Original Article

Splenomegaly during oxaliplatin-based chemotherapy: impact on blood parameters and anti-neoplastic treatment

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Background: Oxaliplatin induces splenomegaly, which can cause blood sequestration and relevant cytopenia, leading to further dose reductions and schedule modifications of chemotherapy. Here, we aimed to explore the changes of spleen volume induced by oxaliplatin as well as its impact on blood parameters and anti-neoplastic treatment in patients with colon cancer.

Methods: We conducted a retrospective analysis of patients with resectable stage II–IV colon cancer who were treated with oxaliplatin and capecitabine at our institution from January 2016 to December 2017. Laboratory tests and computed tomographic (CT) data before, during and up to 18 months after the end of chemotherapy were extracted. Spleen volume was determined by volumetric measurements. Splenomegaly was defined as an over 30% increase in spleen volume from baseline.

Results: Out of 144 patients, 102 patients (70.8%) developed splenomegaly, and 75 (73.5%) recovered at 18 months after the end of chemotherapy. Higher cumulative dose intensity of oxaliplatin (P=0.001) and higher baseline platelet count (P=0.045) were risk factors associated with splenomegaly. Compared to those without splenomegaly, splenomegaly patients experienced more severe reduction in platelet (P<0.001), erythrocyte (P=0.010), neutrophil (P=0.002) and lymphocyte (P=0.006) counts and were more likely to undergo dose reductions of oxaliplatin (21.6% *vs.* 7.1%, P=0.038) as well as interruptions of chemotherapy (18.6% *vs.* 4.8%, P=0.040) due to thrombocytopenia.

Conclusions: Splenomegaly was a common and partly irreversible side effect of oxaliplatin-based therapy in patients with colon cancer. It is correlated with more severe pancytopenia and might exert a negative impact on the efficacy of anti-neoplastic treatment.

Keywords: Splenomegaly; colonic neoplasms; oxaliplatin; pancytopenia; lymphocytopenia

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Introduction

As a third-generation platinum-derivative, oxaliplatin has been widely used in the treatment of gastrointestinal cancer (1-3). The increase in spleen volume during oxaliplatin-based chemotherapy has been observed in a few studies (4-8), which is currently proposed to be secondary to portal hypertension caused by portal sinusoidal vascular disease (9-11). Splenomegaly has emerged as a novel and important mechanism for thrombocytopenia, a major dose-limiting toxicity of oxaliplatin with an incidence up to 70% (12). Considering that spleen is a site for blood cell storage as well as the largest secondary lymphoid organ in the human body, its enlargement might result in reductions in other blood cells. Data evaluating oxaliplatin-induced splenomegaly and its potential effect on anti-neoplastic therapy is also insufficient. In this study, we aimed to explore the change of spleen volume as well as its impact on blood parameters and anti-neoplastic treatments in patients receiving oxaliplatin-based chemotherapy. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-83/rc).

Methods

Patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of China National Cancer Center (No. GCP-SOP-03-01) and individual consent for this retrospective analysis was waived. Included in this retrospective study were patients with resectable stage II–IV primary colon cancer treated with oxaliplatin and capecitabine as postoperative chemotherapy in China National Cancer Center from January 2016 to December 2017. Other eligibility criteria included age ≥18 years, complete resection of tumor lesions (for stage IV patients, complete resection of both primary and metastatic lesions), and availability of computed tomographic (CT) scans and laboratory tests before, during and at least within 3 months after oxaliplatin-based chemotherapy. Exclusion criteria included recurrence during chemotherapy, administration of other chemotherapy agents, prior splenectomy, active viral hepatitis, prior diagnosed cirrhosis, prior noncirrhotic portal hypertension (right heart failure, constrictive pericarditis, Budd-Chiari syndrome, portal or splenic vein thrombus, etc.), or prior hematological disease.

Clinical information

Clinical information including demographic data, smoking and drinking habits, past medical histories, pathological information, laboratory data and treatment information were extracted from the electronic medical record system of China National Cancer Center. Laboratory and CT data were collected until disease recurrence or until 24 months after the initiation of oxaliplatin-based chemotherapy.

Laboratory tests including complete blood count and comprehensive metabolic panel were performed at least once each cycle for all patients. Decrease ratio of blood cell counts was calculated as minimum blood cell counts during surveillance period divided by baseline value. Thrombocytopenia was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (13). Elevated liver enzymes were defined as either serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels above the upper limit of normal.

Patients received a maximum of 12 cycles biweekly or a maximum of 8 cycles triweekly oxaliplatin-based chemotherapy regimens. The biweekly regimen was administrated as 2-hour infusion of oxaliplatin (85 mg/m^2) on day 1 followed by capecitabine (1,000 mg/m^2) twice daily on 10 consecutive days, which was repeated every 2 weeks. The triweekly oxaliplatin-based chemotherapy was administrated as 2-hour infusion of oxaliplatin (130 mg/m^2) on day 1 followed by capecitabine (1,000 mg/m^2) twice daily on 14 consecutive days, which was repeated every 3 weeks.

Spleen volume measurement

Spleen volume was measured by radiologists who were blinded to remaining clinical information at the workstation equipped with software enabling automatic spleen volume measurements (Advanced Workstation VolumeShare v5.0, General Electric Medical System, Milwaukee, WI, USA). CT images were loaded onto the workstation where the spleen outline was determined on each axial image, combined with the slice thickness, the spleen volume was then measured. Increased ratio of spleen volume was calculated as maximum spleen volume divided by baseline value. The predictive efficacy for thrombocytopenia by different increased ratios of spleen volume was assessed. Among all potential cut-off values (1.2 to 1.6), the increased ratio of 1.3 had both satisfactory Youden index (0.297) and sensitivity (0.789) and therefore an increased ratio over

1.3 was defined as splenomegaly. We defined the recovery of splenomegaly as the spleen volume returned to within 1.1 times the baseline value (5).

Statistical analyses

Continuous variables were described as median [interquartile range (IQR), p25–p75] or median (range). Categorical variables were described as absolute value and percentages. Median value and ranges of continuous variables were compared by Mann-Whitney U test. Categorical variables were compared by chi-square test or Fisher exact test, as appropriate. Cut-off values were calculated using the Youden index for receiver operating characteristic (ROC) analysis. Unconditional logistic regression was performed to explore the correlation between the following clinical variables and development of splenomegaly: age, sex, body mass index (BMI), drinking habit, presence of chronic viral hepatitis, liver metastases, baseline spleen volume, baseline blood cell counts (erythrocyte, neutrophil, platelet, lymphocyte counts), abnormal liver function and cumulative dose intensity of oxaliplatin. In logistic regression analysis, the median value of blood cell count and biochemical index were utilized to convert these continuous variables into categorical variables with two groups. Variables with P value <0.10 in univariate analysis were further included in the multivariate analysis. All data analyses were performed using SPSS 25.0 for windows (SPSS institute, Chicago, IL, USA) and P value <0.05 was considered statistically significant.

Results

Changes in spleen volume

A total of 249 patients were preliminarily screened, and 144 patients met the inclusion and exclusion criteria and were thus enrolled, whose demographic characteristics and treatment information were summarized in *Table 1*. One hundred and two patients (70.8%) developed splenomegaly with a median increase of 68% (IQR, 46–96%) in spleen volume, of whom 22 (21.6%) had over 100% increase (*Figure 1*). Out of the 144 patients, 37 (25.7%), 91 (63.2%) and 102 (70.8%) developed splenomegaly within 3, 6 and 9 months after initiation of chemotherapy, respectively (*Figure 2*). For splenomegaly patients, the spleen volume increased rapidly after the initiation of chemotherapy and reached 1.74 (IQR, 1.46–2.11) times of the baseline at 6 months, and gradually declined to 1.08 (1.01–1.34) times of the baseline value at the end of the surveillance. While in the non-splenomegaly group, the spleen volume increased modestly to 1.16 (IQR, 1.03–1.25) times of the baseline at 4.5 months, and rapidly recovered to 1.03 (0.98–1.11) times of the baseline value at 9 months (*Figure 3*). Recovery of splenomegaly, which was defined as spleen volume returned to within 1.1 times the baseline value, occurred in 23 (22.5%), 51 (50.0%) and 75 (73.5%) patients at 12, 18 and 24 months after the initiation of chemotherapy, respectively.

Risk factors correlated with development of splenomegaly

In the univariate analysis, higher cumulative dose intensity of oxaliplatin [odds ratio (OR) 1.004; 95% CI: 1.002–1.005; P<0.001], higher baseline erythrocyte count ($\geq 4.50\times10^{12}$/L *vs.* $<4.50\times10^{12}$/L; OR 2.28; 95% CI: 1.09–4.79; P=0.030) and higher baseline platelet count ($\geq 237.5\times10^{9}$/L *vs.* $<237.5\times10^{9}$/L; OR 2.64; 95% CI: 1.24–5.59; P=0.011) were significantly correlated with the development of splenomegaly. In the multivariate analysis, higher cumulative dose intensity of oxaliplatin (OR 1.003; 95% CI: 1.001–1.005; P=0.001) and higher baseline platelet count (OR 2.33; 95% CI: 1.02–5.31; P=0.045) were confirmed as independent risk factors (*Table 2*).

Thrombocytopenia and its negative impact on chemotherapy

Thrombocytopenia appeared in 83 patients (57.6%). Among them, grade 1 or 2 thrombocytopenia occurred in 54 patients (52.9%) with splenomegaly and in 16 (38.1%) without splenomegaly (P=0.105). Grade 3 or 4 thrombocytopenia occurred in 13 patients (12.7%) with splenomegaly while none in the non-splenomegaly group (P=0.011). Splenomegaly patients underwent a more severe decrease in platelet count compared with non-splenomegaly patients [0.36-fold of baseline value (IQR, 0.27–0.43) *vs.* 0.54-fold (IQR, 0.40–0.66), P<0.001] (*Figures 3*,*4*). For patients who developed splenomegaly within the first three months of chemotherapy, the incidence of thrombocytopenia within the first three months was higher than the rest (54.1% *vs.* 31.7%, P=0.016). Continuous thrombocytopenia was observed in 3 patients at 12 months after initiation of chemotherapy, all in the splenomegaly group.

Due to thrombocytopenia, 25 patients (24.5%) with splenomegaly and 4 (9.5%) without splenomegaly

Table 1 Demographic characteristics and treatment information of patients

Variables	Total (n=144)	S group (n=102)	NS group (n=42)	P[a]
Demographic characteristics				
Age, median [range], years	58.0 [29–76]	58.1 [29–75]	56.4 [33–76]	0.577
Sex (male: female)	92:52	68:34	24:18	0.279
BMI, median (IQR), kg/m^2	23.3 (21.5–25.6)	23.3 (21.6–25.9)	23.3 (20.1–24.3)	0.120
BSA, median (IQR), m^2	1.76 (1.61–1.86)	1.78 (1.65–1.87)	1.66 (1.59–1.82)	0.045
Smoking habit (never: past: current)	95:17:32	64:14:24	31:3:8	0.482
Drinking habit (never: past: current)	92:11:41	60:9:33	32:2:8	0.164
Comorbidities, No. (%)				
Hypertension	38 (26.4)	28 (27.5)	10 (23.8)	0.652
Cardiovascular disease	7 (4.9)	4 (3.9)	3 (7.1)	0.416
Diabetes	20 (13.9)	17 (16.7)	3 (7.1)	0.133
Chronic viral hepatitis	6 (4.2)	5 (4.9)	1 (2.4)	0.672
Primary tumor site, No. (%)				
Ascending colon and cecum	42 (29.2)	29 (28.4)	13 (31.0)	0.899
Transverse colon	13 (9.0)	10 (9.8)	3 (7.1)	
Descending colon	11 (7.6)	7 (6.9)	4 (9.5)	
Sigmoid colon	71 (49.3)	50 (49.0)	21 (50.0)	
Multiple colons	7 (4.9)	6 (5.9)	1 (2.4)	
Pathological stage, No. (%)				
II	33 (22.9)	21 (20.6)	12 (28.6)	0.279
III	94 (65.3)	70 (68.6)	24 (57.1)	
IV	17 (11.8)	11 (10.8)	6 (14.3)	
Liver metastases	16 (11.1)	11 (10.8)	5 (11.9)	0.846
Ovary metastases	1 (0.7)	0 (0.0)	1 (2.4)	0.292
Baseline spleen volume, median (IQR), mm^3	202.5 (148.9–263.6)	204.4 (148.8–262.1)	200.4 (146.7–266.3)	0.686
Baseline laboratory data, median (IQR)				
Platelet count, 10^9/L	237.5 (198.5–290.8)	251.5 (200.0–298.0)	212.5 (187.3–263.5)	0.036
Erythrocyte count, 10^{12}/L	4.50 (4.18–4.76)	4.52 (4.24–4.81)	4.34 (4.16–4.62)	0.066
Neutrophil count, 10^9/L	3.00 (2.44–3.82)	3.15 (2.54–3.83)	2.82 (2.36–3.74)	0.182
Lymphocyte count, 10^9/L	1.90 (1.48–2.40)	1.97 (1.51–2.45)	1.81 (1.41–2.35)	0.173
ALT, (U/L)	16.0 (11.0–24.0)	17.0 (12.0–24.0)	14.5 (9.0–24.0)	0.175
AST, (U/L)	17.0 (14.0–21.0)	17.0 (14.0–21.0)	14.0 (16.5–22.3)	0.982
Elevated liver enzymes No. (%)	55 (38.2)	41(40.2)	14 (33.3)	0.441

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=144)	S group (n=102)	NS group (n=42)	P[a]
Chemotherapy information				
Regimen (biweekly: triweekly)	56:88	40:62	16:26	0.900
Cycles of biweekly regimen, median [range]	10 [4–12]	10 [4–12]	6 [4–10]	<0.001
Cycles of triweekly regimen, median [range]	7 [3–8]	8 [3–8]	7 [3–8]	0.052
Cumulative dose intensity of oxaliplatin, median (IQR), mg/m^2	778.6 (606.8–937.5)	837.0 (670.6–957.2)	629.3 (445.9–879.7)	<0.001

P[a], indicate differences between S group and NS group. P<0.05 was considered statistically significant. S group, splenomegaly group; NS group, non-splenomegaly group; BMI, body mass index; BSA, body surface area; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

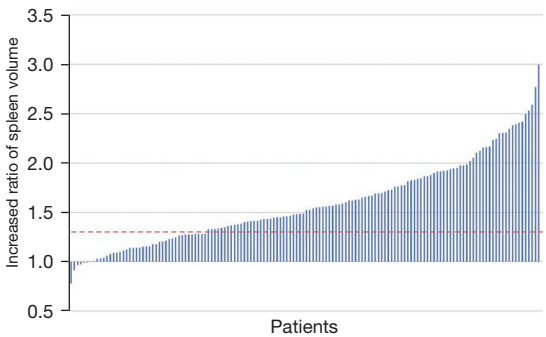

Figure 1 Changes in spleen volume in all 144 patients. Increased ratio indicates maximum spleen volume divided by baseline value. The red dotted line represents an increased ratio of 1.30, which is the thresholds value that defined splenomegaly.

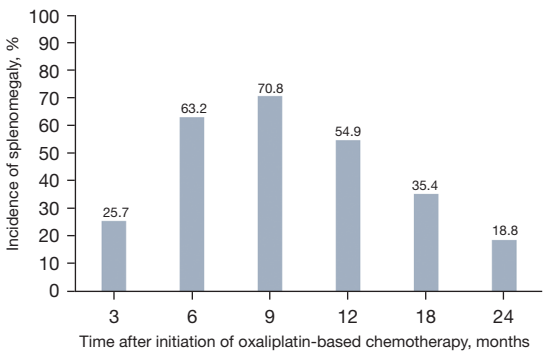

Figure 2 Incidence of splenomegaly over time.

underwent dose reduction of oxaliplatin (P=0.042). Moreover, the interruptions or terminations of oxaliplatin-based chemotherapy occurred in 19 patients (18.6%) with splenomegaly and 2 (4.8%) without splenomegaly due to

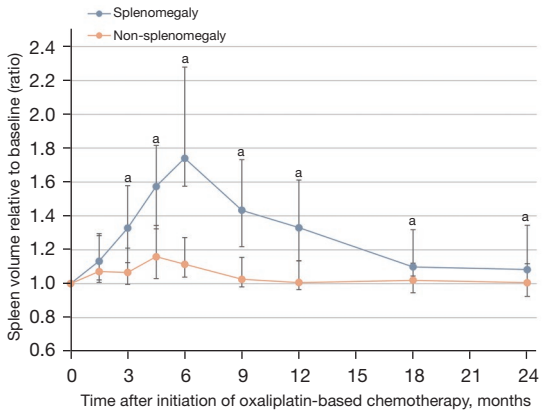

Figure 3 Changes in the spleen volume over time in splenomegaly and non-splenomegaly groups. [a], P<0.05 for splenomegaly *vs.* non-splenomegaly.

thrombocytopenia (P=0.040), including 6 patients in the splenomegaly group and 2 in the non-splenomegaly group who underwent continuous grade 2 thrombocytopenia persisting over 2 weeks.

Splenomegaly and changes of other blood cell counts

Patients with splenomegaly experienced more severe reduction in erythrocyte count (P=0.010), neutrophil count (P=0.002) and lymphocyte count (P=0.006) than patients without splenomegaly (*Figure 4*). Overall, oxaliplatin-based chemotherapy resulted in a reduction in all four blood parameters in 85 patients (81.7%) in the splenomegaly group and 24 (57.1%) in the non-splenomegaly group (P=0.001). At the time of 12 months after initiation of chemotherapy, 13 patients (12.7%) in the splenomegaly

Table 2 Univariate and multivariate analyses of the correlation between clinical variables and development of splenomegaly

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P[a]	Odds ratio	95% CI	P[a]
Age	0.99	0.95–1.03	0.632			
Female	0.67	0.32–1.39	0.281			
BMI	1.12	0.99–1.27	0.077	1.09	0.95–1.26	0.218
Drinking habit						
Never	1.00					
Past	2.40	0.49–11.78	0.281			
Current	2.20	0.91–5.32	0.080	1.80	0.68–4.79	0.240
Chronic viral hepatitis	2.11	0.24–18.66	0.501			
Liver metastases	0.90	0.29–2.75	0.846			
Baseline spleen volume	1.00	0.99–1.00	0.308			
Baseline erythrocyte count ≥4.50×10^{12}/L	2.28	1.09–4.79	0.030	1.69	0.72–3.94	0.227
Baseline neutrophil count ≥3.00×10^{9}/L	1.98	0.95–4.13	0.069	1.70	0.74–3.89	0.209
Baseline platelet count ≥237.5×10^{9}/L	2.64	1.24–5.59	0.011	2.33	1.02–5.31	0.045
Baseline lymphocyte count ≥1.90×10^{9}/L	1.72	0.83–3.57	0.144			
Elevated liver enzymes	1.34	0.63–2.86	0.442			
Cumulative dose intensity of oxaliplatin	1.004	1.002–1.005	<0.001	1.003	1.001–1.005	0.001

[a], P<0.05 was considered statistically significant. BMI, body mass index.

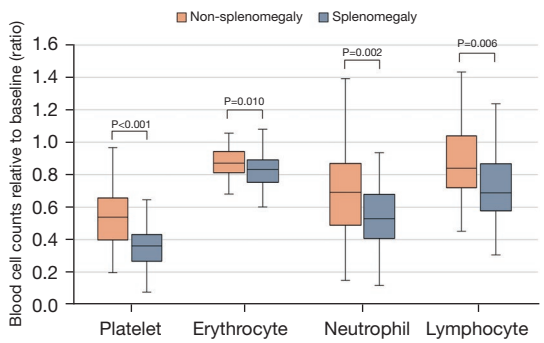

Figure 4 Reductions in blood cell counts in splenomegaly and non-splenomegaly groups. Patients with splenomegaly experienced more severe reductions in platelet (P<0.001), erythrocyte (P=0.010), neutrophil (P=0.002) and lymphocyte (P=0.006) counts after oxaliplatin-based chemotherapy.

group and 5 (11.9%) in the non-splenomegaly group still had over 30% reduction from baseline lymphocyte count (P=0.890), while continuous reductions in erythrocyte and neutrophil counts did not persist in either of the groups.

Discussion

There were several major findings from our analyses. First, rapid and reversible splenomegaly was common during oxaliplatin-based chemotherapy. Second, higher cumulative dose intensity of oxaliplatin and higher baseline platelet count were risk factors associated with splenomegaly. Third, patients with splenomegaly experienced a more severe decrease in blood cell counts, especially in platelet count, which further resulting in more frequent dose reductions and interruptions of oxaliplatin-based chemotherapy.

In this retrospective cohort, over 95% of patients experienced an increase in the absolute value of spleen volume, and splenomegaly (≥30% increase from baseline) occurred in 70.8% of patients. Splenomegaly has been previously observed in 24% to 67% of oxaliplatin-treated patients (4-8,14). Direct comparison of the incidence of splenomegaly between studies was difficult, due to different measurement methods of spleen volume and varied definition of splenomegaly. Further, our analysis revealed that oxaliplatin-induced splenomegaly was a rapid and

partly irreversible disease course. One quarter of patients developed splenomegaly within the first three months of chemotherapy and splenomegaly was still present in over one quarter of patients at 18 months after completion of oxaliplatin-based treatment.

Cumulative dose-dependent side effect is a characteristic of oxaliplatin-induced toxicity, such as peripheral neuropathy and hypersensitivity reactions (15,16). Similarly, oxaliplatin-induced splenomegaly is also dose-dependent, as confirmed by our multivariate analysis result. Unexpectedly, patients with higher baseline platelet count were prone to develop splenomegaly. One possible explanation is that sequestrated platelets mechanically stretch the spleen.

Thrombocytopenia was frequently observed in our patients. Given that capecitabine had a minor effect on thrombocytopenia (17,18), oxaliplatin might make the major contribution to thrombocytopenia in our patients. Compared with the control group, patients with splenomegaly experienced more severe thrombocytopenia, which occurred early after the initiation of chemotherapy and could persist for a long time after the end of chemotherapy. This resulted in more frequent dose reductions and interruptions of oxaliplatin-based treatments, and might eventually attenuated the antineoplastic effects (19). Three mechanisms have been proposed to explain oxaliplatin-induced thrombocytopenia: myelosuppression, immune-mediated reaction and splenic sequestration of platelets (12). Immune-mediated reaction is characterized as a sharp decline in platelet counts accompanied by hypersensitivity reactions (16,20), which was not observed in our patients. Thrombocytopenia secondary to myelosuppression is mild or moderate, and usually recover before the next cycle of chemotherapy (12). We thus speculate that splenomegaly played an important role in the severe and prolonged thrombocytopenia. Moreover, as we hypothesized, patients with splenomegaly also experienced more severe reductions in erythrocyte, neutrophil and lymphocyte counts. The combination of oxaliplatin-based chemotherapy and immune checkpoints inhibitors has been used in the treatment of gastrointestinal cancer recently (21,22). However, patients with lower circulating lymphocyte counts appeared to benefit less from immune checkpoints inhibitors (23,24). Thus, whether the benefit from PD-1/PD-L1 inhibitors will be attenuated by oxaliplatin-induced splenomegaly remains an open question.

There are some limitations to this study. The retrospective and non-randomized nature is the major limitation, which may introduce some bias in the analyses. However, accurate measurement of spleen volume by 3-D volumetric technique guaranteed precise and reliable results. Also, multiple measurements of spleen volume (before, during and until 18 months after chemotherapy) enabled a comprehensive description of the changing pattern of spleen volume in oxaliplatin-based chemotherapy.

In conclusion, splenomegaly was a common dose-dependent side effect of oxaliplatin-based treatment, which occurred early and gradually recovered after completion of chemotherapy. Patients with splenomegaly were prone to experience a more severe decrease in blood cell counts, especially in platelet counts, which resulted in more frequent dose-reductions and interruptions of oxaliplatin-based treatment. Further studies concerning this issue are warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-83/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-83/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-83/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-83/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics

Review Committee of China National Cancer Center (No. GCP-SOP-03-01) and individual consent for this retrospective analysis was waived.

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