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ORIGINAL ARTICLE **CME**

Conversion Surgery in Advanced Unresectable Gastric Cancer After Induction Fluorouracil Plus Leucovorin, Oxaliplatin, and Docetaxel

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ABSTRACT

Introduction: *Palliative chemotherapy is the standard treatment for unresectable locally advanced gastric cancer (GC) with poor prognosis. We evaluated the safety and efficacy of a multimodality approach with induction fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) followed by attempted conversion surgery with additional FLOT at a tertiary hospital in Hong Kong.*

Methods: *Medical records of advanced GC patients treated with induction FLOT and attempted conversion surgery between 2017 and 2023 were reviewed. Patients suitable for surgery after chemotherapy underwent resection, followed by adjuvant FLOT for another four cycles. Safety, treatment outcomes and predictive factors for survival were analysed.*

Results: *Thirty-one patients (25 males, median age = 63 years) were included. The median follow-up time was 22.0 months. Disease control rate after induction FLOT was 87.1% (n = 27). Conversion surgery was performed in 23 patients (74.2%), with 20 achieving R0 resection. Patients with conversion surgery had longer median overall survival (OS) and event-free survival than those who could not undergo surgery. Multivariable analysis identified no conversion surgery, higher neutrophil-to-lymphocyte ratio, serum albumin level <35 g/L, body mass index <23 kg/m^2, and clinical nodal stage N3 disease with a worse OS. No treatment-related deaths occurred. The incidence of grade ≥3 toxicities was 51.6%, with neutropenia (29.0%) and febrile neutropenia (12.9%) being most common.*

Conclusion: *Induction FLOT achieved high conversion rates and R0 resections, offering a favourable survival benefit and acceptable safety in unresectable GC. Prospective trials incorporating biomarker-driven therapy may further improve pathological complete response rates and survival.*

Key Words: *Adenocarcinoma; Induction chemotherapy; Stomach neoplasms*

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Ethics Approval: This research was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster, Hong Kong (Ref No.: UW24-514). The requirement for patient consent was waived by the Committee due to the retrospective nature of the research.

中文摘要

晚期不可切除胃癌在接受誘導氟尿嘧啶、亞葉酸鈣、奧沙利鉑及多西他賽治療後的轉化手術

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引言：緩和性化療是預後差的不可切除局部晚期胃癌的標準治療。患者在接受誘導氟尿嘧啶、亞葉酸鈣、奧沙利鉑及多西他賽（FLOT）治療後嘗試進行轉化手術再配合FLOT是一個多模態治療方式，我們評估這治療方式在香港某所三級醫院的安全性及效用。

方法：我們對在2017至2023年間接受誘導FLOT及嘗試轉化手術治療的晚期胃癌患者的醫療紀錄進行回顧性研究。適合在化療後進行手術的患者接受切除，然後進行另外四個療程的輔助FLOT治療。我們分析了安全性、治療結果及存活的預測因素。

結果：本研究包括31名患者（25名男性，年齡中位數 = 63歲）。隨訪時間中位數為22.0個月。在接受誘導FLOT治療後的疾病控制率為87.1%（n = 27）。共有23名患者（74.2%）接受了轉化手術，當中20名達至完全切除（R0）。與不能接受手術的患者相比，接受了轉化手術的患者的整體存活時間及無事件存活時間均較長。多變量分析識別出沒有接受轉化手術、嗜中性白血球與淋巴球比例（NLR）較高、血清白蛋白水平<35 g/L、體重指標（BMI）<23 kg/m²及臨床第N3期胃癌的整體存活較差。本研究沒有發生與治療相關的死亡事件。毒性≥3的發生率為51.6%，當中以嗜中性白血球減少症（29.0%）及嗜中性白血球減少症合併發熱（12.9%）最為常見。

結論：誘導FLOT治療達至高轉化率及完全切除，為不可切除胃癌患者提供了有利的存活獲益及可接受的安全性。結合生物標記驅動治療的前瞻性試驗可進一步改善病理完全緩解率及存活。

INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the sixth leading cause of cancer deaths in Hong Kong.[1] Worldwide, it is the fourth most common leading cause of cancer deaths (7.7%).[2] While surgical resection is the treatment of choice for operable GC, many patients eventually relapse. Thus, combined modality treatment is recommended for resectable GC classified as stage ≥IB disease under the TNM (Tumour, Node and Metastasis) system.[3,4] Unresectable locally advanced/metastatic GC has a poor prognosis with a median overall survival (OS) of about 4 to 6 months with supportive care alone.[5] With the use of various combination chemotherapeutic regimens containing platinum, fluoropyrimidine, taxane, irinotecan, and/or trastuzumab, the median survival time improves to approximately 11 to 15 months.[5-10] Recently, the addition of immunotherapy to chemotherapy has also been shown to improve survival in the first-line advanced/metastatic setting, especially for those with high expression of programmed death ligand 1.[11,12] Currently, the standard of care is palliative in nature, and newer multidisciplinary therapeutic approaches to improve survival and offer a chance of cure for advanced GC are being evaluated.

The role of surgery in advanced GC is a controversial topic. Advanced GC is a heterogeneous disease with varying extents of local invasion, varying locations and extent of lymph node metastases, and diverse metastatic patterns. The REGATTA randomised phase three trial (Reductive Gastrectomy for Advanced Tumour in Three Asian Countries)[13] failed to show a survival advantage with gastrectomy followed by chemotherapy versus chemotherapy alone in advanced GC. This could partly be explained by the decreased tolerance to chemotherapy after gastrectomy, which was similarly shown in the perioperative setting in the MAGIC trial.[14] Conversion surgery, in which patients with unresectable tumours are given neoadjuvant chemotherapy in an attempt to downstage the disease and achieve an R0 resection, is an appealing approach in advanced GC.[15] Besides downstaging the tumour itself, the rationale behind

giving neoadjuvant chemotherapy is to eradicate occult metastatic disease and to take advantage of the improved tolerance of chemotherapy compared to the postoperative setting. Most data on conversion therapy are from single-arm phase two studies and retrospective cohort studies.[16-24] Various neoadjuvant chemotherapy regimens including docetaxel, capecitabine/S-1, and cisplatin/oxaliplatin, have been used as conversion therapy in treating advanced GCs.[16-24] The median survival time of patients following R0 resection is up to 41 to 57 months,[16,18,19,23] dramatically better than that achieved by palliative systemic treatment alone. Perioperative chemotherapy regimens such as S-1 plus cisplatin, and fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) have also been used in conversion therapy and demonstrated favourable outcomes, especially in those with limited metastatic advanced GC.[25,26]

The multidisciplinary approach of using induction FLOT for four cycles followed by attempted conversion surgery for advanced GC has been used in our centre since 2017. Our centre prefers to use FLOT due to our experience with it in the perioperative setting for resectable GC. Perioperative FLOT in resectable GC has been shown to have a high pathological response rate with a reasonable toxicity profile[27,28] and is the preferred regimen in this setting as recommended by the National Comprehensive Cancer Network[4] and the European Society for Medical Oncology.[3] This retrospective study evaluated the safety and efficacy of incorporating FLOT and conversion surgery in advanced GC.

METHODS

Patients

The cases of 31 consecutive patients with clinically unresectable, locoregionally advanced GC (cT2-4bN0-3M0) treated with induction FLOT with the goal of conversion surgery at Queen Mary Hospital, Hong Kong between January 2017 and December 2023 were reviewed. All patients had undergone baseline upper gastrointestinal endoscopy, were diagnosed with histologically confirmed gastric or gastroesophageal junction adenocarcinoma, and had received staging ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (^{18}F-FDG PET/CT) whole-body scans. Disease was staged according to the 7th and 8th TNM staging system developed by the American Joint Committee on Cancer.[29-31] Preoperative exploratory laparoscopy to rule out peritoneal metastases was not mandatory. All cases were deemed clinically unresectable with locoregionally advanced disease after discussion in multidisciplinary meetings comprising of surgeons, oncologists, and radiologists. Hitherto 'unresectable' features included invasion into adjacent organs (clinical tumour stage T4b [stage cT4b] disease), locoregionally advanced/bulky non–stage cT4b disease, or extensive involvement of regional lymph nodes. These groups of patients were targeted as they would otherwise receive palliative systemic treatment. Patients with grossly definite metastases (i.e., visible on ^{18}F-FDG PET/CT or histologically confirmed at surgery) or distant metastases to visceral organs other than lymph nodes were not included, as our centre would treat these patients with multimodality treatment consisting of intraperitoneal chemotherapy or systemic therapy with palliative intent.

Treatment Overview

All patients received induction chemotherapy using FLOT according to the protocol used in the FLOT4 trial.[28] Each cycle of FLOT consisted of intravenous docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, and leucovorin 200 mg/m^2, followed by a 24-hour continuous infusion of fluorouracil 2600 mg/m^2 on day 1. This regimen was given every 2 weeks for four cycles. The dose was adjusted if patient had intolerable side-effects. Prophylactic use of granulocyte colony-stimulating factor (G-CSF) was used as needed.

Evaluation of Response

Clinical response was assessed after four cycles of FLOT with upper gastrointestinal endoscopy and ^{18}F-FDG PET/CT scan. Response measurement was classified according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1.[32] All cases were re-evaluated in multidisciplinary meetings. If the tumour responded well and curative resection was judged to be possible, conversion surgery was scheduled. Patients with tumours that responded unsatisfactorily and were unlikely amenable to curative resection were administered palliative second-line treatments.

Conversion Surgery and Follow-up

All patients included were alive within 10 weeks from the day of last administration of FLOT. Conversion surgery was performed within 10 weeks from the day of last FLOT. If surgical exploration did not reveal unresectable features, R0 resection was attempted. Depending on the location and size of the gastric or gastroesophageal junction tumour, curative resection involved distal or total gastrectomy plus or minus oesophagectomy, along with D2 lymph node dissection. After surgery, another

four cycles of adjuvant FLOT were administered to those with R0 resection. For patients with R1 or R2 resections, subsequent treatments were chosen at the discretion of oncologists.

For patients who underwent conversion surgery and completed adjuvant FLOT, the follow-up schedule consisted of clinical visits at least once every 3 months during the first 2 years, followed by at least once every 6 months. CT or ^{18}F-FDG PET/CT was performed at least once every 6 months for the first 3 years.

Outcome Measures and Statistical Analyses

Relevant clinical and pathological parameters were recorded from clinical notes and the Clinical Management System of the Hospital Authority. These data included age, sex, body mass index (BMI), co-morbidities, baseline blood tests, tumour characteristics, clinical response, pathological response using the Modified Ryan score,[33] and any adverse events from chemotherapy.

All statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing). Treatment outcomes included OS, defined as the period from the time of starting induction FLOT to the date of death or the last follow-up time; and event-free survival (EFS), defined as the period from the time of starting induction FLOT to the date of disease progression, relapse, death or the last follow-up time. Safety was evaluated according to the National Cancer Institute's CTCAE (Common Terminology Criteria for Adverse Events) version 5.0.[34] OS and EFS of the groups with and without conversion surgery were analysed using the Kaplan-Meier method. The differences in survival time were investigated by the log-rank test. Simple and multivariable Cox proportional hazards regression analyses were performed to identify clinical and pathological variables in relation to survival. Each clinical and pathological variable was assessed individually using simple Cox regression and Kaplan-Meier curves with log-rank tests. Significant clinical and pathological variables with p value ≤ 0.1 in simple analysis were incorporated into a multivariable regression model. Multivariable Cox regression model was used to evaluate the independent effect of each factor while adjusting for other variables. Hazard ratios were presented with 95% confidence intervals (95% CIs). A two-sided p value < 0.05 was considered as statistically significant.

RESULTS

Patient Characteristics

During the study period, 31 patients (25 males and 6 females) with recently diagnosed locoregionally advanced and clinically unresectable GC received FLOT. The median age was 63 years (range, 34-80). All patients had an Eastern Cooperative Oncology Group performance status score of ≤2, with majority (93.5%) scoring 1. Fourteen patients (45.2%) had baseline anaemia requiring blood transfusion and seven patients (22.6%) required either feeding tube insertion or gastrojejunostomy for dysphagia. In total, two patients (6.5%) had stage cT3 disease, 16 (51.6%) had stage cT4a disease and 12 (38.7%) had stage cT4b disease. Eight patients (25.8%) had clinical nodal stage N1 (stage cN1) disease, 14 (45.2%) had stage cN2 disease and six (19.4%) had stage cN3 disease. As stated above, reasons for unresectability included invasion into adjacent organs (stage T4b disease) in 12 patients (38.7%) [pancreas, n = 6; liver, n = 3; colon, n = 3; heart, n = 1; spleen, n = 1], locoregionally advanced/bulky non–stage cT4b disease in 15 patients (48.4%), and extensive regional lymph node involvement in 13 patients (41.9%). Seven patients (22.6%) had two unresectable features and one (3.2%) had three unresectable features. Table 1 summarises the baseline characteristics of this study cohort. The median follow-up time was 22.0 months (range, 5.8-80.7). During the follow-up period, 19 (61.3%) of the 31 patients died.

Clinical and Pathological Response and Adverse Events

All patients except one (96.8%) completed the intended four cycles of induction FLOT, with one patient developing grade 3 encephalopathy and only received three cycles. The disease control rate after induction FLOT was 87.1% (n = 27), of which 23 patients (85.2%) had a complete response (CR) or partial response (PR) and four patients (14.8%) had stable disease (SD) on imaging. Conversion surgery was performed in 23 patients (74.2%), with 20 underwent R0 resections, two underwent R1 resections (microscopic distal duodenal margin), and one underwent R2 resection (macroscopic lymph nodes encasing major arteries). Total gastrectomy was performed in seven patients (22.6%), distal gastrectomy in nine (29.0%), and oesophagogastrectomy in seven patients (22.6%). The median time between end of chemotherapy and surgery was 5.4 weeks (interquartile range, 3.8-6.8). Patients not undergoing

Table 1. Baseline characteristics of patients who had induction fluorouracil plus leucovorin, oxaliplatin, and docetaxel (n = 31).*

Sex	
Male	25 (80.6%)
Female	6 (19.4%)
Median age, y (range)	63 (34-80)
ECOG performance status score	
1	29 (93.5%)
2	2 (6.5%)
Charlson Co-morbidity Index	
2-3	7 (22.6%)
4-6	20 (64.5%)
≥7	4 (12.9%)
Dysphagia score (Mellow and Pinkas)	
0	9 (29.0%)
1	7 (22.6%)
2	10 (32.3%)
3	5 (16.1%)
4	0
Anaemia requiring transfusion	14 (45.2%)
Dysphagia intervention	
Feeding tube insertion	5 (16.1%)
Palliative gastrojejunostomy	2 (6.5%)
None	24 (77.4%)
Tumour location	
Oesophagogastric junction	15 (48.4%)
Stomach	16 (51.6%)
Tumour grade	
1	1 (3.2%)
2	3 (9.7%)
3	24 (77.4%)
Missing	3 (9.7%)
Tumour type	
Diffuse	10 (32.3%)
Intestinal	8 (25.8%)
Mixed intestinal tubular	3 (9.7%)
Others	3 (9.7%)
Missing	7 (22.6%)
Signet ring	
Yes	14 (45.2%)
No	17 (54.8%)
Clinical tumour (cT) stage	
cT2	1 (3.2%)
cT3	2 (6.5%)
cT4a	16 (51.6%)
cT4b	12 (38.7%)
Clinical nodal (cN) stage	
cN0	3 (9.7%)
cN1	8 (25.8%)
cN2	14 (45.2%)
cN3	6 (19.4%)
Reasons for induction FLOT (unresectable features)	
Stage cT4b disease	12 (38.7%)
Locoregionally advanced/bulky non–stage cT4b disease	15 (48.4%)
Extensive regional lymph nodes	13 (41.9%)
Unresectable features	
1	23 (74.2%)
2	7 (22.6%)
3	1 (3.2%)
Clinical response to FLOT	
Complete/partial response	23 (74.2%)
Stable disease	4 (12.9%)
Progressive disease	4 (12.9%)
Conversion rate	
Surgery	23 (74.2%)
Inoperable	8 (25.8%)
Pathological response (modified Ryan score) [n = 23]	
0-1 (complete/near complete)	2 (8.7%)
2 (partial)	12 (52.2%)
3 (poor)	9 (39.1%)
HER2	
Positive	5 (16.1%)
Negative	24 (77.4%)
N/A	2 (6.5%)
PD-L1 (CPS)	
≤1	7 (22.6%)
>1	8 (25.8%)
N/A	16 (51.6%)
MMR	
dMMR	2 (6.5%)
Non-dMMR	13 (41.9%)
N/A	16 (51.6%)
EBER	
Positive	1 (3.2%)
Negative	12 (38.7%)
N/A	18 (58.1%)

Abbreviations: CPS = combined positive score; dMMR = deficient mismatch repair; EBER = Epstein-Barr encoding region; ECOG = Eastern Cooperative Oncology Group; FLOT = fluorouracil plus leucovorin, oxaliplatin, and docetaxel; HER2 = human epidermal growth factor receptor 2; MMR = mismatch repair; N/A = not available; PD-L1 = programmed death ligand 1.
* Data are shown as No. (%), unless otherwise specified.

conversion surgery included eight (25.8%) with stable disease with unresolved unresectable features (n = 5) and progressive disease (n = 3). Of these eight patients, one underwent a palliative gastrojejunostomy and one a palliative oesophagogastrectomy.

The pathological response rate was 60.9%, of which two patients (8.7%) had pathological complete response (pCR) or near complete response. All patients with pathological response had radiological PR. Amongst those with poor pathological response, seven had radiological PR, one had radiological SD, and one had radiological progressive disease.

During preoperative FLOT, 20 patients (64.5%) received prophylactic G-CSF support. The incidence of grade 3 or 4 toxicities during FLOT was 51.6%. Neutropenia (n = 9, 29.0%) and febrile neutropenia (n = 4, 12.9%) were the most common; nine of these occurred in those without prophylactic G-CSF. Non-haematologic adverse events of grade ≥3 toxicities were not common in this cohort, with malaise being the most common (9.7%). Treatment was generally well tolerated, and no treatment-related

deaths occurred. Table 2 shows adverse events with grade ≥3 toxicities on FLOT.

Post Surgery

Postoperative complications were infrequent and occurred in four patients (17.4%). They included pneumonia, arrythmia, surgical emphysema, and surgical site infections. No patients died within 30 days after surgery.

Among 20 patients who underwent successful R0 conversion surgery, 19 (95.0%) started postoperative FLOT, with only one (5.3%) not completing the intended four cycles due to malaise. One patient (5.0%) in the R0 resection group did not start postoperative FLOT and received TS-1 and cisplatin instead because of the appearance of new perigastric lymph nodes while on preoperative FLOT, though conversion surgery was still deemed feasible. One of two patients with R1 resection had a postoperative course of TS-1 and chemoradiotherapy with TS-1 to the operative bed, while the other one continued on FLOT. The patient with R2 resection continued on TS-1 alone.

Of the eight patients who did not undergo conversion surgery, seven continued on chemotherapy (two receiving FLOT, and one each receiving irinotecan/ramucirumab, paclitaxel/ramucirumab, cisplatin/capecitabine/trastuzumab, TS-1/cisplatin, and capecitabine/oxaliplatin/pembrolizumab). The other patient received palliative radiation therapy and best supportive care.

Table 2. Adverse events with grade ≥3 toxicities in 16 patients during induction fluorouracil plus leucovorin, oxaliplatin, and docetaxel therapy.

	No. (%)
Malaise	3 (9.7%)
Neutropenia	9 (29.0%)
Anaemia	2 (6.5%)
Febrile neutropenia	4 (12.9%)
Nausea/vomiting	2 (6.5%)
Diarrhoea	2 (6.5%)
Infections	2 (6.5%)
Creatinine increased	2 (6.5%)
Encephalopathy	1 (3.2%)
Syncope	2 (6.5%)
Electrolyte disturbances	1 (3.2%)
Toxic death	0

Survival

For the entire cohort of 31 patients, the median OS was 26.3 months (95% CI = 18.4 to not applicable) and median EFS was 13.5 months (95% CI = 7.3-26.7). Patients undergoing conversion surgery had a longer median OS (median OS = 33.3 months vs. 11.1 months) [Table 3 and Figure 1] and EFS (median EFS = 21.63 months vs. 2.22 months) [Table 3 and Figure 2] than those who did

Table 3. Overall survival and event survival outcomes of patients with induction fluorouracil plus leucovorin, oxaliplatin, and docetaxel (n = 31).

	OS			EFS	
	Median OS, mo (95% CI)	1-year OS	HR (95% CI)	Median EFS, mo (95% CI)	HR (95% CI)
No conversion surgery (n = 8)	11.1 (7.27 to N/A)	42.9%	Ref	2.22 (2.0 to N/A)	Ref
Conversion surgery (n = 23)	33.3 (24.90 to N/A)	95.6%	0.04 (0.01-0.21)	21.63 (13.5 to N/A)	0.02 (0-0.15)

Abbreviations: 95% CI = 95% confidence interval; EFS = event-free survival; HR = hazard ratio; N/A = not applicable; OS = overall survival.

Table 4. Simple and multivariable analyses on factors associated with overall survival.

	Simple		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
BMI <23 kg/m^2	7.42 (2.04-26.96)	0.002	34.01 (3.03-382.03)	0.004
Baseline haemoglobin	0.78 (0.59-1.04)	0.093	1.46 (0.86-2.48)	0.164
NLR	1.29 (1.08-1.54)	0.005	1.53 (1.04-2.26)	0.03
Serum albumin <35 g/L	2.87 (0.97-8.48)	0.056	17.50 (1.31-233.83)	0.03
Clinical tumour (cT) stage cT4b disease	2.39 (0.96-5.91)	0.060	0.74 (0.10-5.3)	0.76
Locoregionally advanced/bulky non–stage cT4b disease	0.30 (0.11-0.8)	0.016	0.21 (0.03-1.52)	0.12
Clinical nodal (cN) stage cN3 disease	6.52 (1.96-21.64)	0.002	14.47 (1.56-134.48)	0.019
No conversion surgery	23.85 (4.74-119.92)	< 0.001	127.59 (9.17-1775.98)	< 0.001

Abbreviations: 95% CI = 95% confidence interval; BMI = body mass index; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio.

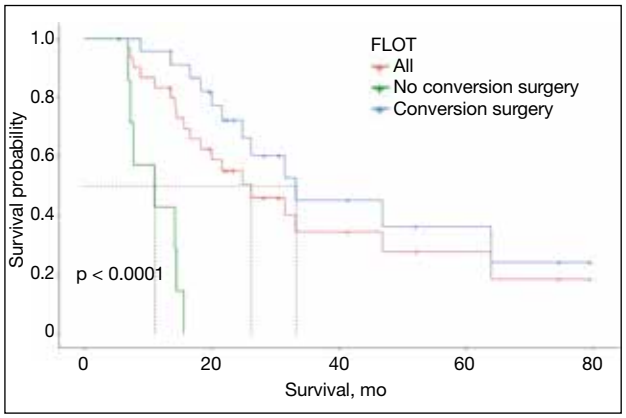

Figure 1. Kaplan-Meier curve of overall survival (n = 31).
Abbreviation: FLOT = fluorouracil plus leucovorin, oxaliplatin, and docetaxel.

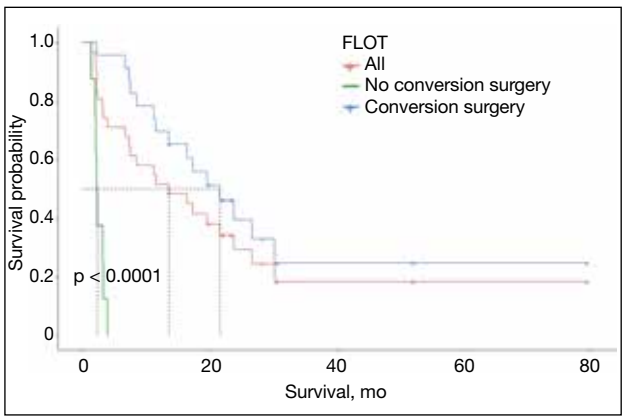

Figure 2. Kaplan-Meier curve of overall event-free survival (n = 31).
Abbreviation: FLOT = fluorouracil plus leucovorin, oxaliplatin, and docetaxel.

not. The 1-year survival proportion was also higher in patients with conversion surgery versus those without (95.6% vs. 42.9%) [Table 3 and Figure 1]. Multivariable analysis showed that low BMI, higher neutrophil-to-lymphocyte ratio (NLR), low serum albumin level, stage cN3 disease, and those without conversion surgery were associated with worse OS (Table 4).

Pattern of Recurrence

Among 20 patients who underwent R0 conversion surgery, 12 developed recurrences. Peritoneum was the most common site of first relapse (n = 7), followed by distant lymph nodes (n = 6) and liver (n = 3). Eight patients went on to have active palliative systemic treatment while four had palliative radiotherapy and best supportive care.

DISCUSSION

This retrospective study demonstrated the high efficacy of induction FLOT and subsequent conversion surgery in unresectable advanced GC, offering a chance of cure with long-term survival benefit with acceptable safety in a hitherto palliative scenario.

Induction FLOT led to a high response rate with disease control rate of 87.1% (85.2% CR/PR and 14.8% SD). No patient died within 10 weeks of last induction FLOT, and it achieved a high conversion rate of 74.2%. Among the 23 patients who underwent conversion surgery, 87.0% (n = 20) achieved R0 resection. These appeared to be slightly better figures compared with the AIO-FLOT3 trial (Arbeitsgemeinschaft Internistische Onkologie-fluorouracil, leucovorin, oxaliplatin, and docetaxel) done in Germany,[26] which reported a response rate of 43% to 60% in patients not upfront resectable, and a 60% conversion rate and 80.6% R0 resection in arm B (patients with limited metastases). It is understandable because our study focused on patients with relatively less advanced stages compared to the AIO-FLOT3 trial while the AIO-FLOT3 trial recruited stage IV patients with more distant metastases.[26] Nevertheless, these are encouraging results as it confirms that a majority of patients may be able to have conversion surgery done with upfront unresectable advanced GC, especially for those with less bulky disease and metastatic burden. The high R0 resection rate in our study is important because R0 resection offers the best chance of cure in GC and is a prognostic factor for survival for patients after preoperative chemotherapy.[25,35,36] Patients with non-R0 tumour resection have a poor prognosis and non-R0 resection should be avoided in advanced GC.[37,38]

Our study showed that induction FLOT was well tolerated. All patients except one completed four cycles of induction FLOT. For those with R0 conversion surgery and planned postoperative FLOT, 95.0% completed four cycles. The high postoperative chemotherapy compliance rate is an important finding in this study as previous trials have reported low compliance with other postoperative chemotherapy regimens due to toxicity after gastrectomy.[14,39,40] The REGATTA trial[13] did not show a survival advantage with gastrectomy followed by chemotherapy versus chemotherapy alone in advanced GC, underscoring the importance and better tolerability of induction chemotherapy. The incidence of grade 3 or 4 toxicities during FLOT was comparable to those in the perioperative setting in resectable GCs.[28]

The FLOT4 trial[28] established perioperative FLOT as standard of care in locally advanced resectable GC. However, the role of perioperative chemotherapy in unresectable advanced GC such as the ones reviewed in this study is uncertain. Conversion therapy for GC is a multimodality strategy garnering attention in recent years.[15] However, definition of conversion therapy varies widely, and studies have included different induction chemotherapy regimens, surgical resection types, and local and metastatic status. A systemic review and meta-analysis[41] found that induction chemotherapy followed by conversion surgery led to survival advantage when compared with chemotherapy alone for advanced GC. However, it also concluded that most patients in the surgery group had only one non-curative clinical factors versus more in the non-surgery group.[41] Those in the surgery group were more often chemotherapy responders and most patients underwent R0 resection.[41] The CONVO-GC-1 study (International Retrospective Cohort Study of Conversion Therapy for Stage IV Gastric Cancer 1)[16] suggested that conversion therapy is a promising approach even for those with stage IV disease involving multiple sites and organs, given that they have a response to chemotherapy and R0 resection can be achieved. Likewise, the AIO-FLOT3 trial[26] demonstrated improved survival in patients with limited metastatic disease.

This study achieved quite a remarkable OS for those patients undergoing conversion surgery after induction FLOT. With this multimodality approach, patients with conversion surgery had tripled the median OS of 33.3 months compared to 11.1 months in those without conversion surgery. The hazard ratios of 0.04 in OS and 0.02 in EFS are remarkable. A total of 95.6% of patients undergoing conversion surgery survived the 1-year mark, more than double that of those who did not undergo conversion surgery (42.9%). Patients who did not undergo conversion surgery essentially had survival time similar to that quoted in the literature for advanced GC (11-15 months).[5-10] The longer survival for those who underwent conversion surgery may not be fully attributable to the surgery itself. It can also be a reflection of biological behaviour of the tumour: patients with chemotherapy-sensitive tumours have better survival than those with relatively chemotherapy-resistant tumours.

Several studies, mainly conducted in Japan, had reported a wide range of median OS from 13 to 48 months with induction chemotherapy followed by conversion surgery approach.[16,19,20,24-26] Most of these studies were done on stage IV advanced GC.[16,20,24-26] Factors associated with longer survival times included negative para-aortic lymph nodes,[20] R0 resection,[20,24,25] positive peritoneal cytology as the only non-curative factor,[25] downstaging, pathological response,[24] and those with only retroperitoneal lymph node metastases.[26] Our study found that low BMI (<23 kg/m^2), higher NLR, low serum albumin level (<35 g/L), stage cN3 disease, and those without conversion surgery were associated with worse OS (Table 4). Most of these factors can be identified at baseline and help with clinical decision making. Hypoalbuminaemia was similarly found to be predictive of worse outcomes in a retrospective study looking at patients receiving CROSS (neoadjuvant carboplatin and paclitaxel with radiotherapy) or FLOT in advanced GC.[42] In the same study, low BMI was not associated with survival.[42] Another study showed that BMI is predictive of survival outcomes in gastroesophageal cancers.[43] This inconsistent finding of BMI as a prognostic factor is likely due to the fact that it may not be a perfect marker for nutrition or that nutrition plays only a small role in affecting survival. NLR is a known blood marker representative of systemic inflammation response, which influences tumour progression.[44] It has been shown to be a prognostic marker in predicting tumour progression for resectable GC.[45] Similarly, our study confirms higher NLR was associated with worse OS.

One unique aspect of our study is that it focused mostly on unresectable advanced GC with advanced local tumour and nodal staging, with almost 40% stage cT4b disease, and almost half with locoregionally bulky non–stage cT4b or extensive regional lymph node metastases. On the other hand, a lot of the studies quoted previously in conversion therapy investigated stage IV advanced GC as a whole, consisting of a lot more patients with distant metastases.[16,17,20,21,23-26] The absence of laparoscopic staging might have resulted in inclusion of more upstaged patients with potentially positive peritoneal cytology or small peritoneal implants, which confer a worse prognosis. Given this limitation, the median OS achieved in our study was still admirable.

In recent years, efforts to improve outcomes of resectable GCs investigated the addition of immune checkpoint inhibitor to perioperative FLOT. Data from both the KEYNOTE-585[46] and MATTHERHORN trials[47] demonstrated an increase in pCRs of about 10% with the addition of pembrolizumab and durvalumab, respectively. Our pCR rate of 8.7% is consistent with the FLOT-only

arm of these two studies.[46,47] Our study showed that poor pathological response had a trend of worse survival. Whether pCR translates to longer survival in advanced GC remains controversial as compared to other tumour types (e.g., triple-negative breast cancer or lung cancer) where pCR is a surrogate for survival. The addition of pembrolizumab showed favourable outcomes in EFS but no difference in OS so far.[48] The MATTERHORN trial[47] is still awaiting long-term results.

Limitations

This study has several limitations. First, it is a single-centre retrospective analysis and there was no control group for comparison. Second, the sample size is small. Third, quality-of-life of the patients and cost-effectiveness were not measured. Taken all together, induction FLOT followed by conversion surgery should be strongly considered if patient has limited burden of baseline incurable factors which responded to chemotherapy and R0 resection is anticipated, as this offers a favourable survival benefit for patients with advanced GC.

CONCLUSION

Our study showed that induction FLOT achieved high conversion rates and R0 resections, providing a favourable survival benefit with acceptable safety in unresectable GC. Future research is warranted to explore whether adding immune checkpoint inhibitors, especially for patients with high programmed death ligand 1 expression, or other more effective biomarker-driven therapy can further improve the conversion rate, pCR rate, and survival.

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