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# Preoperative Capecitabine, Oxaliplatin, and Irinotecan in Resectable Gastric or Gastroesophageal Junction Cancer: Pathological Response as Primary Endpoint and FDG-PET Predictions

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**Keywords**

Gastric cancer · Neoadjuvant chemotherapy · Capecitabine · Oxaliplatin · Irinotecan · Combination chemotherapy · Phase II study · Pathological response · FDG-PET/CT

**Abstract**

***Objectives:*** This phase II trial was aimed at assessing the safety and activity of capecitabine, oxaliplatin, and irinotecan (COI regimen) as a preoperative treatment for resectable gastric cancer (GC) or gastroesophageal junction (GEJ) cancer. ***Methods:*** Patients affected by T3–T4/N0–N+/M0 GC/GEJ cancer were treated with the COI regimen for 4 cycles followed by restaging and gastroresection with D2 lymphadenectomy. Four postoperative cycles were scheduled. The primary endpoint was pathological response rate according to Becker et al. [Cancer 2003;98:1521–1530]. The potential role of fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) as a predictive biomarker of pathological tumor response was assessed in a subgroup of 19 evaluable patients. ***Results:*** Between January 2011 and October 2015, a total of 40 patients were enrolled. After the preoperative phase, 36 out of 40 patients (90%) were considered eligible for surgery: 12 patients (30%) achieved a pathological response. The most frequent grade 3/4 adverse events were diarrhea (27%), nausea (25%), and fatigue (17%). Grade 3 neutropenia occurred in 7.5% of patients. A lower standard uptake value at baseline FDG-PET/CT was associated with pathological response. ***Conclusion:*** COI combination is active with a manageable toxicity profile in patients with resectable GC or GEJ cancer. FDG-PET/CT imaging as a surrogate biomarker of pathological response in this setting appears fascinating but should be further investigated.



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## Introduction

Gastric cancer (GC) is the second most common cause of cancer-related deaths worldwide [1]. Surgical resection is the mainstay of treatment for localized or locally advanced disease, but survival is still unsatisfactory even when achieving R0 resection. Adjuvant or perioperative chemotherapy are widely used for locally advanced disease, although little consensus exists regarding the optimal chemotherapeutic regimen and timing. The early use of chemotherapy in a neoadjuvant approach may offer the advantage of eradication of micrometastatic disease, in vivo assessment of response to chemotherapy, and achievement of tumor downstaging and, consequently, R0 resection. In randomized studies, perioperative chemotherapy conferred a significant outcome improvement when compared to surgery alone [2, 3]. Combinations including third-generation drugs, such as oxaliplatin, oral fluoropyrimidines (capecitabine or S1), docetaxel, and irinotecan, may further improve outcomes given the efficacy in the metastatic setting [4–6]. In phase II studies, pathological response is nowadays widely accepted as a primary endpoint of treatment activity, since it can be used as an immediate surrogate for long-term outcomes [7]. Since the first description by Becker et al. [8], several phase II studies had investigated the activity of newer regimens in order to achieve pathological response [9, 10].

Furthermore, fluorine-18 ($^{18}$F) fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) appears to be a promising tool for the early prediction of pathological response in several tumor types. However, its role in GC patients treated in the preoperative setting is far from being clarified often due to the retrospective nature and small sample size of available studies, the absence of significant FDG avidity in some histotypes (particularly mucinous and diffuse type), and the lack of demonstrated clinical utility [11]. However, the possible use of a noninvasive tool predicting early inactivity of a specific regimen may be useful to switch to a non-cross-resistant treatment in the neoadjuvant setting.

We previously showed that triplet combination of capecitabine, oxaliplatin, and irinotecan (COI regimen) was feasible and promisingly active in metastatic colorectal cancer and metastatic GC [12, 13]. The aim of this study was to evaluate the impact of the COI regimen in the preoperative setting by assessing pathological response in patients with locally advanced, technically resectable GC or gastroesophageal junction (GEJ) cancer. Furthermore, we investigated the potential role of FDG-PET/CT as a predictive biomarker of pathological response in this patient population.

## Material and Methods

This monocentric, single-arm phase II study was approved by the Institutional Review Board of Fondazione IRCCS Istituto Nazionale dei Tumori of Milan (trial registration No. INT 102/14). Written informed consent was obtained from each patient prior to study procedures.

*Study Population*

Patients were enrolled in this study if they had histologically proven resectable GC or GEJ cancer with clinical stage T3–T4 and/or N+, M0. Other inclusion criteria were age between 18 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate hematologic, renal, and hepatic functions. Patients were excluded from the study if they had any other active malignancy with the exception of nonmelanoma skin cancer or in situ cervical cancer, uncontrolled cardiac disease, or another clinically significant uncontrolled illness. Male and female patients with reproductive potential had to use approved contraceptive methods.

*Study Procedures*

Eligible patients were evaluated by physical examination, including nutrition assessment, and staged with CT scan and echoendoscopy. They were treated, in a perioperative strategy, with the COI regimen, consisting of irinotecan (180 mg/m$^2$) on day 1 followed by oxaliplatin (85 mg/m$^2$) on day 2 and capecitabine 1,000 mg/m$^2$/day taken orally twice a day from day 2 to 6 on a biweekly schedule. The preoperative phase consisted of 4 cycles, followed by restaging with the same techniques as used at baseline. After reassessment of resectability in our institutional multi-disciplinary tumor meeting, gastrectomy with standard D2 lymphadenectomy was performed within 4–8 weeks from the last dose of chemotherapy. All resected specimens were reviewed by 2 blinded pathologists. In the postoperative phase, patients received 4 additional cycles of the COI regimen, starting from 4 to 8 weeks after surgery. Radiation therapy with capecitabine at standard radiosensitizing doses (1,650 mg/m$^2$/day) was scheduled for patients with R1 resection and was performed after the end of the whole treatment plan.

Before each treatment cycle, a complete blood count was obtained, and blood urea nitrogen, electrolytes, serum creatinine levels, and liver function were tested. Dose adjustments were made according to the study protocol. The severity of adverse effects was registered according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03) [14].

*Study Endpoints*

The primary endpoint of the study was pathological response rate according to the criteria by Becker et al. [8]. As reported in their paper, response was classified in 3 grades: grade 1, complete (0% residual tumor, grade 1a) or subtotal tumor regression (<10% residual tumor, grade 1b); grade 2, partial tumor regression (10–50% residual); and grade 3, minimal or no tumor regression (>50%

residual tumor). Secondary endpoints were overall response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in patients with measurable disease [15], R0 resection rate, progression-free survival (PFS), overall survival (OS), 3-year OS and PFS rates both in the intent-to-treat (ITT) population and according to pathological response, and, finally, treatment safety.

*FDG-PET/CT Ancillary Study*

In a subgroup of patients, who signed an optional informed consent, an ancillary study with FDG-PET/CT scan was performed using PET-CT Philips 64 TOF Gemini (Philips Healthcare, Andover, MA, USA) or GE Discovery LS (General Electric Healthcare, Milwaukee, WI, USA). A whole-body scan was performed approximately 1 h after intravenous injection of 3–6 MBq/kg of $^{18}$F-FDG. The imaging protocol was composed of the following steps: (1) CT scout view to define the anatomic coverage of the scan (usually from upper third thigh to skull base); (2) low-dose CT scan (120 kV, range 60–80 mA) with the patient breathing normally; and (3) PET scan (2–4 min/bed according to the used PET/CT scan). CT images were used for the reconstruction of attenuated-corrected PET images and anatomic localization of FDG findings. No radiological intravenous contrast agents were administrated. PET-CT images were analyzed by 2 nuclear medicine physicians blinded to study purposes. A positive scan was defined by the presence of an abnormal focal uptake of FDG with anatomic alterations in the corresponding CT image. A semiquantitative analysis of FDG uptake was performed, measuring the standard uptake values (SUVs). The maximum value of SUV ($SUV_{max}$), defined by the highest value of the SUV within a region of interest, was considered. Patients underwent 2 FDG-PET/CT evaluations: at baseline (SUV-1) and prior to surgery (SUV-2). Changes in $SUV_{max}$ values were analyzed as the percentage difference from SUV-1 to SUV-2, and a regression index (RI) was calculated, i.e., (SUV-1 – SUV-2/SUV-1) ×100 [16, 17]. The results were finally correlated with the pathological tumor response.

*Statistical Analysis*

The primary study endpoint was the incidence of pathological response, defined as the frequency of patients with grade 1 and 2 response according to the criteria by Becker et al. [8] over the total number of enrolled patients (ITT population). Using a Simon 2-stage design with a type I error rate of 10% and a power of 85%, a total number of 42 patients was needed to demonstrate an increase in pathological response rate from 10 to 25%. PFS was calculated from randomization to the first event (i.e., disease progression or recurrence, or death from any cause), and OS was calculated from randomization to death. Data on patients who were event free were censored on the date the patient was last seen. Also, the Clopper-Pearson exact method was used for the estimation of the binomial proportion confidence interval. Regarding the ancillary FDG-PET/CT study, SUV-1, SUV-2, and RI were expressed as medians (1st to 3rd quartiles). The differences in all parameters between patients with pathological response and patients with nonpathological response were assessed using the Anderson-Darling test; $p < 0.05$ was considered statistically significant.

**Table 1.** Patients and disease characteristics

| Main characteristics | *n* | % |
|---|---|---|
| Median age (range), years | 59 (33–75) | |
| Gender | | |
| Male | 30 | 75 |
| Female | 10 | 25 |
| ECOG performance status | | |
| 0 | 36 | 90 |
| 1 | 4 | 10 |
| Primary tumor site | | |
| Stomach | 31 | 78 |
| GEJ | 9 | 22 |
| Pretreatment cTNM stage[a] | | |
| cT2N+ | 3 | 7.5 |
| cT3N0 | 3 | 7.5 |
| cT3N+ | 18 | 45 |
| cT4N0 | 4 | 10 |
| cT4N+ | 12 | 30 |
| Histotype (Lauren classification) | | |
| Intestinal type | 24 | 60 |
| Diffuse type | 16 | 40 |

ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction. [a] Staging done via computed tomography scan and echoendoscopy.

## Results

*Patients' Characteristics*

Between January 2011 and October 2015, a total of 40 patients were enrolled at Fondazione IRCCS Istituto Nazionale dei Tumori. Patients' demographics and disease characteristics are shown in Table 1. The median age was 59 years (interquartile range 33–75); 22% of patient had a GEJ localization of the primary tumor, and 24 patients (60%) had an intestinal histotype according to the Lauren classification.

*Tumor-Related Outcomes*

After the preoperative phase, 36 out of 40 patients (90%) were considered eligible for surgery (4 patients had a progressive disease at restaging) and were evaluable for the primary endpoint of pathological response. Twelve patients of the ITT population (30%) achieved a documented pathological response according to the criteria by Becker et al. [7, 8] (95% confidence interval [CI] 16.6–46.5%): there was complete tumor regression (i.e., grade 1a) in 2 cases and partial tumor regression (i.e., grade 2) in the remaining 10 cases. Table 2 summarizes the results in terms of pathological response. Additionally, tumor re-

**Table 2.** Tumor-related outcomes in terms of pathological response and RECIST criteria in patients with measurable disease

| Pathological response | Becker 1a | Becker 1b | Becker 2 | Becker 3 |
|---|---|---|---|---|
| ITT ($n$ = 40) | 2 (5) | 0 | 10 (25) | 24 (60) |
| Resected patients ($n$ = 36)[a] | 2 (6) | 0 | 10 (28) | 24 (66) |
| RECIST 1.1 response | CR | PR | SD | PD |
| Evaluable patients ($n$ = 27) | 0 | 13 (48) | 12 (44) | 2 (8) |

Values are $n$ (%). RECIST, Response Evaluation Criteria in Solid Tumors; ITT, intention to treat; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. [a] Four patients (10%) had a progressive disease at restaging and were not evaluable for the primary endpoint.

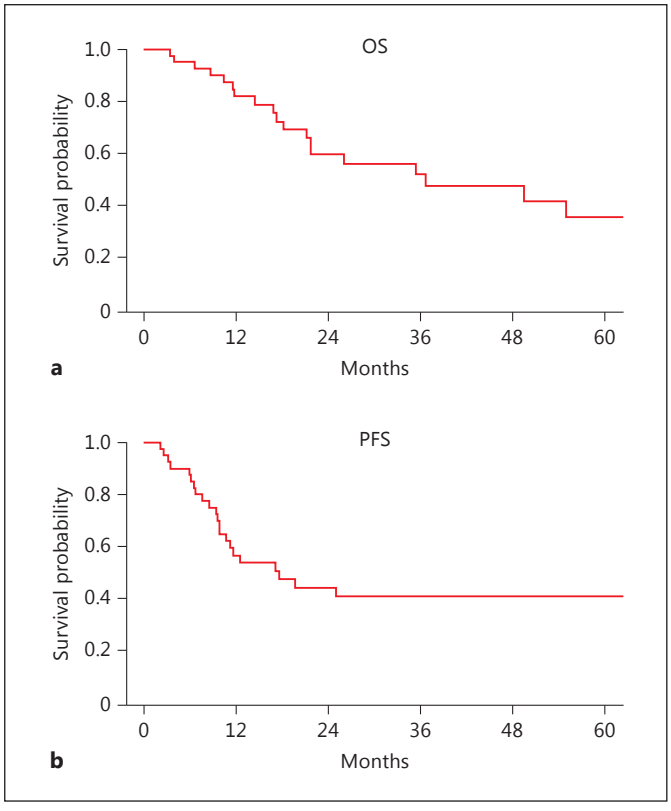


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**Fig. 1.** Kaplan-Meier curves for overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) in the intent-to-treat population.

sponses according to RECIST 1.1 criteria are reported in patients with measurable disease (regional lymph nodes). Overall, R0 resection was achieved in 33 (82%) out of 40 patients.

*Patients-Related Outcomes*

After a median follow-up of 43 months (95% CI 26–79), 21 out of 40 patients (52%) had a documented disease recurrence, and 19 out of 40 patients (47%) died. Of the 21 patients with disease recurrence, 7 patients (33%) received platinum-based chemotherapy, whereas 9 patients (43%) received paclitaxel in monotherapy or combination with ramucirumab. Five patients (24%) were not fit for further treatment. In the ITT population, the median OS and PFS were 36.6 months (95% CI 21.2–not reached) and 17.6 months (95% CI 9.7–not reached), respectively (Fig. 1). Three-year OS and PFS rates were 52.3% (95% CI 37.4–73.1) and 40.9% (95% CI 27.5–61), respectively. If stratified by pathological response, 3-year OS rates were 72.7% (95% CI 50.6–100) in patients with Becker 1 and 2 and 47.9% (95% CI 29.7–77.3) in patients without pathological response ($p$ = 0.161). Furthermore, 3-year PFS rates were 64.8% (95% CI 42.1–99.8) and 34.7% (95% CI 18.9–63.8), respectively ($p$ = 0.109). Kaplan-Meier curves for OS and PFS stratified by pathological response are shown in Figure 2.

*Safety*

All patients were evaluable for safety. The median number of cycles was 6 (range 4–8), and all patients completed the preoperative phase. No chemotherapy-related death was reported. Ten premature study withdrawals occurred only in the postoperative phase: 5 cases (12%) due to chemotherapy-related adverse events (AEs); 4 cases (10%) due to progressive disease at presurgery restaging, and 1 case (2.5%) due to surgery complication (death). Dose reductions or delays related to AEs were reported in 16 patients (40%). However, most AEs were mild to moderate in intensity. The most frequent grade 3/4 AEs were

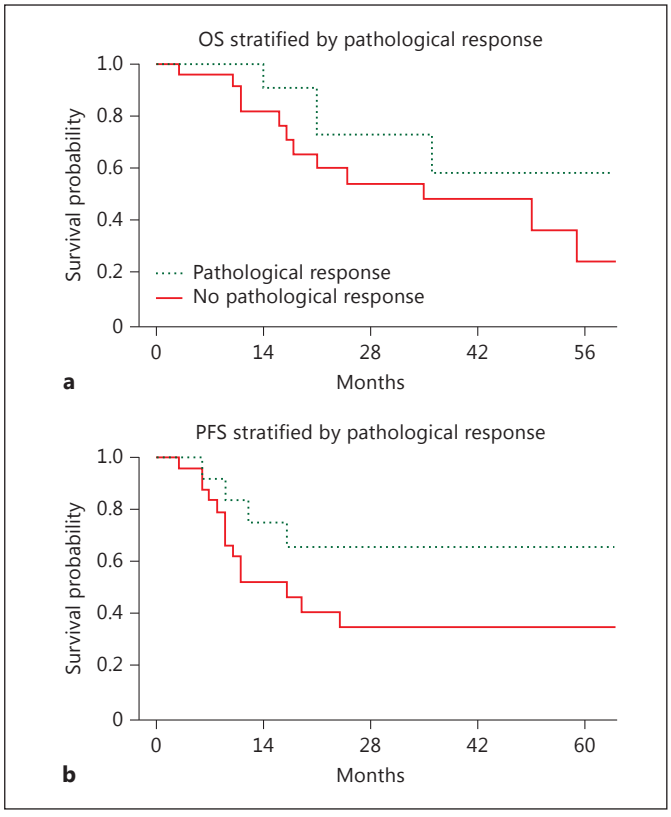


**Fig. 2.** Kaplan-Meier curves for overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) stratified by pathological response in the intent-to-treat population.

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**Table 3.** Treatment-relates adverse events

| Any adverse event | All grades | | Grade 3 or 4 | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Gastrointestinal toxicities | | | | |
| Nausea | 30 | 75 | 10 | 25 |
| Vomiting | 10 | 25 | 3 | 7.5 |
| Diarrhea | 32 | 80 | 11 | 27 |
| Stomatitis | 15 | 37 | 3 | 7.5 |
| Abdominal pain | 12 | 30 | 2 | 5 |
| Hematological toxicities | | | | |
| Neutropenia | 36 | 90 | 3 | 7.5 |
| Anemia | 4 | 10 | 0 | 0 |
| Thrombocytopenia | 2 | 5 | 1 | 2.5 |
| Other adverse events | | | | |
| Anorexia | 20 | 50 | 3 | 7.5 |
| Fatigue | 9 | 22 | 7 | 17 |
| Hand-foot syndrome | 4 | 10 | 1 | 2.5 |

diarrhea – with an incidence of 27% – followed by nausea (25%) and fatigue (17%). Hematologic toxicity was rare, with grade 3 neutropenia occurring in 3 patients (7.5%). Table 3 summarizes the frequency of all grades of AEs during treatment.

Postoperative complications were classified according to the NCI-CTCAE [14]. Complications of any grade occurred in 15 patients (37%). Grade 3 or higher complications occurred in 8 patients (20%): pancreatic juice leakage in 3 patients (7.5%) and intra-abdominal abscess in 2 patients (5%). One patient died of sudden massive bleeding from an aortoenteric fistula at the esophagojejunal anastomosis.

*Results of the FDG-PET/CT Ancillary Study*

Figure 3 shows the diagram of patients included in the FDG-PET/CT ancillary study. The final study population included 19 resected patients with both baseline and presurgical scans. Table 4 shows the median values of the SUV parameters in the overall population. Furthermore, we reported the median SUVs both in the pathological response and nonpathological response groups. A statistical analysis was elaborated: patients with pathological response (Becker 1–2) had significantly lower SUV-1 values than the other group (Becker 3). On the contrary, other FDG-PET/CT parameters (SUV-2 and RI) were not significantly associated with pathological response.

## Discussion

The Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was the first to establish the role of perioperative chemotherapy in patients with locally advanced GC or GEJ cancer, showing a significant PFS and OS benefit with perioperative epirubicin, cisplatin, and fluoropyrimidines (ECF/ECX) as compared to surgery alone [2]. Nowadays, perioperative strategies are a standard of care in this setting. However, the optimal chemotherapy regimen has yet to be defined.

As a matter of fact, in this specific population, several phase II studies have tested the activity of various drug combinations using different primary endpoints: R0 resection rate, radiological response, or pathological response. The available evidence indicates that pathological response may represent the endpoint of choice, since it may be more reproducible than RECIST response. In fact, the use of conventional imaging might be limited in case of nonmeasurable disease, as frequently observed in locally advanced GC. Furthermore, pathological response

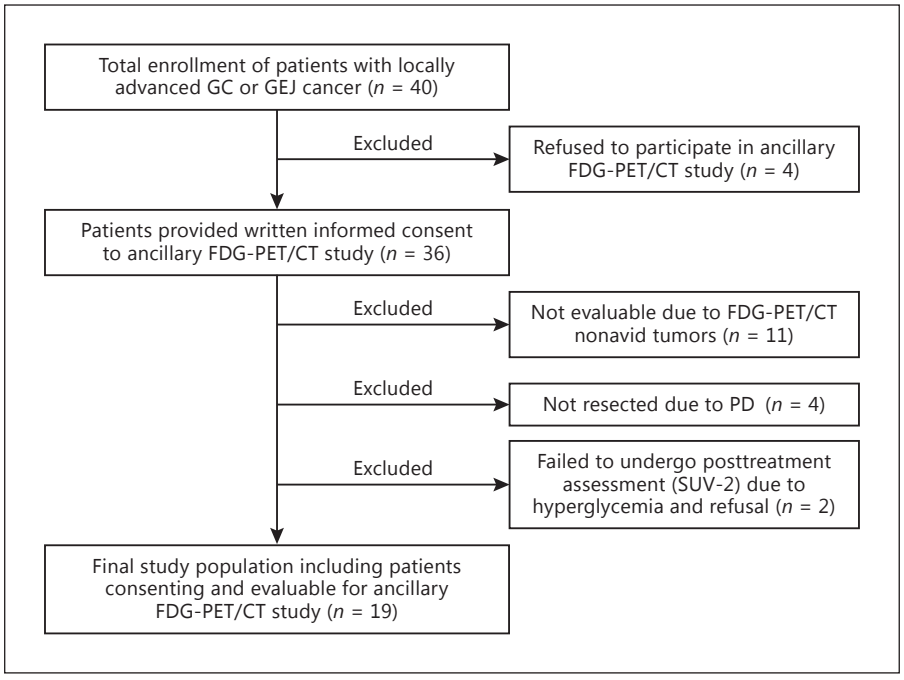


**Fig. 3.** Diagram of patients' selection in the FDG-PET/CT ancillary study. GC, gastric cancer; GEJ, gastroesophageal junction; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; PD, progressive disease.

**Table 4.** FDG-PET parameters in the overall population and by comparison of patients with and without pathological response

| FDG-PET parameter | Overall population ($n$ = 19) | No pathological response ($n$ = 14) | Pathological response ($n$ = 5) | $p$ value[a] |
|---|---|---|---|---|
| SUV-1 | | | | |
| Median | 8.1 | 9.3 | 6.2 | 0.040* |
| 1st–3rd quartile | 6.4–10.9 | 7.25–13.25 | 5.8–6.4 | |
| SUV-2 | | | | |
| Median | 5.8 | 5.45 | 5.7 | 0.838 |
| 1st–3rd quartile | 4.45–7.55 | 4.35–7.39 | 5–5.9 | |
| Regression index, % | | | | |
| Median | 28 | 38.5 | 17 | 0.069 |
| 1st–3rd quartile | 8.75–51.25 | 26.5–52.8 | 1.7–22 | |

FDG-PET, fluorodeoxyglucose positron emission tomography; SUV, standardized uptake value. [a] Anderson-Darling test. * Statistically significant.

may be a good surrogate for OS, and several tumor regression grade systems have been developed over time [8, 18, 19].

Our study was a prospective phase II trial aiming at evaluating pathological response achieved in GC and GEJ cancer patients treated with capecitabine, oxaliplatin, and irinotecan in a perioperative setting. Data published so far have proven the efficacy of triplet regimens including either epirubicin [2] or docetaxel [20]. Whereas the role of anthracyclines has been recently questioned [21], the use of docetaxel in association with a fluoropyrimidine and platinum backbone has shown the highest frequency (up to 20%) of pathologically complete response [20, 22]. To the best of our knowledge, our study was the first to investigate the addition of irinotecan to a fluoropyrimidine- and platinum-based treatment, showing 5% of major pathological response (Becker 1a and 1b). This is in line with historical results of perioperative chemotherapy (usually 3%) [23]. We also demonstrated a pathological response (Becker 1 and 2) of 30% in the ITT population.

Furthermore, a preplanned exploratory analysis of OS and PFS according to pathological response confirmed its prognostic effect, although the low number of patients may have limited the achievement of a statistically significant result.

In addition, the use of irinotecan in lieu of taxanes might be successful from a strategic point of view. In fact, early disease relapse, a frequent event, might still be treated with an effective second-line therapy with paclitaxel and ramucirumab [24].

Concerning the safety profile, it is well established that triplet-drug regimens may be weighted by a higher toxicity burden. Nevertheless, our investigational regimen was revealed to be a feasible strategy in the perioperative setting. In fact, all patients completed the 4 planned cycles prior to surgery, and only 12% had to interrupt the postoperative phase due to AEs.

Our ancillary study prospectively investigated the potential role of FDG-PET/CT to early predict outcomes in terms of pathological response. In GC, there are only few studies using FDG-PET/CT to predict responses to neoadjuvant chemotherapy [11, 17]. Good correlations were reported between early metabolic response (>35% at 2 weeks), pathological response (<10% viable tumor cells in the resected specimen), and patient survival [17]. However, given the low prevalence of major pathological responses in our study and in the clinical practice, we focused on FDG-PET/CT-driven prediction of any-grade pathological response, since also grade 2 regression is associated with an improved outcome as compared to nonresponse. Interestingly, we showed that only baseline SUV, but not posttreatment SUV and RI, was significantly associated with pathological response. Therefore, cancers with minor baseline avidity might have a higher chance of achieving a pathological response, as already shown for other tumor types [25]. Furthermore, the physiologic FDG uptake in the stomach may underestimate tumor response to treatment.

In addition, certain histologic types of GC may not show increased FDG avidity, which could make response evaluation problematic. Besides these limitations, the best time to do posttreatment FDG PET/CT is still a matter of debate. However, early assessment at mid-treatment seems to be useful in distinguishing responders from nonresponders. This strategy may represent, in the future, a tool to select nonresponders and to modify the subsequent chemotherapy regime, optimizing the effectiveness of treatment and avoiding unnecessary side effects.

In conclusion, pathological response and its prediction through FDG-PET/CT imaging should be integrated in future prospective studies conducted in GC and GEJ cancer patients treated with neoadjuvant or perioperative strategies. In this setting, triplet chemotherapy regimens including irinotecan are feasible with promising results that should be investigated in a randomized setting.

## Disclosure Statement

None of the authors has any conflicts of interest to disclose related to this investigation.

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