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Two-center experience comparing the use of the FLOT4 and CROSS schemes for patients with gastric, esophageal, and gastroesophageal junction adenocarcinoma

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Abstract

Introduction. Gastric (GAD), gastroesophageal junction (GEJA), and esophageal adenocarcinoma (EAD) share pathophysiological features. At localized stages, FLOT is used perioperatively for the treatment of GAD and GEJA and CROSS for EAD and some GEJA. Although both therapies have been compared with MAGIC, comparative randomized data on FLOT and CROSS are not yet available.

Material and methods. We retrospectively analyzed and compared 40 patients treated with FLOT and 16 patients treated with CROSS in terms of clinical features and neoadjuvant, surgical, adjuvant, and survival outcomes.

Results. At the time of analysis, 65% of patients treated with FLOT4 and 56.3% with CROSS remained in complete remission. Those who progressed after FLOT4 did so mainly at the peritoneal level (25%) and after CROSS at the bone, lymph node, and peritoneal levels (12.5% respectively). Six patients (37.5%) died after CROSS (median OS of 17.5 months; 95% CI 2–41) and 10 (25%) after FLOT4 (median OS 16.5 months; 95% CI 11–22). For the living patients, the median numbers of months from diagnosis to the follow-up cutoff date were 47.5 (95% CI 11–67) and 27 (95% CI 14–44) for CROSS and FLOT4, respectively. There were no significant differences in median OS estimated by Kaplan Meier analysis [FLOT4: 50 ± 4.6 months (95% CI 40.9–59.2); CROSS: 51.2 ± 7 months (95% CI 37.4–65.0; p = 0.79)].

Conclusions. Although we obtained lower pCR rates; TNM downstaging after neoadjuvant therapy, R0 rates, tolerance, PFS, and OS were similar in both groups and comparable with trial results. The adjuvant compliance rate was high with FLOT4. CROSS allows sequencing with nivolumab in PD-L1+ tumors.

Keywords: CROSS, esophageal adenocarcinoma gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, FLOT

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Introduction

Gastric (GAD), gastroesophageal junction (GEJA), and esophageal adenocarcinoma (EAD) share pathophysiological and molecular similarities. Therefore, treatment regimens used in these locations are sometimes the same.

In the treatment of localized GAD [E. IB–III American Joint Committee on Cancer (AJCC) 8th ed., i.e. > T1, > N0, M0], the 2022 European Society for Medical Oncology (ESMO) guidelines recommend a multimodality treatment with perioperative chemotherapy schemes (level of evidence IA). For GAD, the standard of care is the FLOT4 scheme (docetaxel 50 mg/m^2 plus oxaliplatin 85 mg/m^2 plus leucovorin 200 mg/m^2 plus 5-fluorouracil (5FU) 2600 mg/m^2 in 24-hour infusion, with 4 cycles administered before surgery and 4 cycles after) [1].

The randomized, controlled, blinded phase III clinical trial that led to FLOT4 scheme approval was the FLOT4-AIO trial [2]. The control arm involved the perioperative ECF/ECX chemotherapy schedule (where E corresponds to epirubicin, C to cisplatin, F to 5FU, and X to capecitabine; × 3 cycles pre-surgery and 3 cycles post-surgery), approved following the phase III MAGIC clinical trial [3]. Median overall survival (mOS) was 50 months for the experimental arm and 35 months for the control arm [hazard radtio (HR) = 0.77; p = 0.012]. Five-year overall survival (OS) was significantly superior for the experimental arm (45% *vs.* 36%). The survival benefit was maintained in all subgroups [2].

In the treatment of localized esophageal tumors, the 2022 ESMO guidelines initially distinguish between tumors of squamous histology on the one hand and EAD together with GEJA on the other. In tumors cT2-T4 or N1-3, M0 (which corresponds in the case of esophageal adenocarcinoma to AJCC stages IIA–IVA 8th ed.), there are two recommended options with the same level of evidence IA: the perioperative scheme with FLOT4 (especially used in clinical practice in Siewert III GEJA) and the neoadjuvant CROSS scheme [carboplatin area under the receiver operating characteristic curve = 2 (AUC 2)] plus paclitaxel 50 mg/m^2 weekly concomitant with RT 41.4 Gy, especially used in clinical practice in Siewert I and II (GEJA and EAD) [4].

The phase III clinical trial that led to approval of these schemes was the CROSS trial, where the control arm included only surgery. Median overall survival was 49.4 months for the perioperative chemo-radiotherapy arm followed by surgery, *versus* 24 months for patients included in the surgery arm. Overall survival at 5 years was significantly superior in the experimental arm (47% *vs.* 34%; HR = 0.65; 95% CI 0.49–0.87) [5].

The advantage of the CROSS scheme, as stated in the 2022 ESMO guidelines, is that it allows the option of adjuvant treatment with nivolumab after surgery, approved as a result of the phase III CHECKMATE-577 trial (240 mg fortnightly dose or 480 mg monthly dose, with a total duration of one year), where the control arm was placebo. In that trial, 29% of patients included in each arm had squamous histology and 71% had adenocarcinoma. Median disease-free survival (mDFS) was significantly superior for nivolumab at 22.4 months *vs.* 11 months (HR for risk of recurrence or death of 0.69; 96.4% CI 0.56–0.86) [6].

However, using immunotherapy in the adjuvant setting also means not being able to employ it in the case of relapse in the metastatic setting. In addition, the results of the phase II clinical trial EORTC 1707 VESTIGE presented at the 2023 ESMO gastrointestinal cancer congress, which compared the benefit of adjuvant use of nivolumab (3 mg/kg, q2w, 1 year) plus ipilimumab (1 mg/kg, q6w, 1 year) *vs.* chemotherapy in patients with GEJA at high risk of recurrence (ypN+ and/or R1), whose results favored the use of adjuvant chemotherapy (mDFS: 11.9 months for the use of immunotherapy *vs.* 23.2 months for the use of chemotherapy; HR = 1.8; 95% CI 1.09–2.98), made it clear that further studies are necessary [7].

Like the FLOT4-AIO trial, the randomized controlled blinded phase III clinical trial NEO-AEGIS compared the CROSS scheme primarily with ECF/ECX (157 patients in the control arm), except for 27 patients included from 2018 in whom the FLOT4 scheme was continued [8]. The study demonstrated the non-inferiority of the CROSS scheme with 3-year OS of 57% *vs.* 56%. No significant differences in toxicity were also found, but the CROSS arm achieved better pathological response [42% *vs.* 12.1% for major pathological response and 17.3% *vs.* 5.1% for complete pathological response (pCR)], higher R0 rate (95% *vs.* 82%) and higher nodal downstaging (ypN0 60% *vs.* 43%) [8].

Although both FLOT4 and CROSS schemes have been compared with the MAGIC scheme, comparative data are not yet available. Firstly, the number of FLOT-treated patients included in the NEO-AEGIS trial is not statistically powered as it accounts for only 15% of the control arm [8]. Secondly, we are still awaiting the results of the ESOPEC phase III clinical trial comparing FLOT *versus* CROSS in patients with EAD and GEJA [9]. However, this study design does not consider the possibility of administering adjuvant nivolumab for those receiving CROSS, and, therefore, it will not evaluate the impact on survival that this sequencing may have. Adjuvant nivolumab after CROSS has just begun to be implemented in routine clinical practice, and real-life experience data are scarce.

In this scenario, real-life data become valuable. Therefore, we offer an analysis of the experience of two centers using both schemes between January 2017 and December 2022.

Material and methods

This retrospective two-center descriptive and comparative two-arm study included patients with GA, GEJA, and EAD treated with perioperative FLOT (n = 40) and neoadjuvant CROSS (n = 16) between January 2017 and December 2022 at the Hospital Universitario de Fuenlabrada and the Hospital Universitario Fundación Alcorcón. Radiotherapy for CROSS was provided at the same center (Hospital Universitario de Fuenlabrada) with a total dose of 41.4 Gy.

A total of 51 variables were collected and grouped into the following categories: clinical variables, tumor characteristics at diagnosis, surgical, anatomopathological, and molecular variables, variables related to oncological treatment, and variables related to evolution and survival.

Data analysis was carried out using the IBM SPSS program. Firstly, a stratified descriptive analysis was performed according to the scheme received. Subsequently, a correlation analysis of variables was carried out using the Chi2 test for the FLOT4 population and Kruskal-Wallis for the CROSS population. Then a multinomial logistic regression was made. Finally, analysis of survival (overall and progression-free survival) was performed, including a Kaplan Meier plot.

Results

The descriptive analysis of the sample stratified according to the scheme received is summarized in Tables 1 and 2.

The FLOT4 arm included a higher percentage of elderly patients (27.5% of patients ≥70 years *vs.* 6.3%) and included one patient with Eastern Cooperative Oncology Group (ECOG) 2 (2.5% *vs.* 0%).

Regarding location, the CROSS arm did not include any patients with GA or Siewert III GEJA. EAD predominated in percentage (50%), followed by Siewert I GEJA (37.5%). In the FLOT4 arm, however, most patients had GA (77.5%), but patients with all types of GEJA were also included (Siewert I: 2.5%; Siewert II: 7.5%; Siewert III: 7.5%) as well as two patients with EAD (5%).

Clinical staging was higher in the FLOT4 arm (more than 80% of patients had cT3 or cT4 with 72.5% N+ and 12.5% M1; while in the CROSS arm, more than 80% of patients had cT2 or cT3, 81.3% N+, 0% M1). Forty percent of tumors were defined by endoscopic ultrasound (EUS) in the FLOT arm, with this technique being more often employed in the CROSS arm (62.5%). Metastatic patients included in the FLOT4 arm received perioperative chemotherapy after the multidisciplinary committee of digestive tumors reached a consensus that these patients were potential candidates for curative oncologic surgery.

We found a high percentage of the diffuse Lauren histologic subtype (57.5%), which is associated with worse prognosis. Likewise, signet ring cells were found in 30% of the tumors in the FLOT4 arm and 6.3% of the patients in the CROSS arm. In correlation analysis between these different clinical-histological variables (ECOG, location, cT, cN, cM, molecular markers, histological subtype, and neoadjuvant tolerance variables) and the pCR, only the absence of signet ring cells was associated with a higher pCR rate (chi2 = 21.8; p = 0.000).

Receiving either treatment in neoadjuvant therapy, downstage the TNM Classification of Malignant Tumors (TNM) (22.5% decrease in pT3 + pT4 relative to cT3 + cT4 in the FLOT arm *versus* 25% decrease in pT2 + pT3 relative to cT2 + cT3 in the CROSS arm; 10% decrease in pN+ relative to cN+ in the FLOT4 arm *versus* 43.8% decrease in pN+ relative to cN+ in the CROSS arm). The percentage of clinical M1 was maintained in the anatomopathological analysis in the FLOT4 arm. In the CROSS arm, there was one patient diagnosed with peritoneal carcinomatosis during surgery (unknown until that date). The rate of pCR was higher in the FLOT4 arm, 10% (4 patients) *vs.* only 1 patient in the CROSS arm (6.3%).

Tumor marker determination in the anatomopathological specimen was low. In the CROSS arm, one patient was HER2+ (6.3%) and one had PD-L1 determined by CPS > 5 (6.3%). The PD-L1+ patient received adjuvant nivolumab. In the FLOT4 arm, HER2 was determined in 40% of cases (positive in 7.2%), PD-L1 by CPS in 22.5% (positive in 2.5%), and microsatellite stability (MS) in 37.2% (unstable in 2.5%).

A median of 45.6 ± 4.9 days in the CROSS arm and 43.8 ± 2.7 days in the FLOT4 arm elapsed from diagnosis to the date of neoadjuvant-therapy initiation. The median number of cycles received in neoadjuvant was 5 for CROSS 95% CI (4–5) and 4 for FLOT 95% CI (3–5). The variability in the number of cycles received in neoadjuvant treatment with FLOT is mainly due to the existence of intercurrent complications, such as thromboembolic events, and not due to toxicity directly derived from the treatment.

There was 20% ≥ G3 toxicity in the FLOT4 arm, mostly afebrile neutropenia. In the CROSS arm, chemotherapy caused 6.3% ≥ G3 toxicity (neutropenia) and radiotherapy 12.5% (mucositis/esophagitis).

A mean of 91.4 ± 3.5 days elapsed in the CROSS arm and 92.5 ± 2.9 in the FLOT4 arm from the start of neoadjuvant therapy to the date of surgery.

Table 1. Baseline characteristics of the sample. Clinical, pathological, and molecular characteristics of the tumor

	CROSS (n = 16)			**FLOT4 (n = 40)**		
Age, sex, ECOG	< **60:** 25% (4) **60–69:** 68.8% (11) ≥ **70:** 6.3 % (1)	**M:** 93.8% (15) **F:** 6.3 % (1)	**ECOG 0:** 87.5% (14) **ECOG 1:** 12.5% (2) **ECOG 2:** 0% (0)	< **60:** 22.5% (9) **60–69:** 50% (20) ≥ **70:** 27.5% (11)	**M:** 77.5% (31) **F:** 22.5% (9)	**ECOG 0:** 85% (34) **ECOG 1:** 12.5% (5) **ECOG 2:** 2.5% (1)
Location:	**Gastric adenocarcinoma:** 0% (0) **GEJA, Siewert I:** 37.5% (6) **GEJA, Siewert II:** 12.5% (2) **GEJA, Siewert III:** 0% (0) **Esophageal adenocarcinoma:** 50% (8)			**Gastric adenocarcinoma:** 77.5% (31) **GEJA, Siewert I:** 2.5% (1) **GEJA, Siewert II:** 7.5% (3) **GEJA, Siewert III:** 7.5% (3) **Esophageal adenocarcinoma:** 5% (2)		
cT, cN, cM	**cT2:** 25% (4) **cT3:** 56.3% (9) **cT4**: 18.8% (3) **cTx:** 0% (0)	**cN-:** 18.7% (3) **cN+:** 81.3% (13) **cNx:** 0% (0)	**cM0:** 93.8% (15) **cMx:** 6.3% (1)	**cT2:** 10% (4) **cT3:** 40% (16) **cT4:** 45% (18) **cTx:** 5% (2)	**cN-:** 22.5% (9) **cN+:** 72.5% (29) **cNx:** 5% (2)	**cM0:** 80% (32) **cMx:** 7.5% (3) **cM1. lymph nodes:** 2.5% (1) **cM1. single omentum:** 2.5% (1) **cM1. peritoneal carcinomatosis:** 7.5% (3)
cTN defined by USE	**Yes:** 62.5% (10) **No:** 6.3% (6)			**Yes:** 40% (16) **No:** 60% (24)		
pT, pN, pM	**pT0:** 6.3% (1) **pT1:** 18.8% (3) **pT2:** 37.5% (6) **pT3:** 18.8% (3) **pT4:** 6.3% (1) **No surgery:** 12.5% (2)	**pN-:** 50% (8) **pN+:** 37.5% (6) **No surgery:** 12.5% (2)	**Does not apply:** 81.3%(13) **pM1 peritoneal carcinomatosis:** 6.3% (1) **No surgery:** 12.5% (2)	**pT0:** 15% (6) **pT1:** 7.5% (3) **pT2:** 10% (4) **pT3:** 22.5% (9) **pT4:** 40% (16) **No surgery:** 5% (2)	**pN-:** 32.5% (13) **pN+:** 62.5% (25) **No surgery:** 5% (2)	**Does not apply:** 80% (32) **pM1 peritoneal carcinomatosis:** 7.5% (3) **pM1 other locations:** 5% (2) **pM0:** 2.5% (1) **No surgery:** 5% (2)
pCR, tumor regression grade	**Yes:** 6.3% (1) **No:** 81.3% (13) **No surgery:** 12.5% (2)		**1:** 6.3% (1) **2:** 25% (4) **3:** 43.8% (7) **Unknown:** 20% (4)	**Yes:** 10% (4) **No:** 85% (34) **No surgery:** 5% (2)		**1:** 10% (4) **2:** 5% (2) **3:** 70% (28) **Unknown:** 15% (6)
R	**R0:** 75% (12) **R1:** 12.5% (2) **No surgery:** 12.5% (2)			**R0:** 80% (32) **R1:** 15% (6) **No surgery:** 5% (2)		
Lauren, signet ring cells	**Does not apply**		**Yes:** 6.3% (1) **No:** 93.7% (15)	**Diffuse type:** 57.5% (23) **Intestinal type:** 32.5% (13) **Mixed morphology:** 10% (4)		**Yes:** 30% (12) **No:** 70% (28)
HER 2, PD-L1 (determined by CPS), MS	**HER 2 positive:** 6.3% (1) **Undetermined:** 93.7% (15)	**CPS ≥ 5:** 6.3% (1) **Undetermined:** 93.7% (15)	**MSS:** 6.3% (1) **Undetermined:** 93.7% (15)	**HER 2 positive:** 7.5% (3) **HER 2 negative:** 32.5% (13) **Undetermined:** 60% (24)	**CPS < 1:** 20% (8) **CPS ≥ 5:** 2.5% (1) **Undetermined:** 77.5% (31)	**MSS:** 35% (14) **MSI:** 2.5% (1) **Undetermined:** 65.2% (25)

CPS — combined positive score; CROSS — carboplatin (AUC 2) plus paclitaxel 50 mg/m^2 weekly concomitant with RT 41.4 Gy; ECOG — Eastern Cooperative Oncology Group performance status; FLOT — docetaxel 50 mg/m^2 plus oxaliplatin 85 mg/m^2 plus leucovorin 200 mg/m^2 plus 5-fluorouracil (5FU) 2600 mg/m^2 in 24-hour infusion, with 4 cycles administered before surgery and 4 cycles after; GEJA — gastroesophageal junction adenocarcinoma; MS — microsatellite stability; MSS — microsatellite stable; MSI — microsatellite unstable; pCR — complete pathological response; PD-L1 — programmed cell death ligand 1; USE — endoscopic ultrasound

Table 2. Variables related to the used treatment and survival

		CROSS (n = 16)			FLOT4 (n = 40)		
Number of neoadjuvant cycles, toxicity ≥ G3		**Me** = 5 **95% CI** (4–5)	**% Toxicity ≥ G3 QT:** 6.3% (1) **% Toxicity ≥ G3 RT:** 12.5% (2)		**Me** = 4 **95% CI** (3–5)	**% toxicity ≥ G3:** 20% (8)	
Scheduled oncological surgery (+/- HIPEC if peritoneal carcinomatosis)		**Yes:** 87.5% (14) **Emergent due to perforation/obstruction:** 0% **No, due to progression during neoadjuvant treatment:** 6.3% (1) **No, due to death during neoadjuvant therapy:** 6.3% (1) **Unresectable disease found during surgery:** 0%			**Yes:** 92.5% (37) **Emergent due to perforation/obstruction:** 2.5% (1) **No, due to progression during neoadjuvant treatment:** 2.5% (1) **No, due to death during neoadjuvant therapy:** 2.5% (1) **Unresectable disease found during surgery:** 0%		
Postoperative defunction **Number of re-interventions** **Postoperative days**		**Yes:** 0% **No:** 87.5% (13) **Did not go under surgery:** 12.6% (2)	$\bar{x} = 0.43 \pm 0.25$ **Range:** [0–3] **Moda** = 0	$\bar{x} = 27.2 \pm 6.1$ **Range:** [10–86] **Moda**: 21	**Yes:** 5% (2) **No:** 90% (13) **Did not go under surgery:** 5% (2)	$\bar{x} = 0.18 \pm 0.09$ **Range:** [0–3] **Moda** = 0	$\bar{x} = 19.2 \pm 3.9$ **Range:** [6–103] **Moda**: 10
Adjuvancy, number of adjuvant cycles, toxicity ≥ G3		**Nivolumab:** 6.3% (1) **No:** 93.7% (15)	**Under treatment to date**	**% Toxicidad ≥ G3 IT:** 0%	**FLOT:** 67.5% (27) **No:** 32.5% (13)	**Me** = 4 **95% CI** (0–4)	**% toxicity ≥ G3:** 7.5% (3)
Treatment discontinuation		**No:** 100%			**Yes, during neoadjuvance:** 7.5% (3) **Yes, during adjuvance:** 5% (2) **Yes, during adjuvance, but for late surgical complications:** 2.5% (1) **Yes, after surgery, without beginning adjuvant:** 22.5% (9) **Yes, after surgery, because the patient rejects adjuvant**: 2.5% (1) **No:** 60% (24)		
Median follow-up		**Me** = 41 months **95% CI** (12–54)			**Me** = 19.5 months **95% CI** (14–29)		
Maintains full remission until February 2023?, progression type, DFS [months]		**Maintains full remission until Feb 2023:** 50% (8) **Local:** 6.3% (1) **Lymph nodes:** 12.5% (2) **Peritoneal carcinomatosis:** 12.5% (2) **Two organs involved:** 6.3% (1) **Bone:** 12.5% (2)		**N** = 8 (progress to CROSS, 50%) **Me** = 9.5 **95% CI** (2–25) **Range:** [2–47]	**Maintains full remission until Feb 2023:** 62.5% (25) **Local:** 2.5% (1) **Lymph nodes:** 2.5% (1) **Peritoneal carcinomatosis:** 25% (10) **Two organs involved:** 2.5% (1) **More than two organs involved:** 2.5% (1) **CNS:** 2.5% (1)		**N** = 16 (progress to FLOT4, 40%) **Me** = 7 **95% CI** (5–10) **Range:** [3–34]
Alive in February 2023?	**OS [months]**	**Yes:** 56.3% (9) **No:** 43.7% (7)	**N** = 6 (exitus, CROSS, 37,5%) **Me** = 17,5 **95% CI** (2–41) **Range:** [2–54]		**Yes:** 75% (30) **No:** 25% (10)	**n** =10 (exitus, FLOT4, 25%) **Me** = 16,5 **95% CI** (11–22) **Range:** [3–29] Among them, 4 were cM1 when diagnosed. For the remaining **n** = 6: **Me** = 21.5 **95% CI** (13–28) **Range:** [13–29]	
	Survival from diagnosis to February 2023 [months]		**n** = 10 (alive, CROSS, 62,5%) **Me** = 47,5 **95% CI** (11–67) **Range:** [9–73]			**n** = 30 (alive, FLOT4, 75%) **Me** = 27 **95% CI** (15–44) **Range:** [5–68]	

CI — confidence interval; CNS — central nervous system; CROSS — carboplatin (AUC 2) plus paclitaxel 50 mg/m^2 weekly concomitant with RT 41.4 Gy; DFS — disease-free survival; FLOT — docetaxel 50 mg/m^2 plus oxaliplatin 85 mg/m^2 plus leucovorin 200 mg/m^2 plus 5-fluorouracil (5FU) 2600 mg/m^2 in 24-hour infusion, with 4 cycles administered before surgery and 4 cycles after; G3 — grade three; HIPEC — hyperthermic intraperitoneal chemotherapy; IT — immunotherapy; Me — median; OS — overall survival; QT — chemotherapy; RT — radiotherapy

Most of the patients underwent scheduled surgery, which, in the case of GA, included D2 lymphadenectomy in all cases. The Hospital Universitario de Fuenlabrada is a reference center for peritoneal carcinomatosis surgery, so some oligometastatic patients treated as "locally advanced" were included in the FLOT4 arm, receiving hyperthermic intraperitoneal chemotherapy (HIPEC) during the oncological surgery.

In the FLOT4 arm, one patient did not qualify for surgery due to progression during neoadjuvant therapy and another due to defunction caused by fulminant massive pulmonary thromboembolism.

The perioperative mortality rate was low: 2 postoperative deaths (5%) in the FLOT4 arm and none in the CROSS arm. The range of reinterventions was 0–3, and the mode was zero for both arms. The mean number of days of admission during the postoperative period was 27.2 ± 6.1 for CROSS (mode 21 days) and 19.2 ± 3.9 for FLOT (mode 10 days).

A mean of 48.1 ± 4.3 days elapsed from surgery to the start of FLOT adjuvant treatment, which was performed in 67.5% of patients. The remaining patients presented deterioration in ECOG due to postoperative sequelae and could not receive adjuvant therapy. In addition, one patient (2.5%) had to stop adjuvant treatment due to late surgical suture dehiscence.

Dose adjustments were made in 55% of patients, most of them (30%) during adjuvant treatment due to the patients' post-surgical frailty. Intra-schema progression occurred in 17.5% of patients during neoadjuvant therapy (included in this percentage are also patients whose progression was diagnosed intraoperatively) and 5% in adjuvant therapy.

In the CROSS arm, only one patient underwent adjuvant nivolumab treatment, which was initiated 42 days after surgery. The patient is on treatment to date and has so far received 12 cycles. The regimen was neither modified nor discontinued in any of the 16 cases analyzed in this arm. Two patients (12.5%) progressed during neoadjuvant treatment and did not qualify for surgery.

At the first reassessment after completion or discontinuation of the scheme, 25% of patients in the CROSS arm and 22.5% of patients in the FLOT4 arm had progressed. As of the cutoff date and data analysis (February 2023), 56.3% of patients treated with CROSS and 65% of patients treated with FLOT remained in complete remission.

The location of progression was mostly nodal, peritoneal, or bone in the CROSS arm (12.5% each) and mostly peritoneal in the FLOT4 arm (25%).

Median disease-free survival was 9.5 months (95% CI 2–25) for CROSS and 7 months (95% CI 5–10) for FLOT4.

Six patients (37.5%) died in the CROSS arm (mOS 17.5 months; 95% CI 2–41) and 10 (25%) in the FLOT4 arm (mOS 16.5 months; 95% CI 11–22). Four of the 10 patients who died in the FLOT4 arm were metastatic at diagnosis. For the remaining 6, mOS was 21.5 months (95% CI 13–29).

For the surviving population at the follow-up cutoff date, the median number of months that elapsed from diagnosis to February 2023 was calculated, resulting in 47.5 (95% CI 11–67) and 27 (95% CI 14–44) months for CROSS and FLOT4, respectively.

Kaplan-Meier analysis was performed with no difference in estimated mOS (50 ± 4.6 months; 95% CI 40.9–59.2) for FLOT4 and 51.2 ± 7 months for CROSS (95% CI 37.4–65.0; p = 0.79) (Fig. 1).

Discussion

Currently, we are still awaiting the results of the ESOPEC trial comparing FLOT *versus* CROSS in patients with EAD and GEJA [9]. However, the design of this trial does not allow for sequencing CROSS with adjuvant nivolumab, and, therefore, no data will be provided on the impact on survival that such sequencing may have. In addition, the results of the EORTC 1707 VESTIGE trial have recently been updated, comparing the benefit of adjuvant nivolumab + ipilimumab *versus* chemotherapy in patients with esophagogastric junction adenocarcinoma at high risk of recurrence (ypN+ and/or R1), with a clear survival data benefit towards the use of chemotherapy [7]. These results raise the question of what would happen if nivolumab was compared with adjuvant chemotherapy rather than placebo as was done in CHECKMATE-577 [6]. In this scenario, in which several questions converge, the real-life data acquire an important value.

When comparing the baseline characteristics, we found that our population was older than the recruited in the trials. In the FLOT4 arm, 50% of patients were between 60 and 69 years *vs.* 33% in FLOT4-AIO [2]; and 27.5% ≥70 years *vs.* 24%. In the CROSS arm, 68.8% were between 60–69 years, while in the NEO-AEGIS, the median age was 64 years (range 45–81 years) [8].

Clinical staging was higher than reported by trials. In the FLOT4 arm, 45% presented cT4 (*vs.* 8%) and 40% cT3 (*vs.* 75%) [2]. The cN+ rate was similar, 72.5% *vs.* 78% [2]. Our population included 5 metastatic patients in the FLOT4 arm, while metastases were an exclusion criterion for FLOT4-AIO [2]. However, the phase II clinical trial AIO-FLOT3 is ongoing, in which oligometastatic patients were included [10].

The rate of R0 resections was similar to that obtained in FLOT4-AIO (80% *vs.* 85%) and lower than that obtained in NEO-AEGIS (75% *vs.* 92%) [2, 8].

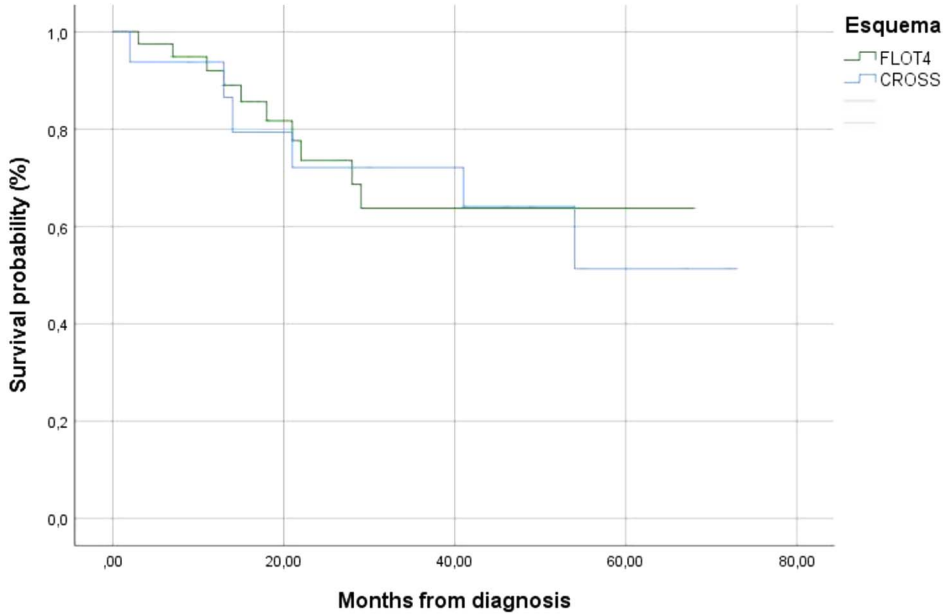

Figure 1. Kaplan-Meier analysis; CROSS — carboplatin (AUC 2) plus paclitaxel 50 mg/m^2 weekly concomitant with RT 41.4 Gy; FLOT — docetaxel 50 mg/m^2 plus oxaliplatin 85 mg/m^2 plus leucovorin 200 mg/m^2 plus 5-fluorouracil (5FU) 2600 mg/m^2 in 24-hour infusion, with 4 cycles administered before surgery and 4 cycles after.

The pCR rate was 17% for both schemes in their respective trials, higher than that obtained in our population (10% for FLOT and 6.3% for CROSS), although, we started from a higher cTNM at diagnosis [2, 5, 8].

The downstaging of TNM was similar to that reported by FLOT4-AIO [2]. In our population, cT3 + + cT4 totaled 80%, with the pathological stage pT3 + + pT4 decreasing to 62.5%, which represents a downstaging of around 20% in the tumor size. However, the percentage of pN0 patients increased by only 10% with respect to the clinical stage, while in FLOT4–AIO, it increased by 30% [2]. We presented higher adjuvant rates of 67.5% (*vs.* 60%), and higher adjuvant completion rates 60% (*vs.* 46%) [2].

TNM Classification of Malignant Tumors downstaging was also similar to that reported by NEO-AEGIS [8]. In the CROSS arm, the rate of pN0 increased by 30% with respect to clinical staging, and T downstaging by 50%, so that 75% of patients had clinical stage pT3 or pT4, with this percentage decreasing to 25% in the pathological stage [8]. One patient received adjuvant nivolumab treatment maintained to date.

Regarding safety analysis, in the FLOT4 arm, the rate of 20% ≥ G3 toxicity in neoadjuvant therapy and 7.5% in adjuvant therapy, added together, is similar to that reported by FLOT4-AIO (25% ≥ G3 toxicity overall) [2]. In the CROSS arm, the 12.5% rate of ≥ G3 toxicity found in our sample was mostly due to mucositis/radical esophagitis processes. In the CROSS trial, the rate of mucositis ≥ G3 was 7.9% [5]. One patient presented G3 neutropenia, which in our sample was 6.3%. In NEO-AEGIS, a rate of ≥ G3 neutropenia of 2.8% and febrile neutropenia ≥ G3 of 0.6% was published [8].

We found no significant differences in estimated mOS in our groups, and it was similar to outcomes evidenced in the respective trials. In FLOT4-AIO, mOS was 50 months 95% CI [38.33 months–not reached (NA)] [2]. These results did not include oligometastatic patients who were considered operable. In arm B of the AIO-FLOT3 trial, oligometastatic patients who were potential candidates for surgery if downstaged after neoadjuvant therapy, were included, with mOS of 31.3 months 95% CI (18.9–NA) [10].

The 5-year OS rate provided by the CROSS trial was 36.3% CI95% (29.5–43%) [5]. The estimated 3-year OS probability was 56% with 95% CI (47–64%) in NEO-AEGIS [8].

Conclusions

Despite obtaining lower pCR rates than those reported in the respective clinical trials, this did not translate into detrimental survival data.

The absence of signet ring cells was the only factor statistically related to a higher pCR rate.

CROSS allowed sequencing with nivolumab in PD-L1+ tumors. This possibility was present in a single patient in our sample, who continues adjuvant treatment to date and, therefore, has no impact on the OS analysis.

TNM Classification of Malignant Tumors downstaging after neoadjuvant therapy, tolerance, and sur-

vival data were similar in both groups and comparable with the results of the respective clinical trials.

Article Information and Declarations

Data availability statement

SPSS data set could be consulted by request.

Ethics statement

This is a retrospective data analysis study.

Author contributions

I.S.L., D.G.A., M.V.T.O.: conceptualization, visualization, methodology, project management, writing: proofreading and editing; E.M.M., I.J.M., A.H.N., A.M.M.F. de S., C. de Z.L., N.S.B., F.E.M., B.L.V., C.P.G., L.R.L., D.M.G., B.J.M., R.H.L., J.C.R., J.A.G.M.: editing.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

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