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Original Article

Pathological response guides adjuvant 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy in surgically resected gastro-oesophageal cancer (SPACE-FLOT): international cohort study

SPACE-FLOT Investigators

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Abstract

Background: Many patients with locally advanced gastro-oesophageal cancers are unable to complete adjuvant 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy, raising questions about its therapeutic utility. The aim of this study was to examine whether pathological response to neoadjuvant FLOT can guide its adjuvant use.

Methods: Patients with non-metastatic gastro-oesophageal adenocarcinoma who received neoadjuvant FLOT and underwent surgery from 1 January 2017 to 1 January 2022 from 43 hospitals across 12 countries were analysed. Pathological response was assessed using tumour regression grading systems, trichotomized into minimal responders (MR; worst category), complete responders (CR; pCR), and partial responders (PR; between MR and CR). Survival outcomes of patients who did and did not receive adjuvant FLOT were compared using Kaplan–Meier, Cox regression, propensity score matched, and sensitivity analysis.

Results: A total of 1887 patients (459 MR, 221 CR, and 1207 PR) were evaluated. The median follow-up was 25.5 (interquartile range 15.0–39.1) months. In the MR group, there was no difference in disease-free survival (DFS; HR 1.03 (95% c.i. 0.78 to 1.36), $P = 0.836$) between those who did and did not receive adjuvant FLOT. Whilst there was a difference in non-adjusted OS, this became statistically non-significant after adjusting for baseline characteristics (HR 0.96 (95% c.i. 0.70 to 1.30), $P = 0.801$). In the CR group, there was no difference in DFS (HR 0.88 (95% c.i. 0.41 to 1.85), $P = 0.724$) or OS (HR 0.69 (95% c.i. 0.31 to 1.54), $P = 0.343$) between those who did and did not receive adjuvant FLOT. In the PR group, adjuvant FLOT conferred a significant DFS (HR 0.68 (95% c.i. 0.55 to 0.86), $P < 0.001$) and OS (HR 0.55 (95% c.i. 0.44 to 0.69), $P < 0.001$) benefit.

Conclusion: Pathological response to neoadjuvant FLOT may guide the use of adjuvant FLOT, enabling personalized approaches to treatment.

Lay summary

Chemotherapy for cancers of the stomach and oesophagus is associated with significant side effects. Being able to predict which patients may benefit or not from further chemotherapy after surgery may optimize its use and reduce harm. In this international study of real-world patients with stomach and oesophageal cancer undergoing surgery and chemotherapy, the authors found that only patients with a partial response to pre-surgery chemotherapy benefited from further chemotherapy after surgery. Patients with a minimal response or no response to pre-surgery chemotherapy, or those whose cancer had been eradicated by pre-surgery chemotherapy, did not benefit from further chemotherapy after surgery. This study suggests that a tumour's response to pre-surgery chemotherapy may guide the use of chemotherapy after surgery.

Introduction

Perioperative chemotherapy significantly improves survival for locally advanced gastro-oesophageal adenocarcinoma[1–3]. As a result of the FLOT4-AIO trial[2], a regimen of four cycles of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) delivered both before and after surgery is the standard of care at many institutions worldwide and is endorsed by international guidelines[4,5]. However, this regimen is difficult to tolerate, as evidenced by 30–50% of patients not completing all treatment cycles[2,6,7].

Tumour regression grading (TRG) histologically examines the resected specimen for response to preoperative chemotherapy, providing an opportunity to predict benefit from adjuvant

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therapy, particularly when identical chemotherapy regimens are applied. This concept is particularly relevant to perioperative FLOT treatment, as 20–30% of resected cancers demonstrate minimal/no response to neoadjuvant FLOT, whilst 10–20% of cancers exhibit complete pathological regression[8]. This questions the utility of adjuvant FLOT for all patients regardless of tumour response. Hence, for cancers with no response to neoadjuvant FLOT, further postoperative FLOT is questionable. Conversely, for cancers with a complete response, the need for further adjuvant FLOT is debatable. However, to date, the role of TRG as a therapeutic biomarker to inform the use of adjuvant FLOT has not been evaluated.

To address this clinical conundrum, the authors established SPACE-FLOT (Survival and PAtterns of Care in the Era of FLOT-based chemotherapy for gastro-oesophageal cancers), an international collaboration of 43 gastro-oesophageal cancer centres. The aim of this study was to examine whether pathological response to neoadjuvant FLOT can guide its adjuvant use.

Methods

Study design

Analysis of prospectively maintained databases of patient-level data was performed for consecutive patients who received neoadjuvant FLOT chemotherapy and underwent radical resection for gastro-oesophageal adenocarcinoma from 1 January 2017 to 1 January 2022. This study involved 43 hospitals in 12 countries (*Table S1*). Complete eligibility criteria are listed in *Fig. 1*. Patients who required dose reductions to their FLOT regimen were included as study participants, but patients who changed regimens and/or received non-FLOT regimens were excluded. This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000180718) and was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC/76492/PMCC) and all sites.

Data collection and quality assurance

Data were collated through an online research electronic data capture (REDCap) database (tested and validated by the Peter MacCallum Data Systems, Research Computing Facility). Training sessions for data collectors, in-program prompting, and real-time data entry support were employed to minimize inter-observer variations. Data cleaning was conducted independently by two investigators. Random auditing of 10% of data fields from all sites, by cross-checking with patient medical records, demonstrated a mean(s.d.) accuracy rate of 97.8(2.3)%.

Study outcomes

The primary endpoint was 2-year disease-free survival (DFS). Secondary endpoints were overall survival (OS), sites of treatment failure, completion rates of neoadjuvant and adjuvant therapy, and reasons for not starting and/or completing perioperative therapy. DFS was calculated from the date of surgery to the date of disease recurrence, as determined by clinical, endoscopic, and/or radiological examinations. OS was calculated from the date of surgery to the date of death from any cause. Those alive at study termination were censored at the time of last contact. All tumours were staged using the Eighth Edition AJCC Cancer Staging Manual[9]. Other study definitions can be found in *Methods S1*.

TRG

Seven well-described TRG systems were identified from all study sites (*Table S2*). All TRG systems were trichotomized a priori by two gastrointestinal pathologists into minimal (worst TRG tier), complete (pCR), and partial (all TRG tiers in-between) responders. Their definitions are detailed in *Table S2*. This pragmatic method of unifying all TRG systems was adopted after considering the regulatory, logistic, economic, and resourcing challenges of centralizing pathology review and/or retraining pathologists to conform to a new TRG system. This approach also allows immediate translatability of this study's findings into clinical practice.

Power calculation

Methods S2 provides extended details on power calculations. Based on FLOT completion rates, survival data, and adjuvant chemotherapy effect sizes from the FLOT4-AIO, MAGIC, and CLASSIC trials[1,2,8,10], we powered for a 2-year 15% DFS (two-sided $\alpha = 0.05$, 80% power) difference between groups, assuming a 40% non-commencement rate of adjuvant FLOT. The sample sizes required for the minimally, partially, and completely responsive cohorts were 370 (adjuvant FLOT *versus* no adjuvant treatment, 230 *versus* 140, 2-year DFS: 55% *versus* 40%), 350 (adjuvant FLOT *versus* no adjuvant treatment, 220 *versus* 130, 2-year DFS: 70% *versus* 55%), and 210 (adjuvant FLOT *versus* no adjuvant treatment, 130 *versus* 80, 2-year DFS: 90% *versus* 75%) respectively.

Statistical analysis

Each tumour-response cohort was analysed as an independent entity. Baseline characteristics between 'adjuvant FLOT' and 'no adjuvant treatment' cohorts were compared using Fisher's exact test and Student's *t* test. For non-parametric data, the Mann-Whitney *U* test was applied. Where comparisons involved more than two categorical variables, the chi-squared test was used. Unadjusted DFS and OS were analysed using the log rank test. Multivariate Cox proportional hazards models were fitted, adjusting for baseline characteristics that were significantly different between study groups on univariate analysis. The proportional hazards assumption was tested for all models. Survival differences were orthogonally validated using 1 : 1 propensity score matching (*Methods S3* and *Figs S1–S3*) and sensitivity analysis. Two-tailed *P* values <0.050 and HRs with 95% confidence intervals that did not cross one were considered statistically significant. Statistical analyses were performed using Prism version 10 (GraphPad Software, San Diego, CA, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 1887 patients were evaluated. Of these, 459 (24.3%), 221 (11.7%), and 1207 (64.0%) had a minimal, complete, and partial pathological response to neoadjuvant FLOT respectively (*Fig. 1*). Detailed study population characteristics are shown in *Tables S3–S6*. The mean(s.d.) age of patients was 63.0(10.4) years and 1416 (75.0%) were male. A total of 1808 patients (95.8%) had locally advanced (cT ≥2 and/or cN1+) cancer and there were 265 (14.0%), 955 (50.6%), and 667 (35.4%) with tumours located in the distal oesophagus, gastro-oesophageal junction, and stomach respectively. The median follow-up duration was 25.5 (interquartile range (i.q.r.) 15.0–39.1) months post-surgery.

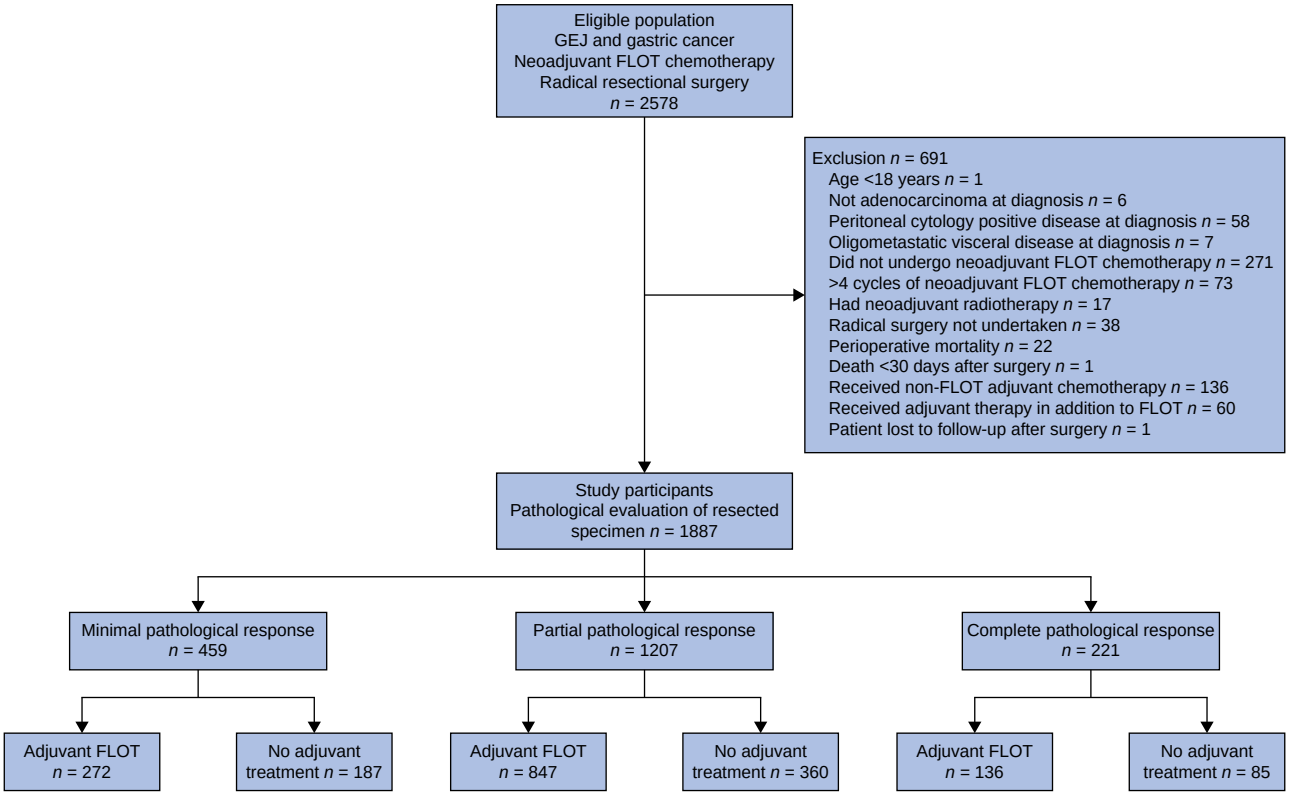

Fig. 1 Study flow chart

GEJ, Gastroesophageal junction; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Perioperative FLOT treatment

Overall, 1564 patients (82.9%) completed all four neoadjuvant FLOT cycles. The most common reason for early cessation of neoadjuvant therapy (*Table S7*) was drug toxicity (41.8%). In total, 632 patients (33.5%) did not receive any adjuvant treatment. This was largely attributed to clinician decision (44.9%) and patient refusal (36.1%) based on tolerance to neoadjuvant therapy, postoperative recovery, and COVID-19-related concerns (*Table S8*). Of the 1255 patients (66.5%) who received adjuvant FLOT, 951 (75.8%) completed all adjuvant treatment. The most common reason for not completing four postoperative cycles (*Table S9*) was drug toxicity (43.8%).

Minimal responders to neoadjuvant FLOT

Of the 459 patients who had a minimal response (worst TRG tier) to neoadjuvant FLOT, 187 (40.7%) did not receive any adjuvant therapy. In the 272 (59.3%) patients who received FLOT after surgery, 215 (79.0%) completed all four adjuvant cycles. *Table 1* and *Table S10* compare the characteristics within this TRG cohort. Patients who received adjuvant FLOT were younger, had a better Charlson co-morbidity index and ECOG status, and completed more neoadjuvant FLOT cycles than those who did not receive adjuvant FLOT. Additional differences in tumour location, resection type, surgical complications, and treatment of recurrent disease are detailed in *Table 1*. Importantly, the prognostic histopathological features were similar between the two groups. The 2-year DFS for patients who did and did not receive adjuvant FLOT was 55.2% and 55.6% respectively. There was no difference in unadjusted DFS (*Fig. S4a*; HR 1.03 (95% c.i. 0.78 to 1.36), $P = 0.836$) between the two groups. This was validated using Cox regression analysis (*Fig. 2a*; HR 1.21 (95% c.i. 0.89 to 1.64), $P = 0.218$) and propensity score matched analysis (*Fig. S4b*; HR 1.07 (95% c.i. 0.81 to 1.42), $P = 0.618$), having adjusted for (using Cox regression analysis) and adequately matched on (using propensity score matched analysis) significantly different characteristics found on univariate comparison (*Table 1*). Whilst there was a difference in unadjusted OS (*Fig. S4c*; HR 0.73 (95% c.i. 0.55 to 0.97), $P = 0.027$) between the two groups, this became non-significant after adjusting for (*Fig. 2b*; HR 0.96 (95% c.i. 0.70 to 1.30), $P = 0.801$) and matching (*Fig. S4d*; HR 0.84 (95% c.i. 0.63 to 1.10), $P = 0.202$) the same patient characteristics. This demonstrates that adjuvant FLOT does not improve DFS and OS in patients with a minimal response to neoadjuvant FLOT. There were no differences in sites of treatment failure between the two groups (*Fig. S5*).

Complete responders to neoadjuvant FLOT

Of the 221 patients who achieved a complete response (best TRG tier) to neoadjuvant FLOT, 85 (38.5%) did not receive any adjuvant therapy. In the 136 patients (61.5%) who received FLOT after surgery, 88 (64.7%) completed all adjuvant cycles. Patients who received adjuvant FLOT were younger, had a better ASA grade, and completed more neoadjuvant FLOT cycles than those who did not receive adjuvant FLOT. Additional differences in tumour location and surgical complications are detailed in *Table 2* and *Table S11*. The 2-year DFS for patients who did and

Table 1 Patient, tumour, treatment, and perioperative characteristics for the minimally responsive cohort

Characteristics	Adjuvant FLOT (*n* = 272)	No adjuvant treatment (*n* = 187)	*P*
Demographics			
Age (years), mean(s.d.)	61.1(10.4)	64.6(9.8)	<0.001*
Sex			1.000
Male	194 (71.3)	134 (71.7)	
Female	78 (28.7)	53 (28.3)	
BMI (kg/m^2), mean(s.d.)	26.6(4.6)	26.8(5.2)	0.607
Charlson co-morbidity index			<0.001*
Index score, median (i.q.r.)	2 (1–3)	3 (2–4)	
Predicted 10-year survival (%), mean(s.d.)	80.4(23.1)	73.6(25.9)	
Smoking status at time of surgery			0.253
Active	42 (15.4)	22 (11.7)	
Former	103 (37.9)	82 (43.9)	
Never	94 (34.6)	55 (29.4)	
Unknown	33 (12.1)	28 (15.0)	
ASA grade at time of surgery, median (i.q.r.)	II (II–III)	II (II–III)	0.178
ECOG status at time of surgery, median (i.q.r.)	0 (0–1)	0 (0–1)	0.046*
Neoadjuvant treatment			
Completed four cycles of FLOT	239 (87.9)	125 (66.8)	<0.001*
FLOT cycles completed (*n*), median (i.q.r.)	4 (4–4)	4 (3–4)	0.007*
Clinical tumour features			
cT category			0.581
cT1	11 (4.1)	7 (3.8)	
cT2–3	228 (83.8)	151 (80.7)	
cT4	33 (12.1)	29 (15.5)	
cN+ status	146 (53.7)	93 (49.7)	0.447
Anatomical location of tumour			0.010*
Distal oesophageal	20 (7.4)	25 (13.4)	
Gastro-oesophageal junction	109 (40.0)	88 (47.0)	
Stomach	143 (52.6)	74 (39.6)	
Surgery and perioperative details			
Surgical approach			0.149
Open	153 (56.2)	118 (63.1)	
Minimally invasive	119 (43.8)	69 (36.9)	
Type of resection			0.003*
Oesophagectomy	102 (37.5)	91 (48.7)	
Total gastrectomy	87 (32.0)	64 (34.2)	
Subtotal gastrectomy	83 (30.5)	32 (17.1)	
Duration of surgery (min), mean(s.d.)	350.6(132.9)	358.3(126.4)	0.581
Surgical complications			<0.001*
None	140 (51.4)	54 (28.9)	
Minor (Clavien–Dindo grades I–II)	85 (31.3)	59 (31.6)	
Major (Clavien–Dindo grades III–IV)	47 (17.3)	74 (39.5)	
Tumour histology			
Histological diagnosis			0.448
Adenocarcinoma	269 (98.9)	185 (99.0)	
Adenocarcinoma with squamous differentiation	3 (1.1)	1 (0.5)	
Undifferentiated carcinoma	0 (0.0)	1 (0.5)	
Lauren classification			0.129
Intestinal	46 (16.9)	41 (21.9)	
Diffuse	79 (29.0)	37 (19.8)	
Mixed	21 (7.8)	15 (8.0)	
Indeterminate	126 (46.3)	94 (50.3)	
Tumour grade			0.523
Well differentiated	18 (6.6)	12 (6.4)	
Moderately differentiated	54 (19.9)	47 (25.1)	
Poorly differentiated	165 (60.7)	99 (53.0)	
Undifferentiated	5 (1.8)	4 (2.1)	
Indeterminate	30 (11.0)	25 (13.4)	
Lymphovascular invasion	164 (60.3)	100 (53.5)	0.151
Perineural invasion	142 (52.5)	89 (47.6)	0.344
Resection margin			0.156
R0	225 (82.7)	143 (76.5)	
R1	41 (15.1)	41 (21.9)	
R2	6 (2.2)	3 (1.6)	
ypT status			0.895
ypT1a	5 (1.8)	9 (4.8)	
ypT1b	9 (3.3)	10 (5.4)	
ypT2	34 (12.5)	15 (8.0)	
ypT3	159 (58.5)	96 (51.4)	
ypT4a	59 (21.7)	47 (25.1)	
ypT4b	6 (2.2)	10 (5.3)	

(continued)

Table 1 (continued)

Characteristics	Adjuvant FLOT ($n = 272$)	No adjuvant treatment ($n = 187$)	P
ypN status			0.602
ypN0	82 (30.2)	57 (30.5)	
ypN1	52 (19.1)	27 (14.4)	
ypN2	58 (21.3)	45 (24.1)	
ypN3	80 (29.4)	58 (31.0)	
Total nodal harvest (*n*), median (i.q.r.)	29 (20–42)	29 (23–39)	0.767
Recurrence details			
ECOG status at recurrence, median (i.q.r.)	1 (0–2)	1 (1–2)	0.034*
First-line treatment, *n* of *n* (%)	80 of 131 (61.1)	37 of 79 (46.8)	0.047*
Second-line treatment, *n* of *n* (%)	25 of 131 (19.1)	10 of 79 (12.7)	0.226
Third-line treatment, *n* of *n* (%)	9 of 131 (6.9)	2 of 79 (2.5)	0.172

Values are *n* (%) unless otherwise indicated. *Statistically significant. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; i.q.r., interquartile range; ECOG, Eastern Cooperative Oncology Group.

did not receive adjuvant FLOT was 87.9% and 86.2% respectively. DFS was similar between these two groups based on unadjusted (*Fig. S6a*; HR 0.88 (95% c.i. 0.41 to 1.85), $P = 0.724$), Cox regression adjusted (*Fig. 2c*; HR 0.79 (95% c.i. 0.35 to 1.79), $P = 0.575$), and propensity score matched (*Fig. S6b*; HR 0.81 (95% c.i. 0.39 to 1.70), $P = 0.579$) analysis. There were no differences in sites of treatment failure (*Fig. S5*). Similarly, OS was comparable between these two groups based on unadjusted (*Fig. S6c*; HR 0.69 (95% c.i. 0.31 to 1.54), $P = 0.343$), Cox regression adjusted (*Fig. 2d*; HR 0.69 (95% c.i. 0.29 to 1.68), $P = 0.417$), and propensity score matched (*Fig. S6d*; HR 0.97 (95% c.i. 0.44 to 2.14), $P = 0.940$) analysis.

Partial responders to neoadjuvant FLOT

Of the 1207 patients who had a partial response (any tier between best and worst TRG) to neoadjuvant FLOT, 360 (29.8%) did not receive any adjuvant therapy. In the 847 (70.2%) patients who received FLOT after surgery, 648 (76.5%) completed all adjuvant cycles. Patients who received adjuvant FLOT were younger, had a better ASA grade, Charlson co-morbidity index, and ECOG status, and completed more cycles of neoadjuvant FLOT. Additionally, prognostic histopathological features were similar between the two groups (*Table 3* and *Table S12*). The 2-year DFS for patients who did and did not receive adjuvant FLOT was 74.5% and 61.9% respectively. In contrast to minimal and complete pathological responders, partial responders derived a significant DFS (*Fig. S7a*; HR 0.68 (95% c.i. 0.55 to 0.86), $P < 0.001$) benefit from adjuvant FLOT. Importantly, this benefit remained after adjusting for (*Fig. 2e*; HR 0.73 (95% c.i. 0.58 to 0.92), $P = 0.007$) and matching on (*Fig. S7b*; HR 0.72 (95% c.i. 0.58 to 0.88), $P = 0.002$) baseline differences (*Table 3*). Moreover, adjuvant FLOT significantly increased OS based on unadjusted (*Fig. S7c*; HR 0.55 (95% c.i. 0.44 to 0.69), $P < 0.001$), Cox regression adjusted (*Fig. 2f*; HR 0.63 (95% c.i. 0.50 to 0.79), $P < 0.001$), and propensity score matched (*Fig. S7d*; HR 0.66 (95% c.i. 0.54 to 0.82), $P < 0.001$) analysis. Compared with the adjuvant FLOT group, patients who did not receive adjuvant treatment had a significantly higher risk of peritoneal, nodal, bone, central nervous system, and chest wall recurrence (*Fig. S5*).

Sensitivity analysis

A sensitivity analysis was undertaken, examining subgroups of different TRG systems, different operative approaches, different tumour locations, and patients who completed all neoadjuvant/adjuvant FLOT cycles. Irrespective of TRG system (5-tiered Mandard or 4-tiered TRG), surgical approach (gastrectomy or esophagectomy), or tumour location (distal oesophageal/gastro-oesophageal junction or stomach), and for patients who completed all neoadjuvant/adjuvant FLOT cycles, only partial responders derived a significant therapeutic benefit from adjuvant FLOT (*Fig. S8*).

Finally, further analysis within the partially responsive group suggested that adjuvant FLOT improves DFS regardless of age, co-morbidities, performance status, completion (or not) of four adjuvant cycles, and the extent of lymphadenectomy (*Fig. S9*). Additionally, female sex, completion of neoadjuvant therapy, tumours with moderate to poor differentiation, lymphovascular invasion, perineural infiltration, advanced ypT category, positive ypN category, *HER2* negativity, and proficient mismatch repair status correlated with relative therapeutic benefit from adjuvant FLOT in patients with a partially responsive tumour.

Discussion

In this international cohort study, it was demonstrated that pathological response to neoadjuvant FLOT predicts the efficacy of adjuvant FLOT. These findings can be used to personalize the perioperative management of patients with resected gastro-oesophageal adenocarcinoma.

Personalizing perioperative FLOT therapy is important for several reasons. First, this approach is biologically plausible, as gastro-oesophageal cancers exhibit a spectrum of sensitivity to this regimen, with some patients achieving a pCR to only four cycles and others experiencing early disease relapse despite the full eight cycles of chemotherapy. Tailoring adjuvant FLOT therapy to chemo-sensitivity may therefore avoid overtreatment or undertreatment of patients. Second, perioperative FLOT treatment incurs substantial acute toxicities, which may adversely impact commencement and/or completion of planned adjuvant therapy, in addition to carrying a risk of toxic death. Third, adjuvant FLOT may diminish patients' performance status and confer permanent toxicities (for example peripheral neuropathy) that can limit future therapeutic options. Therefore, to maximize therapeutic efficacy and minimize harm, the present findings advocate using pathological TRG to tailor adjuvant FLOT therapy.

This study can be applied in several ways. First, using contemporary real-world data stratified by TRG, patients' prognoses were modelled and the therapeutic efficacy of adjuvant FLOT was estimated. This can inform patient counselling in the postoperative interval. Second, for FLOT-refractory disease, the present data question the benefit of postoperative FLOT, particularly in patients who are borderline for adjuvant therapy. Third, for complete responders, the data suggest that neoadjuvant FLOT and surgery achieves a cure in

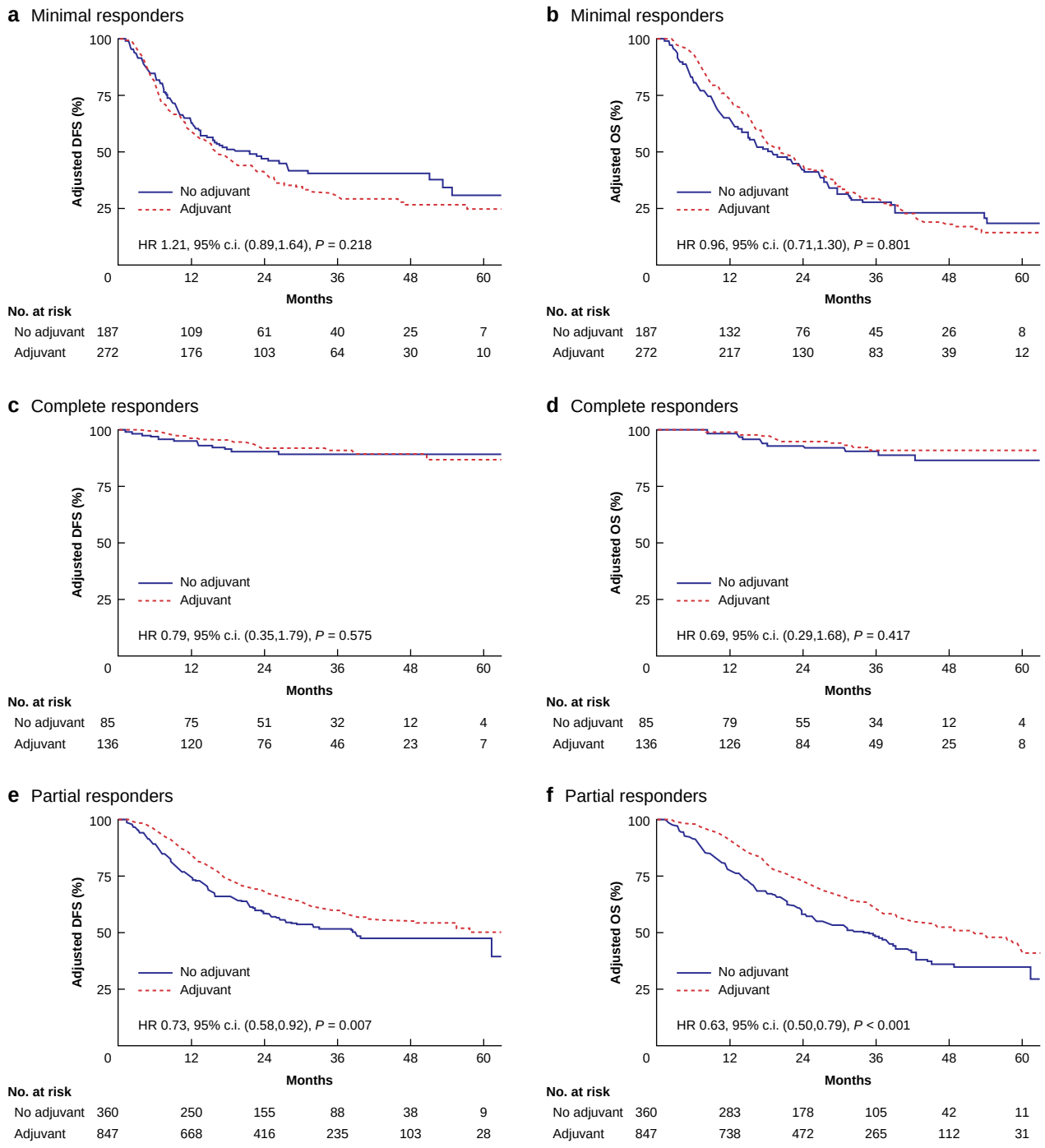

Fig. 2 Adjusted DFS and OS

a and **b** For the minimally responsive cohort. **c** and **d** For the completely responsive cohort. **e** and **f** For the partially responsive cohort. Survival curves adjusted using multivariable Cox regression analysis based on significantly different variables found in *Table 1* (for **a** and **b**), *Table 2* (for **c** and **d**), and *Table 3* (for **e** and **f**). DFS, disease-free survival; OS, overall survival.

80% of patients and that adjuvant FLOT may not confer additional therapeutic benefit. However, it should be acknowledged that the power calculation has not allowed for a smaller but true survival advantage to be detected in both response subgroups. Therefore, in fit patients, it would be reasonable to deliver adjuvant therapy to further minimize disease recurrence. In contrast, for patients with borderline fitness, the findings of the present study support a nuanced discussion to withhold adjuvant treatment. Finally, for tumours that partially respond to neoadjuvant FLOT, this study strongly advocates pursuing adjuvant FLOT due to the significant DFS and OS benefit, particularly for patients with poor prognostic pathological features, *HER2* negativity, and proficient mismatch repair disease.

To the authors' knowledge, this is the first study to examine the role of adjuvant chemotherapy, stratified by TRG, in the FLOT era. Until now, three studies have explored the benefit of further adjuvant treatment, utilizing older regimens of perioperative chemotherapy[11–13]. Two of these were single-institution studies, limited by insufficient power, heterogeneous patient populations and treatment regimens, inconsistent disease

Table 2 Patient, tumour, treatment, and perioperative characteristics for the completely responsive cohort

Characteristics	Adjuvant FLOT (*n* = 136)	No adjuvant treatment (*n* = 85)	*P*
Demographics			
Age (years), mean(s.d.)	62.5(10.7)	65.4(8.8)	0.036*
Sex			0.269
Male	97 (71.3)	67 (78.8)	
Female	39 (28.7)	18 (21.2)	
BMI (kg/m^2), mean(s.d.)	27.3(4.7)	26.6(4.8)	0.275
Charlson co-morbidity index			0.081
Index score, median (i.q.r.)	2 (1–3)	3 (2–3)	
Predicted 10-year survival (%), mean(s.d.)	78.6(24.7)	74.1(26.2)	
Smoking status at time of surgery			0.945
Active	15 (11.0)	8 (9.4)	
Former	55 (40.5)	36 (42.4)	
Never	49 (36.0)	32 (37.6)	
Unknown	17 (12.5)	9 (10.6)	
ASA grade at time of surgery, median (i.q.r.)	II (II–III)	III (II–III)	0.016*
ECOG status at time of surgery, median (i.q.r.)	0 (0–1)	0 (0–1)	0.427
Neoadjuvant treatment			
Completed four cycles of FLOT	123 (90.4)	67 (78.8)	0.018*
FLOT cycles completed (*n*), median (i.q.r.)	4 (4–4)	4 (4–4)	0.104
Clinical tumour features			
Histological diagnosis			0.560
Adenocarcinoma	135 (99.3)	83 (97.6)	
Adenocarcinoma with squamous differentiation	1 (0.7)	2 (2.4)	
cT category			0.273
cT1	17 (12.5)	5 (5.9)	
cT2–3	106 (77.9)	73 (85.9)	
cT4	13 (9.6)	7 (8.2)	
cN+ status	64 (47.1)	43 (50.6)	0.679
Anatomical location of tumour			0.019*
Distal oesophageal	20 (14.7)	26 (30.5)	
Gastro-oesophageal junction	69 (50.7)	36 (42.4)	
Stomach	47 (34.6)	23 (27.1)	
Surgery and perioperative details			
Surgical approach			0.272
Open	63 (46.3)	46 (54.1)	
Minimally invasive	73 (53.7)	39 (45.9)	
Type of resection			0.848
Oesophagectomy	84 (61.8)	56 (65.9)	
Total gastrectomy	24 (17.6)	14 (16.5)	
Subtotal gastrectomy	28 (20.6)	15 (17.6)	
Duration of surgery (min), mean(s.d.)	408.1(126.7)	660.0(379.4)	0.126
Surgical complications			<0.001*
None	67 (49.3)	28 (32.9)	
Minor (Clavien–Dindo grades I–II)	46 (33.8)	21 (24.7)	
Major (Clavien–Dindo grades III–IV)	23 (16.9)	36 (42.4)	
Total nodal harvest (*n*), median (i.q.r.)	27 (20–35)	26 (20–39)	0.895
Recurrence details			
ECOG status at recurrence, median (i.q.r.)	1 (0–1)	1 (1–2)	0.176
First-line treatment, *n* of *n* (%)	13 of 17 (76.5)	6/12 (50.0)	0.140
Second-line treatment, *n* of *n* (%)	5 of 17 (29.4)	3 of 12 (25.0)	0.794
Third-line treatment, *n* of *n* (%)	3 of 17 (17.6)	2 of 12 (16.7)	1.000

Values are *n* (%) unless otherwise indicated. *Statistically significant. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; i.q.r., interquartile range; ECOG, Eastern Cooperative Oncology Group.

staging, the absence of DFS data, and they lacked statistical adjustments for confounders[9,10]. The present findings are consistent with those reported by Deng *et al.*[13], who utilized the US National Cancer Database to identify gastric cancer patients treated with perioperative chemotherapy before the FLOT era. In this independent patient cohort, Deng *et al.*[13] found that adjuvant chemotherapy was significantly associated with increased OS in patients with chemo-sensitive disease (comparable to partial responders in the present study), but not in patients with refractory disease (comparable to minimal responders in the present study) or those who achieved a pCR.

The findings of the present study are particularly relevant considering the recently reported ESOPEC trial[6,14,15], which demonstrated superiority of perioperative FLOT over neoadjuvant chemoradiation for gastro-oesophageal adenocarcinomas. Moreover, as multiple perioperative chemo-immunotherapy trials have not reached or achieved their survival endpoints[16–18], the FLOT regimen remains the current standard of care. With improvements in predictive biomarkers for immunotherapy, and a potential shift to delivering neoadjuvant immunotherapy, we anticipate that a subset of adenocarcinomas may respond to checkpoint inhibitors in combination with chemotherapy; however, utilizing TRG to guide benefit from adjuvant FLOT will still be useful to personalize the chemotherapy component of the regimen.

Importantly, the present study highlights an area of unmet need for patients with FLOT-refractory disease, as this group has the worst prognosis amongst the three tumour-response

Table 3 Patient, tumour, treatment, and perioperative characteristics for the partially responsive cohort

Characteristics	Adjuvant FLOT (*n* = 847)	No adjuvant treatment (*n* = 360)	*P*
Demographics			
Age (years), mean(s.d.)	61.7(10.5)	66.1(9.7)	<0.001*
Sex			0.824
Male	650 (76.7)	274 (76.1)	
Female	197 (23.3)	86 (23.9)	
BMI (kg/m^2), mean(s.d.)	26.8(4.9)	27.3(5.3)	0.101
Charlson co-morbidity index			<0.001*
Index score, median (i.q.r.)	2 (1–3)	3 (2–4)	
Predicted 10-year survival (%), mean(s.d.)	79.9(22.0)	72.1(25.0)	
Smoking status at time of surgery			0.729
Active	122 (14.5)	56 (15.6)	
Former	339 (40.0)	147 (40.8)	
Never	274 (32.3)	91 (25.3)	
Unknown	112 (13.2)	66 (18.3)	
ASA grade at time of surgery, median (i.q.r.)	II (II–III)	III (II–III)	<0.001*
ECOG status at time of surgery, median (i.q.r.)	0 (0–1)	0 (0–1)	0.006*
Neoadjuvant treatment			
Completed four cycles of FLOT	765 (90.3)	245 (68.1)	<0.001*
FLOT cycles completed (*n*), median (iq.r.)	4 (4–4)	4 (4–4)	<0.001*
Clinical tumour features			
cT category			0.151
cT1	30 (3.6)	9 (2.5)	
cT2–3	682 (80.5)	307 (85.3)	
cT4	135 (15.9)	44 (12.2)	
cN+ status	430 (50.8)	197 (54.7)	0.232
Anatomical location of tumour			<0.001*
Distal oesophageal	95 (11.2)	59 (16.4)	
Gastro-oesophageal junction	356 (42.0)	178 (49.4)	
Stomach	396 (46.8)	123 (34.2)	
Surgery and perioperative details			
Surgical approach			0.567
Open	495 (58.4)	204 (56.6)	
Minimally invasive	352 (41.6)	156 (43.4)	
Type of resection			<0.001*
Oesophagectomy	369 (43.6)	207 (57.5)	
Total gastrectomy	276 (32.6)	92 (25.6)	
Subtotal gastrectomy	202 (23.8)	61 (16.9)	
Duration of surgery (min), mean(s.d.)	365.2(118.7)	357.5(123.8)	0.371
Surgical complications			<0.001*
None	461 (54.4)	111 (30.8)	
Minor (Clavien–Dindo grades I–II)	253 (29.9)	117 (32.5)	
Major (Clavien–Dindo grades III–IV)	133 (15.7)	132 (36.7)	
Tumour histology			
Histological diagnosis			0.165
Adenocarcinoma	840 (99.2)	359 (99.9)	
Adenocarcinoma with squamous differentiation	5 (0.6)	1 (0.1)	
Undifferentiated carcinoma	2 (0.2)	0 (0.0)	
Lauren classification			0.200
Intestinal	272 (32.1)	110 (30.6)	
Diffuse	168 (19.8)	57 (15.8)	
Mixed	64 (7.6)	24 (6.6)	
Indeterminate	343 (40.5)	169 (47.0)	
Tumour grade			0.111
Well differentiated	80 (9.4)	26 (7.2)	
Moderately differentiated	228 (26.9)	94 (26.2)	
Poorly differentiated	391 (46.2)	155 (43.0)	
Undifferentiated	4 (0.5)	2 (0.6)	
Indeterminate	144 (17.0)	83 (23.0)	
Lymphovascular invasion	334 (39.4)	131 (36.4)	0.333
Perineural invasion	271 (32.0)	108 (30.0)	0.588
Resection margin			0.051
R0	768 (90.6)	314 (87.2)	
R1	76 (9.0)	38 (10.6)	
R2	3 (0.4)	8 (2.2)	
ypT category			0.379
ypT0	4 (0.5)	2 (0.6)	
ypT1a	56 (6.6)	25 (6.9)	
ypT1b	113 (13.3)	45 (12.5)	
ypT2	175 (20.6)	64 (17.8)	
ypT3	398 (47.0)	170 (47.2)	
ypT4a	92 (10.9)	44 (12.2)	

(continued)

Table 3 (continued)

Characteristics	Adjuvant FLOT (*n* = 847)	No adjuvant treatment (*n* = 360)	*P*
ypT4b	9 (1.1)	10 (2.8)	
ypN category			0.321
ypN0	401 (47.4)	179 (49.7)	
ypN1	210 (24.8)	60 (16.7)	
ypN2	135 (15.9)	66 (18.3)	
ypN3	101 (11.9)	55 (15.3)	
Total nodal harvest (*n*), median (i.q.r.)	30 (21–41)	29 (22–40)	0.714
Recurrence details			
ECOG status at recurrence, median (i.q.r.)	1 (0–2)	1 (1–2)	0.001*
First-line treatment, *n* of *n* (%)	146 of 249 (58.6)	66 of 138 (47.8)	0.041*
Second-line treatment, *n* of *n* (%)	35 of 249 (14.1)	18 of 138 (13.0)	0.756
Third-line treatment, *n* of *n* (%)	14 of 249 (5.6)	5 of 138 (3.6)	0.468

Values are *n* (%) unless otherwise indicated. *Statistically significant. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; i.q.r., interquartile range; ECOG, Eastern Cooperative Oncology Group.

cohorts (*Fig. S10*), with no alternative adjuvant standard of care. The recently reported VESTIGE trial[18,19], which examined a cohort of patients with gastro-oesophageal cancers at high risk of recurrence (ypN1–3 and/or R1) after neoadjuvant FLOT and surgery, compared adjuvant immunotherapy (nivolumab plus ipilimumab) with FLOT chemotherapy. Adjuvant immunotherapy was found to be inferior to adjuvant FLOT therapy. It needs to be emphasized that the VESTIGE trial did not stratify patients according to TRG. Consistent with the present study, one would expect that a significant proportion of the VESTIGE study population were partial responders to neoadjuvant FLOT (63% of the partial responders in the present study were ypN1–3 and/or R1) and therefore benefited from adjuvant FLOT.

Several limitations regarding this study should be acknowledged. As this is a retrospective analysis, there may be factors that influenced the decision to administer adjuvant FLOT that were not captured or adjusted for (for example postoperative ECOG status) in the analysis. However, to minimize the impact of bias, stringent data-quality measures were applied, the findings were validated using three statistical approaches, and eligibility criteria were refined to ensure a relatively homogeneous yet internationally relevant patient population. In this study, real-world data were used, powered to detect differences in survival for each pathological-response cohort, to inform current practice. Whilst a randomized trial would provide a higher level of evidence, the duration and resources required to achieve sufficient power within each response subgroup would render such a study impractical to run, with findings that may no longer be informative to clinical practice. Due to regulatory, economical, logistical, and resourcing reasons, it was not possible to undertake central review of TRG. However, it is recognized that each TRG system carries variable inter-observer agreement in grading pathological response[20–24]. To address this, a sensitivity analysis of five-tier only (Mandard) and four-tier only (Becker, AJCC, College of American Pathologists, and Modified Ryan—as they have comparable tiered definitions) TRG systems was performed (*Fig. S8*) to validate the primary analysis. Multimodal assessment of tumour response to neoadjuvant FLOT was not evaluated. This is because PET is not the standard of care for restaging of gastro-oesophageal cancers at most institutions. Finally, pathological response within resected lymph nodes was not examined[25], as this aspect is not routinely practiced or standardly reported.

In summary, this study has demonstrated that pathological response to neoadjuvant FLOT correlates with the efficacy of adjuvant FLOT. These findings suggest that pathological tumour response to neoadjuvant FLOT may guide the use of adjuvant FLOT and help inform future studies to personalize postoperative therapy.

Collaborators

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data dictionary, study protocol, and statistical analysis plan will be available online with the publication of this manuscript on the journal's website. Individual deidentified participant data will only be shared after approval of a proposal by all study investigators, the clinical research sponsorship committee, the research governance office, and the human research ethics committee.

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