68	0.56-0.76	Beta	34
5-10 years in PFS for FLOT arm	0.81	0.648-0.972	Beta	33
Beyond 10 years for 2 arms	1	-	-	35
PS in two arms	0.5	0.4-0.6	Beta	34
PFS =Progression-free survival; PS = Progression survival.				
[b] The range was assumed to be varied ± 20%				

RESULT

The economic and health results calculated by the model are displayed in Table 4. The QALYs associated with the FLOT (4.08QALYs) chemotherapy was longer than that with ECF/ECX (3.0QALYs), and the FLOT achieved an increase of 1.08QALYs over the course of disease. Compared with the cost of ECF/ECX regimen of $45,311.91, the direct medical costs of FLOT regimen was increased by $921.51 （$46,233.42 vs $45,311.91）. The corresponding ICER of the FLOT regimen was $850.68 per QALY. A detailed analysis of cost breakdown (Table 5), shows that FlOT increased the Second lines of treatment and suppotive treatment costs in $1080.41, plus $473.34 in drug costs, but allows to save $1264.89 in the management of the patient. Other cost groups were similar between treatments.

Table 4.The base-case model results for two treatments

Model outcome	**Treatment strategy**	
	ECF/ECX	**FLOT**
Costs in PFS($)	16,250.09	16,060.58
Costs in PS($)	29,061.82	30,172.84
Costs of total($)	45,311.91	46,233.42
QALYs in PFS(QALY)	2.44	3.5
QALYs in PS(QALY)	0.56	0.58
QALYs of total(QALY)	3	4.08
CER($/QALY)	15,103.97	11,331.72059
ICER for FLOT ($/QALY)	-	850.68

Table 5. Cost Breakdown Base-case Results

Cost breakdown($)	**FLOT**	**ECF/ECX**	**Incremental**
Cost of administration	380.28	336.72	43.56
Cost of management	493.33	1758.22	-1264.89

Second lines of treatment & suppotive treatment	29341.43	28261.02	1080.41
Cost of adverse events	748.36	453.18	295.18
Cost of surgery	13019.22	12725.29	293.93
Drug costs	2250.81	1777.47	473.34

Tornado diagram (Figure 3) revealed that the HR of OS was the most influential parameter in our model. When the HR of OS was increased from 0.63 to 0.94, the ICERs ranged from $3,868.18 per QALY to $-16,856.98 per QALY. Other influential parameters included the HR of PFS, the proportion of surgery patients in the ECF/ECX chemotherapy group and the discount rate. Parameters that have a minor influence on the model included the proportion of AEs, such as nausea, diarrhoea and vomiting (grade 3 or 4). In generally, the ICERs remained below the WTP $31513 (three times of China's per capita GDP) within the fluctuation of all parameters.

The ICER scatter plot (Figure 4) shows the results of the probabilistic sensitivity analyses, including a set of points representing the incremental cost and benefit value pairs in Monte Carlo simulation (10,000 repetitions). The slash is the WTP threshold line, and 95% confidence intervals of the estimates are surrounded by the ellipse. It can be seen from Figure 4 that ICER is mostly distributed in the first and fourth quadrants and below the threshold line. The plot below the threshold line accounted for 99.5% of all scatter plots, indicating that the possibility of FLOT chemotherapy regimen being cost-effective compared with the ECF/ECX treatment was 99.5%.

The CEAC (Figure 5) shows the cost-effectiveness probabilities of the FLOT chemotherapy generated by Markov Model simulation at different cost-effectiveness thresholds. The cost-effectiveness probability of the FLOT chemotherapy was increased with the increasing WTP thresholds. When the WTP threshold was greater than $699.2/QALY, the probability of the FLOT chemotherapy being cost-effective was nearly 50% for patients with resectable gastric or gastroesophageal junction cancer. When the threshold exceeded $17,090/QALY, the cost-effectiveness possibility of the FLOT chemotherapy reached 99%.

Discussion

Since 2018, the FLOT chemotherapy regimen has occupied an important position in the CSCO guidelines in China and the National Comprehensive Cancer Network (NCCN) in the United States[17,18]. Although previous chemotherapy has proved to be effective in improving the overall survival of patients with advanced gastric cancer after resection, the prognosis of later-stage patients (stage III B and III C) are still suboptimal. Therefore, further clinical studies are needed to find more effective perioperative treatment for gastric cancer.

In recent years, the use of anthracycline and platinum drugs has sprouted in the field of perioperative treatment of resectable gastric cancer. Two published phase III studies have demonstrated the clinical efficacy of docetaxel in the treatment of advanced gastric cancer, involving DOS (docetaxel, oxaliplatin, S-1) and DS (docetaxel combined with S-1) [47,48]. Moreover, oxaliplatin has showed favorable safety in the treatment gastrointestinal tract, liver, kidney, and bone marrow than cisplatin and carboplatin. Therefore, oxaliplatin has gradually replaced cisplatin in the current commonly used chemotherapy regimens. In the ARTIST- Ⅱ trail, the SOX regimen (oxaliplatin combined with S-1) showed superiority over single drug (S-1) in prolonging patient's survival[49]. Two pivotal phase III trial from Japan and South Korea also found that oxaliplatin combined with folic acid and S-1was associated with a clinically significant improvement among patients with advanced gastric cancer, when compared with S-1 plus cisplatin[50]. Based on these positive results, docetaxel and oxaliplatin have been introduced into FLOT chemotherapy regimen. At present, FLOT regimen is considered as a preferred strategy for perioperative chemotherapy combined with surgery, including three chemotherapeutic drugs that suitable for patients with good performance status. Notably, for patients with good to moderate performance status and patients who is not able to tolerate the combination regimen of these three drugs, the two drug combination regimen is recommended.

In China, the climbing incidence and mortality of gastric cancer have imposed considerable physical, psychological and economic burdens on the society, patients and their families. Therefore, it is very crucial to study the economic significance of this chemotherapy strategy in the field of medicine and policy. In this economic

evaluation that compared with the ECF/ECX, the use of FLOT in patients with gastric and gastroesophageal junction adenocarcinoma achieved additional 1.08QALY at an incremental cost of $921.51, resulting in an ICER of $850.68/QALY. Based on the WTP threshold set for this analysis, the FLOT strategy was considered to be cost-effective. However, due to the extreme imbalance of economic development in Chinese Mainland, the per capita GDP of the 32 provincial-level administrative regions varies greatly. The highest per capita GDP was reported in Beijing's per capita GDP ($23,968), and the lowest was reported in Gansu's ($5,238)[51]. For the whole Chinese Mainland the per capita GDP was $10,504, and three times the per capita GDP was $31,513. Because the ICERs of the FLOT strategy were much lower than three times the per capita GDP in Gansu Province ($15,714). This suggests that the FLOT perioperative chemotherapy regimen is more cost-effective than ECF/ECX in the treatment of locally advanced resectable gastric or gastroesophageal junction adenocarcinoma in all provincial-level administrative regions in Chinese Mainland.

The one-way sensitivity analysis showed that the most influential parameter on the model results was the hazard ratio (HR) of overall survival. Specifically, when the HR decreased from 0.94 to 0.63, the ICER of FLOT strategy versus ECF/ECX strategy ranged from $-16,856.98 per QALY to $3,868.18 per QALY. The other sensitive parameters included the hazard ratio of progression-free survival, the proportion of patients with ECF/ECX who underwent surgery, and the discount rate. The change of HR for overall survival made ICER fluctuate the most, but the ICER was still less than WTP ($10,504/QALY). Moreover, the ICER of FLOT strategy versus ECF/ECX strategy was always much lower than WTP regardless of the large fluctuation of model parameters. Consequently, we can conclude the uncertainty of parameters will not affect the robustness of our results.

It should be noted that, docetaxel prices played a more important role than the prices of other drugs in our model. From the perspective of cancer patients, the use of high-priced new drugs might impose a heavy financial burden on the both social and patients, which likely leads to delay, abandonment, and discontinuation of treatment[52]. In recent years, the Chinese government has conducted a series of price

negotiation with many pharmaceutical enterprises with the aim of reducing the price of oncology drugs. Fortunately, docetaxel passed the price negotiation and the consistency evaluation of generic drugs successfully in March 2021[53]. This means that the market price of docetaxel will drop, which will make docetaxel less costly and more widely used in China. Since the implementation of the national drug centralized procurement policy and the generic drug consistency evaluation, we can expect that cancer patients may benefit from these policies in China. To our best knowledge, this study is the first cost-effectiveness analysis of FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction adenocarcinoma.

There are some limitations in the current study. Firstly, there is uncertainty regarding the outcomes of patients with gastric and gastroesophageal junction adenocarcinoma beyond the trial period, despite the use of validated extrapolation techniques. Secondly, some potential bias lied in only direct medical costs were incorporated in the model, however, our sensitive analysis found that our results were almost unaffected by changes in costs. Thirdly, another limitation of the current economic analysis was that other treatment strategies for advanced resectable gastric cancer have not been fully explored. With the successful application of targeted therapy and immunotherapy for advanced gastric cancer clinically, the pattern of perioperative treatment of resectable gastric cancer have been refreshed. For example, the research on treatment of HER-2 positive gastric cancer has attracted considerable attentions in recent years. Meanwhile, combining the perioperative chemotherapy with targeted treatment, was found to increase the pathological complete remission rate and improve overall survival benefit, while the safety is acceptable[54,55]. Therefore, we can expect that receiving higher cost targeted therapy can increase more cost-effectiveness.

Author affliations

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Study design and supervision were contributed by H.Q. Zeng and X.H. Zeng; data analysis and interpretation were contributed by H.Q. Zeng, X.H. Zeng and Li-Ying Song; data collection was contributed by H.Q. Zeng, Chunjiang Wang; manuscript writing was contributed by H.Q. Zeng, X.H. Zeng , Su-Jie Jia and Q. Liu; final approval of the manuscript was contributed by all of the authors.

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Figure 1. Markov model structure of FLOT and ECF/ECX strategies for the treatment of patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma

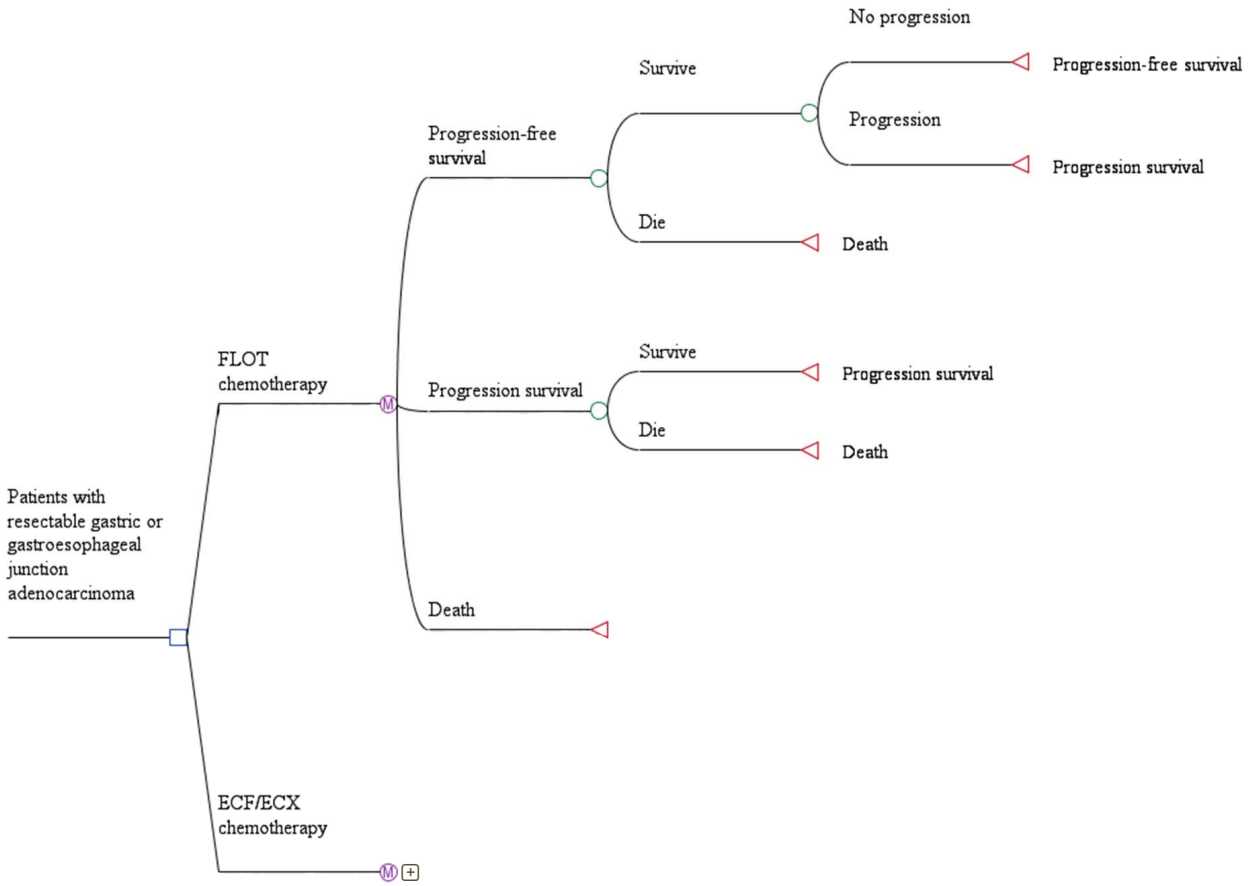
Figure 2. The Log-Logistic curves of (A) disease-free survival and (B) overall survival.

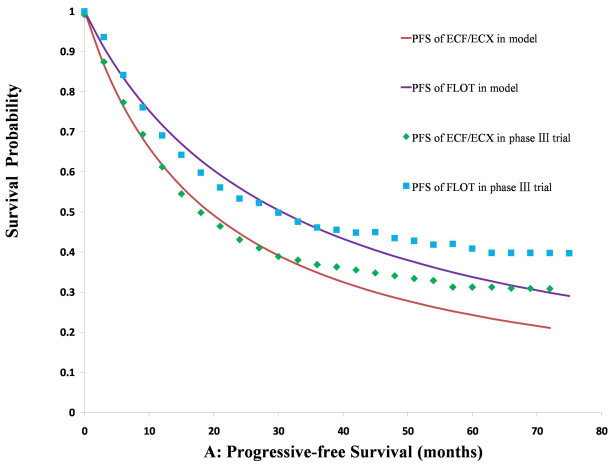
Figure 3. Tornado diagram for univariable sensitivity analyses. The grey dotted line represents the ICER of $850.6842 per QALY from the base-case results. ICER incremental cost-efectiveness ratio, QALY quality-adjusted life-year.

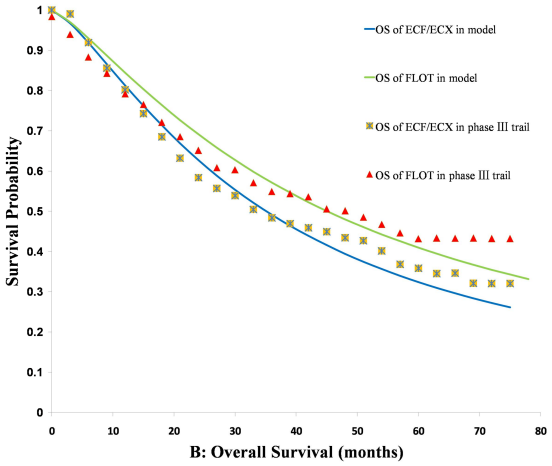
Figure 4. The results of Monte Carlo probabilistic sensitivity analysis for the strategies of FLOT VS ECF/ECX in scatter plots. The solid lines indicate the $31,513 threshold. The estimates of 95% were surrounded in the ellipses.

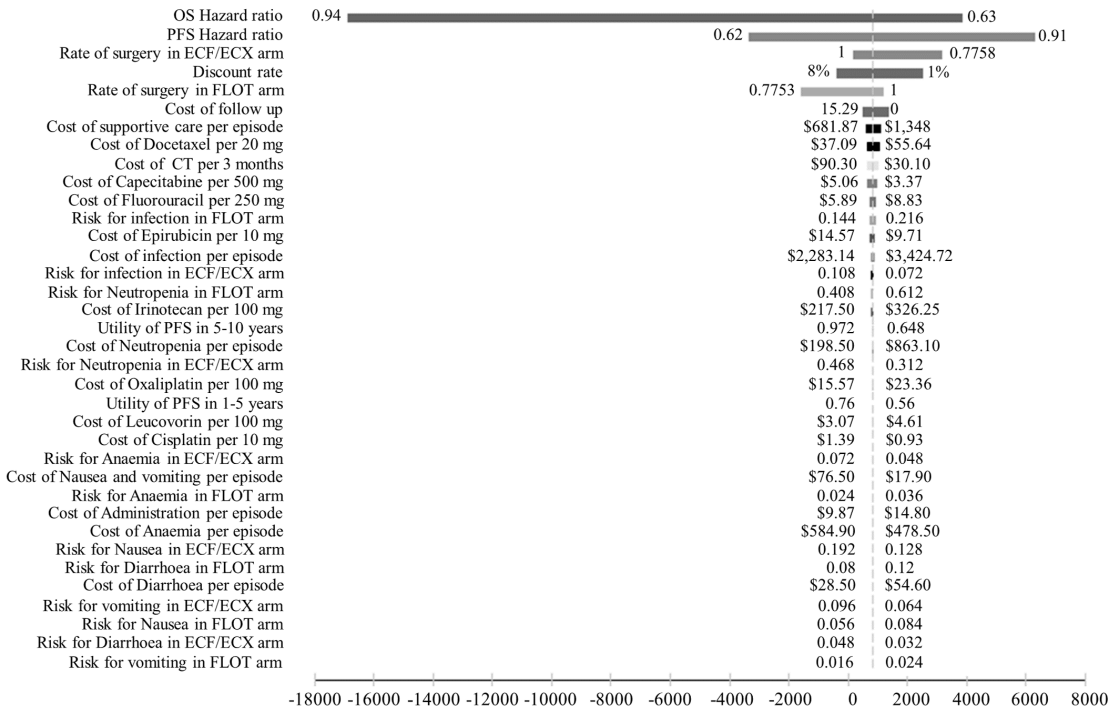
Figure 5. Acceptability curves for the two strategies at willingness-to-pay (WTP) thresholds in locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma patients. The vertical dashed line represent the threshold that the cost-effectiveness probability of FLOT chemotherapy reached 99%, and the solid line

represent the WTP threshold of $10504 (the per capita GDP in China).


Patients with resectable gastric or gastroesophageal junction adenocarcinoma
FLOT chemotherapy
ECF/ECX chemotherapy
Progression-free survival
Progression survival
Death
Survive
Die
No progression
Progression
Progression-free survival
Progression survival
Death
Survive
Die
Progression survival
Death






OS Hazard ratio 0.94 0.63
PFS Hazard ratio 0.62 0.91
Rate of surgery in ECF/ECX arm 1 0.7758
Discount rate 8% 1%
Rate of surgery in FLOT arm 0.7753 1
Cost of follow up 15.29 0
Cost of supportive care per episode $681.87 $1,348
Cost of Docetaxel per 20 mg $37.09 $55.64
Cost of CT per 3 months $90.30 $30.10
Cost of Capecitabine per 500 mg $5.06 $3.37
Cost of Fluorouracil per 250 mg $5.89 $8.83
Risk for infection in FLOT arm 0.144 0.216
Cost of Epirubicin per 10 mg $14.57 $9.71
Cost of infection per episode $2,283.14 $3,424.72
Risk for infection in ECF/ECX arm 0.108 0.072
Risk for Neutropenia in FLOT arm 0.408 0.612
Cost of Irinotecan per 100 mg $217.50 $326.25
Utility of PFS in 5-10 years 0.972 0.648
Cost of Neutropenia per episode $198.50 $863.10
Risk for Neutropenia in ECF/ECX arm 0.468 0.312
Cost of Oxaliplatin per 100 mg $15.57 $23.36
Utility of PFS in 1-5 years 0.76 0.56
Cost of Leucovorin per 100 mg $3.07 $4.61
Cost of Cisplatin per 10 mg $1.39 $0.93
Risk for Anaemia in ECF/ECX arm 0.072 0.048
Cost of Nausea and vomiting per episode $76.50 $17.90
Risk for Anaemia in FLOT arm 0.024 0.036
Cost of Administration per episode $9.87 $14.80
Cost of Anaemia per episode $584.90 $478.50
Risk for Nausea in ECF/ECX arm 0.192 0.128
Risk for Diarrhoea in FLOT arm 0.08 0.12
Cost of Diarrhoea per episode $28.50 $54.60
Risk for vomiting in ECF/ECX arm 0.096 0.064
Risk for Nausea in FLOT arm 0.056 0.084
Risk for Diarrhoea in ECF/ECX arm 0.048 0.032
Risk for vomiting in FLOT arm 0.016 0.024
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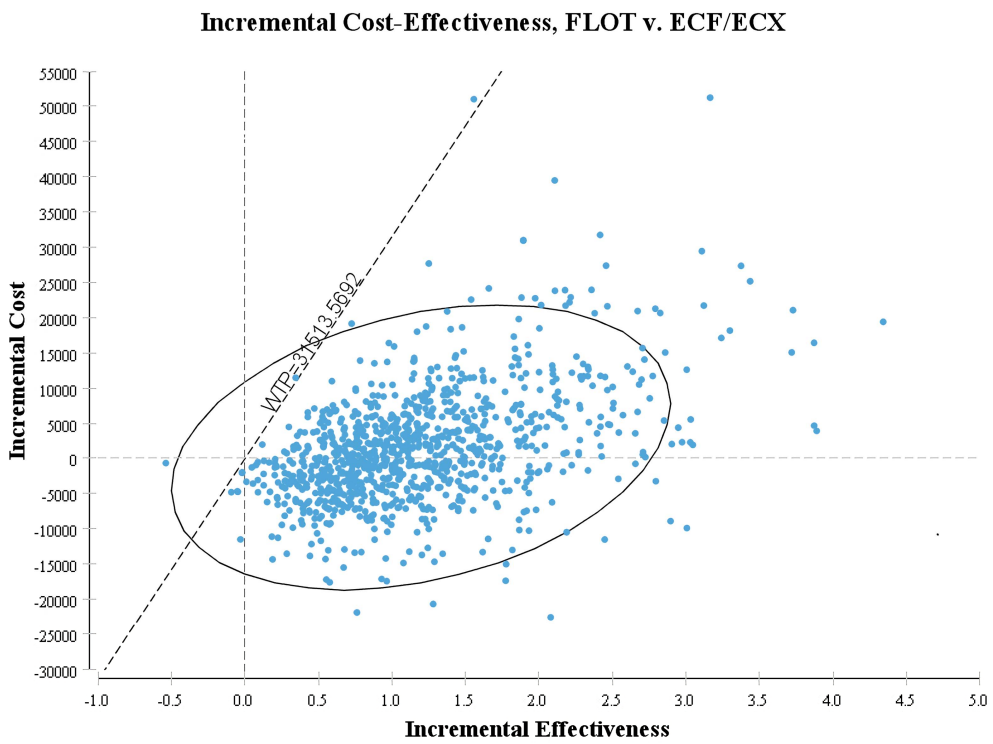
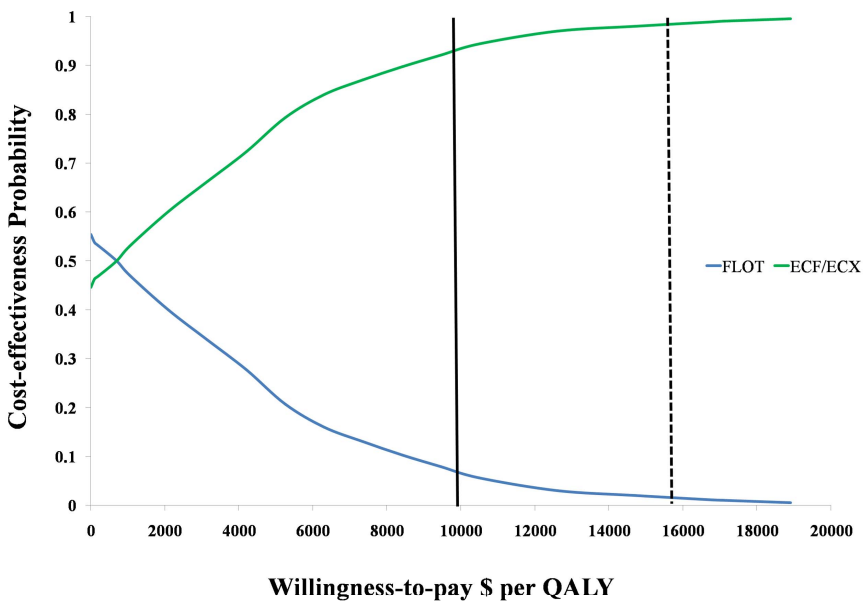

Incremental Cost-Effectiveness, FLOT v. ECF/ECX
Incremental Cost
Incremental Effectiveness
WTP=31513.5692
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
-25000
-30000
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0


Cost-effectiveness Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
FLOT
ECF/ECX
Willingness-to-pay $ per QALY

Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	2
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	3
Methods			

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	7
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	6
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	6-7
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	n/a
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	'n/a'
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	9

Methods

Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	6
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	6
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	10
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	12
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	12

Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	'n/a'
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	'n/a'
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-16
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	17
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	17