Short-Term Survival and Safety of Apatinib Combined With Oxaliplatin and S-1 in the Conversion Therapy of Unresectable Gastric Cancer

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Research Article

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Abstract

Background

To investigate the short-term efficacy and safety of apatinib combined with oxaliplatin and S-1 in the treatment of unresectable gastric cancer.

Patients and methods

Previously untreated patients with unresectable HER-2-negative advanced gastric cancer were selected. All the patients received six cycles of S-1 and oxaliplatin and five cycles of apatinib, which were administered at intervals of three weeks. The surgery was performed after six cycles of drug treatment. The primary endpoints were radical resection (R0) rate and safety. This study was registered with the China Trial Register, number ChiCTR-ONC-17010430(01/12/2016-01/12/2022).

Results

A total of 39 patients were enrolled. Efficacy evaluation was feasible for 37 patients. One patient achieved complete response (CR, 2.7%), 26 patients achieved partial response (PR, 70.3%), three patients had stable disease (SD, 8.1%) and seven patients had progressive disease (PD, 18.9%). The objective response rate (ORR) was 73.0% and the disease control rate (DCR) was 81.1%. 22 patients underwent surgery, among which 14 patients underwent radical resection (R0), with a R0 resection rate of 63.6%. The 1-year survival rate of the surgical group (22 patients) was 71.1% and the 2-year survival rate was 41.1%. The median survival time was 21 months. The incidence of adverse reactions (AEs) was 100%. Leucopenia (65.3%) and granulocytopenia (69.2%) were the most common hematological AEs. The most common non-hematological AEs were fatigue (51.3%) and oral mucositis (35.9%).

Conclusion

Apatinib combined with oxaliplatin and S-1 showed good short-term survival and acceptable safety in the conversion therapy of unresectable gastric cancer.

Background

In China, unresectable gastric cancer accounts for 10% of the total number of gastric cancer cases [1]. At present, palliative chemotherapy is the main treatment option. The median survival time is 5–12 months, and the 5-year survival rate is about 9.4% [2]. In unresectable gastric cancer, the primary focus of gastric cancer infiltrates into the extraserous or surrounding tissues and organs, and distant metastasis occurs, such as paraaortic, liver, peritoneum, etc. Therefore, radical resection is difficult from the perspective of surgical technology and oncology. The conversion therapy provides a new therapeutic option in clinical practice. Through multidisciplinary treatment (MDT) mode, the patients are given reasonable chemotherapy, radiotherapy and targeted treatment, so that the initial non-resectable tumor can be transformed into radical resection, in order to prolong the survival outcome and improve the quality of life

of the patients. Sym et al [3]. used docetaxel + capecitabine + cisplatin to treat unresectable gastric cancer, and found that the response rate of chemotherapy was 65%, the conversion rate of operation was 74%, the R0 resection rate was 63%, and the median recurrence-free survival period of patients after R0 resection was 54.3 months, while the total survival period of patients without R0 resection was only 11.5 months. Kinoshita et al [4]. reported that the response rate of docetaxel + cisplatin + S-1 regimen was 73.7%, the conversion rate of operation was 59.6%, and the R0 resection rate was 79.4%. The median survival time after operation was significantly longer than that of chemotherapy alone (29.9 months vs. 9.6 months).

The combination of oxaliplatin and S-1 (SOX) has been widely used in neoadjuvant and postoperative chemotherapy of gastric cancer [5–7]. Apatinib, a new small molecular inhibitor of vascular endothelial growth factor receptor, which is a third-line treatment option for advanced gastric cancer, has achieved reliable results [8]. The combination of SOX and apatinib has also been applied in neoadjuvant chemotherapy of advanced gastric cancer [9, 10]. However, there are few reports on its application in transformation therapy, especially on the survival rate. Therefore, this study examined the short-term survival effect and safety of apatinib combined with oxaliplatin and S-1 in the treatment of unresectable gastric cancer.

Patients And Methods

Patients

All the patients were confirmed to be adenocarcinoma by biopsy under gastroscopy, and HER-2 negative by immunohistochemistry. Inclusion criteria were: age 18–70 years; confirmed by pathology as gastric adenocarcinoma, and met one of the following non-resectable conditions: peritoneal metastasis, liver metastases, Krukenberg tumor, distant lymph node metastasis, N3, extensive or bulky lymph nodes, local progression; CT/MRI before operation or color ultrasound, PET-CT, if necessary, laparoscopic exploration to clearly diagnose the above-mentioned staging of gastric cancer; diagnosed patients who had not received prior radiotherapy, chemotherapy, targeted treatment or immunotherapy; ECOG 0–1; expected survival time ≥ 3 months; no severe center of gravity, lung and liver dysfunction; no jaundice and digestive tract obstruction; no acute infection; normal function of main organs; no pregnancy; no other clinical research before and during treatment.

Treatment

The patients were treated with apatinib, oxaliplatin and S-1. Oxaliplatin: 130 mg/m2, IVGTT, d1; apatinib: 500 mg/day, P.O, QD, d1-d21; S-1: according to the body surface area, the dosage (< 1.25 m^2, 40 mg, bid; 1.25–1.50 m^2, 50 mg, bid; > 1.50 m^2, 60 mg, bid, P.O, bid, d1-d14) was given for three weeks from the first day of chemotherapy. The short-term efficacy was evaluated every two cycles. The operation was performed when the requirements of surgical resection were met. All the patients received six cycles of transformation therapy (the last cycle stopped using apatinib). According to RECIST 1.1, complete

response (CR) and partial response (PR) were regarded as objective remission rate (ORR), while CR, PR and stable disease (SD) were regarded as disease control rate (DCR). The adverse reactions were divided into 0-IV degrees according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE 4.0).

Three weeks after the therapy, the doctors performed conventional laparotomy or laparoscopic exploration, and decided the operation plan based on the situation. D2 radical resection was the first choice. Palliative resection and/or short circuit operation of digestive tract were selected if radical resection of local cancer was not feasible. In the surgical group, the original treatment was continued for two cycles after operation, and then S-1 and apatinib were taken orally for six months. The pathological response of the surgical group was in accordance with the 14th edition of Japanese gastric cancer treatment protocol, in which the pathological response rate (PRR) refers to the survival of tumor cells in less than two-third of the tumor area (IB or above). Tumor staging (cTNM and ypTNM) was according to the AJCC seventh edition.

Each patient was followed-up once every three months post-operation until death. The follow-up methods included telephone, SMS, outpatient visit, etc. The follow-up included survival, endoscopy, abdominal enhanced CT, tumor markers and routine laboratory tests.

Statistical analysis

SPSS 19.0 statistical software was used for statistical analysis. All measurement data with normal distribution are expressed in ($x \pm s$). The mean value of the two groups was compared by the Student's *t*-test, and the count data were tested by the $\chi 2$ test or the *Fisher* exact probability method. *Kaplan-Meier* method was used for survival analysis, and the survival rate was compared by *Log-rank* test. A *p-value* < 0.05 indicated statistically significant difference.

Results

Patient characteristics

Between December 2016 and May 2019, 39 patients with advanced unresectable gastric cancer were selected. The average age of the patients was 58 years. The pathological types were signet ring cell carcinoma and poorly differentiated adenocarcinoma. The major non-resectable factors were peritoneal metastasis, N3, liver metastasis and local progression, as shown in Table 1.

Table 1
Baseline characteristics of the patients

Variable	Patients (N = 39)
Age (years), median (range)	58 (30–68)
Gender, N (%)	
Male	19 (48.7)
Female	20 (51.3)
ECOG performance status, N (%)	
0	12 (30.8)
1	27 (69.2)
Non resectable factors, N (%)	
N3 lymph node metastasis	2 (5.1)
Distant lymphatic metastasis	4 (10.3)
Invasion of peripheral organs (T4b)	4 (10.3)
Liver metastasis	2 (5.1)
Peritoneal carcinomatosis	27 (69.2)
Pathological type, N (%)	
Moderately differentiated adenocarcinoma	5 (12.8)
Poorly differentiated adenocarcinoma	17 (43.6)
Mucinous adenocarcinoma	3 (7.7)
Signet ring cell carcinoma	14 (35.9)
Tumor site, N (%)	
Antrum gastric angle	11 (28.2)
Gastric body	11 (28.2)
Fundus cardia	10 (25.6)
Iiffuse whole stomach	7 (17.9)

Efficacy evaluation

No patient was lost to follow-up. The follow-up time was 12–40 months up to April 2020. After pre-operative treatment, 37 patients could be evaluated (one case was retreated due to IV myelosuppression, and one case was retreated due to acute upper gastrointestinal perforation). Among the 37 patients, one

patient achieved CR (2.7%), 26 achieved PR (70.3%), three had SD (8.1%) and seven had PD (18.9%). The ORR was 73.0%, and DCR was 81.1%.

A total of 22 patients underwent surgery (59.6%), of which 14 underwent radical resection (R0). The rate of R0 resection was 63.6% (Table 2). PET-CT changes of one case with liver metastasis alone before and after the transformation treatment are shown in Fig. 1. The images of exploration of another case of peritoneal metastasis before and after the transformation treatment are shown in Fig. 2.

Table 2
Efficacy evaluation

Variable	Patients, N (%)
CR	1(2.7)
PR	26(70.3)
SD	3 (8.1)
PD	7(18.9)
ORR	27(73.0)
DCR	30(81.1)
Surgical conversion	22(59.5)
R0 resection	14(63.6)

Safety and adverse reactions

The incidence of adverse reactions (AEs) was 100%. Leucopenia (65.3%), granulocytopenia (69.2%) and thrombocytopenia (15.4%) were the most common hematological AEs. The most common non-hematological AEs included fatigue (51.3%), oral mucositis (35.9%), and hypertension (25.6%). No serious surgical complications were observed (Table 3).

Table 3
Incidence of adverse reactions

Variable	Patients (N = 29)	
	Any grade, N (%)	Grade III or IV, N (%)
Leukopenia	27(73.0)	0(0)
Granulocytopenia	29(78.4)	0(0)
Thrombocytopenia	6(16.2)	1(2.7)
Elevated transaminase	9(24.3)	0(0)
Hand-foot syndrome	9(24.3)	0(0)
Stomatitis	14(37.8)	0(0)
Fatigue	20(54.1)	0(0)
Proteinuria	4(10.8)	0(0)
Gastrointestinal hemorrhage	2(5.4)	1(2.7)
Hypertension	10(27.0)	1(2.7)
Neurotoxicity	10(27.0)	0(0)

Postoperative pathological examination

In terms of postoperative pathological response, seven cases were Grade IA (31.8%), nine cases were Grade IB (40.9%), five cases were Grade II (22.7%), one case was Grade III (4.5%), and the pathological response rate (PRR) was 68.2% (Table 4).

Table 4
Postoperative pathological examination

Variable	Patients, N (%)
Histologic grade (N = 22)	
G1. Well differentiated	0 (0)
G2. Moderately differentiated	3 (13.6)
G3. Poorly differentiated	18 (64.3)
G_X. Not evaluated	1 (4.6)
Pathological response (N = 22)	
Grade 0 (no effect)	0 (0)
Grade I (slight effect)	16 (72.7)
Grade I a (very slight effect)	7 (31.8)
Grade I b (slight effect)	9 (40.9)
Grade II (considerable effect)	5 (22.7)
Grade III (complete response)	1 (4.6)

Short-term survival efficacy

The 1-year survival rate of the surgical group (22 patients) was 71.1%, the 2-year survival rate was 41.1%, and the median survival time was 21 months. The 1-year survival rate of the non-surgical group (15 patients) was 61.4%, the 2-year survival rate was 24.5%, and the median survival time was 12 months. There was a significant difference between the two groups in short-term survival (p = 0.026) (Fig. 3a).

Among the 27 patients with peritoneal metastasis, the 1-year survival rate was 77.5%, the 2-year survival rate was 34.0%, and the median survival time was 18 months. Among the 12 patients without peritoneal metastasis, the 1-year survival rate was 75.0%, the 2-year survival rate was 40.0%, and the median survival time was 17 months. There was no significant difference between the two groups in short-term survival (p = 0.084) (Fig. 3b).

In the surgical group, 14 cases received R0 resection. The 1-year survival rate was 88.9%, the 2-year survival rate was 74.1%, and the median survival time was 21 months. Eight cases received R1/R2 resection. The 1-year survival rate was 62.5%, the 2-year survival rate was 0% in two years, and the median survival time was 14 months. There was a significant difference between the two groups in short-term survival (p = 0.049), but there was no significant difference between the non-surgical group and the R1/R2 resection group (p = 0.186) (Fig. 3c).

In the surgical group, seven cases were diagnosed with pathological grade 0-Ia. The 1-year survival rate was 30.0%. The 2-year survival rate was 0%. The median survival time was 12 months; 15 cases were diagnosed with grade Ib-III. The 1-year survival rate was 84.6%, 2-year survival rate was 47.0%. The median survival time was 21 months. There was significant difference between the two groups in short-term survival ($p = 0.031$) (Fig. 3d).

Discussion

This was a single arm, phase II clinical study. The main purpose of this study was to evaluate the conversion effect of SOX regimen combined with apatinib in the treatment of unresectable gastric cancer. The primary endpoints were R0 resection rate and safety. The secondary outcome measures were the objective response rate (ORR) and overall survival rate (OSR) of the whole group. Although the follow-up time was < 5 years, we believe that the analysis of short-term survival effect would help to identify the improvement of prognosis of the combined regimen at an earlier stage.

In terms of safety, given that the pre-operative course of transformation treatment was up to six cycles, and oral maintenance was needed for half a year after operation, only three patients (8.1%) in this study had adverse reactions of grades III and IV, one patient withdrew due to grade IV severe thrombocytopenia, one patient withdrew due to emergency operation for upper gastrointestinal hemorrhage and perforation, and one patient with grade III hypertension could maintain the treatment after drug reduction. Apatinib is an anti-angiogenic drug that may induce gastrointestinal perforation and bleeding, which is most likely to cause treatment interruption. However, in this study, except for one patient with upper gastrointestinal hemorrhage and perforation, only one patient had black stool symptoms in the sixth cycle of pre-operative treatment. After short-term conservative treatment with apatinib, the patient recovered and successfully underwent R0 resection. Therefore, the combined therapy does not highlight the side effects of apatinib on anti-angiogenesis. The main adverse reactions were myelosuppression, oral mucositis and asthenia. Myelosuppression was mainly leukopenia and granulocytopenia, mostly grade I and II, which were tolerable. Oral mucositis was also mild, and could be relieved after vitamin C treatment and local symptomatic treatment. The incidence of adverse reactions was not higher than that of oxaliplatin and S-1 alone [5, 7]. The incidence of asthenia, hypertension, albuminuria and hand foot syndrome was higher than that of oxaliplatin and S-1 alone reported in the literature [5, 7], but could be easily controlled due to the mild degree of I and II, which did not affect its clinical use.

Among the patients who underwent R0 resection, one patient achieved pathological complete remission (PCR), which indicated that the scheme had a good conversion effect. No serious complications occurred in any patient during the peri-operative period. The pathological response rate (PRR) reached 68.2%. This standard is widely used in postoperative pathological evaluation of gastric cancer in Asia [11–13]. For the evaluation of primary gastric cancer, the PRR objectively reflects the effectiveness of the combined treatment scheme for patients with advanced gastric cancer.

In terms of survival benefits, the 1-year survival rate of the surgical group was 71.1%, and the 2-year survival rate was 41.1%. The median survival time was 21 months, which was much longer than that of the non-surgical group in this study, and also longer than patients with advanced gastric cancer who received chemotherapy alone reported in the literature [2, 4], suggesting that the successful conversion and concurrent operation can improve the prognosis of the patients. However, there was no significant difference in survival between the peritoneal and non-peritoneal metastasis patients after treatment, suggesting that anti-angiogenesis therapy combined with chemotherapy is also one of the feasible schemes of conversion therapy, even for peritoneal metastasis patients. The 1-year survival rate and 2-year survival rate of the R0 resection group were 88.9% and 74.1%, respectively, which were similar to the short-term survival of stage III gastric cancer [14–20], which is the ultimate goal of gastric cancer transformation treatment. However, the R1/R2 resection group did not show survival advantage compared with the non-surgical group, which indirectly indicated that if the patients fail to achieve R0 resection after the conversion therapy, surgery may not improve the prognosis. The 1-year survival rate of patients who achieved PRR was 84.6%, while the 1-year survival rate of patients who failed to achieve PRR was only 30.0%, which means that the PRR is not only an objective index of efficacy evaluation but also an option for prognosis evaluation.

Conclusions

In summary, apatinib combined with oxaliplatin and S-1 showed a good short-term survival effect and acceptable safety, especially in patients who were able to undergo R0 resection and grade Ib-III of pathological response after resection.

List Of Abbreviations

R0
radical resection
CR
complete response
PR
partial response
SD
stable disease
PD
progressive disease
ORR
objective response rate
DCR
disease control rate
AEs

adverse reactions
MDT
multidisciplinary treatment
SOX
oxaliplatin and S-1
PRR
pathological response rate
OSR
overall survival rate
PCR
pathological complete remission

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Fujian Medical University Cancer Hospital (No. 2017-037-03). Written informed consent was obtained from the patients.We confirm that all methods were performed in accordance with the relevant guidelines and regulations by including a statement in the Declaration section.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZY and YZ wrote the main manuscript text and collected data; ZY, ZW and SC participated in the data analysis; SW, YW, SC and ZL performed the statistical analysis, interpretation of the data, and statistical expertise; ZY and LC carried out the design of the study. All authors reviewed and approved the manuscript.

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Figures

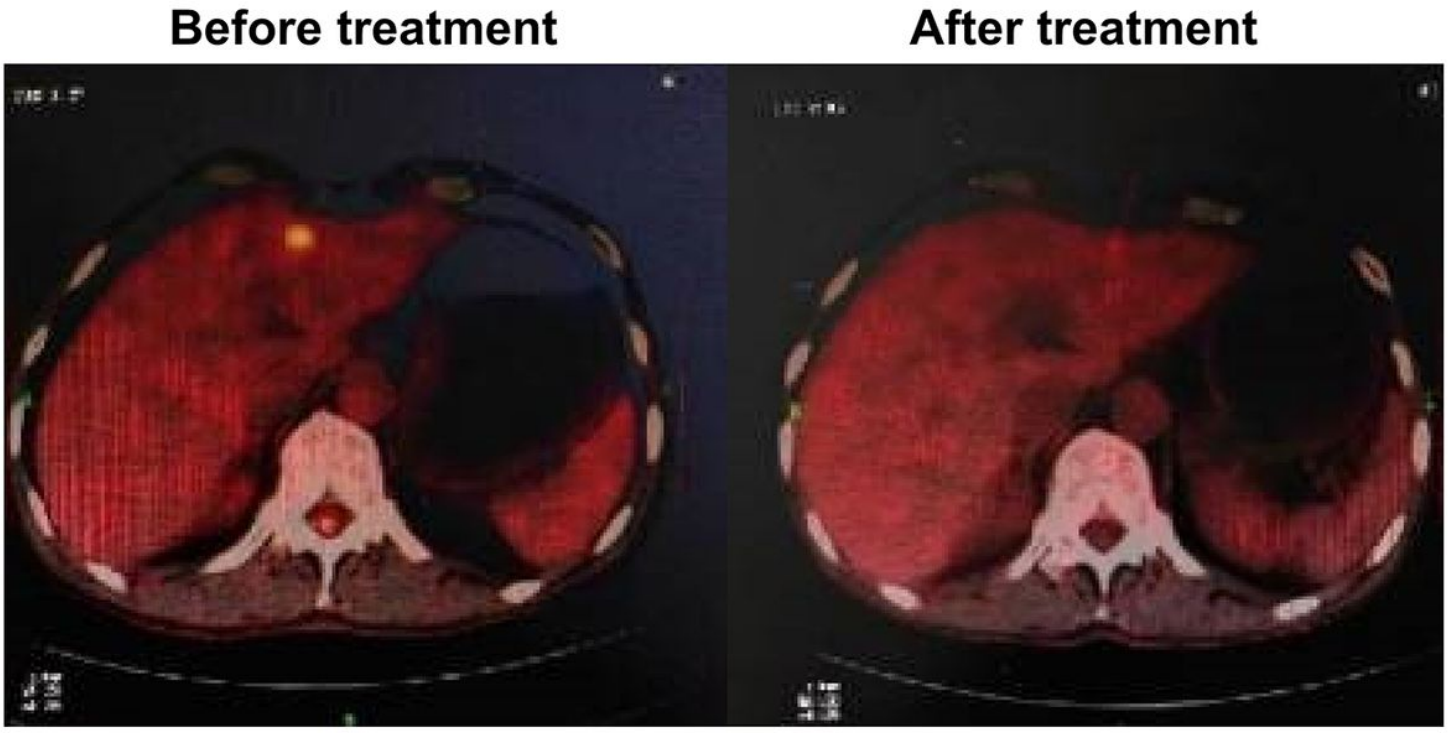

Figure 1

Case 1 (liver metastasis alone).

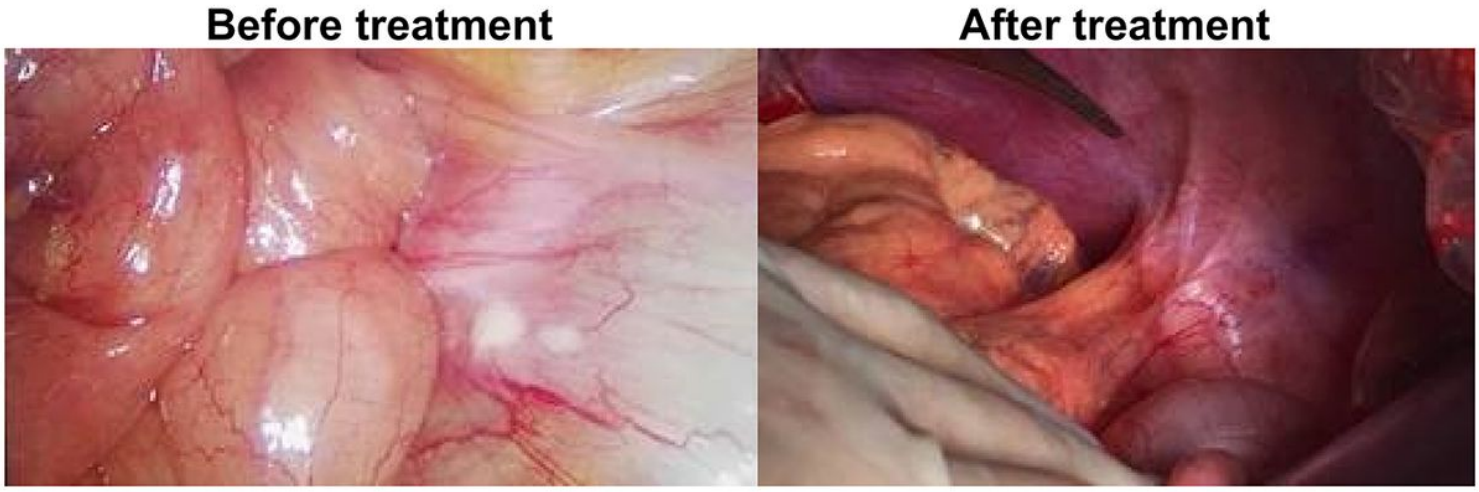

Figure 2

Case 2 (Peritoneal metastasis).

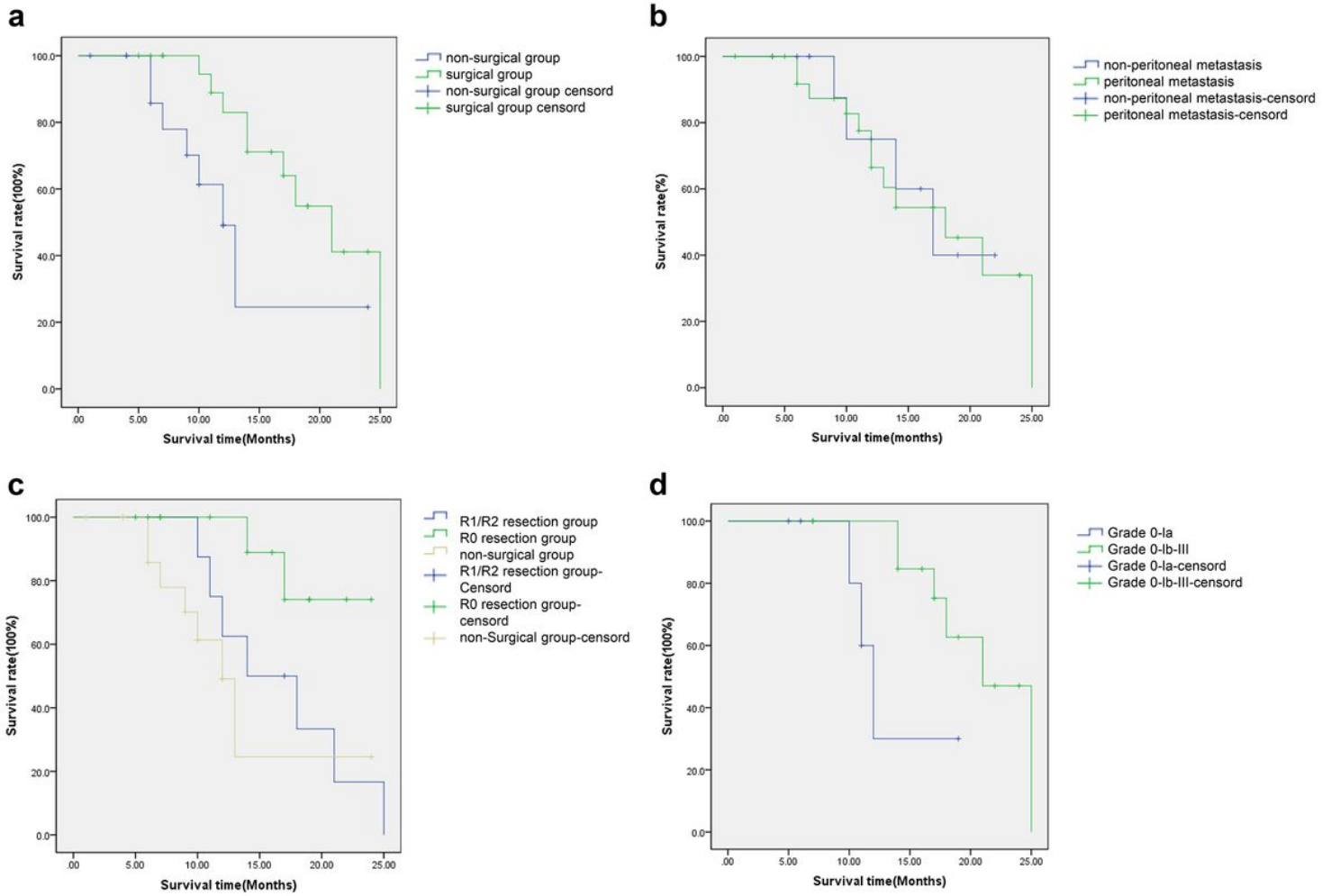

Figure 3

Shor-term survival effect. a Overall survival curves of the non-surgical and surgical groups; b Overall survival curves of the non-peritoneal metastasis and peritoneal metastasis groups; c Overall survival curves of the R1/R2 resection group, R0 group and non-surgical group; d Overall survival curves of the different pathological responses.