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Practical Insights into Risk-Adapted Implementation of Perioperative FLOT for Resectable Gastroesophageal Adenocarcinoma

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Abstract

Background : Perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) is expected to become an increasingly important standard approach for locally advanced gastroesophageal adenocarcinoma (GEA), including in Asia. However, practical management strategies for elderly or vulnerable patients in Asia remain unclear.

Methods: We retrospectively reviewed patients with GEA who received perioperative FLOT through January 2025. Patients were categorized into three age groups: <60, 60–74, and ≥75 years.

Results: Among 147 patients, 19.0%, 51.7%, and 29.3% were aged <60, 60–74, and ≥75 years, respectively. Initial dose reduction increased with age (0%, 10.5%, and 67.4%, respectively), whereas neoadjuvant completion rates and pathological complete response rates were comparable across groups. In contrast, initiation and completion of adjuvant FLOT declined with age. The most common grade ≥3 adverse events were neutropenia (35.4%), anorexia (7.5%), and febrile neutropenia (5.4%), without apparent age-related increases. Intravenous fluid support was most frequently required during cycle 1 and increased with age. Prophylactic pegylated granulocyte colony-stimulating factor was associated with lower rates of severe neutropenia and febrile neutropenia, while prophylactic olanzapine was associated with lower anorexia rates.

Conclusions: Individualized dose modification and proactive supportive care may facilitate safe implementation of perioperative FLOT, particularly for elderly or vulnerable patients. These findings may help optimize the real-world use of FLOT-based perioperative strategies in Asia.

Introduction

Clinical management of resectable gastroesophageal adenocarcinoma (GEA) has historically differed between Western and Eastern countries. Following the FLOT4 trial, perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) became the standard of care in Western countries [1], whereas upfront gastrectomy followed by adjuvant chemotherapy has remained the predominant approach in many Asian countries [2–7]. More recently, global collaborative efforts have begun to bridge this gap, and the phase III MATTERHORN trial demonstrated that perioperative durvalumab plus FLOT (D-FLOT) significantly improved clinical outcomes, supporting its emergence as a new global standard [8, 9].

Despite this shift toward global standardization, the applicability of FLOT-based regimens in Asian clinical practice remains a matter of ongoing debate partly because clinical experience with this regimen was limited in many Asian countries before MATTERHORN. In particular, the feasibility of D-FLOT in elderly or vulnerable patients remains uncertain.

We previously demonstrated that perioperative FLOT can be delivered safely in Japan with appropriate dose modification and prophylactic use of pegylated granulocyte colony-stimulating factor (peg-G-CSF)

[10]. However, practical guidance for optimizing its implementation in real-world Asian settings remains limited.

Accordingly, this study aimed to provide practical insights into the management of perioperative FLOT in clinical practice, with a particular focus on risk-adapted strategies—primarily based on age and clinical vulnerability—to improve feasibility across a broader patient population.

Patients and Methods

Study Design and Patient Selection

We reviewed consecutive patients with GEA who received at least one dosing of perioperative FLOT between February 2020 and January 2025 at National Cancer Center Hospital East, Kashiwa Japan. The eligibility criteria were the presence of histologically proven adenocarcinoma of esophageal, gastroesophageal junction (GEJ) and stomach; clinical stage T ≥ 3 and/or nodal positive, and no clinical evidence of distant metastases; no prior systemic chemotherapy for GEA. The exclusion criteria were advanced malignancy other than GEA with potential to impact management of these diseases. All patients provided written informed consent for treatment and prospective biomarker study (UMIN000019129). The study protocol was approved by the ethics committee of the National Cancer Center Hospital East Institutional Review Board (Approval ID: 2025 – 139, Approval date: August 6, 2025). This study was conducted in accordance with the Declaration of Helsinki guidelines for biomedical research, and an opt-out option was provided on the institutional website.

Treatment Plan

The FLOT regimen consisted of docetaxel (50 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (200 mg/m^2), and fluorouracil (2600 mg/m^2 as a 26-h continuous infusion), every 2 weeks for 4 neoadjuvant cycles followed by 4 adjuvant cycles. Treatment was discontinued in cases of unacceptable adverse events (AEs), disease progression, or patient's request. All patients received antiemetic premedication with palonosetron (0.75 mg intravenous [iv] on day 1), aprepitant (125 mg orally on day 1 and 80 mg orally on days 2–3) or fosaprepitant (150 mg iv on day 1), and dexamethasone (6.6 mg iv on day 1 and 2 or 4 mg orally on days 2–3). Prophylactic peg-G-CSF has been implemented since August 2021.

Assessments

Patients were categorized into three age groups: aged < 60, 60–74, and ≥ 75 years. Treatment-related AEs (TRAEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Computed tomography scans and upper gastrointestinal endoscopy were performed both before and after neoadjuvant FLOT. Clinical and pathological stages were determined according to the Japanese Classification of Gastric Cancer (15th edition) [11] or Japanese Classification

of Esophageal Cancer (11th/12th edition) [12, 13]. Histopathologic effects were evaluated according to the Japanese Classification of Gastric Cancer (15th edition) or Japanese Classification of Esophageal Cancer (11th/12th edition) as follows: grade 3 (corresponds to pathological complete response [pCR], no residual tumor cells), grade 2 (tumor cells remain in < 1/3; in gastric cancer, subdivided into grade 2a [tumor cells remain in ≥ 1/10 but < 1/3] and grade 2b [tumor cells remain in < 1/10]), grade 1b (tumor cells remain in ≥ 1/3 but < 2/3), grade 1a (tumor cells remain in ≥ 2/3), and grade 0 (no histologic evidence of treatment effect) [11, 12, 14]. The relative dose intensity (RDI) was calculated as the percentage of the delivered dose intensity divided by the standard intensity.

Human epidermal growth factor receptor 2 (HER2), mismatch repair (MMR), claudin-18 isoform 2 (CLDN18.2) status, and programmed death-ligand 1 (PD-L1) combined positive score (CPS) were assessed as previously described [15].

Statistical Analysis

Categorical variables were presented as numbers and percentages and were compared using the chi-squared test or Fisher's exact test, as appropriate between adjacent age groups. A *P*-value of less than 0.05 was considered statistically significant, whereas a *P*-value of less than 0.10 was interpreted as indicating a trend toward significance. All statistical analyses were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 152 patients who received FLOT were identified. Three patients with concurrent malignancies requiring active treatment and two patients with retrospectively suspected metastatic disease were excluded, leaving 147 patients eligible for analysis. During this period, 77 patients were enrolled in clinical trials; 45 patients received FLOT-based treatments and were not included in this analysis. Baseline characteristics are summarized in Table 1. A total of 28 (19.0%), 76 (51.7%), and 43 (29.3%) patients were categorized as aged < 60, 60–74, and ≥ 75 years, respectively. The proportions of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 (3.6%, 11.8%, and 27.9% in patients aged < 60, 60–74, and ≥ 75 years, respectively), presence of comorbidities (17.9%, 38.2%, and 51.2%, respectively), creatinine clearance < 60 mL/min (10.7%, 25.0%, and 69.8%, respectively), and tumors with deficient MMR (dMMR) (0%, 5.3%, 7.0%) increased with advancing age.

Table 1
Baseline patient characteristics

		Overall	< 60 years	60–74 years	≥ 75 years
		n = 147 (%)	n = 28 (%)	n = 76 (%)	n = 43 (%)
Age (years)	Median (range)	70 (28–84)	51 (28–59)	70 (60–74)	78 (75–84)
Sex	Male	111 (75.5)	22 (78.6)	58 (76.3)	31 (72.1)
	Female	36 (24.5)	6 (21.4)	18 (23.7)	12 (27.9)
ECOG PS	0	125 (85.0)	27 (96.4)	67 (88.2)	31 (72.1)
	1	22 (15.0)	1 (3.6)	9 (11.8)	12 (27.9)
Primary tumor location	Gastric	84 (57.1)	12 (42.9)	45 (59.2)	27 (62.8)
	Esophagus and GEJ	63 (42.9)	16 (57.1)	31 (40.8)	16 (37.2)
Primary tumor stage	Non-T4	96 (65.3)	19 (67.9)	53 (69.7)	24 (55.8)
	T4	51 (34.7)	9 (32.1)	23 (30.3)	19 (44.2)
Clinical lymph-node status	Positive	135 (91.8)	26 (92.9)	70 (92.1)	39 (90.7)
	Negative	12 (8.2)	2 (7.1)	6 (7.9)	4 (9.3)
Lauren classification	Diffuse	92 (62.6)	18 (64.3)	43 (56.6)	31 (72.1)
	Intestinal	55 (37.4)	10 (35.7)	33 (43.4)	12 (27.9)
Histological types	Non-signet ring cell carcinoma	121 (82.3)	18 (64.3)	68 (89.5)	35 (81.4)
	Signet ring cell carcinoma	26 (17.7)	10 (35.7)	8 (10.5)	8 (18.6)
Comorbidity[a]	No	91 (61.9)	23 (82.1)	47 (61.8)	21 (48.8)
	Yes	56 (38.1)	5 (17.9)	29 (38.2)	22 (51.2)
CCr (ml/min)	Median (range)	69 (33–211)	103 (36–211)	73 (36–126)	53 (33–79)

ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; PD-L1, programmed death-ligand 1; CPS, combined positive score; CLDN18.2, claudin-18 isoform 2; CCr, creatinine clearance.

[a] Comorbidities included ischemic heart disease, cerebrovascular disease, obstructive lung disease, and restrictive lung disease.

		Overall	< 60 years	60–74 years	≥ 75 years
		n = 147 (%)	n = 28 (%)	n = 76 (%)	n = 43 (%)
	≥ 60	95 (64.6)	25 (89.3)	57 (75.0)	13 (30.2)
	≥ 30 to < 60	52 (35.4)	3 (10.7)	19 (25.0)	30 (69.8)
HER2 status	Negative	138 (93.9)	26 (92.9)	71 (93.4)	41 (95.3)
	Positive	9 (6.1)	2 (7.1)	5 (6.6)	2 (4.7)
MMR status	Proficient	140 (95.2)	28 (100)	72 (94.7)	40 (93.0)
	Deficient	7 (4.8)	0 (0)	4 (5.3)	3 (7.0)
PD-L1 CPS	CPS ≥ 1	132 (89.8)	25 (89.3)	67 (88.2)	40 (93.0)
	CPS < 1	14 (9.5)	3 (10.7)	8 (10.5)	3 (7.0)
	Unknown	1 (0.7)	0 (0)	1 (1.3)	0 (0)
CLDN18.2 status	Negative	100 (68.0)	20 (71.4)	52 (68.4)	28 (65.1)
	Positive	47 (32.0)	8 (28.6)	24 (31.6)	15 (34.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; PD-L1, programmed death-ligand 1; CPS, combined positive score; CLDN18.2, claudin-18 isoform 2; CCr, creatinine clearance.

[a] Comorbidities included ischemic heart disease, cerebrovascular disease, obstructive lung disease, and restrictive lung disease.

Treatment Exposure in Neoadjuvant Phase

An overview of treatment delivery for perioperative FLOT is shown in Table 2. Among the 147 patients, 129 patients (87.8%) completed 4 cycles of neoadjuvant FLOT, whereas 18 patients (12.2%) discontinued due to AEs (n = 11), disease progression (n = 6), and patient refusal (n = 1). The completion rate of neoadjuvant FLOT was comparable across age groups (89.3%, 88.2%, and 86.0% in patients aged < 60, 60–74, and ≥ 75 years, respectively). The patterns and clinical background of initial dose modifications are summarized in Supplementary Table S1. Initial dose modification was increasingly adopted with advancing age and was primarily guided by clinical vulnerability factors, including impaired renal function, comorbidities, and poor performance status. Initial dose reduction was implemented in 67.4% and 10.5% of patients aged ≥ 75 and 60–74 years, respectively, whereas all patients aged < 60 years were initiated without dose reduction. Among patients aged ≥ 75 years, all patients with ECOG PS 1 received initial dose reduction, compared with 55.6% of those aged 60–74 years. Similarly, among patients with comorbidities or creatinine clearance < 60 mL/min, initial dose reduction was more frequently adopted in

patients aged ≥ 75 years than in those aged 60–74 years. Dose modifications during neoadjuvant phase also increased with age (Supplementary Table S2). RDI was higher in patients who received prophylactic peg-G-CSF than in those who did not during neoadjuvant phase (Supplementary Table S3).

Table 2
Treatment delivery of perioperative FLOT

	Overall	**< 60 years**	**60–74 years**	**≥ 75 years**
	n = 147 (%)	**n = 28 (%)**	**n = 76 (%)**	**n = 43 (%)**
Completed all neoadjuvant FLOT	129 (87.8)	25 (89.3)	67 (88.2)	37 (86.0)
Reasons for neoadjuvant FLOT discontinuation				
Adverse events	11 (7.5)	1 (3.6)	6 (7.9)	4 (9.3)
Disease progression	6 (4.1)	1 (3.6)	3 (3.9)	2 (4.7)
Patient refusal	1 (0.7)	1 (3.6)	0 (0)	0 (0)
Received any adjuvant FLOT	101 (68.7)	26 (92.9)	53 (69.7)	22 (51.2)
Completed all adjuvant FLOT	83 (56.5)	21 (75.0)	45 (59.2)	17 (39.5)
Reasons for adjuvant FLOT discontinuation				
Adverse events	14 (9.5)	2 (7.1)	7 (9.2)	5 (11.6)
Disease recurrence	2 (1.4)	1 (3.6)	1 (1.3)	0 (0)
Patient refusal	2 (1.4)	2 (7.1)	0 (0)	0 (0)

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Surgical Outcomes

Surgical outcomes are shown in Supplementary Table S4. Among the 147 patients, 137 patients (93.2%) proceed to surgery, whereas two patients aged 60–74 years and one patient aged ≥ 75 years with dMMR tumors who showed an inadequate response to FLOT did not undergo surgery and switched to immune checkpoint inhibitor therapy. The operative procedures were subtotal gastrectomy in 72 patients (49.0%), esophagectomy in 40 patients (27.2%), and total gastrectomy in 25 patients (17.0%). Median time from cycle 1 day1 until surgery was 12 (range, 6–23) weeks. The R0 resection rate (100%, 92.1%, and 86.0%, respectively) and pCR rate (10.7%, 7.9%, and 11.6%, respectively) were comparable across age groups.

Treatment Exposure in Adjuvant Phase

After radical surgery, 101 patients (68.7%) received at least one cycle of adjuvant FLOT. Adjuvant treatment was not initiated because of AEs during the neoadjuvant phase (n = 17, 11.6%), postoperative decline in general condition or surgical complications (n = 15, 10.2%), or other reasons (n = 4, 2.7%). The proportion of patients who initiated adjuvant FLOT decreased with advancing age (92.9%, 69.7%, and 51.2% in patients aged < 60, 60–74, and ≥ 75 years, respectively).

Overall, 83 patients (56.5%) completed four cycles of adjuvant FLOT, whereas 18 patients (12.2%) discontinued treatment because of AEs (n = 14), disease recurrence (n = 2), or patient refusal (n = 2). Completion rates also declined with advancing age (75.0%, 59.2%, and 39.5%, respectively). Initial and subsequent dose modifications during adjuvant treatment were more frequently required in older patients (Supplementary Table S2). RDI was higher in patients who received prophylactic peg-G-CSF than in those who did not during adjuvant phase (Supplementary Table S3).

Safety

TRAEs are summarized in Table 3. Hematologic and nonhematologic AEs of any-grade tended to occur more frequently in younger patients and less frequently in older patients. This trend was most pronounced for neutropenia, with grade ≥ 3 neutropenia observed in 53.6%, 36.8%, and 20.9% of patients aged < 60, 60–74, and ≥ 75 years, respectively. In contrast, grade ≥ 3 AEs were generally infrequent across all age groups, most occurring in fewer than 5% of patients. However, among patients who developed AEs, older patients tended to experience a higher proportion of severe toxicity. This trend was particularly notable for anorexia, in which grade ≥ 3 events occurred in 9.3% of patients aged ≥ 75 years, corresponding to 4 of 33 patients (12.1%) who developed anorexia.

Table 3
Treatment-related adverse events

	Overall		< 60 years		60–74 years		≥ 75 years	
	n = 147 (%)		n = 28 (%)		n = 76 (%)		n = 43 (%)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
Hematologic adverse events								
Platelet count decreased	107 (72.8)	7 (4.8)	21 (75.0)	1 (3.6)	52 (68.4)	3 (3.9)	34 (79.1)	3 (7.0)
Anemia	98 (66.7)	3 (2.0)	20 (71.4)	0 (0)	48 (63.2)	2 (2.6)	30 (69.8)	1 (2.3)
Neutropenia	64 (43.5)	52 (35.4)	16 (57.1)	15 (53.6)	36 (47.4)	28 (36.8)	12 (27.9)	9 (20.9)
Febrile neutropenia	8 (5.4)	8 (5.4)	1 (3.6)	1 (3.6)	6 (7.9)	6 (7.9)	1 (2.3)	1 (2.3)
Nonhematologic adverse events								
Anorexia	105 (71.4)	11 (7.5)	22 (78.6)	2 (7.1)	50 (65.8)	5 (6.6)	33 (76.7)	4 (9.3)
Fatigue	82 (55.8)	2 (1.4)	19 (67.9)	0 (0)	42 (55.3)	1 (1.3)	21 (48.8)	1 (2.3)
Diarrhea	78 (53.1)	2 (1.4)	18 (64.3)	1 (3.6)	45 (59.2)	1 (1.3)	15 (34.9)	0 (0)
Nausea	68 (46.3)	6 (4.1)	19 (67.9)	1 (3.6)	34 (44.7)	3 (3.9)	15 (34.9)	2 (4.7)
Vomiting	4 (2.7)	1 (0.7)	2 (7.1)	1 (3.6)	1 (1.3)	0 (0)	1 (2.3)	0 (0)

Supportive Care Management and Occurrence of Adverse Events

The associations between prophylactic supportive care and AEs are shown in Fig. 1. Prophylactic peg-G-CSF was associated with significantly lower rates of grade ≥ 3 neutropenia (6.7% vs 80.7%, $P < 0.001$) and febrile neutropenia (2.2% vs 10.5%, $P = 0.038$), and unplanned hospitalization due to febrile neutropenia (1.1% vs 5.3%) compared with no prophylactic peg-G-CSF use (Fig. 1A). This benefit was consistently observed across all age groups.

Prophylactic olanzapine was administered in 12 patients (8.2%). Although the number of patients receiving prophylactic olanzapine was limited and age-stratified analyses were not feasible, prophylactic olanzapine was associated with lower rates of any-grade nausea (33.3% vs 47.4%), any-grade anorexia

(41.7% vs 74.1%, *P* = 0.024), and unplanned hospitalization due to anorexia (0% vs 8.9%) compared with no prophylactic olanzapine use (Fig. 1B).

Additional IV fluid support is summarized in Fig. 2A. During the neoadjuvant phase, IV fluid support was most frequently required during cycle 1 across all age groups and increased with advancing age (10.7%, 30.3%, and 46.5% in patients aged < 60, 60–74, and ≥ 75 years, respectively; Fig. 2A). A similar age-related trend was observed during cycles 2–4 (3.6%, 21.1%, and 32.5%, respectively). Consistent with these findings, unplanned hospitalizations during the neoadjuvant phase also occurred most frequently during cycle 1, although the incidence remained below 10% across all age groups (Fig. 2B). Among patients who did not require additional supportive interventions during cycle 1, 88.0% did not require such interventions in subsequent neoadjuvant phase.

In contrast, during the adjuvant phase, no clear age-related differences in IV fluid administration or unplanned hospitalization were observed. However, patients who underwent total gastrectomy tended to require IV fluid support more frequently than those who underwent other procedures (32.0% vs 18.8%, *P* = 0.143; Fig. 2A), while postoperative unplanned hospitalization was significantly more frequent after total gastrectomy (20.0% vs 3.6%, *P* = 0.010; Fig. 2B). Among patients who did not require additional supportive interventions during cycle 5, 86.6% did not require such interventions in subsequent adjuvant phase.

Discussion

In the post-MATTERHORN era, practical management strategies for perioperative FLOT are essential for the safe implementation of D-FLOT in routine clinical practice, particularly in Asian populations and elderly or vulnerable patients. In this study, we described a risk-adapted strategy for perioperative FLOT delivery according to age subgroup and clinical vulnerability factors, including PS, comorbidities, and renal function. Notably, pCR rates were maintained across age groups despite more frequent dose modifications in older patients, suggesting that individualized modification may allow feasible neoadjuvant FLOT delivery without apparent compromise in pathological response. Our findings also highlight the importance of timely supportive care intervention, particularly during treatment initiation and the first postoperative cycle of FLOT, when unplanned hospitalization and IV fluid support were most frequently required. Based on treatment tolerability and clinical course, interim outpatient visits could subsequently be individualized or omitted in selected patients (Fig. 3).

In the MATTERHORN trial, the median age of participants was 62 years (range, 26–84 years), and only 8.4% of patients were aged ≥ 75 years. In addition, a creatinine clearance of ≥ 50 mL/min was required for study eligibility [8]. As the global population ages, the number of older patients with GEA is expected to increase markedly [16, 17]. These findings underscore the need for risk-adapted strategies to extend FLOT-based perioperative treatment beyond the selected populations enrolled in clinical trials. Previous observational studies evaluating perioperative FLOT in older patients generally used an age cutoff of 65 years [18–20]. In our cohort, however, comorbidities were more common and reduced creatinine

clearance was substantially more frequent among patients aged ≥ 75 years. Therefore, stratifying patients using a 75-year cutoff and discussing age-specific management strategies may provide more practical insights for clinical practice. At the same time, as treatment decisions for older adults have increasingly shifted from chronological age toward individualized assessment, incorporation of geriatric assessment may further refine risk stratification and treatment selection within the ≥ 75-year population [21, 22].

The present study suggests that appropriate supportive care, including prophylactic peg-G-CSF and olanzapine, may improve the safety and feasibility of perioperative FLOT. Prophylactic peg-G-CSF may be particularly important in Asian patients. In the MATTERHORN trial, Asian patients receiving FLOT had a 25-percentage-point higher incidence of grade ≥ 3 neutropenia than the overall study population (69% vs 44%) [23]. In addition, febrile neutropenia occurred in 12% of Asian patients in the D-FLOT arm despite the younger age of the Asian cohort compared with our study population. Prophylactic peg-G-CSF may therefore help reduce severe neutropenia, prevent febrile neutropenia, avoid treatment delays, and maintain RDI. Antiemetic management is another key component of supportive care. Although FLOT is classified as a moderately emetogenic regimen [24, 25], its emetogenic potential may be comparable to that of highly emetogenic chemotherapy [26]. Given that international guidelines recommend olanzapine-containing antiemetic prophylaxis for highly emetogenic regimens [27–29], incorporating olanzapine into supportive care may improve the tolerability and treatment feasibility of FLOT.

In our cohort, 83 of 147 patients (56.5%) completed all eight planned cycles of FLOT, a completion rate comparable to that observed in MATTERHORN. However, the proportion of patients who initiated adjuvant FLOT declined with increasing age (92.9%, 69.7%, and 51.2% in patients aged < 60 years, 60–74 years, and ≥ 75 years, respectively). In contrast, among patients who initiated adjuvant FLOT, discontinuation rates in adjuvant phase were similar across age groups (19.2%, 15.1%, and 22.7%, respectively). Lower completion rates of adjuvant FLOT in elderly patients may reflect not only reduced chemotherapy tolerability but also postoperative factors, such as surgical complications, delayed recovery, and functional decline, underscoring the importance of maximizing feasible preoperative treatment delivery, particularly in elderly patients. Furthermore, delivery of adjuvant FLOT after total gastrectomy remained challenging regardless of age. However, this challenge is commonly encountered after total gastrectomy, regardless of the perioperative treatment strategy.

The limited feasibility of postoperative treatment highlights the need for risk-adapted de-escalation strategies. Emerging evidence suggests that selected patients may derive limited benefit from intensive postoperative therapy. Given the findings of the prospective observational SPACE-FLOT study, patients who achieve pCR may be candidates for omission of adjuvant FLOT [30]. Furthermore, patients who achieved pCR in the D-FLOT arm of the MATTERHORN study demonstrated a favorable prognosis, with a 24-month event-free survival rate of 94.5% [31]. However, these findings should not be interpreted as evidence supporting routine omission of postoperative therapy in patients with pCR outside prospective trials.

This study has several limitations. First, this was a retrospective, single-center study conducted in Japan. Although the overall sample size was substantial for a Japanese real-world FLOT cohort, the number of patients in each subgroup was relatively small, requiring caution when interpreting subgroup analyses. Second, the higher prevalence of dMMR tumors among older patients and subsequent treatment changes to immunotherapy may have affected preoperative FLOT completion rates. Third, no formal geriatric assessment was performed, highlighting the need for future studies incorporating comprehensive geriatric assessment. Finally, selection bias cannot be excluded because this study was conducted at a specialized cancer center and excluded patients enrolled in clinical trials. Nevertheless, the inclusion of patients potentially underrepresented in clinical trials provides valuable insights into FLOT feasibility in routine clinical practice.

In conclusion, as FLOT-based perioperative treatment becomes more widely adopted in the post-MATTERHORN era, practical risk-adapted strategies will be essential to ensure its safe implementation beyond clinical trial populations. Individualized dose modification and proactive supportive care may enable broader and safer delivery of FLOT-based chemoimmunotherapy, particularly in Asian, elderly, and clinically vulnerable patients, thereby maximizing the clinical benefit of immune checkpoint inhibitor–containing perioperative regimens in routine practice.

Declarations

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Author Contributions

Conception and design: Rika Uchino, Mashiro Okunaka, Izuma Nakayama, and Kohei Shitara

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Provision of study materials or patients: Not applicable

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Manuscript writing: All authors

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Conflicts of Interest

R. Uchino has no conflicts of interest.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

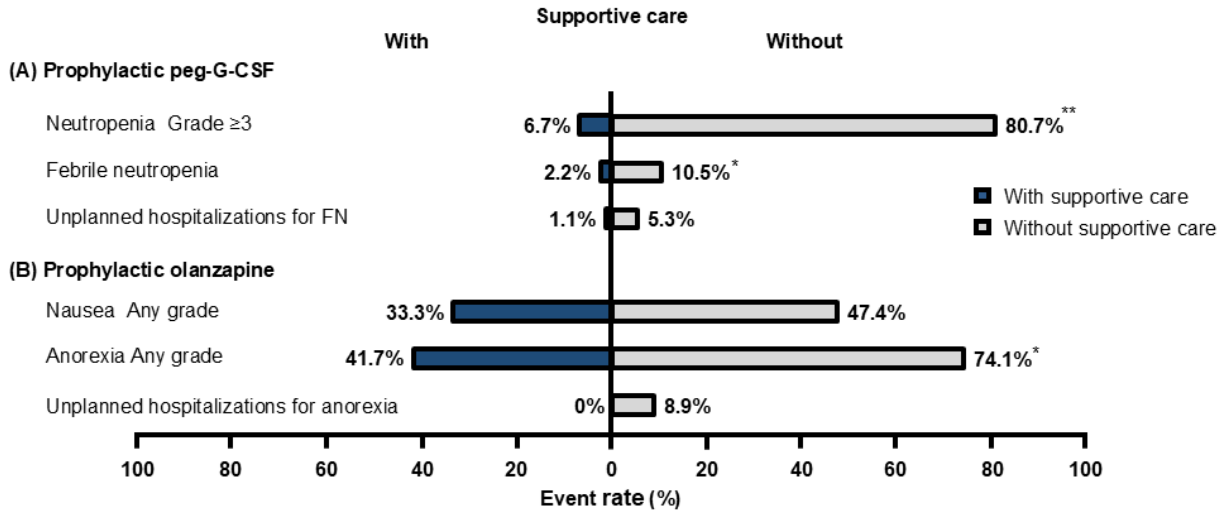


Figure 1

Prophylactic management and occurrence of adverse events

Incidence of adverse events according to prophylactic use: (A) peg-G-CSF and (B) olanzapine. Colors indicate prophylactic supportive care use: blue for with, and gray for without.

peg-G-CSF, pegylated granulocyte colony-stimulating factor; FN, febrile neutropenia. $^{**}P < 0.01$, $^{*}P < 0.05$.

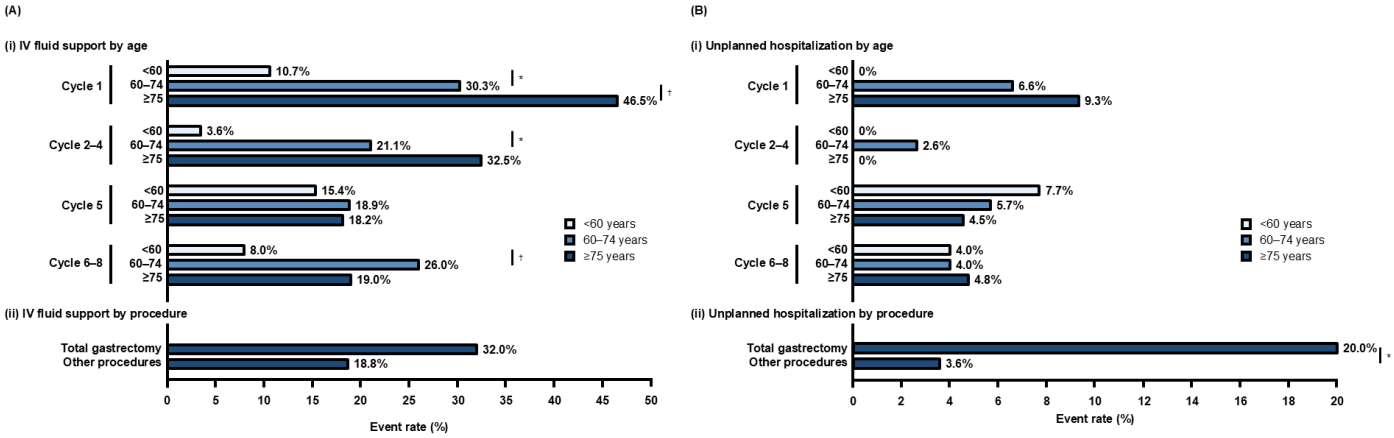


Figure 2

Incidence of additional supportive interventions

Incidence of additional supportive interventions: (A) IV fluid support and (B) unplanned hospitalization. Panel (i) shows differences by age group. Colors indicate age groups: light blue for aged< 60 years, medium blue for aged 60–74 years, and dark blue for aged≥ 75 years. Panel (ii) shows differences by procedure.

IV, intravenous. *$P < 0.05$, †$P < 0.10$.

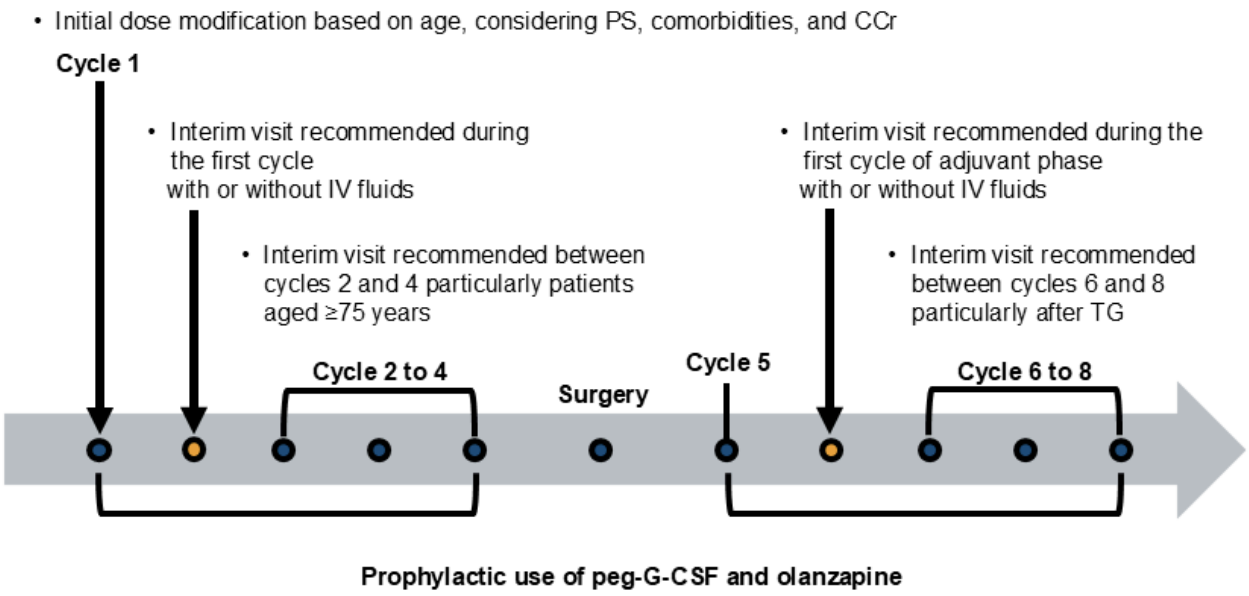


Figure 3

Practical management strategy for perioperative FLOT

Our treatment strategy for implementing FLOT in daily clinical practice.

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; PS, performance status; CCr, creatinine clearance; IV, intravenous; TG, total gastrectomy; peg-G-CSF, pegylated granulocyte colony-stimulating factor.