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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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4 **Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in**
5 **patients with resectable gastric or gastroesophageal junction adenocarcinoma**
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60 **ABSTRACT**

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4 **Objective:** The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin,
5 docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for
6 gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction
7 adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy has not been
8 evaluated in China. The analysis aimed to compare the cost-effectiveness between FLOT and
9 ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine) in patients with locally advanced
10 resectable tumors.
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17 **Design:** We developed a Markov model to compare the health and economic outcomes of FLOT
18 and ECF/ECX in resectable gastric or gastroesophageal junction adenocarcinoma. The cost was
19 estimated from the perspective of Chinese healthcare system. The clinical and utility inputs were
20 derived from the FLOT4 phase II/III clinical trial or published literature. Sensitivity analyses were
21 employed to assess the robustness of our result. The annual discount rate for costs and health
22 outcomes was set at 5%.
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29 **Outcome measures:** The primary outcome of incremental cost-effectiveness ratios (ICERs) was
30 calculated as the cost per quality-adjusted life years(QALYs).
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33 **Results:** The base-case analysis showed that compared with ECF/ECX, the use of FLOT
34 chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of
35 \$851/QALY. The probabilistic sensitivity analysis demonstrated that FLOT was more likely to be
36 cost-effective compared with ECF/ECX at a willingness-to-pay WTP value of \$31,513/QALY.
37 Sensitivity analysis results suggested that the hazard ratio (HR) of overall survival (OS) and
38 progression-free survival (PFS) had the greatest impact on the ICER.
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44 **Conclusions:** For patients with locally advanced resectable tumors, the FLOT chemotherapy is a
45 cost-effective treatment option comparing with ECF/ECX in China.
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48 **Trial registration number:** NCT01216644.
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52 **Keywords:** Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy,
53 FLOT, ECF/ECX , Cost-effectiveness.
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55 56 57 **Strengths and limitations of this study**

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59 ➤ Perioperative FLOT improved overall survival compared with perioperative
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4 ECF/ECX in patients with locally advanced, resectable gastric or
5 gastro-oesophageal junction adenocarcinoma. However, the cost-effectiveness of
6 perioperative FLOT in treating these patients remains unknown.
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10 ➤ To our knowledge, this is the first cost-effectiveness analysis comparing FLOT
11 with ECF/ECX for patients with resectable gastric or gastroesophageal junction
12 adenocarcinoma.
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15 ➤ The use of data in clinical trials may not represent the data in real clinical practice,
16 because clinical trials have certain time constraints. For example, we used
17 Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the
18 trial.
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24 **SUBHEADLING: Economic evaluation of FLOT chemotherapy in patients with**
25 **resectable gastric or gastroesophageal junction adenocarcinoma**
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30 **INTRUODOCTION**
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32 According to the latest global cancer burden data in 2020 released by the
33 international agency for research on cancer (IARC) of the World Health Organization,
34 China ranked first in the cancer-related deaths with approximately 480,000 cases
35 recorded. Gastric cancer is the third most prevalent malignant tumor in the world and
36 the third leading cause of cancer-related death in China^[1].
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42 Although significant progress has been made in early detection, the prognosis of
43 patients with resectable gastric and gastroesophageal junction adenocarcinoma is still
44 poor^[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant
45 chemoradiotherapy were demonstrated they have significantly improved overall
46 survival (OS) in patients with this cancer as compared with a simple surgery^[3-6].
47 Based on this, perioperative chemotherapy is recommended as the preferred treatment
48 for locally resectable diseases^[3,7-9]. Postoperative chemoradiotherapy is the preferred
49 treatment for patients with less surgical scope than D2 lymph node dissection^[6,10,11].
50 Other treatment strategies, such as postoperative chemotherapy, are suitable for
51 patients who have experienced primary lymph node dissection^[12-14]. In Asian
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4 countries, accumulating research evidence has shown that adjuvant chemotherapy
5 after a D2 surgery significantly improves the tumor remission rate and R0 resection
6 rate compared with D2 gastrectomy alone, and is associated with a
7 favorable safety profile^[15,16].
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11 The Medical Research Council adjuvant gastric infusion chemotherapy (MAGIC)
12 trial was the first and largest clinical trial that confirmed the survival benefits of
13 perioperative chemotherapy^[3]. In this trial, 503 patients with locally advanced
14 resectable gastric and gastroesophageal junction adenocarcinoma were enrolled and
15 were assigned to either the three cycles of epirubicin, cisplatin and fluorouracil (ECF)
16 chemotherapy or the surgery alone. The survival rate in the chemotherapy group was
17 significantly higher compared to the simple surgery group (5-year survival, 36% vs
18 23%). The FNCLCC/FFCD II/III trial also found that perioperative chemotherapy for
19 gastric cancer provided greater survival benefits than the surgery alone^[3]. According
20 to the trial evidence, the National Comprehensive Cancer Network Clinical (NCCN)
21 Guidelines recommended perioperative chemotherapy as a routine regimen for
22 advanced gastric cancer (class I evidence) in 2010, and a standard model of adjuvant
23 chemotherapy for gastroesophageal adenocarcinoma^[17]. Subsequently, the Chinese
24 Society of Clinical Oncology (CSCO) Guidelines^[18] recommended several
25 chemotherapy regimens as preferred schemes. This includes cisplatin combined with
26 fluorouracil (PF)^[4], improved ECF scheme^[19], oxaliplatin combined with capecitabine
27 (XELOX)^[20], oxaliplatin combined with fluorouracil (FLOFOX)^[21], and oxaliplatin
28 combined with S-1 (SOX)^[22]. Although the great progression had been made
29 on chemotherapies, the clinical prognosis of patients with advanced gastric or
30 gastroesophageal junction cancer is still unsatisfactory, especially those with
31 advanced cancers. In view of this, there is a pressing need for any novel
32 chemotherapy regimen with a greater effectiveness than the existing ones.
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54 In the phase II/III clinical trials of FLOT4, the researchers compared the
55 perioperative chemotherapy FLOT (docetaxel, oxaliplatin, leucovorin, fluorouracil)
56 with the standard chemotherapy ECF/ECX (epirubicin, cisplatin, fluorouracil or
57 capecitabine)^[23,24]. Fluoropyrimidine and platinum combined with or without
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4 anthracycline are the most used chemotherapeutic regimen. In a large prospective
5 phase II/III randomized controlled trial of FLOT4, docetaxel was added to triple-drug
6 regimen (FLOT regimen) and showed to improved survivals among patients with
7 resectable gastric or gastroesophageal junction cancer with clinical stage CT2 or
8 higher and lymph node positive (CN+) as compared with ECF/ECX regimen (50
9 months vs 35 months; HR = 0.77; 95% confidence interval, 0.63-0.94). In this phase
10 II/III trial, the proportion of patients with complete regression of pathology was
11 significantly higher in the FLOT group than that in the ECF/ECX group. In addition,
12 compared with the ECF/ECX group, patients in the FLOT group had a lower
13 incidence of grade 3-4 adverse events (AEs), including neutropenia, leucopenia,
14 nausea, infection, fatigue and vomiting (25% vs 40%), but had the same incidence of
15 serious chemotherapy-related AEs (27% in both groups).
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27 Based on the clinical trial evidence, FLOT chemotherapy is recommended for
28 patients with resectable gastric or gastroesophageal junction adenocarcinoma (Class
29 IIA) by the Chinese society of clinical oncology (CSCO) Guidelines for gastric cancer
30 (2018 Edition). However, its financial impact has not been studied yet from the
31 perspective of Chinese healthcare system. Considering the high incidence and
32 prevalence of gastric or gastroesophageal junction cancer, and limited health
33 resources in China, the therapeutical benefits of FLOT chemotherapy must be
34 weighed against the economic burden that it has imposed. This study aimed to
35 evaluate whether the perioperative chemotherapy FLOT is cost-effective compared
36 with ECF/ECX among patients with gastric and gastroesophageal junction
37 adenocarcinoma from the perspective of Chinese medical system, based on the
38 clinical result of the FLOT4 trial.
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51 52 **METHODS**

53 54 55 **Patients and regimens**

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58 The patient population analyzed in this study mirrored the patient enrolled in the
59 FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and
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4 ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction
5 adenocarcinoma. In this study, a total of 716 patients were randomly assigned to
6 receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group
7 received three 3-week cycles preoperative chemotherapy and three 3-week cycles
8 postoperative chemotherapy. Each 3-week cycle included epirubicin 50mg/m² on day
9 1, cisplatin 60mg/m² on day 1, and continuous intravenous infusion of fluorouracil
10 200mg/m² or oral capecitabine 1250mg/m² on days 1 to 21 at the discretion of
11 investigators. Patients in the FLOT group received four 2-week cycles preoperative
12 chemotherapy and four 2-week cycles postoperative chemotherapy, each of which
13 included docetaxel 50mg/m² on day 1, oxaliplatin 85mg/m² on day 1, calcium folinate
14 200mg/m² on day 1 and 5-FU 2600mg/m² as 24-h infusion on day 1.

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

32 33 34 35 36 37 38 39 **Patient and public involvement**

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

43 44 45 46 47 **Analytic Model**

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49 Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro
50 2018 software to estimate the clinical and outcomes of two perioperative
51 chemotherapy regimens (FLOT and ECF/ECX) for patients with gastric and
52 gastroesophageal junction adenocarcinoma in China(Figure 1).

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60 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

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4 model, the whole cohort was in PFS state, and the transitions between health states in
5 the model may occur during each Markov cycle. From the perspective of Chinese
6 medical system, we used a lifetime horizon and a half-cycle correction to estimate the
7 total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio
8 (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the
9 annual discount rate for costs and health outcomes was set at 5% [26]. All costs used in
10 the model were adjusted based on the consumer price index provided by the the
11 People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar =
12 6.88 Chinese Yuan)^[27]. According to the recommendation of World Health
13 Organization (WHO), we used 3 times per capita GDP as the WTP threshold^[28].
14 Given that China's per capita GDP was \$10,504 in 2020, the WTP threshold used in
15 the model was \$31,513^[29].
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18 PFS and OS data were obtained from the Kaplan Meier survival curve in the trial.
19 First, we used GetDataGraph Digitizer software version 2.24 to extract datapoints
20 from published PFS and OS curves in the publications
21 (<http://getdata-graph-digitizer.com>). These extracted point data were used to fit
22 different parametric survival models (including Exponential, Weibull, Lognormal and
23 Log-logistic). According to the result of statistical goodness-of-fit test using Akaike
24 information standard (AIC) and Bayesian information criterion (BIC), the
25 Log-logistic distribution was selected to fit these data points. The two parameters of
26 Log-logistic distribution, scale parameters (θ) and shape parameters (κ) are shown
27 in Table 1. Then, we used the parameters to calculate survival rate, which is
28 $S(t) = \{1 + e^{\theta t^{\kappa}}\}^{-1}$, where t is time. Figure 2 shows the fitted Log-logistic survival
29 curves for the FLOT and ECF/ECX regimens.
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53 **TABLE1 Input parameters for the model**

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Parameters	Values
Log-Logistic survival model of PFS	
ECF/ECX	$\theta=0.05168663$ $\kappa=1.004703$
FLOT	$\theta=0.03274242$ $\kappa=0.9957772$
Log-Logistic survival model of OS	
ECF/ECX	$\theta=0.02849954$ $\kappa=1.369613$
FLOT	$\theta=0.022184$ $\kappa=1.279334$
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

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4 healthcare expenditure costs in the model, including drug and administration costs,
5 AE management costs, follow-up examination costs, second-line treatment costs,
6 supportive treatment costs and surgery treatment costs. Data of drug and
7 administration costs, follow-up examination costs and drug price were extracted from
8 the local health system [35]. To calculate the dosage of chemotherapeutic drug, we
9 assumed that a baseline patient has a weight of 65kg and a body surface area of 1.72
10 square meters[36].
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17 Based on the data reported in the FLOT4 trial, after disease progressed, 25% of
18 the patients in both groups who would receive second-line treatment and the
19 second-line chemotherapy regimen was selected from the FLOT4 trial[37]. When
20 patient experienced a further progression, they would receive supportive treatments
21 until death[38]. The second-line chemotherapy regimen included intravenous injection
22 of irinotecan 180mg/m² on days 1, calcium folinate 400 mg/m² on days 1, fluorouracil
23 400mg/m² on day 1, continuous intravenous injection of fluorouracil 1200mg/m² for
24 more than 24 hours on day 1 and 2, and circulation every 14 days[25,39,40]. Data of the
25 costs for drug administration, supportive and surgery treatments were extracted from
26 published literature[41-43]. The follow-up examination included CT or MRI every three
27 months until disease progression, recurrence or death. The price of CT or MRI came
28 from the local health system[35]. According to expert suggestions and clinical practice,
29 we correlated the grade 3-4 adverse events with a significant difference (P>0.05)
30 between the two groups with the total cost. Therefore, according to the data provided
31 by FLOT4 trial, the following AEs were included in the model: vomiting, nausea,
32 neutropenia, anaemia, infections, diarrhoea. The costs of AE management were
33 estimated by multiplying the management cost per event by the incidence of each AE.
34 The incidence of AE was obtained from the FLOT4 trial and the unit cost was based
35 on the published literature[32,41,44]. Table 2 lists all direct costs in the experiment.
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55 **Table 2. Baseline costs, risks, and utility values with ECF/ECX and FLOT perioperative**
56 **chemotherapy in patients with resectable gastric or gastroesophageal junction**
57 **adenocarcinoma in China.**
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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 \pm 50%.				
^b The range was assumed to be varied \pm 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 (\pm 20% or \pm 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

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4 increased with the increasing WTP thresholds. When the WTP threshold was greater
5 than \$699.2/QALY, the probability of the FLOT chemotherapy being cost-effective
6 was nearly 50% for patients with resectable gastric or gastroesophageal junction
7 cancer. When the threshold exceeded \$17,090/QALY, the cost-effectiveness
8 possibility of the FLOT chemotherapy reached 99%.
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13 14 15 **Discussion**

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19 In the past decade, ECF and ECX were recommended as a class I regimen for
20 patients with resectable gastric or gastroesophageal junction adenocarcinoma. After
21 2018, the FLOT chemotherapy regimen was included into the CSCO guidelines in
22 China and the National Comprehensive Cancer Network (NCCN) in the United
23 States^[17,18]. According to the NCCN guidelines, combined therapy
24 (surgery+chemotherapy) has been proved to significantly improve the survival rate of
25 gastric cancer patients with local regional diseases and perioperative chemotherapy is
26 recommended as preferred approach for the treating locally resectable diseases. The
27 CSCO in China pointed out that the standard treatment for resectable advanced gastric
28 cancer was D2 surgical resection combined with postoperative adjuvant
29 chemotherapy. For patients with late stage (clinical stage III or above), the
30 perioperative chemotherapy mode was selected. Moreover, this standard treatment has
31 been fully recognized and recommended by East Asian countries. Although this
32 treatment regimen has been proved to be effective in improving the overall survival of
33 patients with advanced gastric cancer after resection, the survival states of patients
34 with late stage (stage III B and III C) are still suboptimal. Therefore, a large number
35 of clinical studies have been carried out in order to figure out how to further optimize
36 the perioperative treatment of gastric cancer.
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56 With the continuing development of chemotherapeutic drugs for gastric cancer,
57 anthracycline drugs and platinum drugs have been introduced into the perioperative
58 treatment of resectable gastric cancer. Docetaxel and oxaliplatin have been introduced
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4 into FLOT chemotherapy scheme. In the PRODIGY study from Korea in East Asia,
5 468 cases of advanced gastric cancer were studied^[45]. The intervention group received
6 preoperative DOS regimen (docetaxel, oxaliplatin, S-1) chemotherapy for 3 cycles,
7 and the control group received postoperative S-1 orally for 1 year. In the JACCRO
8 G-07 study conducted in Japan, 915 cases of pathological stage III gastric cancer
9 undergoing D2 operation were enrolled^[46]. The intervention group was treated with
10 DS regimen (docetaxel combined with S-1) for 6 cycles, followed by S-1 single drug
11 until 1 year after operation, and the control group was treated with S-1 orally until 1
12 year after operation. The above two trials showed that the combining the docetaxel
13 with other chemotherapeutic drugs conferred a greater efficacy than the docetaxel
14 monotherapy. Not only docetaxel was added to the FLOT chemotherapy strategy, but
15 also oxaliplatin was used instead of cisplatin. Oxaliplatin has a lower toxicity to
16 gastrointestinal tract, liver, kidney and bone marrow than cisplatin and carboplatin
17 and is more well tolerated. It also showed a superiority over many other
18 chemotherapy regimens. The ARTIST-II study conducted in Korea compared 8
19 cycles of postoperative SOX regimen (oxaliplatin combined with S-1) with oral S-1
20 for 1 year. The survival data showed that combined chemotherapy was better than
21 single drug ^[47]. In the multi center phase III trial in Japan and South Korea, 711
22 patients with advanced gastric cancer were enrolled^[48]. The intervention group was
23 assigned to oxaliplatin plus folic acid and S-1, and the control group was assigned to
24 S-1 plus cisplatin. Oxaliplatin plus folic acid and S-1 showed a clinically significant
25 beneficial effect. Therefore, at present, FLOT scheme is considered to be one of the
26 preferred schemes of perioperative chemotherapy combined with surgery, including
27 three chemotherapeutic drugs, which is mainly suitable for patients with good
28 performance status. However, for patients with good to moderate performance status
29 and patients who cannot tolerate the combination regimen of these three drugs, the
30 two drug combination regimen can be considered to lower the risk of drug toxicity. In
31 China, the increasing incidence rate and mortality rate of gastric cancer have imposed
32 considerable physical, psychological and economic burdens on the society, patients
33 and their families, especially for the developing countries. Therefore, it is very crucial
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4 to study the economic significance of this chemotherapy strategy in the field of
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6 medicine and policy.
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10 In the FLOT4 trial, compared with the control group, the QALYs in the
11 intervention group was increased by 1.08QALY and the cost per patient was
12 increased by \$921.51, resulting in an ICER of \$850.68/QALY. Based on the current
13 threshold of WTP, the FLOT strategy is more cost-effective. The univariate
14 sensitivity analysis showed that the most influential parameter on the model results
15 was the hazard ratio of overall survival, which could improve the ICER of FLOT
16 strategy by reducing HR. This was followed by the hazard ratio of progression-free
17 survival, the proportion of patients with ECF/ECX who underwent surgery, and the
18 discount rate. The change of HR for overall survival made ICER fluctuate the most,
19 but the ICER was still less than \$10,504/QALY (\$6,330.47/QALY). Moreover, when
20 other number sensitive parameters changed within the specified range, ICER was also
21 lower than WTP. Therefore, we can conclude that the parameters in the intervention
22 have little impact on ICER results. However, there were significant differences in per
23 capita GDP among 32 provinces in mainland China. The maximum difference was
24 \$18,731 (in 2020, the highest was Beijing's per capita GDP of \$23,968, and the lowest
25 was Gansu's per capita GDP of \$5,238)^[49]. For all provinces, the per capita GDP was
26 \$10,504, and three times the per capita GDP was \$31,513. Therefore, the ICERs of
27 the FLOT strategy were much lower than that of China's per capita GDP in 2020 and
28 less than that of Gansu Province. This suggests that the FLOT perioperative
29 chemotherapy regimen is much more cost-effective than ECF/ECX in the treatment of
30 locally advanced resectable gastric or gastroesophageal junction adenocarcinoma in
31 China. To our best knowledge, this study is the first cost-effectiveness analysis of
32 FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction
33 adenocarcinoma.
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57 There are some limitations in the current study. Firstly, we used Log-logistic
58 distribution to extrapolate survival beyond the lifetime horizon of the trial. However,
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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 intervention. 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.

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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

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11 **Ethical Approval Statement:**

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

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25 **Patient consent for publication** Not required

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27 **Competing interests** None declared.

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capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393:1948-1957.

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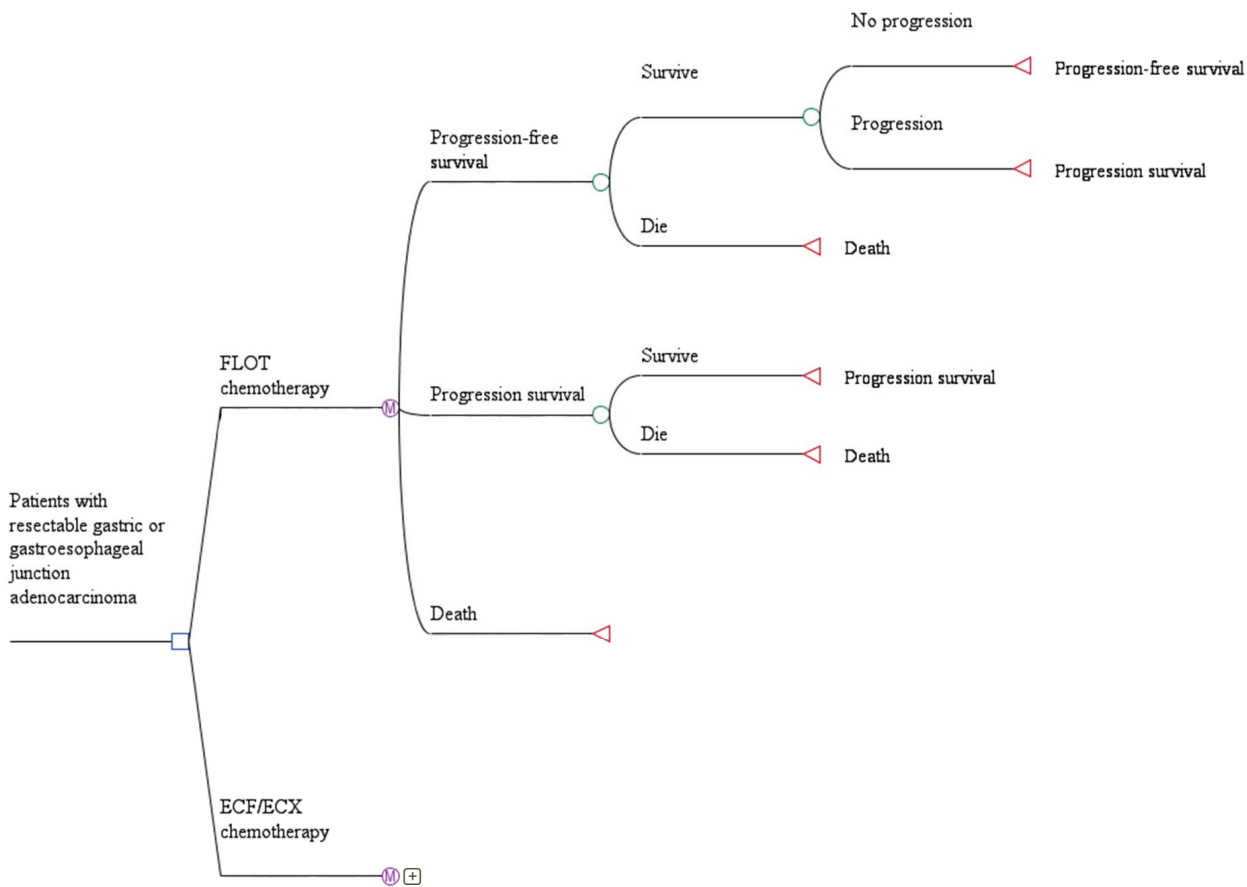
Figure 1. Markov model structure of FLOT and ECF/ECX strategies for the treatment of patients with locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma

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

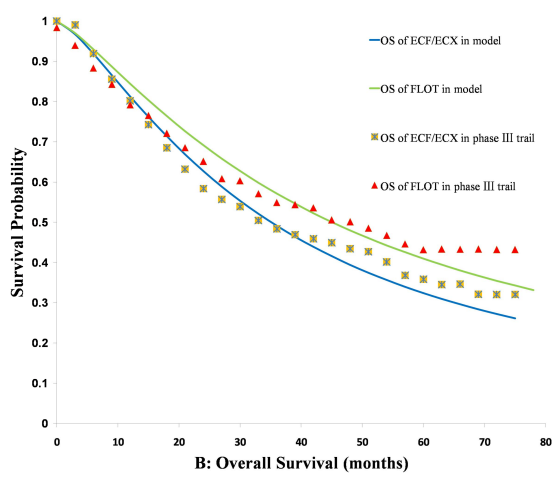
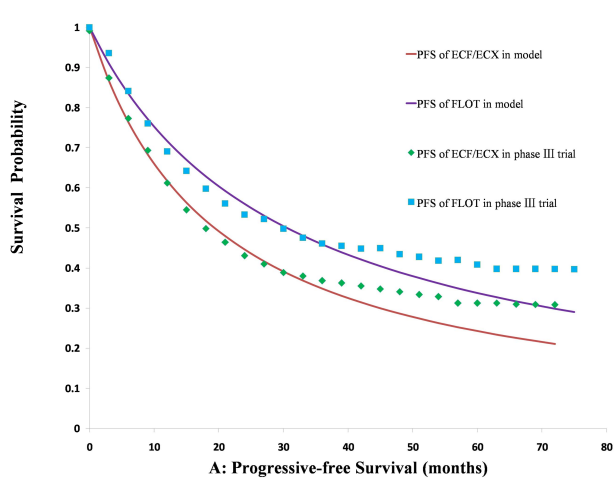
Figure 3. Tornado diagram for univariable sensitivity analyses. The grey dotted line represents the ICER of \$850.6842 per QALY from the base-case results. ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-year.

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).

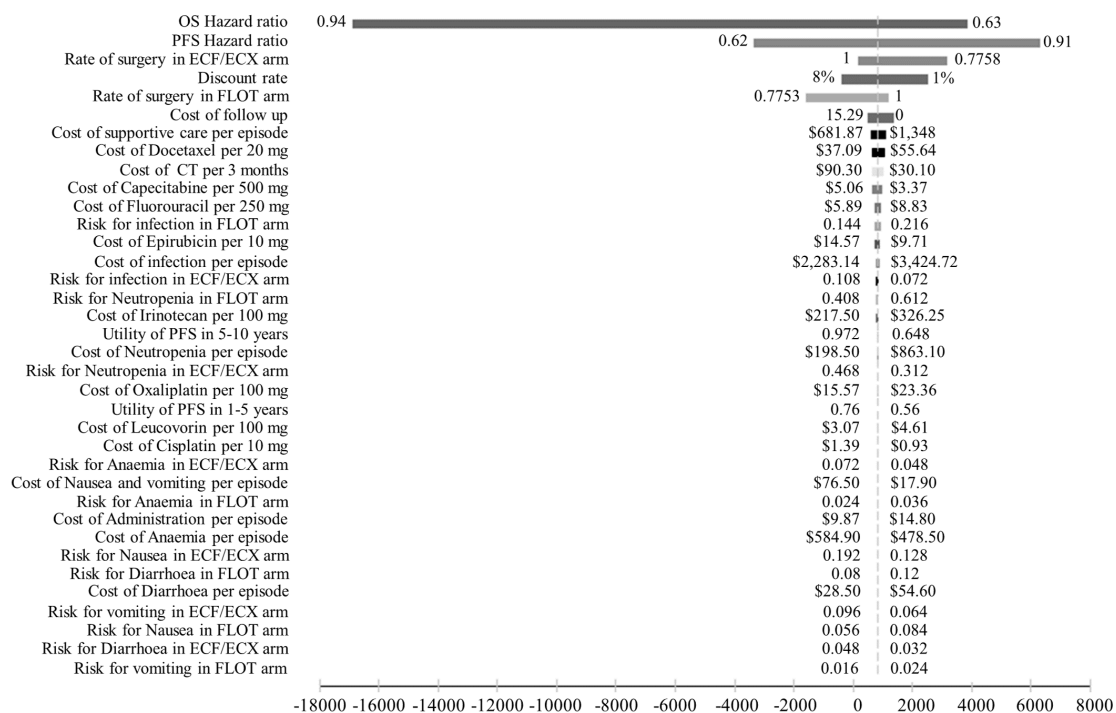


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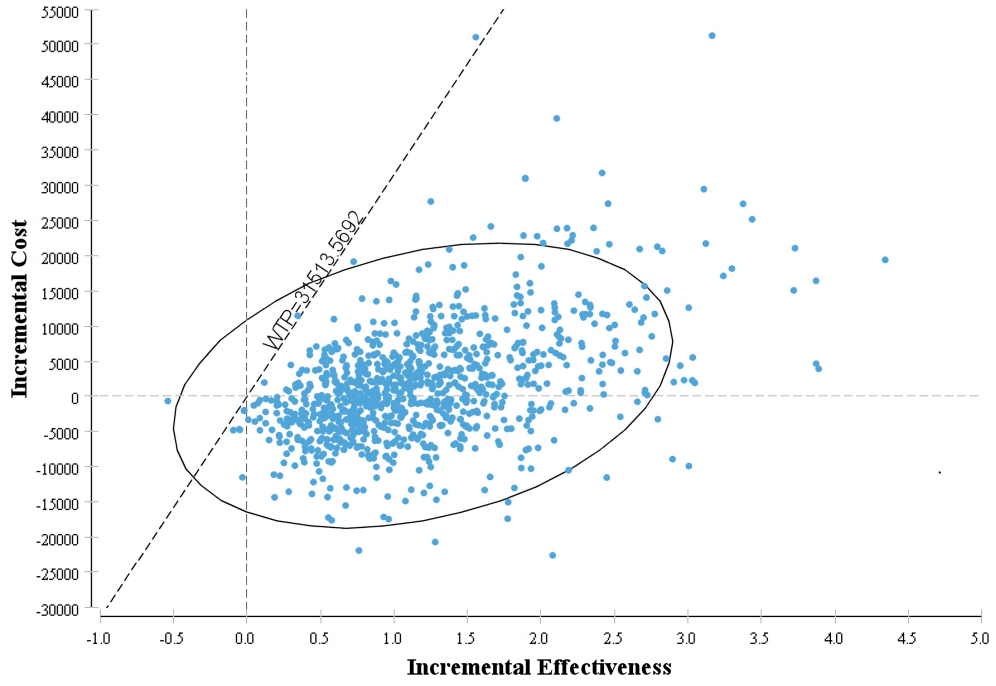
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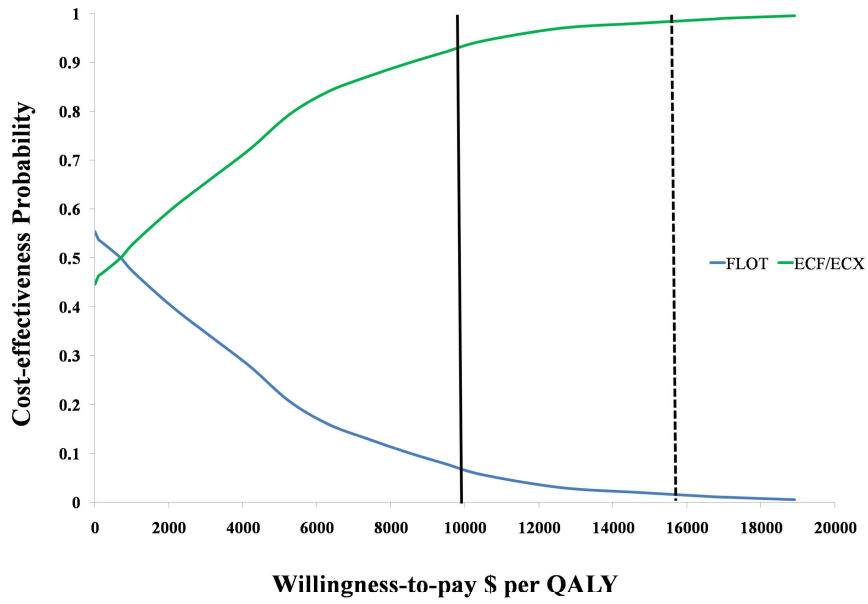
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Incremental Cost-Effectiveness, FLOT v. ECF/ECX



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Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

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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		

1	Target population and	#4	Describe characteristics of the base case population and subgroups	5
2	subgroups		analysed, including why they were chosen.	
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5	Setting and location	#5	State relevant aspects of the system(s) in which the decision(s)	5
6			need(s) to be made.	
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9	Study perspective	#6	Describe the perspective of the study and relate this to the costs	5
10			being evaluated.	
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12	Comparators	#7	Describe the interventions or strategies being compared and state	6
13			why they were chosen.	
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16	Time horizon	#8	State the time horizon(s) over which costs and consequences are	6
17			being evaluated and say why appropriate.	
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20	Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes	7
21			and say why appropriate	
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24	Choice of health	#10	Describe what outcomes were used as the measure(s) of benefit in	6
25	outcomes		the evaluation and their relevance for the type of analysis	
26			performed	
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29	Measurement of	#11a	Single study-based estimates: Describe fully the design features of	6-7
30	effectiveness		the single effectiveness study and why the single study was a	
31			sufficient source of clinical effectiveness data	
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34	Measurement of	#11b	Synthesis-based estimates: Describe fully the methods used for	n/a
35	effectiveness		identification of included studies and synthesis of clinical	
36			effectiveness data	
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40	Measurement and	#12	If applicable, describe the population and methods used to elicit	'n/a'
41	valuation of preference		preferences for outcomes.	
42	based outcomes			
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45	**Estimating resources			
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47	and costs **			
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50		#13a	Single study-based economic evaluation: Describe approaches	9
51			used to estimate resource use associated with the alternative	
52			interventions. Describe primary or secondary research methods for	
53			valuing each resource item in terms of its unit cost. Describe any	
54			adjustments made to approximate to opportunity costs	
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Methods

1	Estimating resources	#13b	Model-based economic evaluation: Describe approaches and data	9
2	and costs		sources used to estimate resource use associated with model health	
3			states. Describe primary or secondary research methods for valuing	
4			each resource item in terms of its unit cost. Describe any	
5			adjustments made to approximate to opportunity costs.	
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9	Currency, price date,	#14	Report the dates of the estimated resource quantities and unit costs.	9
10	and conversion		Describe methods for adjusting estimated unit costs to the year of	
11			reported costs if necessary. Describe methods for converting costs	
12			into a common currency base and the exchange rate.	
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16	Choice of model	#15	Describe and give reasons for the specific type of decision	6
17			analytical model used. Providing a figure to show model structure	
18			is strongly recommended.	
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21	Assumptions	#16	Describe all structural or other assumptions underpinning the	6
22			decision-analytical model.	
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25	Analytical methods	#17	Describe all analytical methods supporting the evaluation. This	6
26			could include methods for dealing with skewed, missing, or	
27			censored data; extrapolation methods; methods for pooling data;	
28			approaches to validate or make adjustments (such as half cycle	
29			corrections) to a model; and methods for handling population	
30			heterogeneity and uncertainty.	
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35	Results			
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37	Study parameters	#18	Report the values, ranges, references, and, if used, probability	10
38			distributions for all parameters. Report reasons or sources for	
39			distributions used to represent uncertainty where appropriate.	
40			Providing a table to show the input values is strongly	
41			recommended.	
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46	Incremental costs and	#19	For each intervention, report mean values for the main categories	12
47	outcomes		of estimated costs and outcomes of interest, as well as mean	
48			differences between the comparator groups. If applicable, report	
49			incremental cost-effectiveness ratios.	
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53	Characterising	#20a	Single study-based economic evaluation: Describe the effects of	12
54	uncertainty		sampling uncertainty for the estimated incremental cost and	
55			incremental effectiveness parameters, together with the impact of	
56			methodological assumptions (such as discount rate, study	
57			perspective).	
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1	Characterising	#20b	Model-based economic evaluation: Describe the effects on the	'n/a'
2	uncertainty		results of uncertainty for all input parameters, and uncertainty	
3			related to the structure of the model and assumptions.	
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6	Characterising	#21	If applicable, report differences in costs, outcomes, or cost	'n/a'
7	heterogeneity		effectiveness that can be explained by variations between	
8			subgroups of patients with different baseline characteristics or	
9			other observed variability in effects that are not reducible by more	
10			information.	
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14	Discussion			
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17	Study findings,	#22	Summarise key study findings and describe how they support the	13-16
18	limitations,		conclusions reached. Discuss limitations and the generalisability of	
19	generalisability, and		the findings and how the findings fit with current knowledge.	
20	current knowledge			
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23	Other			
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26	Source of funding	#23	Describe how the study was funded and the role of the funder in	17
27			the identification, design, conduct, and reporting of the analysis.	
28			Describe other non-monetary sources of support	
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31	Conflict of interest	#24	Describe any potential for conflict of interest of study contributors	17
32			in accordance with journal policy. In the absence of a journal	
33			policy, we recommend authors comply with International	
34			Committee of Medical Journal Editors recommendations	
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BMJ Open

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

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4 **Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in**
5 **patients with resectable gastric or gastroesophageal junction adenocarcinoma**
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9 Hanqing Zeng¹, Chunjiang Wang¹, Li-Ying Song¹, Su-Jie Jia¹, Xiaohui Zeng², Qiao
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41
42 **ABSTRACT**

43
44 **Objective:** The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin plus
45 docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for
46 gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction
47 adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy in China
48 remains unclear. The analysis aimed to compare the cost-effectiveness of FLOT versus ECF/ECX
49 (epirubicin, cisplatin plus fluorouracil or capecitabine) in patients with locally advanced resectable
50 tumors.
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58 **Design:** We developed a Markov model to compare the healthcare and economic outcomes of
59 FLOT and ECF/ECX in patients with resectable gastric or gastroesophageal junction
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4 adenocarcinoma. Costs were estimated from the perspective of Chinese healthcare system.
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6 Clinical and utility inputs were derived from the FLOT4 phase II/III clinical trial and published
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8 literature. Sensitivity analyses were employed to assess the robustness of our result. The annual
9
10 discount rate for costs and health outcomes was set at 5%.

11 **Outcome measures:** The primary outcome of incremental cost-effectiveness ratios (ICERs) was
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13 calculated as the cost per quality-adjusted life years (QALYs).
14

15 **Results:** The base-case analysis found that compared with ECF/ECX, the use of FLOT
16
17 chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of
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19 \$851/QALY. One-way sensitivity analysis results suggested that the hazard ratio (HR) of overall
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21 survival (OS) and progression-free survival (PFS) had the greatest impact on the ICER.
22
23 Probabilistic sensitivity analysis demonstrated that FLOT was more likely to be cost-effective
24
25 compared with ECF/ECX at a willingness-to-pay (WTP) threshold of \$31,513/QALY.
26

27 **Conclusions:** For patients with locally advanced resectable tumors, the FLOT chemotherapy is a
28
29 cost-effective treatment option compared with ECF/ECX in China.
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31 **Trial registration number:** NCT01216644.
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34 **Keywords:** Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy,
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36 FLOT, ECF/ECX, Cost-effectiveness.
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39 **Strengths and limitations of this study**

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- 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

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

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

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15 **INTRUDOCTION**

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

22
23 Although significant progress has been made in early detection, the prognosis of
24 patients with resectable gastric and gastroesophageal junction adenocarcinoma is still
25 poor^[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant
26 chemoradiotherapy had demonstrated their superior survival benefit in patients with
27 this disease when compared with a simple surgery^[3-6]. Based on this, perioperative
28 chemotherapy is recommended as the preferred treatment for locally resectable
29 diseases^[3,7-9]. For patients whose surgical scope is less than D2 lymph node dissection,
30 postoperative chemoradiotherapy is the preferred treatment ^[6,10,11]. Other treatment
31 strategies, such as postoperative chemotherapy, are applicable patients who have
32 udergone primary lymph node dissection^[12-14]. In Asian countries, accumulating
33 clinical evidence has shown that, compared with D2 gastrectomy alone , adjuvant
34 chemotherapy after a D2 surgery significantly improves the tumor remission rate and
35 R0 resection rate is associated with a favorable safety profile^[15,16].

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52 The Medical Research Council adjuvant gastric infusion chemotherapy (MAGIC)
53 trial was the first clinical trial to confirm the survival benefits of perioperative
54 chemotherapy^[3]. In this trial, 503 patients with locally advanced resectable gastric and
55 gastroesophageal junction adenocarcinoma were enrolled and were randomly assigned
56 to receive three cycles of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy or
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4 surgery alone. The survival rate in the chemotherapy group was significantly higher
5 than the simple surgery group (5-year survival rate, 36% vs 23%). The
6 FNCLCC/FFCD II/III trial also found that perioperative chemotherapy for gastric
7 cancer provided greater survival benefits than the surgery alone^[3]. According to the
8 trial evidence, the National Comprehensive Cancer Network Clinical (NCCN)
9 Guidelines recommended perioperative chemotherapy as a routine regimen for
10 advanced gastric cancer (class I evidence) in 2022, and a standard adjuvant
11 chemotherapy for gastroesophageal adenocarcinoma^[17]. Subsequently, the Chinese
12 Society of Clinical Oncology (CSCO) Guidelines^[18] recommended several
13 chemotherapy regimens as preferred schemes, including cisplatin combined with
14 fluorouracil (PF)^[4], improved ECF scheme^[19], oxaliplatin combined with capecitabine
15 (XELOX)^[20], oxaliplatin combined with fluorouracil (FOLFOX)^[21], and oxaliplatin
16 combined with S-1 (SOX)^[22]. Although the great progress had been made
17 on chemotherapies, the clinical prognosis of patients with advanced gastric or
18 gastroesophageal junction cancer is still unsatisfactory, especially those with
19 advanced cancers. In view of this, there is a pressing need for any novel
20 chemotherapy regimen with a greater effectiveness than the existing ones.

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37 In the phase II/III clinical trials of FLOT4, the researchers compared the
38 perioperative chemotherapy FLOT (fluorouracil, leucovorin, oxaliplatin plus
39 docetaxel) with the standard chemotherapy ECF/ECX (epirubicin, cisplatin,
40 fluorouracil or capecitabine)^[23,24]. Fluoropyrimidine and platinum combined with or
41 without anthracycline are the most used chemotherapeutic regimen. In the FLOT4
42 trial, adding docetaxel to triple-drug regimen (FLOT regimen) was associated with
43 improved survivals among patients with resectable gastric or gastroesophageal
44 junction cancer with clinical stage CT2 or higher and lymph node positive (CN+)
45 when compared with ECF/ECX regimen (50 months vs 35 months; HR = 0.77; 95%
46 confidence interval, 0.63-0.94). In this phase II/III trial, the proportion of patients
47 with complete regression of pathology was significantly higher in the FLOT group
48 than that in the ECF/ECX group. In addition, compared with the ECF/ECX group,
49 patients in the FLOT group had a lower incidence of grade 3-4 adverse events (AEs),
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4 including neutropenia, leucopenia, nausea, infection, fatigue and vomiting (25% vs
5 40%), but had the same incidence of serious chemotherapy-related AEs (27% in both
6 groups).
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10 In response to the positive results from FLOT4 trial, FLOT chemotherapy is
11 recommended for patients with resectable gastric or gastroesophageal junction
12 adenocarcinoma (Class IIA) by the Chinese society of clinical oncology (CSCO)
13 Guidelines for gastric cancer (2018 Edition). However, its financial impact has not
14 been studied yet from the perspective of Chinese healthcare system. Considering the
15 high prevalence of gastric or gastroesophageal junction cancer, and limited health
16 resources in China, the therapeutical benefits of FLOT chemotherapy must be
17 weighed against the economic burden that it has imposed. This study aimed to
18 evaluate whether the perioperative chemotherapy FLOT is cost-effective compared
19 with ECF/ECX among patients with gastric and gastroesophageal junction
20 adenocarcinoma from the perspective of Chinese medical system.
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32 33 **METHODS**

34 35 36 37 **Patients and regimens**

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39 The patient population analyzed in this study mirrored the patient enrolled in the
40 FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and
41 ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction
42 adenocarcinoma. In this study, a total of 716 patients were randomly assigned to
43 receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group
44 received three 3-week cycles preoperative chemotherapy and three 3-week cycles
45 postoperative chemotherapy. The chemotherapy regimen for each 3-week cycle was
46 epirubicin 50mg/m² on the first day, cisplatin 60mg/m² on the first day, and
47 continuous intravenous infusion of fluorouracil 200mg/m² or oral capecitabine
48 1250mg/m² from the first to the 21st days at the discretion of investigators. Patients in
49 the FLOT group received four 2-week cycles preoperative chemotherapy and four
50 2-week cycles postoperative chemotherapy, which were docetaxel 50mg/m² on the
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4 first day, oxaliplatin 85mg/m² on the first day, calcium folinate 200mg/m² on the first
5 day and 5-FU 2600mg/m² as 24-h infusion the first day.
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8 The operation was scheduled 4 weeks after the last preoperative chemotherapy.
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10 The interval between the two groups was 4 weeks (28 days). As per this clinical trial,
11 patients may discontinue treatment due to unacceptable toxicity, disease progression,
12 death, or patient requirements. When patients experienced disease progression, they
13 would receive second-line treatment, including irinotecan, calcium folinate and
14 fluorouracil^[25].
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21 **Patient and public involvement**

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23 There was patient representation in the FLOT4 trial. However, this cost-effectiveness
24 analysis does not involve human participants.
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28 **Analytic Model**

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30 Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro
31 2018 software to estimate the clinical outcomes of two perioperative chemotherapy
32 regimens (FLOT and ECF/ECX) for patients with gastric and gastroesophageal
33 junction adenocarcinoma in China(Figure 1).
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38 The model comprised three mutually exclusive health states: progression-free
39 survival (PFS), progressed survival (PS) and death. The Markov cycle length was set
40 as 2-week to fit the treatment schedule of the two groups. At the beginning of the
41 model, the whole cohort was in PFS state, and the transitions between health states in
42 the model may occur during each Markov cycle. From the perspective of Chinese
43 medical system, we used a lifetime horizon and a half-cycle correction to estimate the
44 total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio
45 (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the
46 annual discount rate for both costs and health outcomes was set at 5% ^[26]. All costs
47 used in the model were adjusted based on the consumer price index provided by the
48 the People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar =
49 6.88 Chinese Yuan)^[27]. According to the recommendation of World Health
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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 $S(t) = \{1 + e^{\theta t^{\kappa}}\}^{-1}$, where t is time. Figure 2 shows the Log-logistic parameters estimated for the FLOT and ECF/ECX regimens.

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

Table 1.
Log-logistic
parameters

Utility

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

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4 FLOT4 trial, the utility related to gastric cancer was taken from the literatures^[20,29].
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6 Gockel et al used the Gastrointestinal Life Quality Index (GLQI) to evaluate the
7
8 quality of life of 338 patients with gastrectomy, and then estimated the utility of
9
10 patients with PFS health state as 0.81^[30]. In addition, Sakamaki et al used the Time
11
12 Trade-Off (TTO) to evaluate the utility of hospitalized patients with gastric cancer^[29].
13
14 In their study, the utilities of patients receiving intravenous chemotherapy and
15
16 advanced care were 0.68 and 0.50, respectively. In the current model, we assumed
17
18 that the utilities of the three health states were identical in both groups. Therefore,
19
20 0.68 (1-5 years) and 0.81 (5-10 years) were used as the utilities of patients with PFS
21
22 health state in both groups. In addition, the utility of patients in PS health state was set
23
24 to 0.5 and the utility of patients who survived for more than 10 years was set to 1.0^[31].
25
26 The disutility of adverse events (AEs) was calculated by multiplying the utility
27
28 decrement due to AEs by the incidence of AEs^[32,33]. We assumed that all AEs
29
30 occurred in the first cycle.
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33 Cost

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35 From the perspective of Chinese medical system, we considered the direct
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37 healthcare expenditure costs in the model, including drug and administration costs,
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39 AE management costs, follow-up examination costs, second-line treatment costs,
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41 supportive treatment costs and surgery treatment costs. Drug and administration costs,
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43 follow-up examination costs and drug price were extracted from the local health
44
45 system^[34]. To calculate the dosage of chemotherapeutic drug, we assumed that a
46
47 baseline patient's weight was 65kg and body surface area was 1.72 square meters^[35].
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50 After disease progressed, 25% of the patients in both groups who would receive
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52 second-line treatment and the second-line chemotherapy regimen was selected from
53
54 the FLOT4 trial^[36]. When patient experienced further disease progression, they would
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56 receive supportive treatments until death^[37]. The second-line chemotherapy regimen
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58 included intravenous injection of irinotecan 180mg/m² on days 1, calcium folinate
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60 400 mg/m² on days 1, fluorouracil 400mg/m² on day 1, continuous intravenous
injection of fluorouracil 1200mg/m² 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 $\pm 50\%$.				

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 ($\pm 20\%$ or $\pm 50\%$ 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-line chemotherapy^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 $\pm 20\%$

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 supportive 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 & supportive 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

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4 C) are still suboptimal. Therefore, further clinical studies are needed to find more
5 effective perioperative treatment for gastric cancer.
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8 In recent years, the use of anthracycline and platinum drugs has sprouted in the
9 field of perioperative treatment of resectable gastric cancer. Two published phase III
10 studies have demonstrated the clinical efficacy of docetaxel in the treatment of
11 advanced gastric cancer, involving DOS (docetaxel, oxaliplatin, S-1) and DS
12 (docetaxel combined with S-1) [44,45]. Moreover, oxaliplatin has showed favorable
13 safety in the treatment gastrointestinal tract, liver, kidney, and bone marrow than
14 cisplatin and carboplatin. Therefore, oxaliplatin has gradually replaced cisplatin in the
15 current commonly used chemotherapy regimens. In the ARTIST- II trail, the SOX
16 regimen (oxaliplatin combined with S-1) showed superiority over single drug (S-1) in
17 prolonging patient's survival^[46]. Two pivotal phase III trial from Japan and South
18 Korea also found that oxaliplatin combined with folic acid and S-1 was associated
19 with a clinically significant improvement among patients with advanced gastric
20 cancer, when compared with S-1 plus cisplatin^[47]. Based on these positive results,
21 docetaxel and oxaliplatin have been introduced into FLOT chemotherapy regimen. At
22 present, FLOT regimen is considered as a preferred strategy for perioperative
23 chemotherapy combined with surgery, including three chemotherapeutic drugs that
24 suitable for patients with good performance status. Notably, for patients with good to
25 moderate performance status and patients who is not able to tolerate the combination
26 regimen of these three drugs, the two drug combination regimen is recommended.
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30 In China, the climbing incidence and mortality of gastric cancer have imposed
31 considerable physical, psychological and economic burdens on the society, patients
32 and their families. Therefore, it is very crucial to study the economic significance of
33 this chemotherapy strategy in the field of medicine and policy. In this economic
34 evaluation that compared with the ECF/ECX, the use of FLOT in patients with gastric
35 and gastroesophageal junction adenocarcinoma achieved additional 1.08QALY at an
36 incremental cost of \$921.51, resulting in an ICER of \$850.68/QALY. Based on the
37 WTP threshold set for this analysis, the FLOT strategy was considered to be
38 cost-effective. However, due to the extreme imbalance of economic development in
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4 Chinese Mainland, the per capita GDP of the 32 provincial-level administrative
5 regions varies greatly. The highest per capita GDP was reported in Beijing's per capita
6 GDP (\$23,968), and the lowest was reported in Gansu's (\$5,238)^[48]. For the whole
7 Chinese Mainland the per capita GDP was \$10,504, and three times the per capita
8 GDP was \$31,513. Because the ICERs of the FLOT strategy were much lower than
9 three times the per capita GDP in Gansu Province (\$15,714). This suggests that the
10 FLOT perioperative chemotherapy regimen is more cost-effective than ECF/ECX in
11 the treatment of locally advanced resectable gastric or gastroesophageal junction
12 adenocarcinoma in all provincial-level administrative regions in Chinese Mainland.
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21 The one-way sensitivity analysis showed that the most influential parameter on
22 the model results was the hazard ratio (HR) of overall survival. Specifically, when the
23 HR decreased from 0.94 to 0.63, the ICER of FLOT strategy versus ECF/ECX
24 strategy ranged from \$-16,856.98 per QALY to \$3,868.18 per QALY. The other
25 sensitive parameters included the hazard ratio of progression-free survival, the
26 proportion of patients with ECF/ECX who underwent surgery, and the discount rate.
27 The change of HR for overall survival made ICER fluctuate the most, but the ICER
28 was still less than WTP (\$10,504/QALY). Moreover, the ICER of FLOT strategy
29 versus ECF/ECX strategy was always much lower than WTP regardless of the large
30 fluctuation of model parameters. Consequently, we can conclude the uncertainty of
31 parameters will not affect the robustness of our results.
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42 It should be noted that, docetaxel prices played a more important role than the
43 prices of other drugs in our model. From the perspective of cancer patients, the use of
44 high-priced new drugs might impose a heavy financial burden on the both social and
45 patients, which likely leads to delay, abandonment, and discontinuation of
46 treatment^[49]. In recent years, the Chinese government has conducted a series of price
47 negotiation with many pharmaceutical enterprises with the aim of reducing the price
48 of oncology drugs. Fortunately, docetaxel passed the price negotiation and the
49 consistency evaluation of generic drugs successfully in March 2021^[50]. This means
50 that the market price of docetaxel will drop, which will make docetaxel less costly
51 and more widely used in China. Since the implementation of the national drug
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4 centralized procurement policy and the generic drug consistency evaluation, we can
5 expect that cancer patients may benefit from these policies in China. To our best
6 knowledge, this study is the first cost-effectiveness analysis of FLOT chemotherapy
7 in patients with resectable gastric or gastroesophageal junction adenocarcinoma.
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11 There are some limitations in the current study. Firstly, there is uncertainty
12 regarding the outcomes of patients with gastric and gastroesophageal junction
13 adenocarcinoma beyond the trial period, despite the use of validated extrapolation
14 techniques. Secondly, some potential bias lied in only direct medical costs were
15 incorporated in the model, however, our sensitive analysis found that our results were
16 almost unaffected by changes in costs. Thirdly, another limitation of the current
17 economic analysis was that other treatment strategies for advanced resectable gastric
18 cancer have not been fully explored. With the successful application of targeted
19 therapy and immunotherapy for advanced gastric cancer clinically, the pattern of
20 perioperative treatment of resectable gastric cancer have been refreshed. For example,
21 the research on treatment of HER-2 positive gastric cancer has attracted considerable
22 attentions in recent years. Meanwhile, combining the perioperative chemotherapy
23 with targeted treatment, was found to increase the pathological complete remission
24 rate and improve overall survival benefit, while the safety is acceptable^[51,52].
25 Therefore, we can expect that receiving higher cost targeted therapy can increase
26 more cost-effectiveness.
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21
22
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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

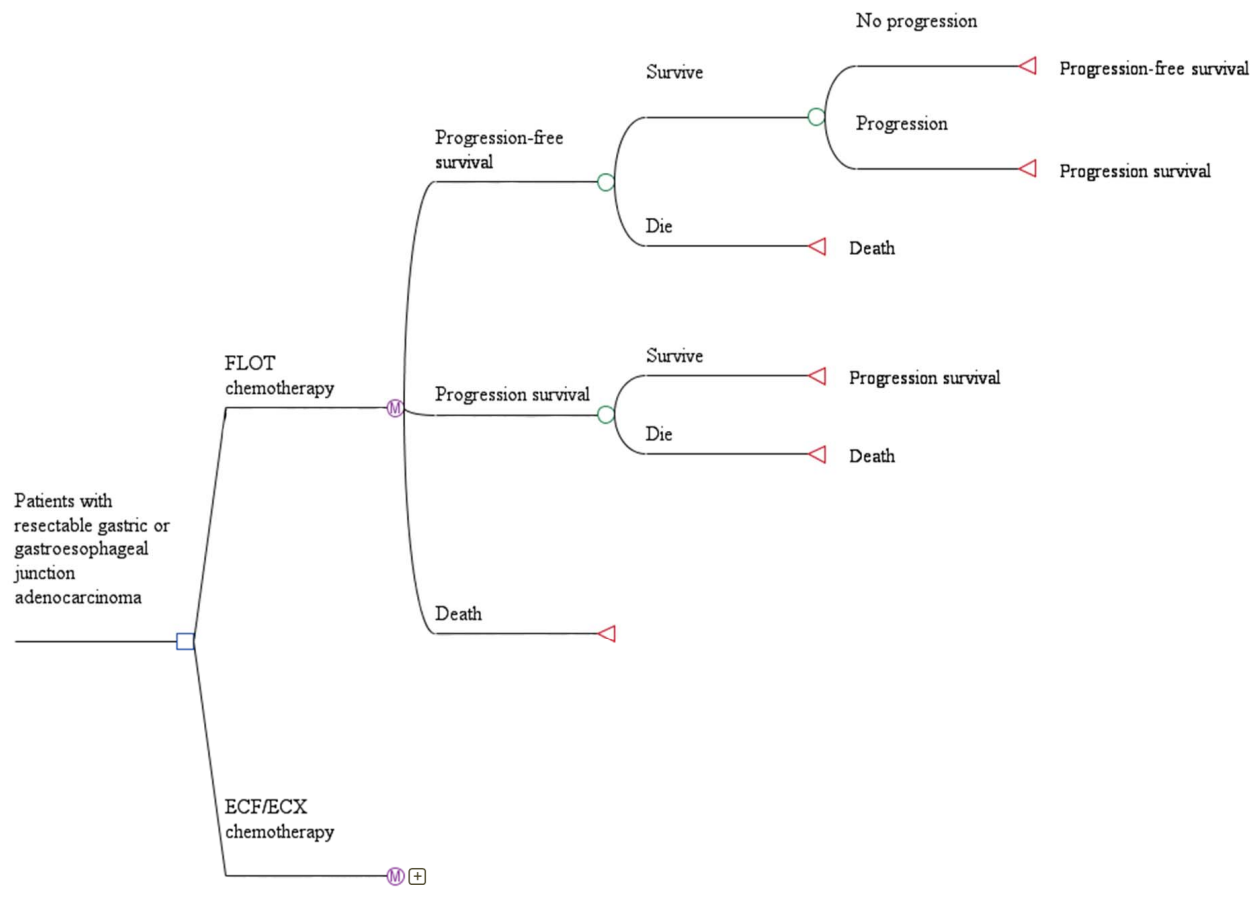
Figure 2. The Log-Logistic curves of (A) disease-free survival and (B) overall survival.

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-effectiveness ratio, QALY quality-adjusted life-year.

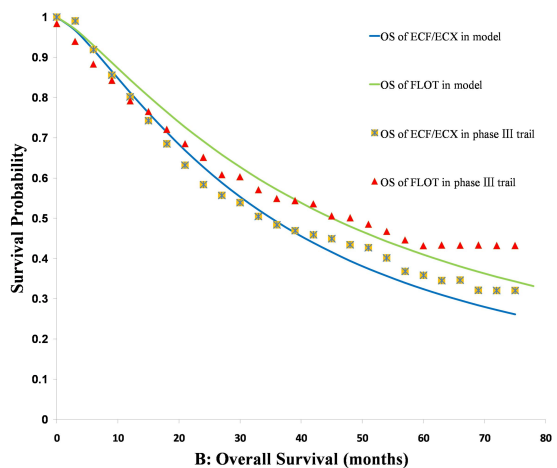
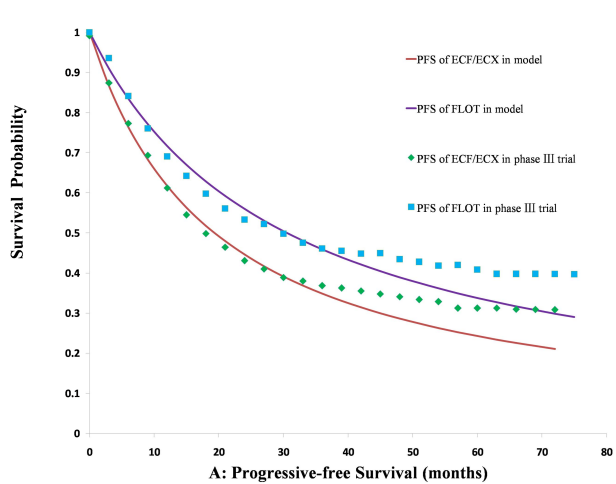
Figure 4. The results of Monte Carlo probabilistic sensitivity analysis for the strategies of FLOT VS ECF/ECX in scatter plots. The solid lines indicate the \$31,513 threshold. The estimates of 95% were surrounded in the ellipses.

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).

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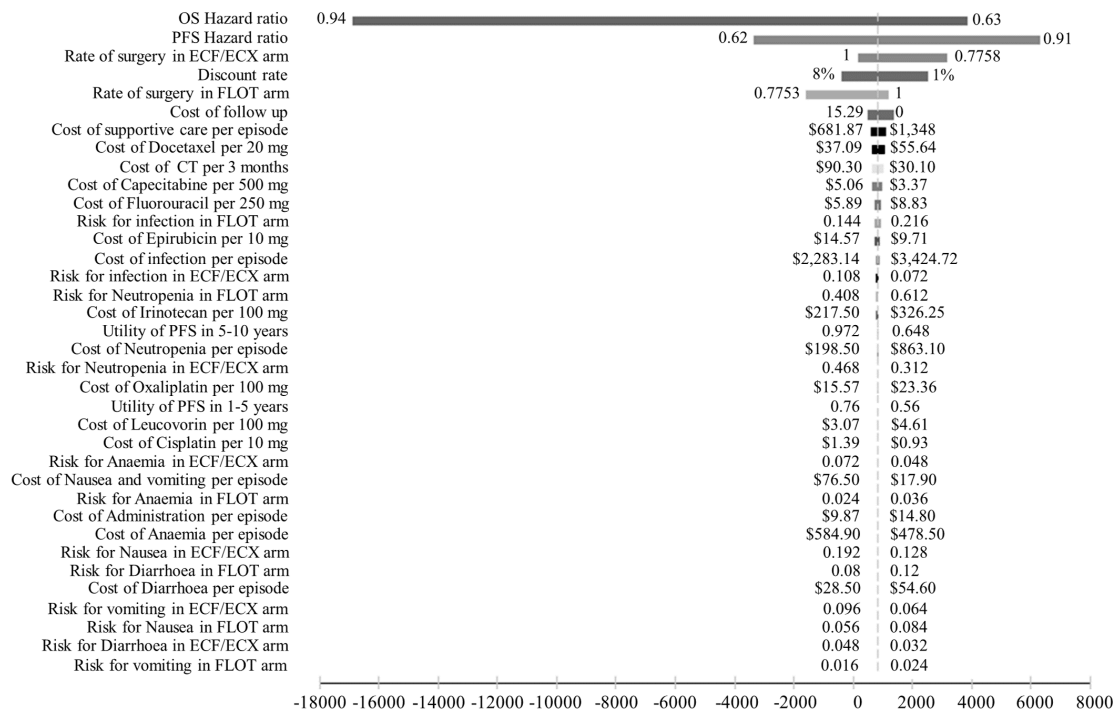


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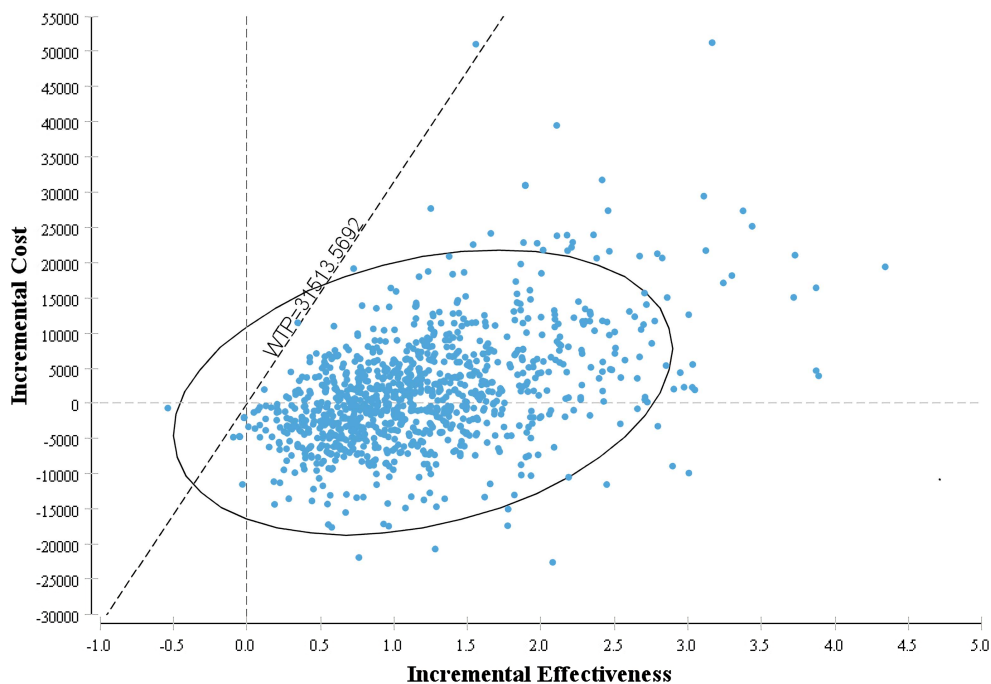
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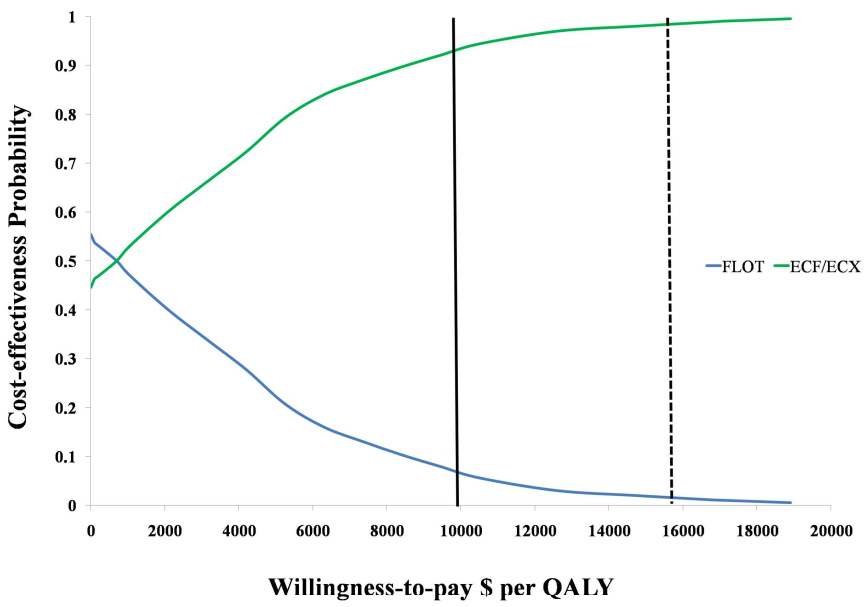
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Incremental Cost-Effectiveness, FLOT v. ECF/ECX



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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		

1	Target population and	#4	Describe characteristics of the base case population and subgroups	5
2	subgroups		analysed, including why they were chosen.	
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5	Setting and location	#5	State relevant aspects of the system(s) in which the decision(s)	5
6			need(s) to be made.	
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9	Study perspective	#6	Describe the perspective of the study and relate this to the costs	5
10			being evaluated.	
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12	Comparators	#7	Describe the interventions or strategies being compared and state	6
13			why they were chosen.	
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16	Time horizon	#8	State the time horizon(s) over which costs and consequences are	6
17			being evaluated and say why appropriate.	
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20	Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes	7
21			and say why appropriate	
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24	Choice of health	#10	Describe what outcomes were used as the measure(s) of benefit in	6
25	outcomes		the evaluation and their relevance for the type of analysis	
26			performed	
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29	Measurement of	#11a	Single study-based estimates: Describe fully the design features of	6-7
30	effectiveness		the single effectiveness study and why the single study was a	
31			sufficient source of clinical effectiveness data	
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34	Measurement of	#11b	Synthesis-based estimates: Describe fully the methods used for	n/a
35	effectiveness		identification of included studies and synthesis of clinical	
36			effectiveness data	
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40	Measurement and	#12	If applicable, describe the population and methods used to elicit	'n/a'
41	valuation of preference		preferences for outcomes.	
42	based outcomes			
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45	**Estimating resources			
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47	and costs **			
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50		#13a	Single study-based economic evaluation: Describe approaches	9
51			used to estimate resource use associated with the alternative	
52			interventions. Describe primary or secondary research methods for	
53			valuing each resource item in terms of its unit cost. Describe any	
54			adjustments made to approximate to opportunity costs	
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Methods

1	Estimating resources	#13b	Model-based economic evaluation: Describe approaches and data	9
2	and costs		sources used to estimate resource use associated with model health	
3			states. Describe primary or secondary research methods for valuing	
4			each resource item in terms of its unit cost. Describe any	
5			adjustments made to approximate to opportunity costs.	
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9	Currency, price date,	#14	Report the dates of the estimated resource quantities and unit costs.	9
10	and conversion		Describe methods for adjusting estimated unit costs to the year of	
11			reported costs if necessary. Describe methods for converting costs	
12			into a common currency base and the exchange rate.	
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16	Choice of model	#15	Describe and give reasons for the specific type of decision	6
17			analytical model used. Providing a figure to show model structure	
18			is strongly recommended.	
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21	Assumptions	#16	Describe all structural or other assumptions underpinning the	6
22			decision-analytical model.	
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25	Analytical methods	#17	Describe all analytical methods supporting the evaluation. This	6
26			could include methods for dealing with skewed, missing, or	
27			censored data; extrapolation methods; methods for pooling data;	
28			approaches to validate or make adjustments (such as half cycle	
29			corrections) to a model; and methods for handling population	
30			heterogeneity and uncertainty.	
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37	Study parameters	#18	Report the values, ranges, references, and, if used, probability	10
38			distributions for all parameters. Report reasons or sources for	
39			distributions used to represent uncertainty where appropriate.	
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46	Incremental costs and	#19	For each intervention, report mean values for the main categories	12
47	outcomes		of estimated costs and outcomes of interest, as well as mean	
48			differences between the comparator groups. If applicable, report	
49			incremental cost-effectiveness ratios.	
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53	Characterising	#20a	Single study-based economic evaluation: Describe the effects of	12
54	uncertainty		sampling uncertainty for the estimated incremental cost and	
55			incremental effectiveness parameters, together with the impact of	
56			methodological assumptions (such as discount rate, study	
57			perspective).	
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1	Characterising	#20b	Model-based economic evaluation: Describe the effects on the	'n/a'
2	uncertainty		results of uncertainty for all input parameters, and uncertainty	
3			related to the structure of the model and assumptions.	
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6	Characterising	#21	If applicable, report differences in costs, outcomes, or cost	'n/a'
7	heterogeneity		effectiveness that can be explained by variations between	
8			subgroups of patients with different baseline characteristics or	
9			other observed variability in effects that are not reducible by more	
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17	Study findings,	#22	Summarise key study findings and describe how they support the	13-16
18	limitations,		conclusions reached. Discuss limitations and the generalisability of	
19	generalisability, and		the findings and how the findings fit with current knowledge.	
20	current knowledge			
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26	Source of funding	#23	Describe how the study was funded and the role of the funder in	17
27			the identification, design, conduct, and reporting of the analysis.	
28			Describe other non-monetary sources of support	
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31	Conflict of interest	#24	Describe any potential for conflict of interest of study contributors	17
32			in accordance with journal policy. In the absence of a journal	
33			policy, we recommend authors comply with International	
34			Committee of Medical Journal Editors recommendations	
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BMJ Open

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

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4 **Economic evaluation of FLOT and ECF/ECX perioperative chemotherapy in**
5 **patients with resectable gastric or gastroesophageal junction adenocarcinoma**
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9 Hanqing Zeng¹, Chunjiang Wang¹, Li-Ying Song¹, Su-Jie Jia¹, Xiaohui Zeng²,
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40 Word count: 3483

41
42 **ABSTRACT**

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44 **Objective:** The perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin plus
45 docetaxel) was recommended by the Chinese society of clinical oncology (CSCO) Guidelines for
46 gastric cancer (2018 Edition) for patients with resectable gastric or gastroesophageal junction
47 adenocarcinoma (Class IIA). However, the economic impact of FLOT chemotherapy in China
48 remains unclear. The analysis aimed to compare the cost-effectiveness of FLOT versus ECF/ECX
49 (epirubicin, cisplatin plus fluorouracil or capecitabine) in patients with locally advanced resectable
50 tumors.
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58 **Design:** We developed a Markov model to compare the healthcare and economic outcomes of
59 FLOT and ECF/ECX in patients with resectable gastric or gastroesophageal junction
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4 adenocarcinoma. Costs were estimated from the perspective of Chinese healthcare system.
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6 Clinical and utility inputs were derived from the FLOT4 phase II/III clinical trial and published
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8 literature. Sensitivity analyses were employed to assess the robustness of our result. The annual
9
10 discount rate for costs and health outcomes was set at 5%.

11 **Outcome measures:** The primary outcome of incremental cost-effectiveness ratios (ICERs) was
12
13 calculated as the cost per quality-adjusted life years (QALYs).
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15 **Results:** The base-case analysis found that compared with ECF/ECX, the use of FLOT
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17 chemotherapy was associated with an additional 1.08 QALYs, resulting in an ICER of
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19 \$851/QALY. One-way sensitivity analysis results suggested that the hazard ratio (HR) of overall
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21 survival (OS) and progression-free survival (PFS) had the greatest impact on the ICER.
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23 Probabilistic sensitivity analysis demonstrated that FLOT was more likely to be cost-effective
24
25 compared with ECF/ECX at a willingness-to-pay (WTP) threshold of \$31,513/QALY.
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27 **Conclusions:** For patients with locally advanced resectable tumors, the FLOT chemotherapy is a
28
29 cost-effective treatment option compared with ECF/ECX in China.
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31 **Trial registration number:** NCT01216644.
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34 **Keywords:** Resectable gastric or gastroesophageal junction adenocarcinoma, Chemotherapy,
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36 FLOT, ECF/ECX, Cost-effectiveness.
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39 **Strengths and limitations of this study**

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41 ➤ Perioperative FLOT significantly improved overall survival compared with
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43 perioperative ECF/ECX in patients with locally advanced, resectable gastric or
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45 gastro-oesophageal junction adenocarcinoma. However, the cost-effectiveness of
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47 perioperative FLOT among Chinese patients remains unknown.
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49 ➤ To our knowledge, this is the first cost-effectiveness analysis comparing FLOT
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51 with ECF/ECX for patients with resectable gastric or gastroesophageal junction
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53 adenocarcinoma in China.
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55 ➤ The use of data in clinical trials may not represent the data in real clinical practice,
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57 because clinical trials have certain time constraints. For example, we used
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4 Log-logistic distribution to extrapolate survival beyond the lifetime horizon of the
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6 trial.

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

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15 **INTRUDOCTION**

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

22
23 Although significant progress has been made in early detection, the prognosis of
24 patients with resectable gastric and gastroesophageal junction adenocarcinoma is still
25 poor^[2]. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant
26 chemoradiotherapy had demonstrated their superior survival benefit in patients with
27 this disease when compared with a simple surgery^[3-6]. Based on this, perioperative
28 chemotherapy is recommended as the preferred treatment for locally resectable
29 diseases^[3,7-9]. For patients whose surgical scope is less than D2 lymph node dissection,
30 postoperative chemoradiotherapy is the preferred treatment ^[6,10,11]. Other treatment
31 strategies, such as postoperative chemotherapy, are applicable patients who have
32 udergone primary lymph node dissection^[12-14]. In Asian countries, accumulating
33 clinical evidence has shown that, compared with D2 gastrectomy alone , adjuvant
34 chemotherapy after a D2 surgery significantly improves the tumor remission rate and
35 R0 resection rate is associated with a favorable safety profile^[15,16].

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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

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

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37 In the phase II/III clinical trials of FLOT4, the researchers compared the
38 perioperative chemotherapy FLOT (fluorouracil, leucovorin, oxaliplatin plus
39 docetaxel) with the standard chemotherapy ECF/ECX (epirubicin, cisplatin,
40 fluorouracil or capecitabine)^[23,24]. Fluoropyrimidine and platinum combined with or
41 without anthracycline are the most used chemotherapeutic regimen. In the FLOT4
42 trial, adding docetaxel to triple-drug regimen (FLOT regimen) was associated with
43 improved survivals among patients with resectable gastric or gastroesophageal
44 junction cancer with clinical stage CT2 or higher and lymph node positive (CN+)
45 when compared with ECF/ECX regimen (50 months vs 35 months; HR = 0.77; 95%
46 confidence interval, 0.63-0.94). In this phase II/III trial, the proportion of patients
47 with complete regression of pathology was significantly higher in the FLOT group
48 than that in the ECF/ECX group. In addition, compared with the ECF/ECX group,
49 patients in the FLOT group had a lower incidence of grade 3-4 adverse events (AEs),
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4 including neutropenia, leucopenia, nausea, infection, fatigue and vomiting (25% vs
5 40%), but had the same incidence of serious chemotherapy-related AEs (27% in both
6 groups).
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10 In response to the positive results from FLOT4 trial, FLOT chemotherapy is
11 recommended for patients with resectable gastric or gastroesophageal junction
12 adenocarcinoma (Class IIA) by the Chinese society of clinical oncology (CSCO)
13 Guidelines for gastric cancer (2018 Edition). However, its financial impact has not
14 been studied yet from the perspective of Chinese healthcare system. Considering the
15 high prevalence of gastric or gastroesophageal junction cancer, and limited health
16 resources in China, the therapeutical benefits of FLOT chemotherapy must be
17 weighed against the economic burden that it has imposed. This study aimed to
18 evaluate whether the perioperative chemotherapy FLOT is cost-effective compared
19 with ECF/ECX among patients with gastric and gastroesophageal junction
20 adenocarcinoma from the perspective of Chinese medical system.
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32 33 **METHODS**

34 35 36 **Patients and regimens**

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38 The patient population analyzed in this study mirrored the patient enrolled in the
39 FLOT4 randomized controlled trial, which assessed the clinical efficacy of FLOT and
40 ECF/ECX chemotherapies in patients with gastric and gastroesophageal junction
41 adenocarcinoma. In this study, a total of 716 patients were randomly assigned to
42 receive FLOT (356 cases) or ECF/ECX (360 cases). Patients in the ECF/ECX group
43 received three 3-week cycles preoperative chemotherapy and three 3-week cycles
44 postoperative chemotherapy. The chemotherapy regimen for each 3-week cycle was
45 epirubicin 50mg/m² on the first day, cisplatin 60mg/m² on the first day, and
46 continuous intravenous infusion of fluorouracil 200mg/m² or oral capecitabine
47 1250mg/m² from the first to the 21st days at the discretion of investigators. Patients in
48 the FLOT group received four 2-week cycles preoperative chemotherapy and four
49 2-week cycles postoperative chemotherapy, which were docetaxel 50mg/m² on the
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4 first day, oxaliplatin 85mg/m² on the first day, calcium folinate 200mg/m² on the first
5 day and 5-FU 2600mg/m² as 24-h infusion the first day.
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8 The operation was scheduled 4 weeks after the last preoperative chemotherapy.
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10 The interval between the two groups was 4 weeks (28 days). As per this clinical trial,
11 patients may discontinue treatment due to unacceptable toxicity, disease progression,
12 death, or patient requirements. When patients experienced disease progression, they
13 would receive second-line treatment, including irinotecan, calcium folinate and
14 fluorouracil^[25].
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21 **Patient and public involvement**

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23 There was patient representation in the FLOT4 trial. However, this cost-effectiveness
24 analysis does not involve human participants.
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28 **Analytic Model**

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30 Based on the FLOT4 trial, a Markov model was constructed using Treeage Pro
31 2018 software to estimate the clinical outcomes of two perioperative chemotherapy
32 regimens (FLOT and ECF/ECX) for patients with gastric and gastroesophageal
33 junction adenocarcinoma in China(Figure 1).
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38 The model comprised three mutually exclusive health states: progression-free
39 survival (PFS), progressed survival (PS) and death. The Markov cycle length was set
40 as 2-week to fit the treatment schedule of the two groups. At the beginning of the
41 model, the whole cohort was in PFS state, and the transitions between health states in
42 the model may occur during each Markov cycle. From the perspective of Chinese
43 medical system, we used a lifetime horizon and a half-cycle correction to estimate the
44 total cost, quality-adjusted life year (QALY) and incremental cost-benefit ratio
45 (ICER). According to the Chinese Guidelines for Pharmacoeconomic Evaluations, the
46 annual discount rate for both costs and health outcomes was set at 5% ^[26]. All costs
47 used in the model were adjusted based on the consumer price index provided by the
48 the People's Bank of China and the US dollar to Chinese Yuan in 2020 (1 US dollar =
49 6.88 Chinese Yuan) ^[27]. A WTP threshold of \$31,513 was used in the current analysis.
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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 $S(t) = \{1 + e^{\theta t^{\kappa}}\}^{-1}$, where t is time. Figure 2 shows the Log-logistic parameters

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

estimated for the FLOT and ECF/ECX regimens.

Table 1.
Log-logistic parameters

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/m² on days 1, calcium folinate 400 mg/m² on days 1, fluorouracil 400mg/m² on day 1, continuous intravenous injection of fluorouracil 1200mg/m² 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 $\pm 50\%$.				

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 ($\pm 20\%$ or $\pm 50\%$ 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-line chemotherapy^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 \pm 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 supportive 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 & supportive 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

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4 Since 2018, the FLOT chemotherapy regimen has occupied an important
5 position in the CSCO guidelines in China and the National Comprehensive Cancer
6 Network (NCCN) in the United States^[17,18]. Although previous chemotherapy has
7 proved to be effective in improving the overall survival of patients with advanced
8 gastric cancer after resection, the prognosis of later-stage patients (stage III B and III
9 C) are still suboptimal. Therefore, further clinical studies are needed to find more
10 effective perioperative treatment for gastric cancer.
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17 In recent years, the use of anthracycline and platinum drugs has sprouted in the
18 field of perioperative treatment of resectable gastric cancer. Two published phase III
19 studies have demonstrated the clinical efficacy of docetaxel in the treatment of
20 advanced gastric cancer, involving DOS (docetaxel, oxaliplatin, S-1) and DS
21 (docetaxel combined with S-1) ^[47,48]. Moreover, oxaliplatin has showed favorable
22 safety in the treatment gastrointestinal tract, liver, kidney, and bone marrow than
23 cisplatin and carboplatin. Therefore, oxaliplatin has gradually replaced cisplatin in the
24 current commonly used chemotherapy regimens. In the ARTIST- II trail, the SOX
25 regimen (oxaliplatin combined with S-1) showed superiority over single drug (S-1) in
26 prolonging patient's survival^[49]. Two pivotal phase III trial from Japan and South
27 Korea also found that oxaliplatin combined with folic acid and S-1 was associated
28 with a clinically significant improvement among patients with advanced gastric
29 cancer, when compared with S-1 plus cisplatin^[50]. Based on these positive results,
30 docetaxel and oxaliplatin have been introduced into FLOT chemotherapy regimen. At
31 present, FLOT regimen is considered as a preferred strategy for perioperative
32 chemotherapy combined with surgery, including three chemotherapeutic drugs that
33 suitable for patients with good performance status. Notably, for patients with good to
34 moderate performance status and patients who is not able to tolerate the combination
35 regimen of these three drugs, the two drug combination regimen is recommended.
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54 In China, the climbing incidence and mortality of gastric cancer have imposed
55 considerable physical, psychological and economic burdens on the society, patients
56 and their families. Therefore, it is very crucial to study the economic significance of
57 this chemotherapy strategy in the field of medicine and policy. In this economic
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4 evaluation that compared with the ECF/ECX, the use of FLOT in patients with gastric
5 and gastroesophageal junction adenocarcinoma achieved additional 1.08QALY at an
6 incremental cost of \$921.51, resulting in an ICER of \$850.68/QALY. Based on the
7 WTP threshold set for this analysis, the FLOT strategy was considered to be
8 cost-effective. However, due to the extreme imbalance of economic development in
9 Chinese Mainland, the per capita GDP of the 32 provincial-level administrative
10 regions varies greatly. The highest per capita GDP was reported in Beijing's per capita
11 GDP (\$23,968), and the lowest was reported in Gansu's (\$5,238)^[51]. For the whole
12 Chinese Mainland the per capita GDP was \$10,504, and three times the per capita
13 GDP was \$31,513. Because the ICERs of the FLOT strategy were much lower than
14 three times the per capita GDP in Gansu Province (\$15,714). This suggests that the
15 FLOT perioperative chemotherapy regimen is more cost-effective than ECF/ECX in
16 the treatment of locally advanced resectable gastric or gastroesophageal junction
17 adenocarcinoma in all provincial-level administrative regions in Chinese Mainland.
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31 The one-way sensitivity analysis showed that the most influential parameter on
32 the model results was the hazard ratio (HR) of overall survival. Specifically, when the
33 HR decreased from 0.94 to 0.63, the ICER of FLOT strategy versus ECF/ECX
34 strategy ranged from \$-16,856.98 per QALY to \$3,868.18 per QALY. The other
35 sensitive parameters included the hazard ratio of progression-free survival, the
36 proportion of patients with ECF/ECX who underwent surgery, and the discount rate.
37 The change of HR for overall survival made ICER fluctuate the most, but the ICER
38 was still less than WTP (\$10,504/QALY). Moreover, the ICER of FLOT strategy
39 versus ECF/ECX strategy was always much lower than WTP regardless of the large
40 fluctuation of model parameters. Consequently, we can conclude the uncertainty of
41 parameters will not affect the robustness of our results.
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52 It should be noted that, docetaxel prices played a more important role than the
53 prices of other drugs in our model. From the perspective of cancer patients, the use of
54 high-priced new drugs might impose a heavy financial burden on the both social and
55 patients, which likely leads to delay, abandonment, and discontinuation of
56 treatment^[52]. In recent years, the Chinese government has conducted a series of price
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4 negotiation with many pharmaceutical enterprises with the aim of reducing the price
5 of oncology drugs. Fortunately, docetaxel passed the price negotiation and the
6 consistency evaluation of generic drugs successfully in March 2021^[53]. This means
7 that the market price of docetaxel will drop, which will make docetaxel less costly
8 and more widely used in China. Since the implementation of the national drug
9 centralized procurement policy and the generic drug consistency evaluation, we can
10 expect that cancer patients may benefit from these policies in China. To our best
11 knowledge, this study is the first cost-effectiveness analysis of FLOT chemotherapy
12 in patients with resectable gastric or gastroesophageal junction adenocarcinoma.
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21 There are some limitations in the current study. Firstly, there is uncertainty
22 regarding the outcomes of patients with gastric and gastroesophageal junction
23 adenocarcinoma beyond the trial period, despite the use of validated extrapolation
24 techniques. Secondly, some potential bias lied in only direct medical costs were
25 incorporated in the model, however, our sensitive analysis found that our results were
26 almost unaffected by changes in costs. Thirdly, another limitation of the current
27 economic analysis was that other treatment strategies for advanced resectable gastric
28 cancer have not been fully explored. With the successful application of targeted
29 therapy and immunotherapy for advanced gastric cancer clinically, the pattern of
30 perioperative treatment of resectable gastric cancer have been refreshed. For example,
31 the research on treatment of HER-2 positive gastric cancer has attracted considerable
32 attentions in recent years. Meanwhile, combining the perioperative chemotherapy
33 with targeted treatment, was found to increase the pathological complete remission
34 rate and improve overall survival benefit, while the safety is acceptable^[54,55].
35 Therefore, we can expect that receiving higher cost targeted therapy can increase
36 more cost-effectiveness.
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17 Song; data collection was contributed by H.Q. Zeng, Chunjiang Wang; manuscript
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19 writing was contributed by H.Q. Zeng, X.H. Zeng, Su-Jie Jia and Q. Liu; final
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26 27 **Ethical Approval Statement:**

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

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23 **Figure 1. Markov model structure of FLOT and ECF/ECX strategies for the treatment**
24 **of patients with locally advanced, resectable gastric or gastro-oesophageal junction**
25 **adenocarcinoma**
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32 **Figure 2. The Log-Logistic curves of (A) disease-free survival and (B) overall survival.**
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37 **Figure 3. Tornado diagram for univariable sensitivity analyses.** The grey dotted line
38 represents the ICER of \$850.6842 per QALY from the base-case results. ICER incremental
39 cost-effectiveness ratio, QALY quality-adjusted life-year.
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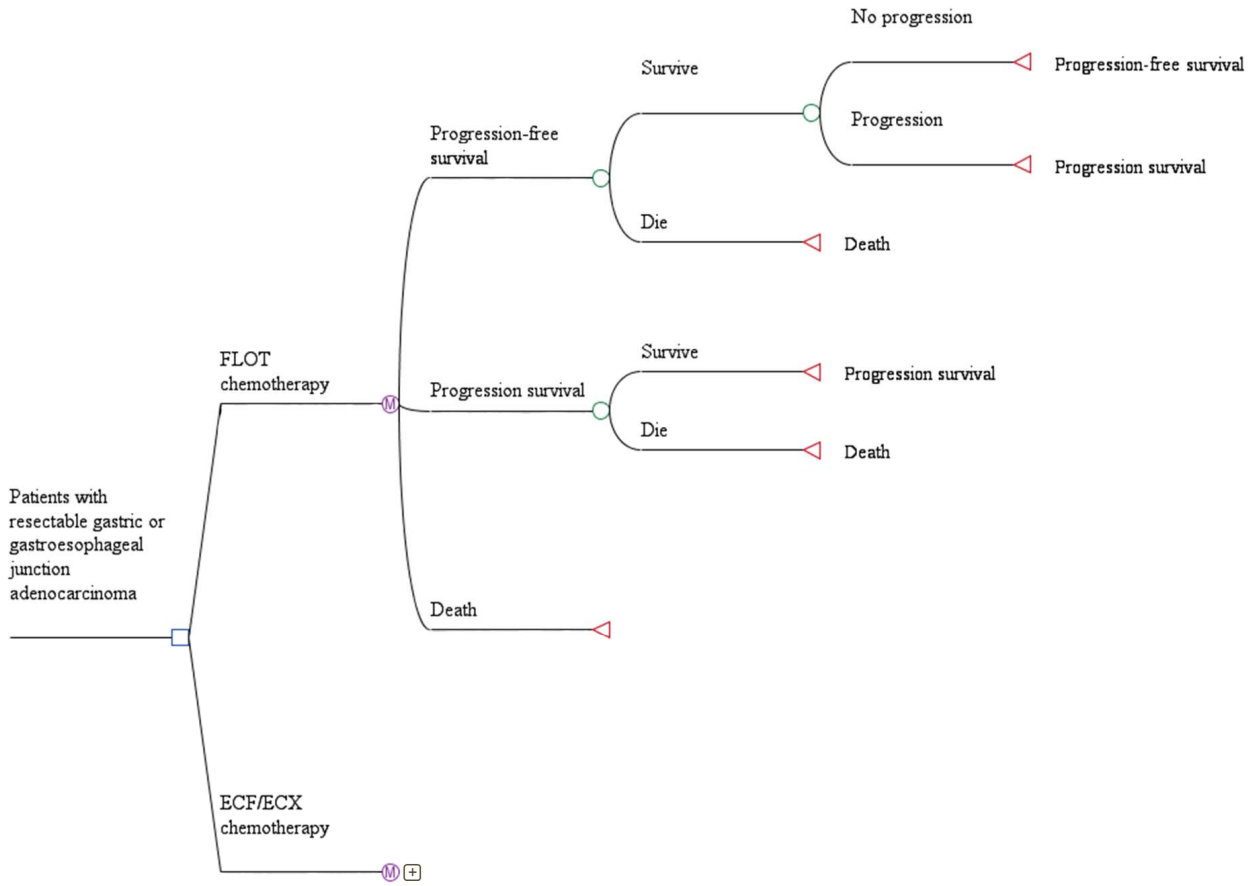
45 **Figure 4. The results of Monte Carlo probabilistic sensitivity analysis for the strategies**
46 **of FLOT VS ECF/ECX in scatter plots.** The solid lines indicate the \$31,513 threshold. The
47 estimates of 95% were surrounded in the ellipses.
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53 **Figure 5. Acceptability curves for the two strategies at willingness-to-pay (WTP)**
54 **thresholds in locally advanced, resectable gastric or gastro-oesophageal junction**
55 **adenocarcinoma patients.** The vertical dashed line represent the threshold that the
56 cost-effectiveness probability of FLOT chemotherapy reached 99%, and the solid line
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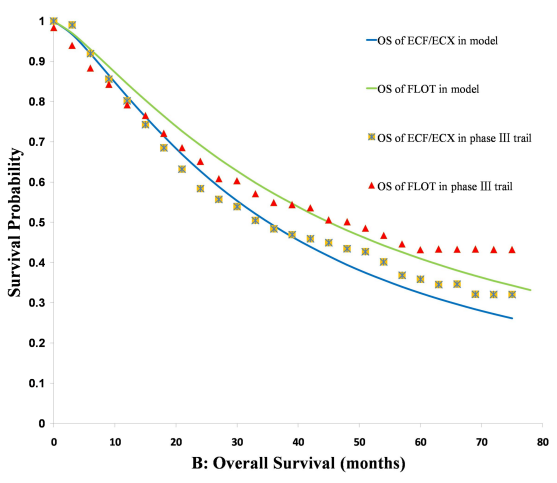
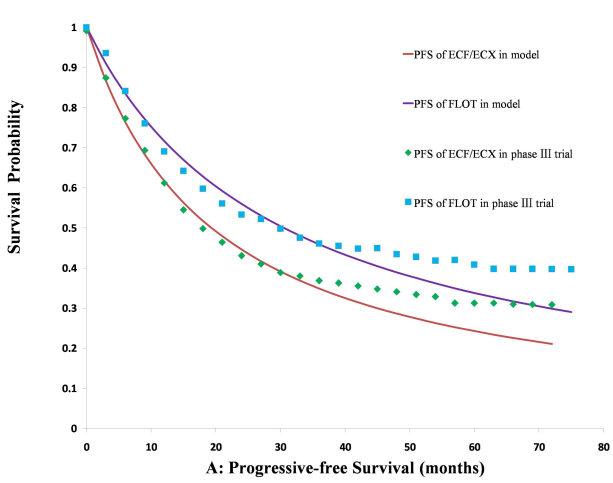
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represent the WTP threshold of \$10504 (the per capita GDP in China).

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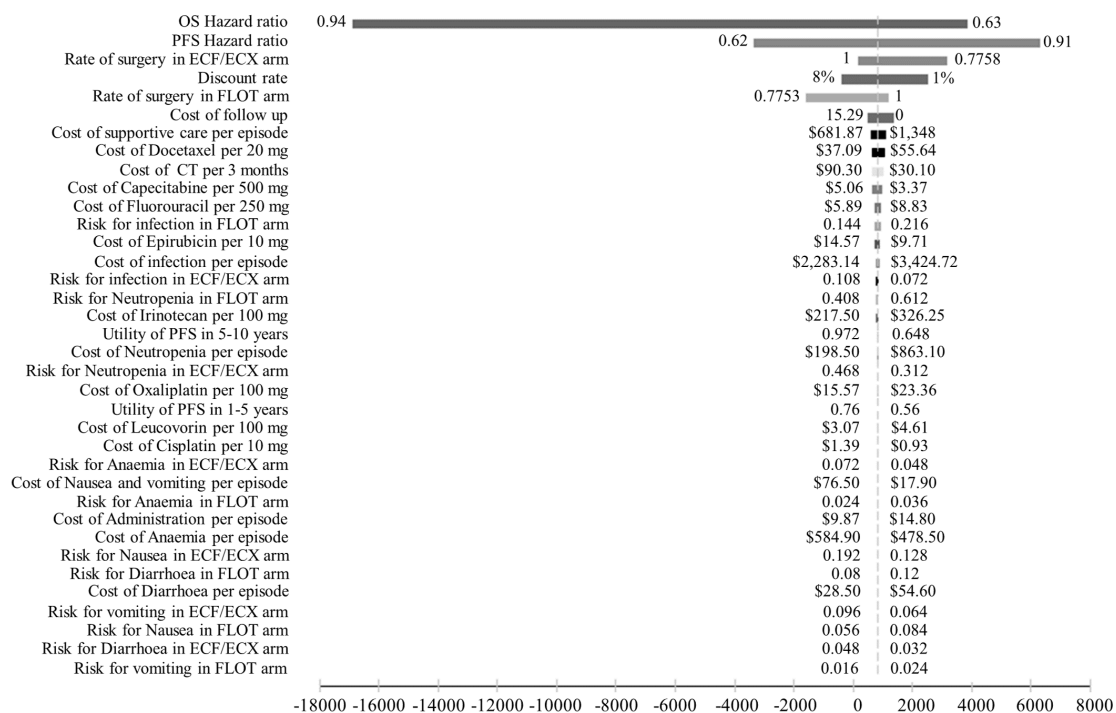


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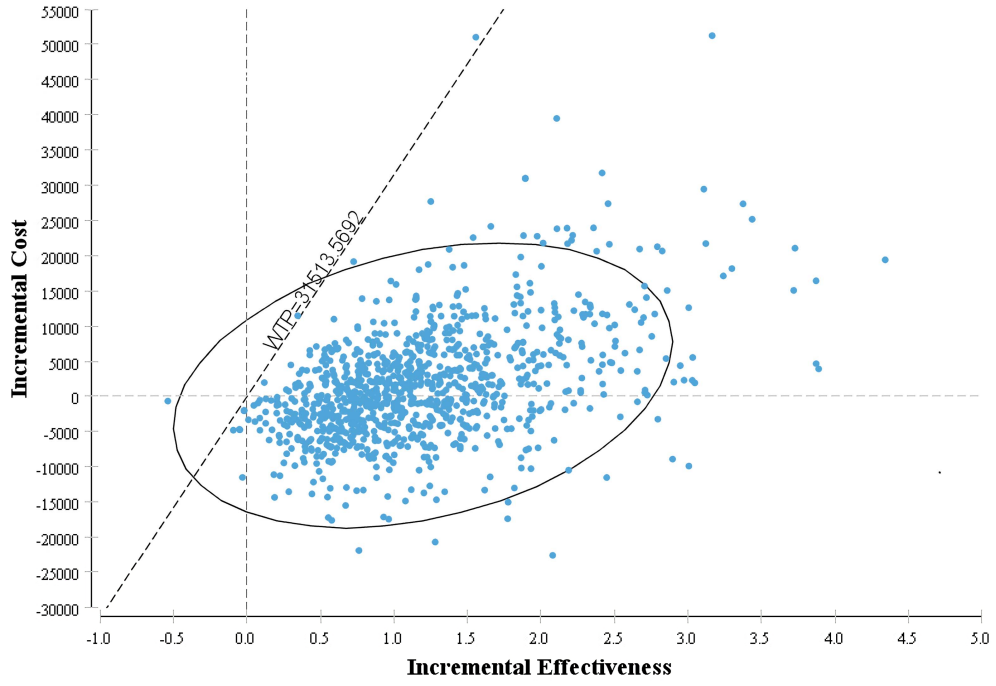
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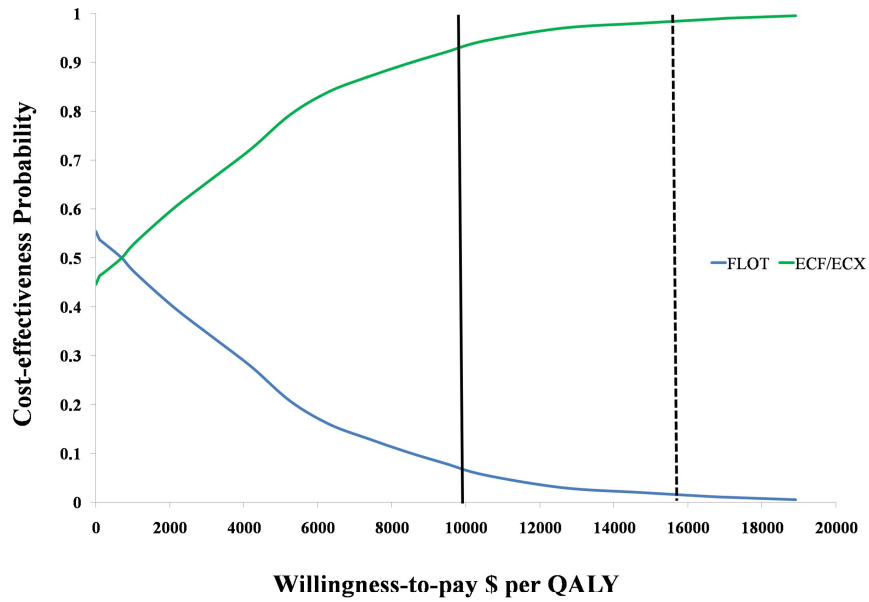


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Incremental Cost-Effectiveness, FLOT v. ECF/ECX





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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		

1	Target population and	#4	Describe characteristics of the base case population and subgroups	5
2	subgroups		analysed, including why they were chosen.	
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5	Setting and location	#5	State relevant aspects of the system(s) in which the decision(s)	5
6			need(s) to be made.	
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9	Study perspective	#6	Describe the perspective of the study and relate this to the costs	5
10			being evaluated.	
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12	Comparators	#7	Describe the interventions or strategies being compared and state	6
13			why they were chosen.	
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16	Time horizon	#8	State the time horizon(s) over which costs and consequences are	6
17			being evaluated and say why appropriate.	
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20	Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes	7
21			and say why appropriate	
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24	Choice of health	#10	Describe what outcomes were used as the measure(s) of benefit in	6
25	outcomes		the evaluation and their relevance for the type of analysis	
26			performed	
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29	Measurement of	#11a	Single study-based estimates: Describe fully the design features of	6-7
30	effectiveness		the single effectiveness study and why the single study was a	
31			sufficient source of clinical effectiveness data	
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34	Measurement of	#11b	Synthesis-based estimates: Describe fully the methods used for	n/a
35	effectiveness		identification of included studies and synthesis of clinical	
36			effectiveness data	
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40	Measurement and	#12	If applicable, describe the population and methods used to elicit	'n/a'
41	valuation of preference		preferences for outcomes.	
42	based outcomes			
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45	**Estimating resources			
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47	and costs **			
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50		#13a	Single study-based economic evaluation: Describe approaches	9
51			used to estimate resource use associated with the alternative	
52			interventions. Describe primary or secondary research methods for	
53			valuing each resource item in terms of its unit cost. Describe any	
54			adjustments made to approximate to opportunity costs	
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Methods

1	Estimating resources	#13b	Model-based economic evaluation: Describe approaches and data	9
2	and costs		sources used to estimate resource use associated with model health	
3			states. Describe primary or secondary research methods for valuing	
4			each resource item in terms of its unit cost. Describe any	
5			adjustments made to approximate to opportunity costs.	
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9	Currency, price date,	#14	Report the dates of the estimated resource quantities and unit costs.	9
10	and conversion		Describe methods for adjusting estimated unit costs to the year of	
11			reported costs if necessary. Describe methods for converting costs	
12			into a common currency base and the exchange rate.	
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16	Choice of model	#15	Describe and give reasons for the specific type of decision	6
17			analytical model used. Providing a figure to show model structure	
18			is strongly recommended.	
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21	Assumptions	#16	Describe all structural or other assumptions underpinning the	6
22			decision-analytical model.	
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25	Analytical methods	#17	Describe all analytical methods supporting the evaluation. This	6
26			could include methods for dealing with skewed, missing, or	
27			censored data; extrapolation methods; methods for pooling data;	
28			approaches to validate or make adjustments (such as half cycle	
29			corrections) to a model; and methods for handling population	
30			heterogeneity and uncertainty.	
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35	Results			
36				
37	Study parameters	#18	Report the values, ranges, references, and, if used, probability	10
38			distributions for all parameters. Report reasons or sources for	
39			distributions used to represent uncertainty where appropriate.	
40			Providing a table to show the input values is strongly	
41			recommended.	
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46	Incremental costs and	#19	For each intervention, report mean values for the main categories	12
47	outcomes		of estimated costs and outcomes of interest, as well as mean	
48			differences between the comparator groups. If applicable, report	
49			incremental cost-effectiveness ratios.	
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53	Characterising	#20a	Single study-based economic evaluation: Describe the effects of	12
54	uncertainty		sampling uncertainty for the estimated incremental cost and	
55			incremental effectiveness parameters, together with the impact of	
56			methodological assumptions (such as discount rate, study	
57			perspective).	
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1	Characterising	#20b	Model-based economic evaluation: Describe the effects on the	'n/a'
2	uncertainty		results of uncertainty for all input parameters, and uncertainty	
3			related to the structure of the model and assumptions.	
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6	Characterising	#21	If applicable, report differences in costs, outcomes, or cost	'n/a'
7	heterogeneity		effectiveness that can be explained by variations between	
8			subgroups of patients with different baseline characteristics or	
9			other observed variability in effects that are not reducible by more	
10			information.	
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14	Discussion			
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17	Study findings,	#22	Summarise key study findings and describe how they support the	13-16
18	limitations,		conclusions reached. Discuss limitations and the generalisability of	
19	generalisability, and		the findings and how the findings fit with current knowledge.	
20	current knowledge			
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23	Other			
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26	Source of funding	#23	Describe how the study was funded and the role of the funder in	17
27			the identification, design, conduct, and reporting of the analysis.	
28			Describe other non-monetary sources of support	
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31	Conflict of interest	#24	Describe any potential for conflict of interest of study contributors	17
32			in accordance with journal policy. In the absence of a journal	
33			policy, we recommend authors comply with International	
34			Committee of Medical Journal Editors recommendations	
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 39 NC. This checklist was completed on 11. January 2022 using <https://www.goodreports.org/>, a tool made by the
 40 EQUATOR Network in collaboration with [Penelope.ai](#)
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