Real Life Experience of Patients With Locally Advanced Gastric and Gastroesophageal Junction Adenocarcinoma Treated With Neoadjuvant Chemotherapy: a Turkish Oncology Group Study

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Abstract

Purpose

Neoadjuvant chemotherapy(NACT) in gastroesophageal junction(GEJ) and gastric cancer(GC) was shown to improve survival in recent studies. We aimed to share our real-life experience of patients who received NACT in order to compare the efficacy and toxicity profile of different chemotherapy regimens in our country.

Methods

This retrospective multicenter study included locally advanced GC and GEJ cancer patients who received NACT, and had pathological response evaluation between 2007 and 2021. Relation between CT regimens and pathological evaluation were analyzed.

Results

A total of 728 patients from 45 oncology centers in Turkey were included. Median age at the time of diagnosis was 60 (range: 18-68). Most frequent NACT regimens used were FLOT (65%), DCF (18%) and ECF (8.1%), respectively.

In the total study group pCR rate was 8.2%, R0 resection rate 88.5%, and D2 dissection rate was 66.8%. Rate of pCR and near-CR (26.4%), and R0 resection (92.6%) were higher in FLOT arm (p= 0.005 and <0.001). Patients who received FLOT had significantly higher chemotherapy-related toxicity rate compared to patients who received other regimens (p=0.02).

Median follow-up time was 17 months (range: 3-106 months). Estimated median overall survival (OS) was 59.4 months (95% CI: 32.9-86.0) and disease-free survival (DFS) was 47.6 months (95% CI: 24.4-70.8). The highest 5-year estimated OS rate was also shown in FLOT arm (58%).

Conclusion

In our real-life study, FLOT regimen has superior survival outcome despite worse toxicity profile. Clinicians should tailor treatment regimens according to patients' multifactorial status and comorbidities for to obtain best outcomes.

Introduction

Gastric cancer (GC) is an important health problem in Turkey. GC is the fifth common cancer, and the third common cause of cancer related death after lung cancer in our country [1]. In addition GC is also a global problem, as it is the third common cause of cancer-related death in the world [2]. It is usually diagnosed in an advanced stage [3]. While 5-year survival rates for stage I patients with curative resection are between 70–75%, it decreases to 25–30% in the locally advanced stage [4]. Therefore, instead of complete resection and lymph node dissection which is known as the only curative treatment in earlier stages, multimodal treatment is a better option for the treatment of locally advanced disease.

Goals of perioperative treatments are to observe the response rates which also gives us hints of the biology of the disease, to eliminate possible micrometastatic disease, to down-stage the primary tumor to increase the chance of R0 resection, and finally to improve survival [5–7].

The United Kingdom Medical Research Council (MAGIC) trial was the first large randomized controlled trial to demonstrate significant benefit of perioperative chemotherapy in GC and gastroesophageal junction (GEJ) cancer. In this study patients who received epirubicin, cisplatin, and 5-fluorouracil (ECF) regimen before surgery survived longer than the ones who were only operated [5]. Subsequent study of "Federation Nationale des Centres de Lutte contre le Cancer" (FLNCC) also demonstrated that cisplatin and 5-fluorouracil (CF) regimen in perioperative setting improved survival compared to surgery alone [6]. Finally, perioperative docetaxel, oxaliplatin, 5-Fluorouracil (FLOT) regimen was shown to be superior for survival when it was compared to ECF in the FLOT4-AIO trial [7].

Still best regimen in neoadjuvant setting needs to be tailored for each patient. Many factors are taken into consideration when choosing neoadjuvant chemotherapy (NACT) regimens in our daily practice such as age, performance status and comorbidities of

patients. Our aim is to share the real-life experiences of patients with gastric and GEJ carcinomas who received different NACT regimens in our country.

Materials And Methods

We retrospectively evaluated 797 patients with locally advanced (clinical T2 or higher, and/or node positive stage) GC and GEJ adenocarcinoma who were treated with NACT between October 2007-March 2021. The study included 728 patients from 45 different oncology centers in Turkey, who were older than 18 years, were operated after NACT, and had evaluable pathology report. Sixty-three patients who were not operated after NACT, five patients who received neoadjuvant chemoradiotherapy (NACRT), and one patient whose tumor was squamous cell histology were excluded.

Demographic, clinicopathologic, efficacy and side effect data of different NACTs were recorded from their files. Clinical staging at presentation was performed according to American Joint of Committee on Cancer (AJCC) staging 7th edition [8]. Collage of American Pathologists (CAP) -Tumor Regression Grading (TRG) were used for pathological evaluation after surgery [9].

- TRG0: Pathological complete response (pCR): no viable cancer cells;

- TRG1: Near complete response (near CR): single cells or small groups of cancer cells;

- TRG2: Partial response (PR): residual cancer outgrown by fibrosis;

- TRG3: Poor response/no response: minimal or no tumor was killed or extensive residual cancer.

Chemotherapy related toxicities were graded according to Common Terminology Criteria for Adverse Event Version 4.03. Different chemotherapy regimens were compared in terms of efficacy, safety and toxicity.

Statistical Analysis

All categorical variables were presented as frequencies and group percentages, ranges were denoted for parameters with a median value. Chi-square test was used to compare categorical variables. Univariate and multivariate cox/logistic regression models were conducted to assess factors that predicting survival and pathological response. Overall survival (OS) was defined as the time interval in months between the diagnosis of disease to death or last outpatient visit if the patient was still alive. Disease free survival (DFS) was defined as the time interval in months between the diagnosis of disease to relapse, or last follow-up if patient was not relapsed. OS and DFS were estimated with Kaplan-Meier method and log-rank test. Confidence interval (CI) was selected as 95% and a 2-sided p value less than 0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS 20.0 software.

Protocols of Chemotherapy Regimens

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel

Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1

Leucovorin 200 mg/m^2 IV on Day 1

Oxaliplatin 85 mg/m^2 IV on Day 1

Docetaxel 50 mg/m^2 IV on Day 1

Cycled every 14 days

FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin

Fluorouracil 2400 mg/m^2 IV continuous infusion over 48 hours on Days 1–2

Fluorouracil 400 mg/m^2 IV on Day 1

Leucovorin 400 mg/m^2 IV on Day 1

Oxaliplatin 85 mg/m^2 IV on Day 1

Cycled every 14 days

CAPEOX: capecitabine and oxaliplatin

Capecitabine 1000 mg/m^2 PO BID on Days 1–14

Oxaliplatin 130 mg/m^2 IV on Day 1

Cycled every 21 days

CF: cisplatin and 5-Fluorouracil

Cisplatin 50 mg/m^2 on Day 1

Fluorouracil 2000 mg/m^2 IV continuous infusion over 48 hours on Days 1–2

Cycled every 14 days

DCF: docetaxel, cisplatin and 5-Fluorouracil

Docetaxel 75 mg/m^2 IV on Day 1

Cisplatin 75 mg/m^2 on Day 1

Fluorouracil 750 mg/m^2 daily IV continuous infusion on Days 1–5

Cycled every 21 days

DCX: docetaxel, cisplatin and capecitabine

Docetaxel 60 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 on Day 1

Capecitabine 1650 mg/m^2 PO on Days 1–14

Cycled every 21 days

ECF: epirubicin, cisplatin, and 5-fluorouracil,

Epirubicin 50 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 IV on Day 1

Fluorouracil 200 mg/m^2 daily IV continuous infusion on Days 1–21

Cycled every 21 days

ECX: epirubicin, cisplatin, and capecitabine

Epirubicin 50 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 IV on Day 1

Capecitabine 825 mg/m^2 PO BID on Days 1–14

Cycled every 21 days

*CAPEOX/FOLFOX, DCF/DCX and ECF/ECX were combined and evaluated as a single group.

Results

Total of 728 patients with GC/GEJ were included in this study, with a male predominance (72.8%). Median age at the time of diagnosis was 60 (range: 18–68). Histology was adenocarcinoma in all, and 55% of patients had gastric primary. All patients were operated and 66.8% had D2 dissection. Patient and tumor characteristics were described in Table 1.

Mostly used NACT regimens were FLOT (65%), DCF (18%) and ECF (8.1%), respectively. Patients received median of 4 cycles of NACT (range: 2–10). Adjuvant chemotherapy was given to 606 (83.2%) patients, and 48 of them received additional adjuvant radiotherapy.

Sixty patients (8.2%) had pCR. Rate of pCR and near-CR (26.4%), and R0 resection (92.6%) were higher in FLOT arm ($p = 0.005$ and < 0.001). Efficacy of different chemotherapy regimens according to clinical stage was not different as presented in Table 2. On the other hand, patients who received FLOT had significantly higher chemotherapy-related toxicity rate compared to patients who received other regimens ($p = 0.002$). Febrile neutropenia was observed in 10 patients after FLOT regimen despite of granulocyte colony-stimulating factor (GCSF) prophylaxis. Comparison of chemotherapy regimens according to pathological response and toxicity profiles are presented in Tables 3 and 4.

Median follow-up time was 17 months (range: 3-106 months). During follow-up, 190 (26.1%) patients were deceased, and 211 (29%) relapsed. Estimated three-year OS rate was 60%. Estimated median OS was 59.4 months (95% CI: 32.9–86.0) and DFS was 47.6 months (95% CI: 24.4–70.8). Although it was not statistically significant, the highest 5-year estimated OS rate was shown in FLOT arm (58%). Kaplan Meier survival curves presented in Figs. 1 and 2. Three most common relapse sites were peritoneal carcinomatosis (40.8%), liver metastasis (22.7%) and loco-regional relapses (10.4%). Results of survival analysis according to chemotherapy regimens is presented in Table 5.

As we presented in Table 6, positive surgical margins in surgery and no pathological response to NACT were determined as independent poor prognostic factors for both OS and DFS in multivariate analysis.

In addition, not receiving adjuvant treatment was also determined as independent poor prognostic factor for OS.

Discussion

In recent years, multimodal approach has been preferred in the treatment of GC and GEJ carcinomas which have aggressive biology and poor prognosis. NACT had valuable advantages such as downstaging of tumor, possibly preventing micrometastatic disease, increasing R0 resection rate, and as a result of all improving survival.

In randomized controlled trials, it has been shown that higher rate of R0 resection and D2 dissection improved survival via improving pathological responses [10]. While MAGIC and French FNCLCC/FFCD trials did not include a proper extended lymphadenectomy in the majority of cases, FLOT-AIU trial had mostly D2 dissection. In all these three landmark studies R0 resection rates were higher in selected arms. We observed that 66.8% of our patients had D2 dissection, and R0 resection rates according to NACT were 92% with FLOT, 86% with DCF, 83% with CF, 78% with FOLFOX and 73% with ECF, which were consistent with the literature.

In our pathological evaluation; we observed higher pCR rates with FLOT regimen (9.1%), but this was lower than 16% of pCR seen in FLOT4-AIO trial [11]. Near-CR rate was also higher in FLOT4-AIO trial (37%) than our study (26.4%).

In FLOT4-AIO trial, distribution of diagnostic age and ECOG-PS were similar with our study. On the other hand, 3.2% of patients in FLOT4-AIO trial could not be operated due to various reasons. These poor prognostic patient group was excluded from our study

cohort. In addition, patients having clinical lymph node positive disease were also higher in FLOT4-AIO trial than our study (78% vs. 55%, respectively). Therefore FLOT4-AIO trial seemed to have more patients with aggressive disease characteristics than our study. Nevertheless, 90% patients in FLOT4-AIO trial completed all cycles of allocated chemotherapy, while this rate was only 77.4% in our study. We believe that failure to complete all cycles of chemotherapy is the most important factor affecting our lower pathological response rate.

Perioperative chemotherapy for GE and GEJ adenocarcinoma was shown to improve survival in the literature. First study was reported in 2006, the MAGIC [5] trial showed significant improvement in 5-year OS rate with perioperative ECF treatment over surgery alone (36% *vs* 23%). Second study came out on 2011, French FNCLCC/FFCD trial [6], reported patients who received CF before and after surgery resulting in a significant improvement of 5-year DFS and OS over surgery alone (DFS: 34% vs 19%, and OS: 38% *vs* 24%, respectively). Finally, the FLOT4-AIO trial compared FLOT and ECF/ECX regimens as perioperative treatment in advanced GC and GEJ cancer with clinical resectable tumors, stage cT2 or higher, or nodal positive stage, or both, with no evidence of distant metastases. Results of this landmark study published in 2016 and updated in 2019, showed a 5-year OS rate improvement with FLOT regimen (45% *vs* 36%, respectively) [7, 11, 12]. Besides these randomized trials, Li et al. demonstrated perioperative FOLFOX regimen improved survival [13]. In this prospective non-randomized study, locally advanced GC patients received a total of 6 cycles of FOLFOX chemotherapy perioperatively vs. postoperatively with a 4-year OS rate of 78% vs. 51%, respectively. DCF regimen usually investigated on advanced GC and GEJ tumors. V325 Phase II/III trial demonstrated significantly improved OS, time to progression, and quality of life over CF regimen [14]. Two-year survival rate was 18% with DCF and 9% with CF. All these pivotal trials summarized in Table 7.

Our study is different from other studies, as we compared five different NACT regimens frequently used in daily practice. In our study population, 1-, 2-, and 5-year estimated survival rates were 89%, 72%, and 52%, respectively. According to NACT regimens, estimated 5-year OS rates were 58% with FLOT, 55% with CF, 54% with DCF and 39% with ECF, and estimated 3-year OS rate was 70% for FOLFOX. We observed higher survival rates compared to the literature. Patients who were included in our retrospective cohort were all operated after NACT. Most of the patients with progressive disease on neoadjuvant treatment could not be operated, and expected to live shorter. Also, some might have died during the NACT, either related to side effects or secondary to rapid disease progression. Excluding these patients with primary resistant disease could have affected our results. Besides these, patients having clinical positive lymph nodes (cN+) who were expected to have poor prognosis were lower in our study population. In addition, our patient cohort had higher D2 dissection rate (66.8%) that effected higher survival rates.

However, since patients with complete retrospective data were included in the study, patients with possibly had poor prognosis and had incomplete data were excluded due to investigator's bias.

In the literature it has been shown that completion of planned chemotherapy is as important as selected regimen on efficacy. Dose modifications or interrupt treatment and failure to continue with adjuvant chemotherapy adversely affected on survival outcomes.

Although perioperative FLOT is considered as standard-of-care for locally advanced resectable GC and GEJ adenocarcinomas, its' toxicity profile and intolerance jeopardize completion of the planned 8 cycles. Only 46% of patients completed all cycles (pre and post-operative treatment) in the initial phase 2/3 trial (FLOT-AIO) [11].

Good performance patients were carefully selected for these trials. It was demonstrated that grade 3 or 4 neutropenia was 52%, and febrile neutropenia was 2% in FLOT-AIU trial. Despite higher primary GCSF prophylaxis in our study (34% in FLOT-AIU trial, 92% in ours), we observed higher grade 3 or 4 neutropenia (62%) and febrile neutropenia (2.1%). It may be due to low socioeconomical level and lack off self-care in our country. In our study we also observed grade 3 or 4 chemotherapy-related adverse events and interruption of treatment most frequently with FLOT regimen (28.5% and 6.3%).

On the other hand, the least grade 3 or 4 chemotherapy-related adverse events and interruption of treatment was observed with ECF (11.8% and 0%). Most common grade 3 or 4 adverse event was nausea (6.7%). It was 6.4% in MAGIC study and 16% in FLOT-AIU study. Most common toxicity being nausea consistent with the literature, might have been induced by cisplatin.

Adding docetaxel to CF resulted increasing toxicity as well as adding epirubicin to CF has been described in the literature (especially leukopenia for all) [14, 15]. Hence, CF replaces ECF and DCF in guidelines as neoadjuvant setting. Higher CF toxicity results compared to both ECF and DCF may be due to the small number of patients in that arm in our study.

Enzinger et al. [16] confirmed in the CALGB 80403/E1206 study, that the FOLFOX regimen had similar effectiveness and better tolerance than the ECF regimen. Efficacy of FOLFOX regimen on neoadjuvant setting was also determined in other recent studies [17–20]. Al-Batran et al. [18] and Vita et al. [20] showed that FOLFOX regimen did not lead more grade 3 or 4 toxicities.

In our study we observed that FOLFOX/CAPEOX regimens are well-tolerated. In this arm, grade 3 or 4 adverse events occurred 15.6% of patients, and most common side effect was neutropenia (6.1%). In FOLFOX group, patients older than 65-years was 50% of the group, and it was higher than other chemotherapy arms. It was striking that FOLFOX was a more tolerable regimen.

The limitations of our study are its' retrospective design and shorter follow-up period. Despite the pathological evaluation was demonstrated one by one ypT and ypN in the landmark trials, we only have combined ypTN data in patients' files. It is difficult for us to compare pathological results in detail. Our survival rates were estimation, and with longer follow-up period, survival results can be altered.

Conclusion

Here, we investigated perioperative chemotherapy preferences in locally advanced GC and GEJ tumors in our country, and aimed to share the real-life experience in efficacy and tolerability of different regimens. We still do not know which NACT regimen is the best choice for daily practice. Clinicians should be aware of potential side-effects of the regimens and tailor it wisely for the patient. We believe that better results will be obtained with determining correct patient-treatment pairs.

Declarations

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Conflict of Interest

The authors declare that they have no conflict of interest

Availability of Data and Material

Available

Ethics Approval

All procedures performed were in accordance with ethical standards of institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical committee approval was obtained from our institute with a number of: 09.2020.1108.

Consent to participate and for publication

All authors approved the final version of manuscript. They all consent to participate and consent for publication.

Author Contributions

TB: designed research, analyzed datas, wrote article

CE, AS, EÖ, DÇ, EÇ, DTÖ, MA, MAŞ, MD, BÖ, MKE, ÖE, EŞT, ND, ÖD, MÖ, İH, İÖ, ETB, HÇY, ŞY, SP, EY, AA, MÖ, AO, EA, BK, ND, MD, DE, NA, Aİ, DKS, AG, TK, ÖÖ, ÖA, ÇÜ, ST, YK: collected datas from their centers

PFY: supervisor of study, designed study, edited english writing

All authors read and approved the manuscript

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Tables

Table 1

Characteristics of Patients and Tumors

Descriptives	n = 728, n(%)
Gender	
Female	198(27.2)
Male	530(72.8)
ECOG-PS	
0	418(57.4)
1	288(39.6)
2	22(3.0)
Age at Diagnosis	
< 65	506(69.5)
≥ 65	222(30.5)
Smoking History	
Current/Past	303(41.6)
Location of Tumor	
GEJ	324(44.5)
Gastric	404(55.5)
Fundus	47(6.5)
Corpus	8(25.8)
Antrum	9(23.2)
Clinical Stage	
cT1-2N+	26(3.6)
cT3-4N0	328(45.1)
cT3-4N+	374(51.4)
Type of Surgery	
Total gastrectomy	511(70.2)
Subtotal gastrectomy	208(28.6)
Palliative	9(1.2)
Lymph Node Dissection	
D1	242(33.2)
D2	486(66.8)
Resection	
R0	644(88.5)
R1	55(7.6)
R2	29(4)
LVI	390(53.6)
PNI	335(46)
Grade Groups	
Grade 1	53(7.2)
Grade 2	387(53.2)
Grade 3	261(35.9)
Pathological Response	
CR	60(8.2)
Near CR	105(14.4)
PR	284(39)
No response	279(38.3)

ECOG-PS: Eastern Cooperative Oncology Group Performance Status, GEJ: gastroesophageal junction, LVI: lymphovascular invasion, PNI:perineural invasion, CR: complete response, PR: Partial response

Table 2

Efficacy of Chemotherapy Regimens According to Clinical Stage

Chemotherapy Regimens	cT1-2N+ n = 26 (RR%)	cT3-4N0 n = 324 (RR%)	cT3-4N+ n = 364 (RR%)
FLOT	4(20)	73(31.9)	48(21.4)
FOLFOX/CAPEOX	0	4(19)	1(10)
DCF/DCX	1(33.3)	6(11.5)	14(18.4)
CF/CX	-	1(11.1)	2(22.2)
ECF/ECX	0	1(7.7)	11(24.4)
p value	0.85	0.05	0.84

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel, FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin, CAPEOX: capecitabine and oxaliplatin, CF: cisplatin and 5-Fluorouracil, DCF: docetaxel, cisplatin and 5-Fluorouracil, DCX: docetaxel, cisplatin and capecitabine, ECF: epirubicin, cisplatin, and 5-fluorouracil, ECX: epirubicin, cisplatin, and capecitabine, RR: response rate (complete response and near complete response)

Table 3

Comparison of Chemotherapy Regimens According To Pathological Evaluation

Chemotherapy Regimens	Location		n = 728(%)	Pathological Response			Resection Rate		
	GEJ, n (%)	Gastric, n (%)		CR, n (%)	CR+ nearCR, n (%)	PR+ poor/no response, n (%)	R0, n (%)	R1, n (%)	R2, n (%)
FLOT	223(47.1)	250(52.9)	473(65)	43(9.1)	125(26.4)	163(34.5)	438(92.6)	22(4.7)	13(2.7)
FOLFOX/CAPEOX	12(37.5)	20(62.5)	32(4.4)	2(6.3)	5(15.6)	13(40.6)	25(78.1)	4(12.5)	3(10.3)
DCF/DCX	51(38.9)	80(61.1)	131(18)	7(5.3)	21(16)	61(46.6)	113(86.3)	15(11.5)	3(2.3)
CF/CX	10(55.6)	8(44.4)	18(2.5)	1(5.6)	3(16.7)	9(50)	15(83.3)	2(11.1)	1(5.6)
ECF/ECX	21(35.6)	38(64.4)	59(8.1)	3(5.1)	12(20.3)	28(47.5)	43(72.9)	11(18.6)	5(8.5)

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel, FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin, CAPEOX: capecitabine and oxaliplatin, CF: cisplatin and 5-Fluorouracil, DCF: docetaxel, cisplatin and 5-Fluorouracil, DCX: docetaxel, cisplatin and capecitabine, ECF: epirubicin, cisplatin, and 5-fluorouracil, ECX: epirubicin, cisplatin, and capecitabine, GEJ: gastroesophageal junction CR: complete response, PR:partial response, R0: microscopically margin-negative resection, R1: microscopically margin-positive resection, R2: macroscopically margin-positive resection

Table 4

Comparison of Chemotherapy Regimens According To Toxicity Profiles

Chemotherapy Regimens	Adverse Events, n (%)		Most Common Adverse Events, (%)		FN, n (%)	Stop/Interrupt treatment, n (%)
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4		
FLOT	228(48.2)	135(28.5)	Anemia (71.1)	Neutropenia (62)	10 (4.3)	30 (6.3)
FOLFOX/CAPEOX	13(40.6)	5(15.6)	Neuropathy (65.8)	Neutropenia (19.1)	0	1 (3.1)
DCF/DCX	48(36.6)	32(24.4)	Neutropenia (55.5)	Neutropenia (42.4)	0	5 (3.8)
CF/CX	4(22.2)	5(27.8)	Trombositopenia (15.2)	Anemia (16.7)	0	0 (0)
ECF/ECX	31(52.5)	7(11.8)	Neutropenia (15.9), Nausea (23.1)	Nausea (6.7)	0	0 (0)

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel, FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin, CAPEOX: capecitabine and oxaliplatin, CF: cisplatin and 5-Fluorouracil, DCF: docetaxel, cisplatin and 5-Fluorouracil, DCX: docetaxel, cisplatin and capecitabine, ECF: epirubicin, cisplatin, and 5-fluorouracil, ECX: epirubicin, cisplatin, and capecitabine, FN: Febrile neutropenia,

Table 5

Survival Analysis

Chemotherapy regimen	n (%)	Median DFS (months) (95% CI)	5 Year DFS Rate (%)	Median OS (months) (95% CI)	5 Year OS Rate (%)
All patients	728(100)	47.6 (24.4–70.8)	43	59.4 (32.9–86.0)	52
FLOT	473(65)	NR(NR)	53	NR(NR)	58
FOLFOX/CAPEOX	32(4.4)	NR(NR)	-	NR(NR)	
DCF/DCX	131(18)	85.7 (37.7-133.8)	43	107.9 (12.3-203.6)	54
CF/CX	18(2.5)	NR(NR)	43	NR(NR)	55
ECF/ECX	59(8.1)	7.6 (19.7–49.6)	37	37.7 (31.6–43.8)	39

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel, FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin, CAPEOX: capecitabine and oxaliplatin, CF: cisplatin and 5-Fluorouracil, DCF: docetaxel, cisplatin and 5-Fluorouracil, DCX: docetaxel, cisplatin and capecitabine, ECF: epirubicin, cisplatin, and 5-fluorouracil, ECX: epirubicin, cisplatin, and capecitabine, OS:Overall Survival, DFS: Disease Free Survival, NR:non-reached, CI: Confidence Interval, NR: Non reached

Table 6

Univariate and Multivariate Analyses of Factors That Predicting Survival

Factor	Univariate analysis for OS		Univariate analysis for DFS		Multivariate analysis for OS		Multivariate analysis for DFS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Gender (male vs. female)	1.28 (0.93–1.75)	0.003	1.26(0.94–1.69)	0.12	2.0(1.40–3.01)	0.10	-	-
Age at Diagnosis (≥ 60 vs. <60)	1.23 (0.78–1.93)	0.366	1.04(0.77–1.40)	0.79	-	-	-	-
Clinical Stage (lymph nodes positive vs. negative)	1.00 (0.75–1.35)	0.953	1.39(1.05–1.84)	0.01	-	-	1.29(0.97–1.71)	0.73
Location (Gastric vs. GEJ)	1.34(0.92–1.97)	0.126	1.05(0.79–1.38)	0.72	-	-	-	-
Surgical margin (positive vs. negative)	3.24(1.77–5.91)	0.000	1.75(1.19–2.58)	0.008	3.51(2.13–5.78)	0.000	1.83(1.24–2.70)	0.002
Lymph Nodes Dissection Type (D1 vs D2)	1.50(1.02–2.26)	0.036	1.24(0.94–1.63)	0.12	1.06(0.73–1.43)	0.67	-	-
Perineural invasion (yes vs. no)	1.39(0.94–2.04)	0.090	1.43(1.09–1.88)	0.009	-	-	1.05(0.76–1.46)	0.72
Lymphovascular invasion (yes vs. no)	1.29(0.89–2.25)	0.075	1.50(1.13–1.98)	0.004	-	-	1.28(0.96–1.71)	0.88
Receiving Adjuvant Treatment (no vs. yes)	1.99(1.43–2.77)	0.000	1.39(0.97–1.98)	0.07	1.98(1.40–2.79)	0.000	-	-
Pathological Response (No response vs. others) (Others vs Complete response)	1.90(1.48–2.62) 1.97(0.97–4.03)	0.000 0.057	1.88(1.42–2.44) 1.26(0.73–2.17)	0.000 0.38	2.12(1.59–2.84)	0.000	1.73(1.30–2.29)	0.000

HR: Hazard ratio, CI: Confidence interval, GEJ: gastroesophageal junction

Table 7

Comparison of Pivotal Trials Using Perioperative Treatment

Trial	Chemotherapy regimen	n(%)	pCR rate (%)	D2 dissection rate (%)	R0 resection rate (%)	Median DFS (months); HR (%95CI) (p)	Median OS (months); HR (%95CI)
MAGIC(5)	ECF + Surgery Surgery	250 253	Not reported	42.5 40.4	81.9 66.7	Estimated surival rate was given HR 0.66 (0.53 to 0.81) p < 0.001	Estimated surival was given HR 0.75 (0.60 to 0.93) p = 0.009
French FNCLCC/FFCD(6)	CF + Surgery Surgery	113 111	Not reported	Not reported	84 74	HR 0.65 (0.48 to 0.89) p = 0.003	HR 0.69 (0.50 to 0.95) p = 0 .02
FLOT4/AIO(7)	FLOT ECF/ECX	356 360	16 6	57 53	85 78	30 months 18 months HR 0.75 (0.62 to 0.91) p = 0.003	50 months 35 months HR 0·77 (0.63 to 0·94) p = 0.012
Li et al(13)	Perioperative FOLFOX Adjuvant FOLFOX	36 37	6.1 -	Not reported Not reported	86 55	Survival rate was given p = 0.031	Survival rates were given p = 0.022
Basoglu et al	FLOT Others	473 255	9.1 5.5	70.6 59.6	68 32	NR(NR) 47.6 months (21.6 to 73.7) HR 0.93(0.70 to 1.24) p = 0.65	NR(NR) 59.4 months (31.2 to 87.7) HR 1.0(0.74 to 1.35) p = 0.98

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel, FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin, CAPEOX: capecitabine and oxaliplatin, CF: cisplatin and 5-Fluorouracil, DCF: docetaxel, cisplatin and 5-Fluorouracil, DCX: docetaxel, cisplatin and capecitabine, ECF: epirubicin, cisplatin, and 5-fluorouracil, ECX: epirubicin, cisplatin, and capecitabine, pCR: pathological complete response, HR: hazard ratio, CI: Confidence interval

Figures

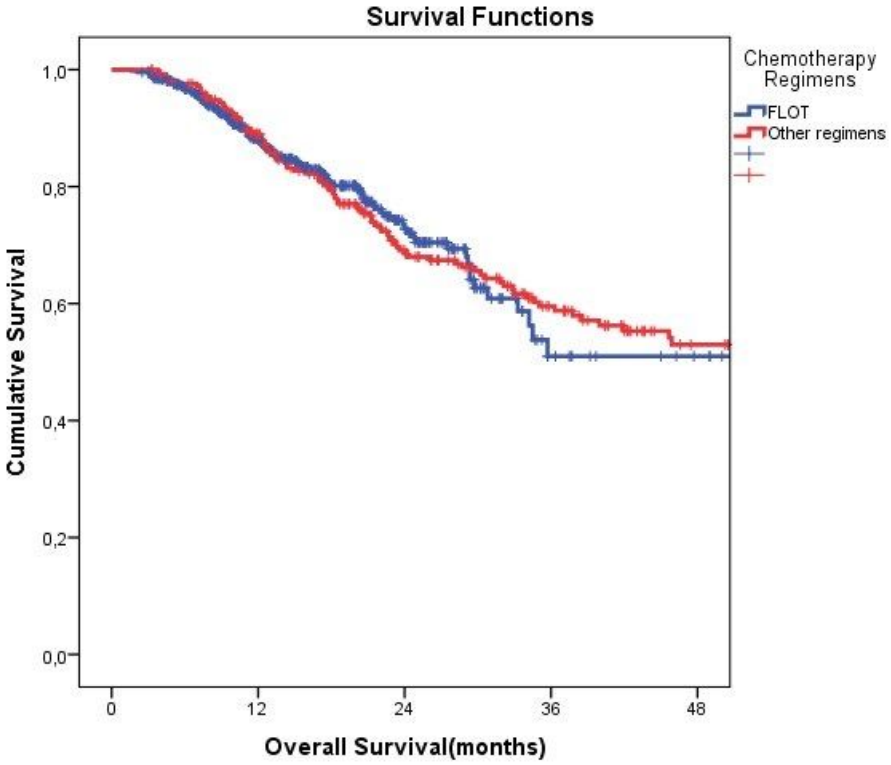

Figure 1

Kaplan-Meier Curve FLOT vs Other Chemotherapy Regimens Predicting Overall Survival p=0.98

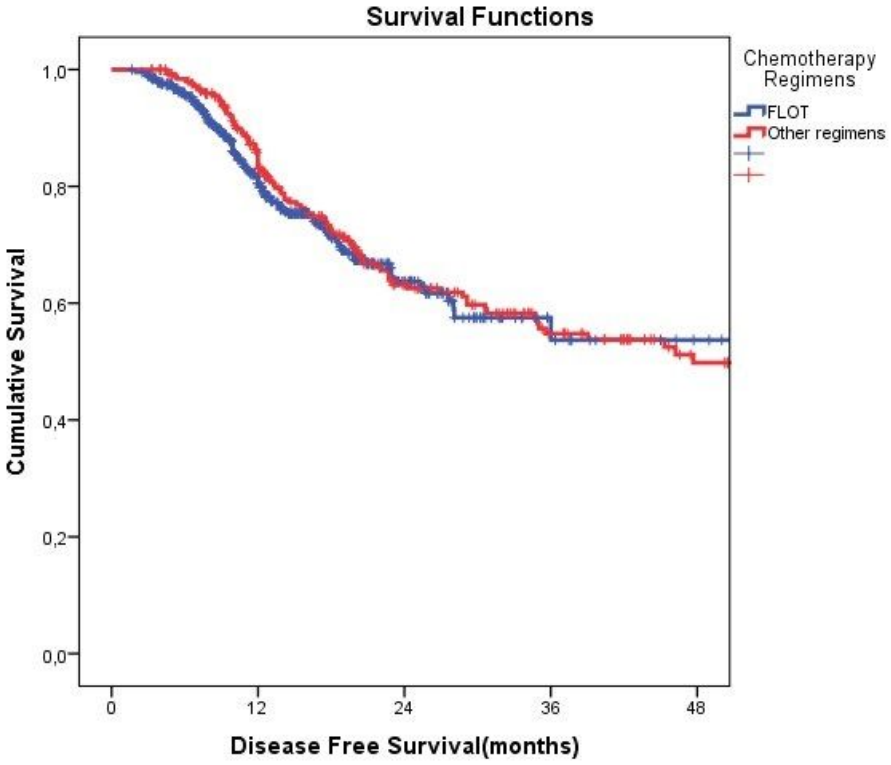

Figure 2

Kaplan-Meier Curve FLOT vs Other Chemotherapy Regimens Predicting Disease Free Survival p=0.65