

Clinical efficacy of irinotecan plus raltitrexed chemotherapy in refractory esophageal squamous cell cancer: a retrospective study

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Research article

Keywords: Esophageal cancer, Irinotecan, Raltitrexed, Chemotherapy

Posted Date: September 5th, 2019

DOI: <https://doi.org/10.21203/rs.2.13923/v1>

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Abstract

Background: The optimal chemotherapy regimen for refractory esophageal squamous cell cancer patients is uncertain. Our retrospective study assessed the efficacy and safety of irinotecan plus raltitrexed in esophageal squamous cell cancer patients who were previously treated with multiple systemic therapies.

Methods: Between January 2016 and December 2018, records of 38 esophageal squamous cell cancer patients who underwent irinotecan plus raltitrexed chemotherapy after at least one line of chemotherapy were reviewed. Efficacy assessment was performed every two cycles according to the RECIST version 1.1.

Results: A total of 95 cycles of chemotherapy were administered, and the median course was 3 (range 2–6). There was no treatment-related death. Nine patients had partial response, 21 had stable disease and 8 had progressive disease. The overall objective response rate was 23.68% (9/38) and the disease control rate was 78.94% (30/38). After a median follow-up of 18.5 months, the median progression-free survival and overall survival were 105 days and 221 days respectively. There were 5 patients (13.15%) with grade 3/4 leukopenia, 3 patients (7.89%) with grade 3/4 neutropenia and 1 patient (2.63%) with grade 3/4 diarrhea.

Conclusions: The combination of irinotecan plus raltitrexed was effective for pretreated esophageal squamous cell cancer patients. Further studies are needed to determine the optimal dose of the two drugs.

Background

Esophageal cancer ranks seventh in terms of incidence and sixth in leading cause of cancer death globally [1]. In Asia, esophageal squamous cell cancer (ESCC) accounts for more than 90% of all esophageal cancer cases. China has the largest number of both newly diagnosed esophageal cancer cases and esophageal cancer-related deaths. Despite the evolution of multidisciplinary treatments, the prognosis of esophageal cancer has not improved much with a five-year survival rate only about 19% [2].

At present, platinum-based chemotherapy, 5-fluorouracil (5-FU) and taxanes are the most widely used as first-line chemotherapeutic agents for advanced esophageal cancer, with response rates ranging from 34% to 72.7%[3–5]. However, many patients who responded initially to chemotherapy or chemoradiotherapy ultimately develop progressive disease. Currently, there are no standard second line chemotherapeutic options for these patients. Second-line chemotherapy used in clinical practice include docetaxel, paclitaxel, irinotecan, and fluorouracil plus irinotecan or pembrolizumab. Response rates remain low, ranging from 21.2% to 29.6%[6–8]. Therefore, there is a need of development for more active drug combinations to treat refractory or relapsed advanced esophageal cancer.

Irinotecan (CPT–11) is a topoisomerase I inhibitor, which has been proven to significantly improve survival and quality of life in 5-FU refractory colorectal cancer[9]. In addition, CPT–11 was considered as

a second-line option in the treatment of advanced gastric cancer refractory to platinum plus fluoropyrimidine[10]. In esophageal cancer, CPT-11 was also active as a single drug in the treatment of cisplatin-refractory cases[11]. In a retrospective study by Wang X et al[6] the efficacy and safety of irinotecan combined with a fluorouracil-based regimen as second or third-line chemotherapy in the treatment of recurrent/metastatic ESCC who were refractory to prior paclitaxel plus platinum chemotherapy was evaluated. The response rate was 29.6%, while the median progression-free survival (PFS) and overall survival (OS) were 4.8 and 10.5 months respectively. This indicates that this combination was effective as a second or third-line treatment for ESCC[6].

However, the use of 5-FU has several disadvantages, such as the requirement for a venous catheter system and infusion pump, risk for cardiac toxicity (overall incidence: 0.55%~19%)[12, 13], and frequent hospital visits. Moreover, it was reported that 5-FU could result in severe toxicity (such as stomatitis and severe pancytopenia) for patients who are deficient in dihydropyrimidine dehydrogenase which is involved in the degradation of 5-FU.

Raltitrexed, a thymidylate synthase (TS) inhibitor, has been considered as a potential substitute for 5-FU. In patients with advanced colorectal cancer, a meta-analysis conducted by Liu et al[14] showed that raltitrexed-based chemotherapeutic regimen led to equivalent response rates and overall survival when compared to traditional 5-FU-based regimen. Furthermore, raltitrexed combined with either CPT-11 or oxaliplatin is also active against 5-FU-refractory advanced colorectal cancer, with overall objective response rates (ORR) ranging from 15.4% to 33.3% and is well-tolerated[15–17]. In addition, raltitrexed alone or in combination with other chemotherapeutic drugs was shown to be a safe option for cancer patients who had experienced prior cardiac toxicity when treated with 5-FU. A systematic review has shown that no cardiotoxicity associated with raltitrexed was reported and no patients who were switched to raltitrexed because of cardiac symptoms from 5-FU experienced further cardiac toxicity[13].

In this light, the combination of irinotecan and raltitrexed might be an effective and safe treatment as a second- or later-line for ESCC. But there is currently no study on the efficacy of this combination in the treatment of recurrent/metastatic ESCC. The goal of this retrospective study was to evaluate the clinical efficacy and safety of irinotecan plus raltitrexed as second or later-line chemotherapy in ESCC patients who had been previously treated with multiple systemic therapies which included standard first-line chemotherapy with or without intensity modulated radiation therapy.

Methods

Patient population

Between January 2016 to December 2018, a total of 38 consecutive patients who were histologically diagnosed as ESCC and had progressed after at least one-line treatment were treated by irinotecan plus raltitrexed as a second or later-line chemotherapy from our institution of clinical medical college, Yangzhou University. The medical records of total 38 patients were reviewed for this study. During

pretreatment evaluation, detailed medical history was collected. Laboratory studies included bone marrow function, hepatic function and kidney function. For disease evaluation and responses assessment, chest computerized tomography, ultrasound examination and/or X-ray barium swallow were performed. All patients gave written informed consent before administering the chemotherapy.

Treatment schedule

Patients were treated with irinotecan in a 90-min infusion on day 1, and raltitrexed in a 30-min infusion on day 2. The treatment was repeated every 3 weeks up to a maximum of 6 cycles or until either unacceptable side-effects or progressive disease (PD) occurred.

Treatment evaluation

Tumor responses and toxicity were evaluated every two cycles of chemotherapy according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1) criteria and National Cancer Institute Common Toxicity Criteria (NCI-CTC) respectively. Diameter changes of the target lesion were measured on computerized tomography imaging. Complete response (CR) was considered as the disappearance of all evaluable disease, and partial response (PR) meant that the target lesions were reduced by 30% or more. We regarded PD as the target lesions increased at least 20% or there were one or more new lesions, and stable disease (SD) as the target lesions reduced by less than 30% and increased by less than 20%. The ORR was defined as the percentage of cases with either CR or PR. The disease control rate (DCR) was defined as the percentage of cases which achieved CR, PR or SD. Furthermore, we calculated PFS from the beginning of the regimen to the first documented disease progression or death, and we defined the time between the initiation of the regimen and the date of dead or the last follow-up assessment as OS. All patients were followed up until death or loss to follow-up.

Statistical analysis

Results were analyzed using the SPSS software package (SPSS 25.0). The Kaplan-Meier method was performed to estimate PFS and OS. Fisher's Exact Test used in comparing the response rates of different subgroups.

Ethical statement

This study was approved by the ethics committee of clinical medical college, Yangzhou University. The study was performed in accordance with the Declaration of Helsinki.

Results

Patients' characteristics

The 38 patients' characteristics were summarized in Table 1. There were 34 males and 4 females. The median age was 63 years old, and ECOG performance status was 0–2. The primary tumors were all located in the thoracic esophagus. Twenty-seven patients had metastatic disease, among which, 22 patients had single organ metastasis and 5 patients had multi-organ metastasis. The main metastatic sites were lung (23 patients) and liver (5 patients). Eleven patients had local recurrences. Prior treatments included surgery plus chemoradiotherapy (12/38, 31.58%), surgery plus adjuvant chemotherapy (3/38, 7.89%), chemoradiotherapy (18/38, 47.37%), and chemotherapy alone (5/38, 13.16%). Twenty-two (57.89%) cases were receiving irinotecan plus raltitrexed chemotherapy as second-line treatment and 16 (42.11%) cases as third or latter line treatment.

Treatment summary

A total of 95 cycles of irinotecan plus raltitrexed were administered, and the median number of treatment cycle was 3 (range 2–6). The median doses of irinotecan and raltitrexed were 178 mg/m² (118–217) and 2.7 mg/m² (2.17–3.07) respectively. Because of the hematological toxicity, fifteen cycles (15.79%) chemotherapy were delayed, and two cycles (2.11%) chemotherapy required 25% dose reduction.

Response and survival

Details for treatment response are listed in Table 2 and the percentage changes of lesion size in each patient are shown in Figure 1. In all 38 patients, there was no CR, 9(23.68%) patients had PR, 21(55.26%) patients had SD, and 8(21.06%) patients had PD. After a median follow-up of 18.5 months (2 to 32 months), two (5.26%) patients were lost to follow-up and no early treatment related death was observed. The median PFS was 105 days (25 to 357, Figure 2), and 3 months, 6 months and 9 months PFS rate were 52.94%, 29.41% and 14.71% respectively. The median OS was 221 days (32 to 632, Figure 2), and 3 months, 6 months, 9 months, 12 months and 18 months OS rate were 85.29%, 61.76%, 38.24%, 14.71% and 5.88% respectively.

In the 20 patients who received prior chemotherapy without 5-FU, 7(35.00%) patients achieved PR, 9(45.00%) patients had SD, and 4(20.00%) patients had PD. The median PFS and OS were 154 days (53 to 357, Figure 3A) and 290 days (67 to 632, Figure 3B) respectively. In the remaining 18 patients who previously received chemotherapy containing 5-FU, 2(11.11%) patients achieved PR, 12(66.67%) patients had SD, and 4(22.22%) patients had PD. The median PFS and OS were 66 days (25 to 343, Figure 3A) and 150 days (32 to 431, Figure 3B) respectively. The ORR in patients who previously received chemotherapy without 5-FU was numerically higher than the one in patients who previously received chemotherapy containing 5-FU, but was not statistically significant ($P = 0.088$, Table 3). The PFS and OS were also similar between the two groups (PFS: $P = 0.278$; OS: $P = 0.300$, Figure 3A and 3B). In the 30 patients who previously received chemoradiotherapy, 6(20.00%) patients achieved PR, 17(56.67%) patients had SD,

and 7(23.33%) patients had PD, while among 8 patients who previously received chemotherapy only, 3(37.50%) patients achieved PR, 4(50.00%) patients had SD, and 1(12.50%) patient had PD. The ORR between the two groups showed no statistical difference ($P = 0.275$, Table 3). Furthermore, the PFS and OS had no significant difference between the two groups (PFS: $P = 0.259$; OS: $P = 0.222$, Figure 3C and 3D). In the 22 patients who received the study drug combination as a second-line treatment, 7(31.82%) patients achieved PR, 9 (40.91%) patients had SD, and 6(27.27%) patients had PD, while among 16 patients who received the study drug combination as third or later-line treatment, 2(12.50%) patients achieved PR, 12(75.00%) patients had SD, and 2(12.50%) patients had PD. The ORR between these two groups also showed no statistical difference ($P = 0.160$, Table 3). And the PFS and OS still had no significant difference between the two groups (PFS: $P = 0.470$; OS: $P = 0.663$, Figure 3E and 3F). Details for subgroup analyses were shown in Table 3.

Toxicity

Treatment-related toxicities are shown in Table 4. Grade 1–2 leukopenia, anemia and nausea–vomiting were the most common toxicities. For grade 3–4 hematological toxicity, 5 patients had grade 3/4 leukopenia (1 had fever), 3 patients had grade 3/4 neutropenia, and 1 patient had grade 3/4 thrombocytopenia. For non-hematological toxicities, 1(2.63%) patient had grade 3/4 diarrhea, and 1(2.63%) patient had grade 3/4 allergic reaction. Two patients had grade 1/2 cholinergic syndrome. There was no treatment-related death in this study.

Discussion

We conducted this retrospective study to evaluate clinical efficacy and safety of irinotecan plus raltitrexed as salvage therapy in a group of 38 ESCC patients who had progressed after the failure of multiple systemic therapies. Our data showed an encouraging ORR of 23.68% and DCR of 78.94%, as well as less than 15% incidence of grade 3/4 toxicities. Median PFS was 105 days and the median OS was 221 days. These results indicate that this combination might be an option for refractory ESCC patients.

In preclinical study, it had been demonstrated a significant schedule-dependent synergism between irinotecan and raltitrexed in vitro. [Aschele et al\[18\]](#) found that greatest synergism was observed when SN–38 (an active metabolite of irinotecan) was administered 24 hours before raltitrexed by comparing ED_{50} (the dose required for 50% inhibition of cell growth) in different intervals (1h, 4h, and 24h), while smaller enhancement or nearly additive interactions was found when the two drug were switched or used simultaneously. Thereafter, several clinical studies employed 24h or 1h earlier schedule to treat different cancer[9, 16, 19]. In the present study, we administered irinotecan and raltitrexed in a suggested 24h earlier schedule to observe its clinical efficacy and safety in the treatment of ESCC.

Currently, no standard second or third-line chemotherapy has been well established in the treatment of ESCC. Although there are a few reports on raltitrexed combination chemotherapy in patients with

advanced gastro-esophageal adenocarcinoma[20, 21], the clinical experience of raltitrexed in patients with ESCC is still unavailable. Recently, [Ding](#) et al reported that raltitrexed could decrease cell viability and proliferation, cause apoptosis and enhance the radiosensitivity of ESCC cells[22]. In patients with advanced colorectal cancer, raltitrexed has produced comparable efficacy as first line treatment when compared to 5-FU-based regimen[9] and still showed activity when combined with irinotecan as second line chemotherapy[16]. Since 5-FU plus irinotecan was an effective combination as a second line chemotherapy in ESCC[6], and raltitrexed was considered as a potential substitute for 5-FU, we investigated the clinical efficacy and safety of irinotecan plus raltitrexed and its potential utility as second or later-line therapy in ESCC patients.

Our data showed that the ORR was 23.68% and the DCR was 78.94%, which were slightly higher than results in colorectal cancer and pancreas cancer (ORR: 16%–16.7%, DCR: 56.7%–58%)[16, 19]. The survival results (median PFS and median OS) were similar to recently reported results from a prospective randomized, multicenter, open-labeled phase3 ESWN 01 trial[23]. Together with the previous reports, our results, showed that irinotecan plus raltitrexed could be a possible alternative regimen for previously treated ESCC patients.

Unlike our present study, only patients with no prior exposure to irinotecan or 5-FU were enrolled in the retrospective study conducted by Wang X et al[6] and the prospective ESWN 01 trial[23]. The reason might be partly because of similar action and thus similar resistance mechanisms associated with 5-FU and raltitrexed. In our present study, we found that patients without prior 5-FU exposure are sensitive to irinotecan plus raltitrexed chemotherapy with an ORR of 35.00%, which was numerically higher than the ORR in patients with prior 5-FU exposure. [However](#), 5-FU inhibits TS through its metabolite 5-fluoro-deoxyuridine monophosphate, while raltitrexed directly and specifically inhibits TS without requiring any modulating agent[24]. Therefore, incomplete cross-resistance between 5-FU and raltitrexed has been confirmed in both preclinical research[25] and clinical studies[16]. In 5-fluorouracil refractory advanced colorectal cancer, irinotecan plus raltitrexed had a moderate improvement in response rate when compared indirectly with data from trial of second-line CPT–11 monotherapy[16, 26]. Our present study shown that patients with prior 5-FU exposure are still sensitive to irinotecan plus raltitrexed chemotherapy with an ORR of 11.11%. This matter of cross-resistance between 5-FU and raltitrexed in irinotecan treatment is an interesting question to further study. In general, irinotecan plus raltitrexed was effective in heavily treated (previous two-line or more chemotherapy or chemoradiotherapy) patients. However, the results provided are from a limited number of cases. To provide more evidence, [a large-scale study](#) is needed in the future.

In this study, we had lower toxicity compared with other reports[9, 16, 19, 27]. Hematological and gastrointestinal toxicities were the main toxicities. Grade 3/4 leukopenia occurred in 5 (13.15%) patients. According to previous reports, most studies used 300–350 mg/m² irinotecan in the treatment of colorectal cancer[28, 29]. A lower dose of irinotecan (200mg/m²) combined with raltitrexed was administered to treat patients with advanced pancreatic adenocarcinoma from a randomized multicenter phase II study[19]. However, there was no study to determine the maximum tolerated dose of this

combination in esophageal cancer. In a multicenter phase II study, 130 mg/m² irinotecan combined with cisplatin were used to treat metastatic, unresectable esophageal cancer[30]. A slightly higher dose of 160 mg/m² irinotecan combined with S-1 were used to treat Chinese esophageal cancer patients from a prospective randomized, multicenter, open-labeled phase 3 trial[23]. In our study, the median dose of irinotecan was 178 mg/m² (118–217 mg/m²). Compared with the ESWN 01 trial, both survival results and incidences of grade 3–4 leukopenia/neutropenia in the present study were similar. This indicates that irinotecan plus raltitrexed is a safe choice in previously treated recurrent/metastatic ESCC. However, the number of patients included in our study is small. And prospective clinical studies of irinotecan plus raltitrexed in patients with refractory ESCC are needed to determine the maximum tolerated dose and clinical efficacy of this combination.

Conclusions

In conclusion, the combination of irinotecan and raltitrexed was effective as second or later-line chemotherapy with controllable toxicity for ESCC patients after the failure of multiple systemic therapies. Due to the limitations in the study design and sample size, a prospective randomized clinical trial detecting the merits of irinotecan combined with raltitrexed should be conducted in the future.

Abbreviations

5-FU: 5-fluorouracil; CPT-11: irinotecan; CR: complete response; DCR: disease control rate; EC: esophageal cancer; ESCC: esophageal squamous cell cancer; NCI-CTC: National Cancer Institute Common Toxicity Criteria; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Declarations

Ethics approval and consent to participate

Ethical approvals were acquired from the ethics committee of clinical medical college, Yangzhou University and informed consent was obtained from participating patients before administering the chemotherapy. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

All authors consent to its publication.

Availability of data and materials

All datasets are presented in the main manuscript or additional supporting files.

Competing interests

The authors declare no conflict of interest.

Funding

This work is supported by the project of Jiangsu Provincial Medical Youth Talent (QNRC2016319); the Natural Science Foundation of Yangzhou City (YZ2014044) and Science, Education and Health Foundation of Yangzhou City (ZDRC201846).

Authors' contributions

Conception and design of the study: Chen Y, Liu M, Jia QQ, Wang XL, Sun CJ, Min LF, Yang JQ, Zhang XZ and Gubat JA.

Data collection, analysis and interpretation: Chen Y, Liu M, Li Y, Zhu CY, Chen YL.

Draft of manuscript: Chen Y, Liu M, Jia QQ and Wang XL.

Revision and approval of manuscript: Chen Y, Liu M, Jia QQ, Wang XL, Sun CJ, Li Y, Zhu CY, Chen YL, Min LF, Yang JQ, Zhang XZ and Gubat JA.

Accountability for all aspects of the study: Chen Y, Liu M, Jia QQ, Wang XL, Sun CJ, Li Y, Zhu CY, Chen YL, Min LF, Yang JQ, Zhang XZ and Gubat JA.

Acknowledgements

We express our appreciation to Medical Oncology of Clinical Medical College of Yangzhou University for supporting in this study.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

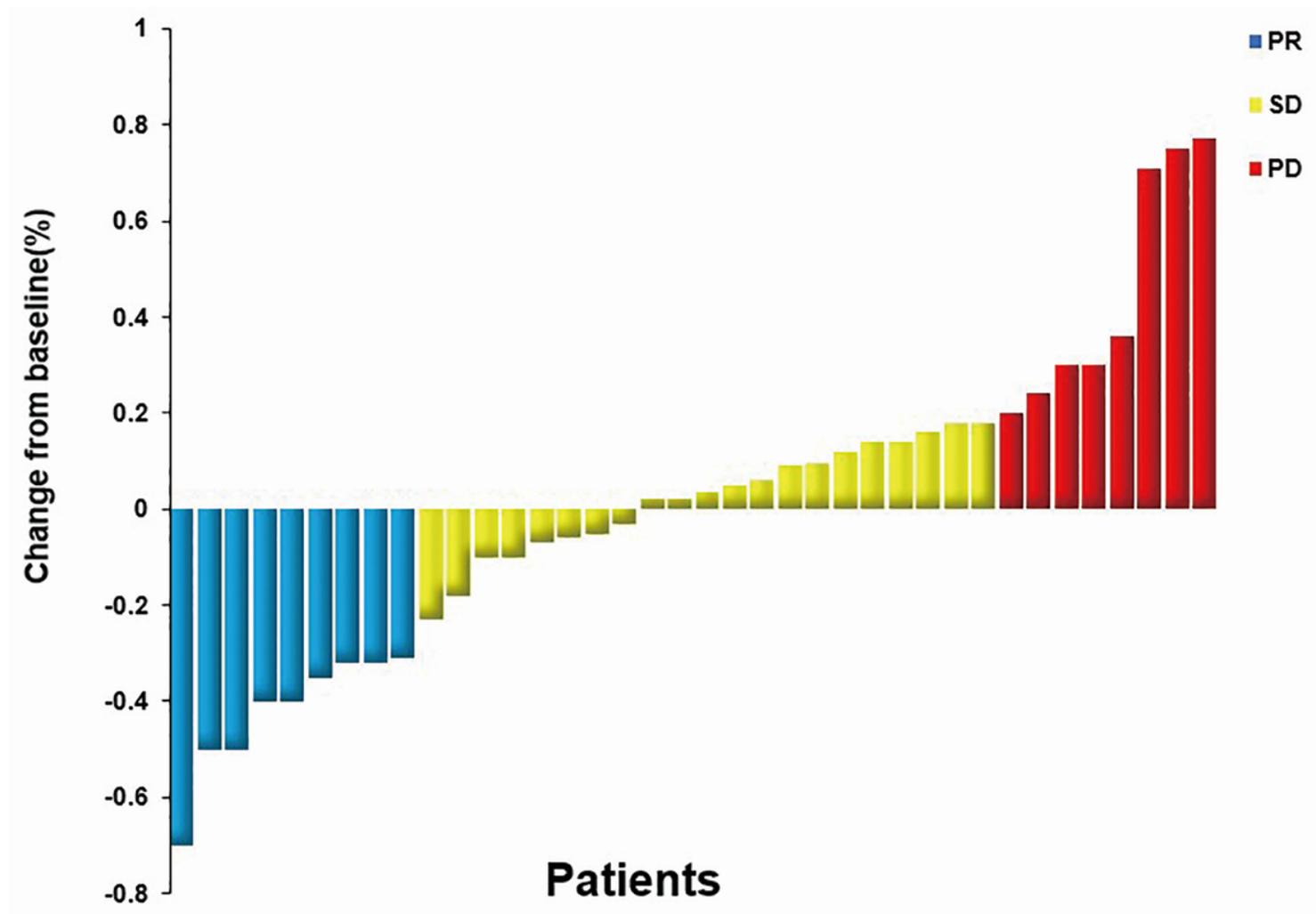


Figure 1

Percentage change from baseline in tumor size. Each bar represents one case (n=38) and bars represent best response in dimension of target lesions.

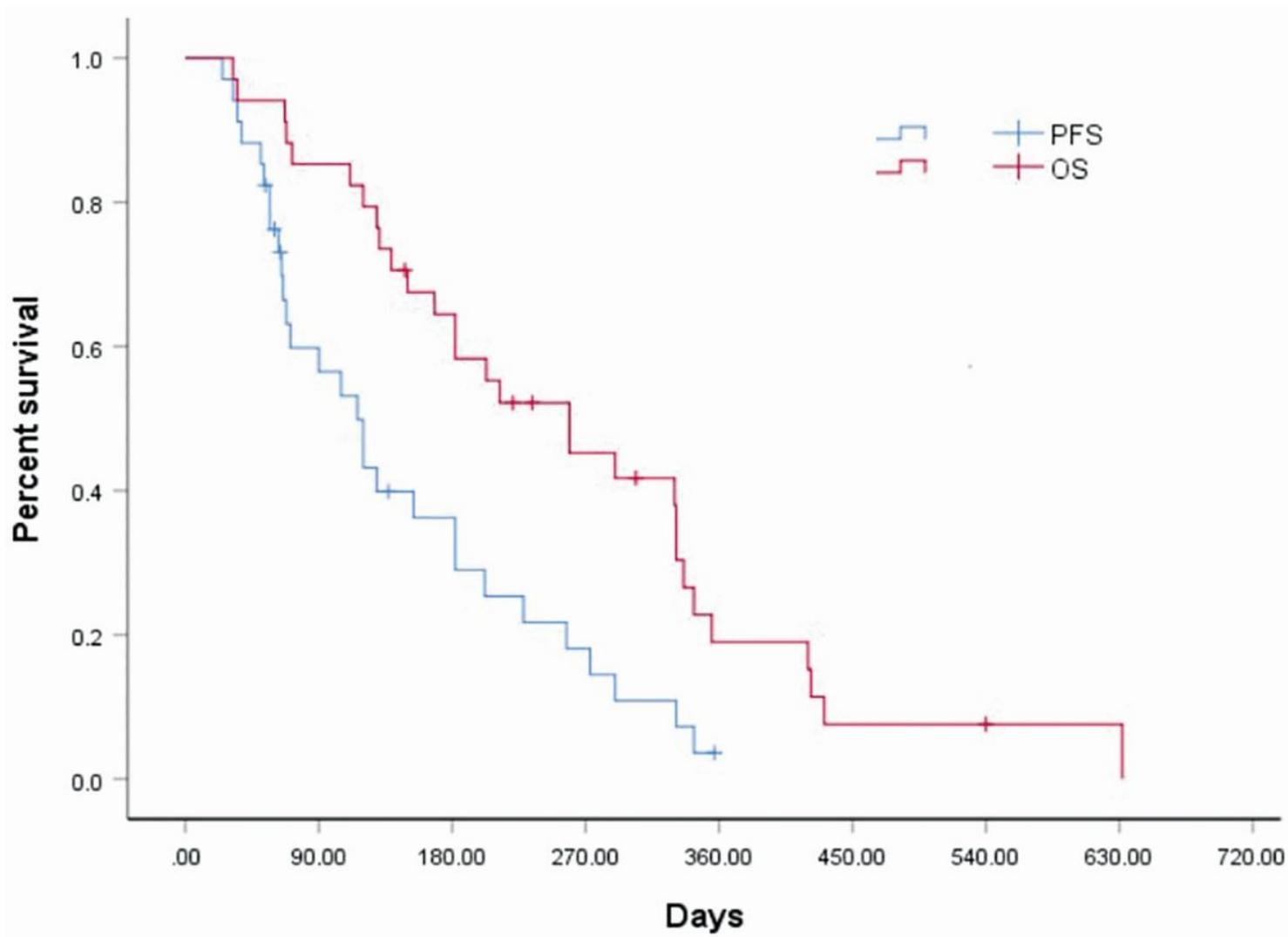


Figure 2

Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) in all patients. The median PFS and OS were 105 days and 221 days respectively.

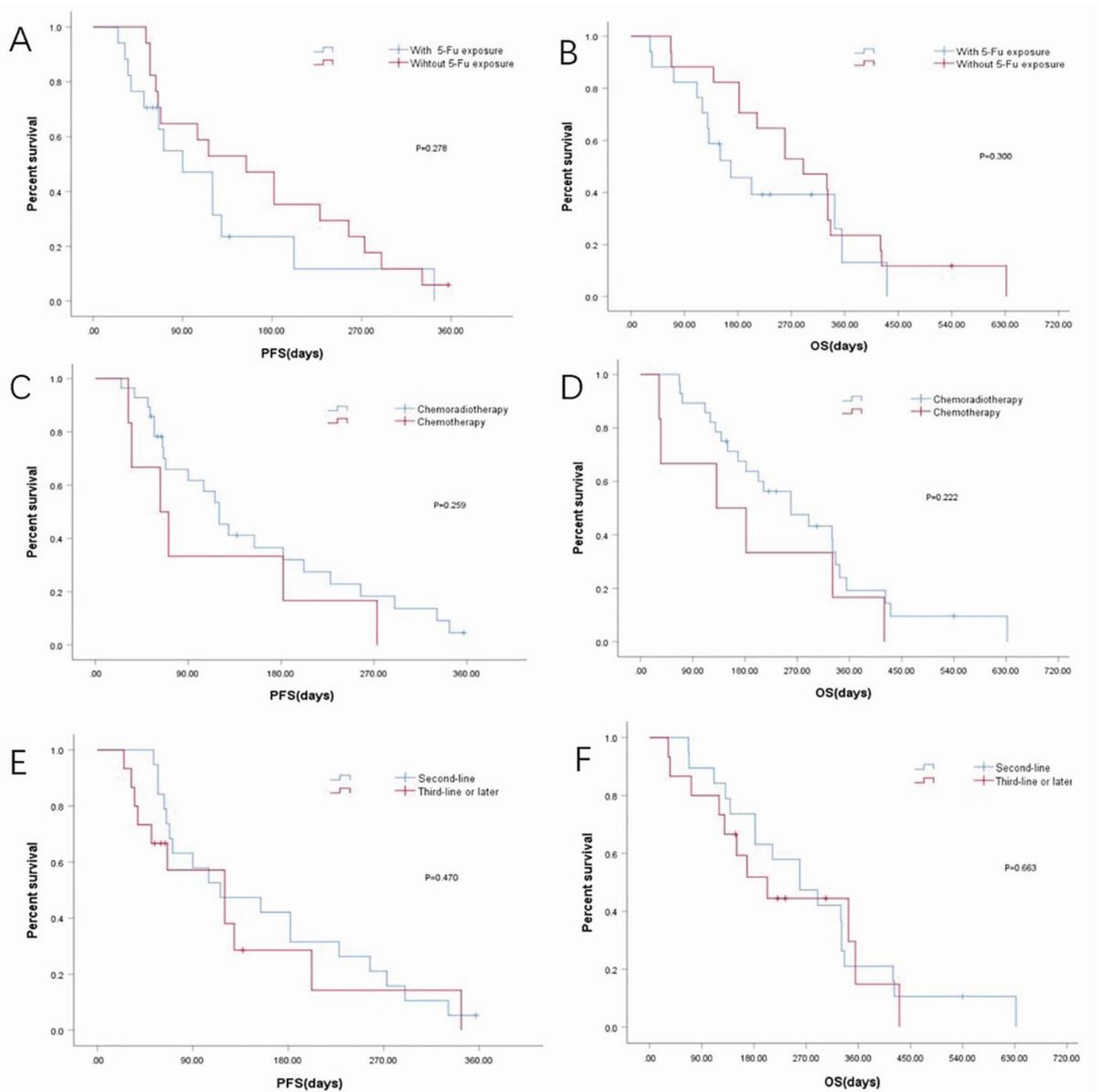


Figure 3

Subgroups analyses of survival between different groups. A Kaplan–Meier estimates of PFS in patients who previously received chemotherapy containing 5-FU or not. B Kaplan–Meier estimates of OS in patients who previously received chemotherapy containing 5-FU or not. C Kaplan–Meier estimates of PFS in patients who previously received chemotherapy or chemoradiotherapy. D Kaplan–Meier estimates of OS in patients who previously received chemotherapy or chemoradiotherapy. E Kaplan–Meier estimates

of PFS in patients who previously received different lines of treatment. F Kaplan–Meier estimates of OS in patients who previously received different lines of treatment.

Supplementary Files

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

- [Table2.doc](#)
- [Table4.doc](#)
- [Table3.doc](#)
- [Table1.doc](#)