

Prediction of Esophagogastric Varices Associated with Oxaliplatin Administration

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Abstract

Background: Oxaliplatin is a key drug for the chemotherapy of colorectal cancer; however, it is also known to cause non-cirrhotic portal hypertension. We aimed to identify the characteristics of patients who developed esophagogastric varices (EGV) after treatment with oxaliplatin.

Methods: This study retrospectively analysed patients with colorectal cancer who were treated with chemotherapy including oxaliplatin between 2010 and 2016. All patients were evaluated by contrast-enhanced computed tomography (CT) every 3 months both during and after treatment, and endoscopy was performed when appearance of portal hypertension was suspected.

Results: A total of 106 patients were divided into 2 groups: EGV formation (n=6) and EGV non-formation (n=100). In the EGV group, platelet counts decreased and the size of the spleen calculated by CT (CT-SI) increased markedly. The highest area under the receiver operating characteristic curve (AUC) for the change in platelet counts was 0.81 (80% sensitivity and 83% specificity) at 3 months posttreatment and the maximum AUC for CT-SI was 0.89 (79% sensitivity and 83% specificity) at 6 months posttreatment.

Conclusions: EGV formation could be predicted by assessment of platelet counts and CT-SI not only during but also after completion of the treatment.

Background

Oxaliplatin is one of the main chemotherapeutic agents currently used for gastrointestinal neoplasia[1, 2]. The addition of oxaliplatin or irinotecan to 5-fluorouracil (5-FU)/leucovorin therapy (FU/LV) has been shown to improve response rates, progression-free survival, and overall survival in patients with stage IV or recurrent colorectal cancer[3]. However, hepatotoxicity induced by oxaliplatin has been reported by surgeons[4–6] and should be carefully considered along with liver function because of the high incidence of postoperative complications. Therefore, oxaliplatin is now recognized as a hepatotoxic drug, based on pathological evidence of sinusoidal endothelial injury in the liver[7]. Recently, it has also become widely known that oxaliplatin may lead to the development of portal hypertension and esophagogastric varices (EGV). Some case reports, including from our group, have shown that EGV formation or rupture during or after oxaliplatin-containing chemotherapy can make it difficult to continue the treatment and may worsen the prognosis[8–12]. However the prevalence of and risk for developing EGV after oxaliplatin treatment is unclear. We therefore evaluated clinical features predictive of the development of EGV in colorectal cancer patients treated with oxaliplatin-based chemotherapy.

Methods

Patients and regimen of oxaliplatin-based chemotherapy

We retrospectively reviewed clinical data for 203 consecutive patients with colorectal cancer who were treated with systemic chemotherapy including oxaliplatin, as first-line therapy, due to advanced or

recurrent colorectal cancer between October 2010 and January 2016. Subjects included in the present study were chemotherapy-naïve patients who completed at least 4 cycles of initial chemotherapy including oxaliplatin, and patients who had never received previous chemotherapy.

The patients in this study were treated with: 5-FU, LV, and oxaliplatin (FOLFOX); FOLFOX plus bevacizumab (FOLFOX/Bev); FOLFOX plus cetuximab (FOLFOX/Cet); or FOLFOX plus panitumumab (FOLFOX/Pan). The FOLFOX regimen consisted of 85 mg/m² oxaliplatin and 200 mg/m² LV via 2-hour infusion, followed by a bolus injection of 400 mg/m² FU and 46-hour infusion of 2,400 mg/m² FU. The FOLFOX/Bev regimen consisted of FOLFOX plus bevacizumab (5 mg/kg via 90-minute infusion on day 1). The FOLFOX/Cet regimen consisted of FOLFOX plus cetuximab (400 mg/kg via 120-minute infusion on day 1 for the first cycle and 250 mg/kg via 60-minute infusion thereafter). The FOLFOX/Pan regimen consisted of FOLFOX plus panitumumab (6 mg/kg via 60-minute infusion on day 1). The treatments were continued in 2-week cycles until disease progression.

The protocol for the present study was approved by the local ethics committee of St. Marianna University School of Medicine, in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments, and written informed consent was obtained from all patients (Approval No. 4897).

Data collection and assessments

As routine care, all patients underwent blood sampling for analysis of aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, albumin, and platelet count every 2 weeks, and were evaluated by contrast-enhanced computed tomography (CE-CT) every 3 months both during and after treatment. If portal hypertension (i.e., collateral vessels, spleen enlargement, and EGV on CE-CT) was suspected, esophagogastroduodenoscopy (EGD) was performed.

Spleen size (CT spleen index)

Spleen size was measured by helical CT scan at areas of the axial portal venous phase images created by consecutive sequential 5-mm-thick slices. The CT spleen index (CT-SI) was calculated based on the maximal width and thickness at the hilum of the spleen on CT[13]. In brief, measurements of the maximal width (A–B) and a cross-sectional area of the spleen, and the thickness at the hilum (C–D) determined on a plane perpendicular to the maximal splenic width and through the hilum were multiplied (see Additional file 1). Changes in spleen size were determined for each CT time point during and after therapy by comparison with the pre-treatment value.

Statistical analyses

Data are presented as the median with range for continuous data and numerically for categorical data. Continuous variables were compared between groups using non-paired t-test or Mann-Whitney *U*-test. Categorical variables were compared between groups using Fisher's exact probability test. Cut-off values were calculated using the Youden index for receiver operating characteristic (ROC) analysis. All *p* values for statistical tests were 2-tailed, and values of < 0.05 were considered statistically significant. All

statistical analyses were performed using Prism 5 software for Windows (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Study cohort and patients characteristics

Of the 203 patients screened, 14 were excluded because CE-CT scans had not been performed routinely, while 189 cases underwent complete follow-up up to 6 months after the end of chemotherapy. Among these cases, 83 patients were excluded because of the presence of diffuse liver metastases, signs of mild liver damage (T-Bil > 2.0 mg/dL or ALT > 100 IU/L) including liver cirrhosis, signs of portal hypertension (EGV and/or ascites), or portal vein occlusion before initial chemotherapy. Ultimately, 106 patients were included, and no patients had radiological signs of portal hypertension prior to chemotherapy. The cohort was divided into 2 groups with or without EGV based on CE-CT and/or EGD; an EGV group (n = 6) and non-EGV group (n = 100), and clinical features of these groups were analyzed and compared retrospectively (Fig. 1).

Comparison of baseline characteristics between patients with and without EGV formation

The clinical characteristics of the 106 patients treated with systemic chemotherapy containing oxaliplatin for colorectal cancer are summarized in Table 1. The group with EGV (n = 6) had a median age of 60 years (range, 49–73) and comprised 5 males and 1 female. The group without EGV (n = 100) had a median age of 66 years (range, 27–87) and comprised 69 males and 31 females. There was no significant difference in tumor location between the 2 groups. In the EGV group, 33% (n = 2) received FOLFOX and 67% (n = 4) received FOLFOX/Bev, FOLFOX/Cet, or FOLFOX/Pan, while in the non-EGV group, the percentages were 63% (n = 63) and 37% (n = 37), respectively. The EGV and non-EGV groups showed no apparent difference in the mean number of cycles (11 vs 13 cycles, respectively) or duration of oxaliplatin administration (5.5 vs 6 months, respectively). As a result of disease progression, other chemotherapy following FOLFOX was continued in 51 patients (51%) without EGV and 5 patients (83%) with EGV.

Table 1
 Characteristics of patients treated with systemic chemotherapy containing oxaliplatin as first-line treatment for colorectal cancer

	non-EGV (n = 100)	EGV (n = 6)
Age, (years, median)	66 (27–87)	60 (49–73)
Sex (male/ female), n (%)	69/ 31 (69/ 31)	5/ 1 (83/ 17)
Location of tumor Rectum/ colon/ cecum (%)	43/ 55/ 2	33/ 67/ 0
Therapeutic regimen of the first line chemotherapy	63 (63%)	2 (33%)
FOLFOX*	37 (37%)	4 (67%)
FOLFOX + Bev, Cet, Pan**		
Administration of oxaliplatin-based chemotherapy	5.5 (1.5–22)	6 (4–17)
Duration of therapy (months, median)	11 (3–44)	13 (9–26)
Number of therapeutic cycles (times, median)		
Other chemotherapy followed by FOLFOX*	49 (49%)	1 (17%)
None	51 (51%)	5 (83%)
Additional therapy (second and third line chemotherapy)		
*FOLFOX; 5-fluorouracil, leucovorin, and oxaliplatin		
**Bev; Bevacizumab, Cet; cetuximab, Pan; panitumumab		
EGV; esophagogastric varices,		

Liver damage caused by oxaliplatin-based chemotherapy

None of the 106 patients included in the evaluation had laboratory signs of liver damage before chemotherapy; i.e., elevated serum ALT, AST, total bilirubin, or albumin levels or abnormal platelet counts. Following completion of oxaliplatin-based chemotherapy, serum ALT, AST, and total bilirubin levels were significantly increased but within normal range (Fig. 2a – 2c). There was no significant difference in serum albumin levels before versus after chemotherapy (Fig. 2d). However platelet counts were significantly decreased and the interquartile range of platelet counts at the end of oxaliplatin administration was not completely within the normal limits (Fig. 2e).

Collectively, the data showed no clinical evidence of liver damage induced by oxaliplatin treatment, but the treatment did appear to have an effect on platelet counts.

Features of cases that developed EGV following oxaliplatin administration

As confirmed by EGD, 6 patients developed EGV detected at a median of 25 months (range, 0–47 months) after the end of oxaliplatin administration; of these, 4 had received FOLFOX/Bev and 2 had received FOLFOX (Table 1). The 6 patients had received a median of 13 cycles (range, 9–26 cycles) of oxaliplatin-based chemotherapy at a median total oxaliplatin dosage of 1,750 mg (range, 1,240–2,600 mg).

Among the cases with EGV, the serum levels of ALT, AST, total bilirubin, and albumin before and after oxaliplatin treatment showed almost no change (Fig. 3a – 3d), but platelet counts were decreased and CT-SI was markedly increased (Fig. 3e and 3f).

Change in platelet counts and CT-SI

Platelet counts during oxaliplatin-based chemotherapy are shown in Fig. 4a. Although the platelet count in the non-EGV group seemed to recover slightly after oxaliplatin treatment, the EGV group showed no recovery and the counts progressively decreased after completing treatment, with more than the half cases receiving other chemotherapy followed by FOLFOX in both groups (Table 1). At every time point after 3 months post oxaliplatin treatment, change from in platelet counts differed significantly among the 2 groups ($p < 0.01$). Similarly, the change in CT-SI from during to after oxaliplatin treatment also significantly differed among the 2 groups ($p < 0.001$) except at 2 years posttreatment (Fig. 4b).

The changes in platelet counts and CT-SI in the 6 patients who developed EGV compared with the 100 patients without EGV indicated that continuous progression of decreased platelet counts and/or increased CT-SI after oxaliplatin treatment could signify the development of EGV.

Flow charts with details on EGV formation caused by oxaliplatin in relation to changes in platelet counts and CT-SI is shown in Fig. 5a and 5b. A decrease in platelet counts of less than 10% and an increase in CT-SI of more than 10% were discriminated at the end of and 6 months after the completing of chemotherapy. As a result, EGV formation could only develop in cases of progressive splenomegaly and thrombocytopenia.

Predictive factors for EGV formation

To predict EGV formation after oxaliplatin-based chemotherapy, we calculated the cut-off values, area under the curve (AUC), sensitivity, and specificity of the change in platelet counts and CT-SI after oxaliplatin treatment using ROC analysis (Fig. 6). The optimal cut-off value, sensitivity, specificity, and AUC of changes in platelet counts for predicting EGV formation in response to oxaliplatin treatment are shown in Table 2. At the end of treatment cut-off of 62.5%, the sensitivity, specificity and AUC were 61%, 67% and 0.65, respectively. At the 3 months posttreatment cut-off of 61%, the sensitivity, specificity, and

AUC were 80%, 83% and 0.81, respectively. At the 6 months posttreatment cut-off of 64%, the sensitivity, specificity and AUC were 75%, 83% and 0.79, respectively. Similarly, the optimal cut-off value, sensitivity, specificity and AUC of changes in CT-SI for predicting EGV formation in response to oxaliplatin treatment are also shown in Table 2. At the end of treatment cut-off of 133%, the sensitivity, specificity and AUC were 74%, 67% and 0.77, respectively. At the 3 months posttreatment cut-off of 128%, the sensitivity, specificity, and AUC were 73%, 83%, and 0.85, respectively. At the 6 months posttreatment cut-off of 129%, the sensitivity, specificity, and AUC were 79%, 83% and 0.89, respectively.

Table 2

Predicted values for EGV formation after oxaliplatin-based chemotherapy using the change of platelet counts and computed tomography spleen index (CT-SI)

Comparison with pre-treatment value	Cut-off value (% of pre-treatment)	AUC	Sensitivity	Specificity
Platelet counts after oxaliplatin-based chemotherapy				
End of chemotherapy	62.5	0.65	61	67
Post 3 months	61.0	0.81	80	83
Post 6 months	64.0	0.79	75	83
CT-SI after oxaliplatin-based chemotherapy				
End of chemotherapy	133	0.77	74	67
Post 3 months	128	0.85	73	83
Post 6 months	129	0.89	79	83
EGV; esophagogastric varices, AUC; area under the receiver operating characteristic curve				

Therefore, the response at 3 or 6 months posttreatment, rather than immediately completing treatment, could be a predictor for EGV formation caused by oxaliplatin-based chemotherapy.

Discussion

In the current study, we found that EGV formation occurred after oxaliplatin administration in patients with progressive splenomegaly and thrombocytopenia. In contrast, EGV formation did not occur in patients with transient splenomegaly and/or thrombocytopenia (Fig. 5). Furthermore, we also found that platelet counts and CT-SI were useful markers for predicting EGV formation caused by oxaliplatin-based chemotherapy 3 or 6 months posttreatment (Fig. 6).

In general, drug-induced liver injury (DILI) presents with extremely diverse histologic features, including necroinflammatory, cholestatic, steatotic, and vascular patterns. Vascular liver disease, also referred to as

toxic sinusoidal injury, sinusoidal obstruction syndrome, or veno-occlusive disease, comprises a commonly recognized vascular pattern of DILI[7]. Consequently, it is well-known that drug-induced sinusoidal endothelial injury may be a consequence of the use of drugs such as busulfan, cyclophosphamide, azathioprine, and oxaliplatin, and non-cirrhotic portal hypertension may develop subsequently[14]. Recently, a group of experts on behalf of the Vascular Liver Disease Interest Group (VALDIG) proposed the term porto-sinusoidal vascular disease (PSVD) to describe this condition[15]. The definition of PSVD is based on the absence of cirrhosis with or without signs of portal hypertension or histological lesions, and the term has been used to describe a form of idiopathic non-cirrhotic portal hypertension. The epidemiology of this entity is unknown; however, the main etiological factors identified in association with the development of PSVD are immunological disorders, infections, human immunodeficiency virus, drugs (azathioprine, oxaliplatin), toxins, genetic predisposition, and thrombophilia[16–19]. In agreement with a recent description[15], EGV after oxaliplatin treatment can be one of the clinical features of PSVD with portal hypertension[20].

The current study was retrospective and based on clinical manifestation of PSVD without a specific pathological confirmation. However, EGV were accurately evaluated by EGD (i.e., a case shown in Additional file 2), and collateral vessel development, spleen enlargement, or EGV on CE-CT were confirmed to have developed gradually and to have not been present before oxaliplatin administration. Our study, in agreement with a previous study[20], showed that PSVD leading to the development of portal hypertension is quite common in patients receiving oxaliplatin-based chemotherapy. In our study cohort, 5.7% (6/106) of patients receiving oxaliplatin-based chemotherapy developed apparent EGV. However the incidence rate of developing EGV after oxaliplatin treatment was not determined because our study consisted of a small number of patients and had inclusion criteria aimed at excluding patients who were followed for less than 6 months from the end of oxaliplatin treatment. Furthermore, while previous studies have reported that the development of non-cirrhotic portal hypertension after oxaliplatin treatment seems to be dose-dependent[20, 21], the data from our cohort showed that the development of EGV after treatment bears no obvious relationship with the total dosage of oxaliplatin. Further study is needed to address this point.

In our study, both platelet counts and CT-SI tended to improve after the completion of chemotherapy in the non-EGV group. In contrast, progressive thrombocytopenia and splenomegaly occurred in the EGV group, indicating the possibility that the development of EGV can be predicted by evaluating platelet counts and CT-SI. In the EGV group, there were no obvious changes in biochemical signs of liver damage, such as AST, ALT and total bilirubin. Huang and colleagues suggested that oxaliplatin-related portal hypertension is characterized by massive ascites, splenomegaly, gastric varices, concomitant arterio-portal fistula, and relatively normal liver function[11]. This report supported our data, together indicating that the absence of signs of liver damage could delay the detection of EGV. Therefore, it is important to assess changes in platelet counts and spleen size on CT scan in patients treated with oxaliplatin-based chemotherapy.

Given that only 6 patients developed EGV, risk factors for developing EGV after oxaliplatin treatment could not be identified, but splenomegaly and thrombocytopenia, especially when occurring after the end of chemotherapy, might be predictive of EGV. Early detection of high risk groups and evaluation by EGD in patients receiving oxaliplatin may prevent worsening of the prognosis associated with EGV rupture, and it might be possible to treat EGV using endoscopic therapy.

Conclusions

Assessment of platelet counts and CT-SI can enable prediction of EGV formation not only during treatment but also after treatment has been completed.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate transaminase; AUC, area under the curve; Bev, bevacizumab; CE-CT, contrast-enhanced computed tomography; Cet, cetuximab; CT-SI, computed tomography spleen index; DILI, drug-induced liver injury; EGD, esophagogastroduodenoscopy; EGV, esophagogastric varices; FOLFOX, 5-FU, LV, and oxaliplatin; FU/LV, 5-fluorouracil/leucovorin; LV, leucovorin; Pan, panitumumab; PSVD; porto-sinusoidal vascular disease; ROC, receiver operating characteristic; 5-FU, 5-fluorouracil

Declarations

Ethics approval and consent to participate: This study has been approved by the research ethics committee of St. Marianna University School of Medicine.

Consent for publication: Not applicable.

Availability of data and material: The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: Takuro Mizukami received honorarium from TAIHO pharmaceutical, Eli Lilly Japan, Ono pharmaceutical, Otsuka pharmaceutical Factory, Asahi Kasei pharmaceutical, Merck Biopharma, Sanofi, Takeda pharmaceutical. Yu Sunakawa received honorarium from Takeda pharmaceutical, Eli Lilly Japan, Chugai pharmaceutical, Taiho pharmaceutical, Merck Biopharma, Yakult Honsha, Sanofi, Bayer Yakuhin,Ltd. The other authors declare that they have no competing interests.

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Authors' contributions: YS and RS: statistical analysis, data interpretation and drafting the article; TW: study concept, design, data acquisition, data interpretation and drafting the article; TM, TT, TS, TE, NH, HK, KN, HI, KM, HT, NM, CO, MS, YS, and HY: sample collection; FI: critical revision of the article for important intellectual content; All authors: approval of the final version of the manuscript.

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Figures

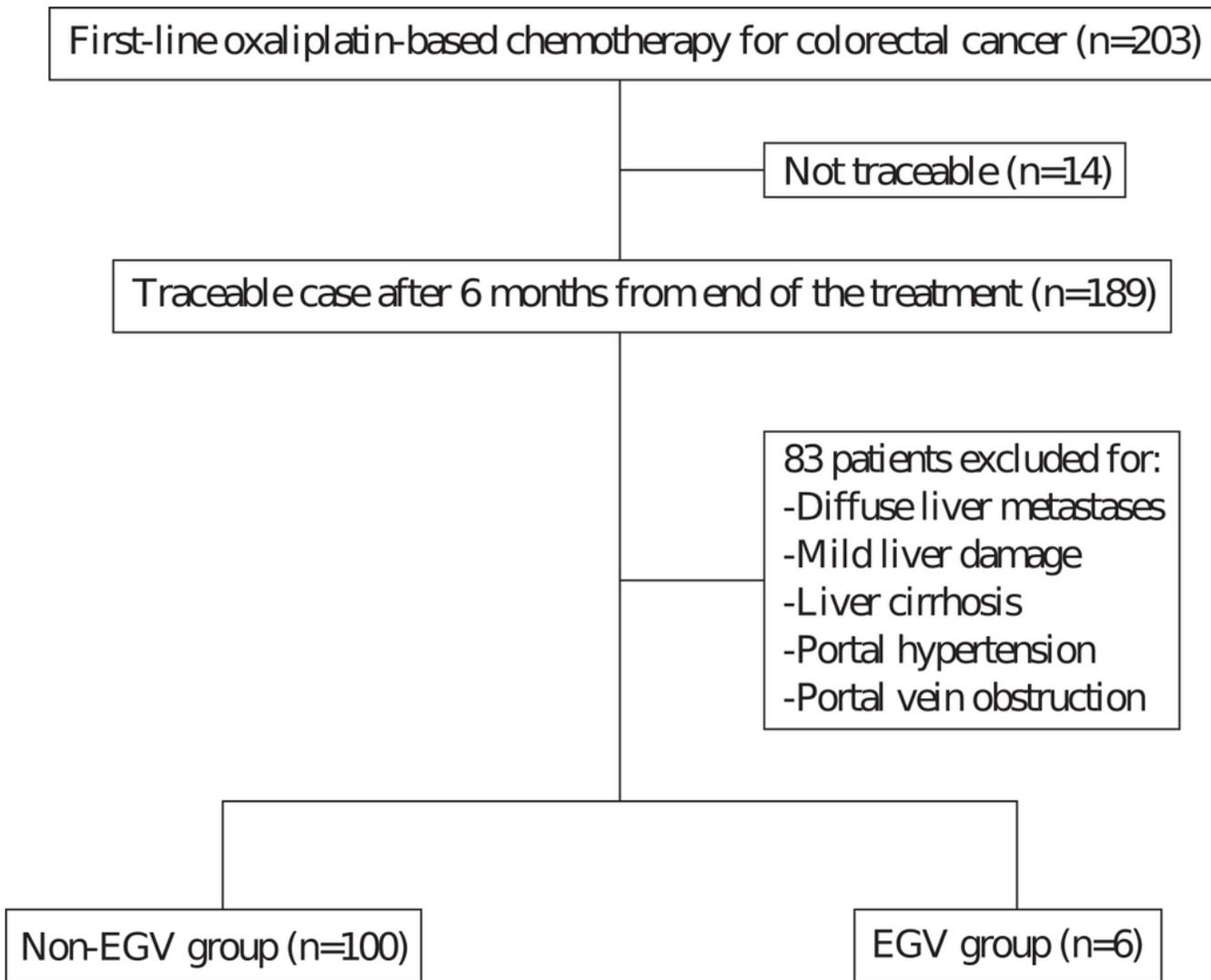


Figure 1. Satta et al.

Figure 1

Patient flow chart

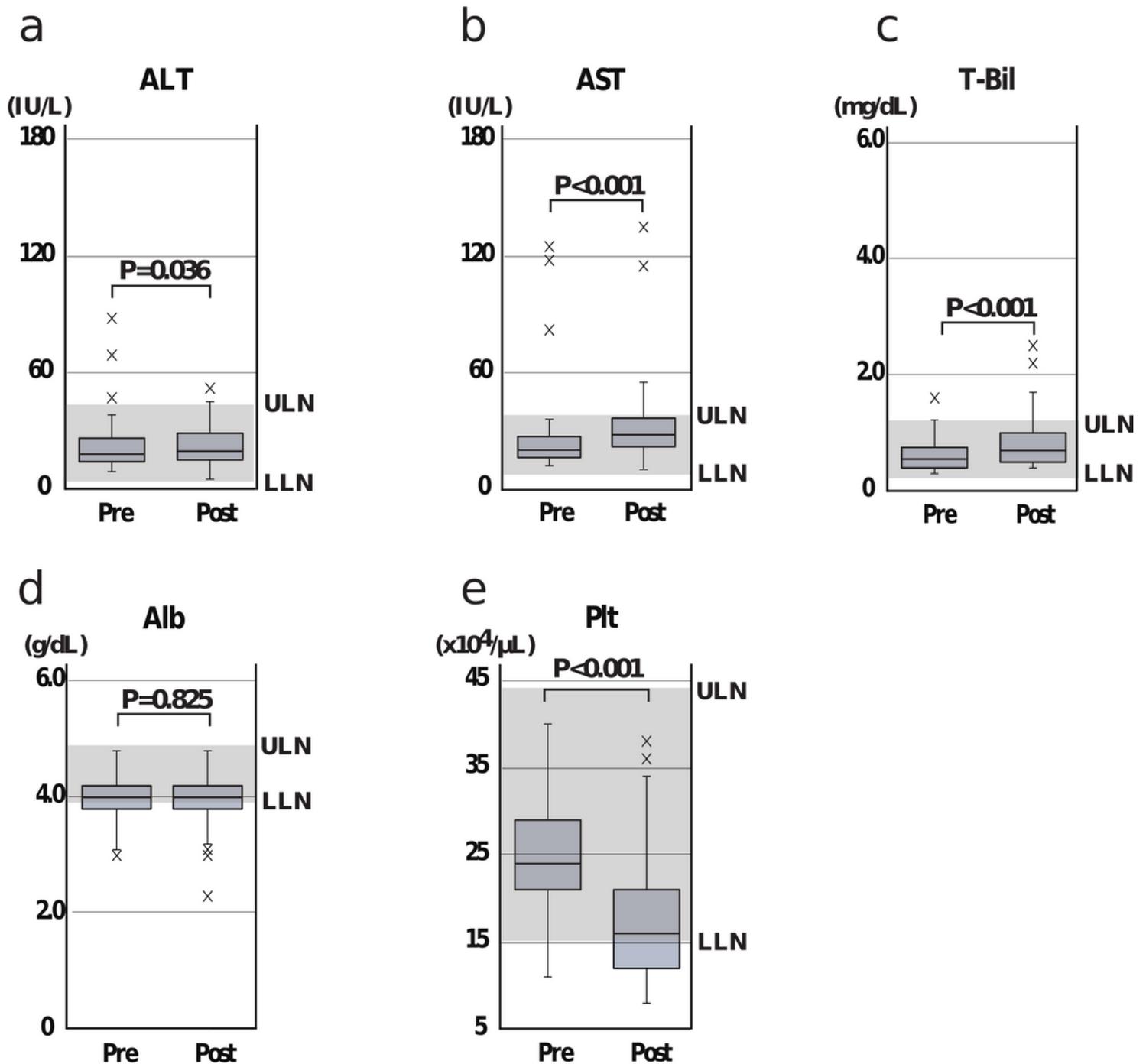


Figure 2. Satta et al.

Figure 2

Laboratory values before and after chemotherapy The mean serum ALT, AST, and total bilirubin (T-Bil) values were significantly increased posttreatment but were within normal ranges (a-c). The mean albumin (Alb) level before and after chemotherapy did not differ significantly (d). However, the mean platelet count (Plt) was significantly decreased after chemotherapy and displayed apparent clinical significance (e). The grey areas represents the normal range. ULN, upper limits of normal. LLN, lower limits of normal.

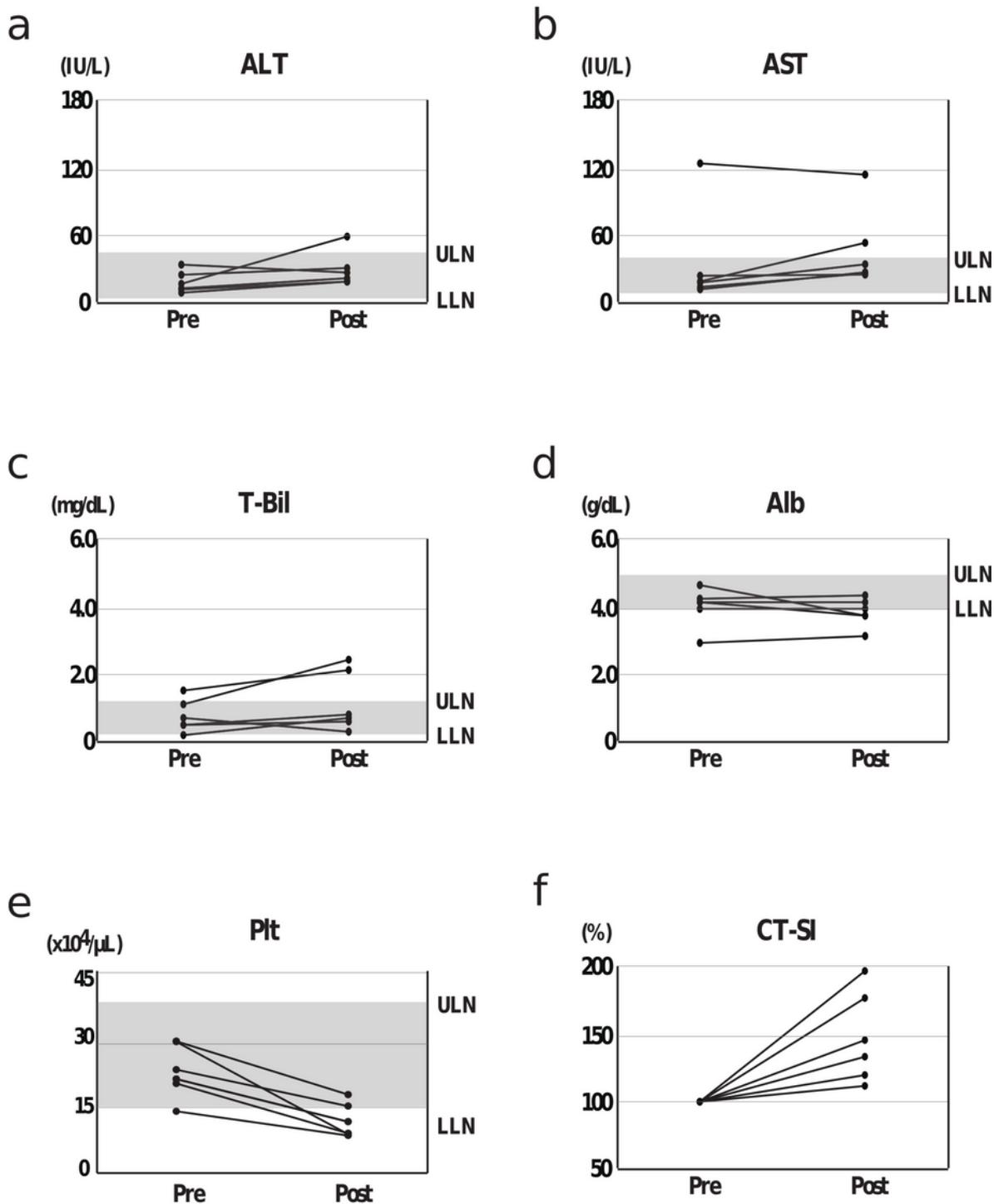


Figure 3. Satta et al.

Figure 3

Liver damage before and after chemotherapy in the EGV group Among the group of patients who developed EGV after oxaliplatin-based chemotherapy, the serum levels of AST, ALT, total bilirubin (T-Bil), and albumin (Alb) pre- and post chemotherapy (a–d). However, there was an apparent decrease in platelet counts (Plt) and increase in the CT spleen index (CT-SI) (e, f). The gray area represents the normal range. ULN, upper limits of normal. LLN, lower limits of normal.

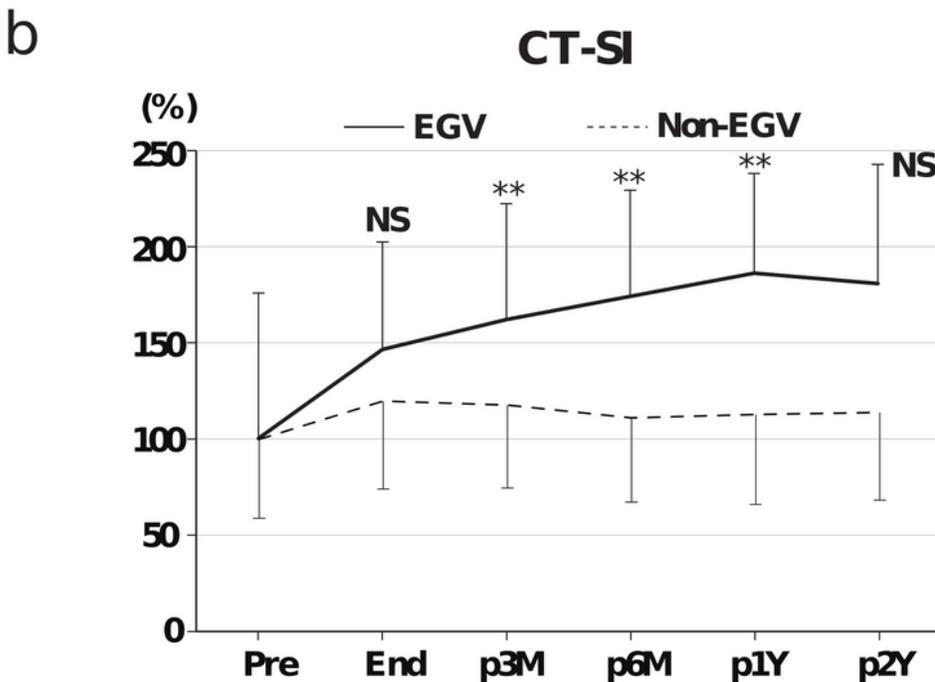
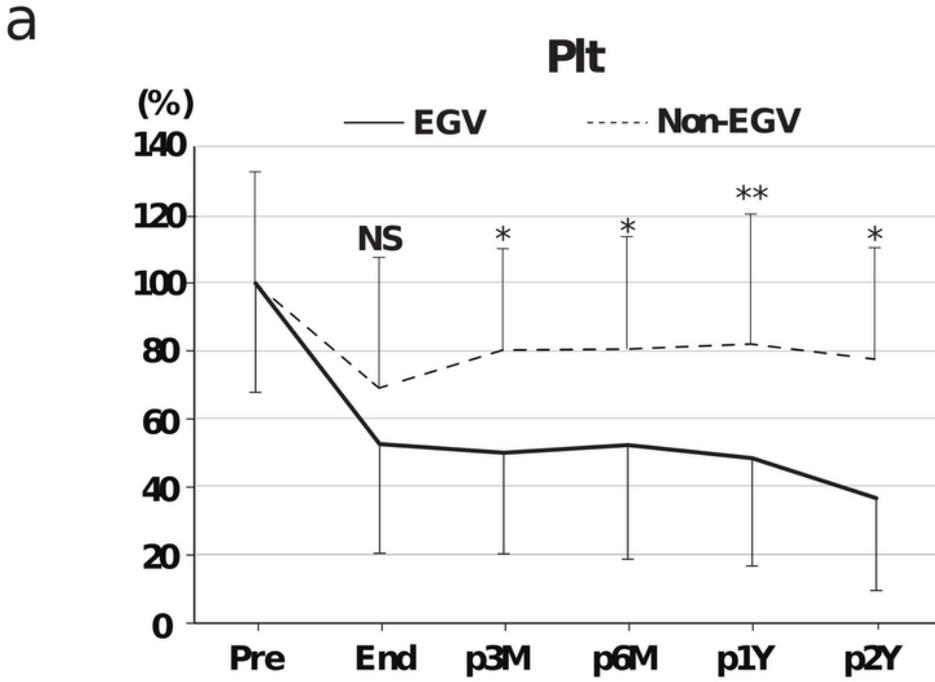


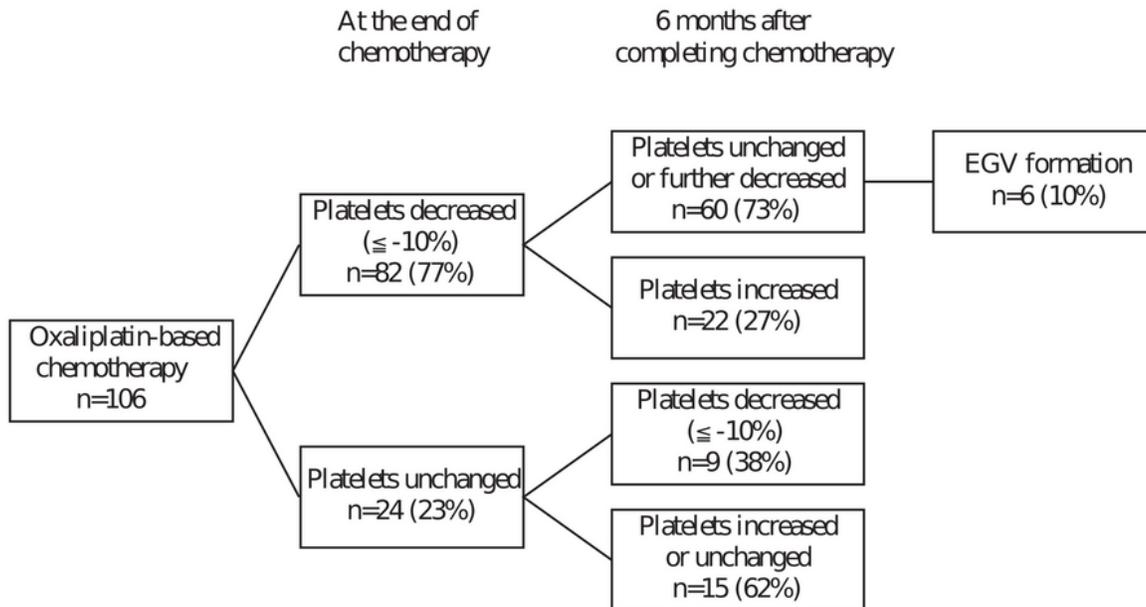
Figure 4. Satta et al.

Figure 4

Platelet counts and CT spleen index in patients treated with oxaliplatin-based chemotherapy (a) Changes in platelet counts in the EGV and non-EGV groups. Although the platelet count recovered after cessation of oxaliplatin treatment in the non-EGV group, it continued to decrease after treatment in the EGV group. (b) Change in CT spleen index (CT-SI) in the EGV and non-EGV groups. Although CT-SI improved after the end of oxaliplatin treatment in the non-EGV group, it continued to increase after treatment in the EGV

group. NS; not significant, * $p < 0.01$, ** $p < 0.001$ Pre, pre-chemotherapy. End, end of chemotherapy. p3M, after 3 months post treatment. p6M, after 6 months post treatment. p1Y, after 1 year post treatment. p2Y, after 2 years post treatment.

a



b

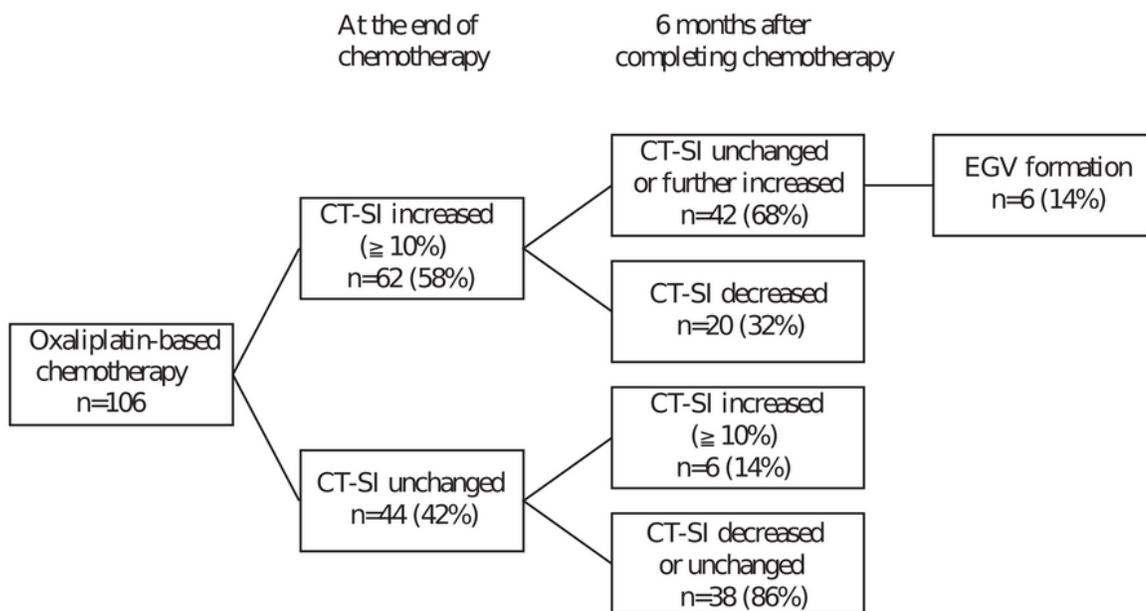


Figure 5. Satta et al.

Figure 5

Occurrence of EGV formation in patients receiving first-line oxaliplatin-based chemotherapy for colorectal cancer CT-SI, CT spleen index.

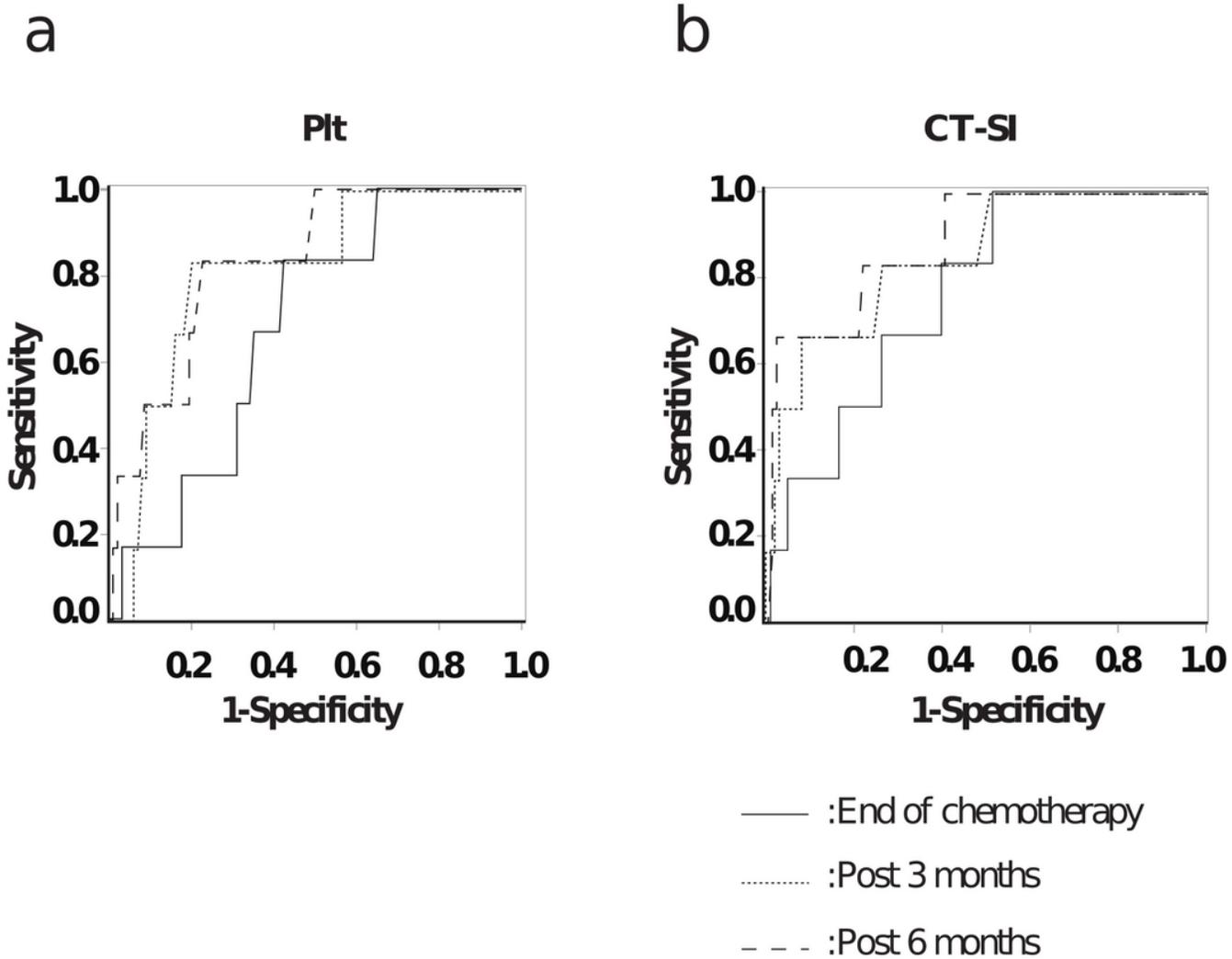


Figure 6. Satta et al.

Figure 6

Prediction of EGV formation after oxaliplatin-based chemotherapy ROC curves for platelet counts and CT spleen index (CT-SI) at the end of chemotherapy, and at 3 months and 6 months after the end of chemotherapy are shown.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.pdf](#)
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