Prognostic biological factors of radiation pneumonitis after stereotactic body radiation therapy combined with pulmonary perfusion imaging

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Abstract. Radiation pneumonitis (RP) is one of the most common dose-limiting toxicity syndromes in patients with thoracic malignant tumors receiving radiotherapy. The present study aimed to identify biological factors for the prediction of RP. Pulmonary perfusion imaging is capable of reflecting the differential functional activity of various regions of the lung, and in the present study, radiotherapy plans that were established on the basis that pulmonary perfusion images have high biological conformality, which may identify regions vulnerable to RP to spare them from radiation. A total of 46 patients with non-small cell lung cancer (NSCLC), exhibiting high and low levels of apurinic/apyrimidinic endonuclease-1 (Ape-1), intercellular adhesion molecule (ICAM)-1 and interleukin (IL)-17A prior to treatment, with SBRT with respective cut-off values of 4.2, 3.0 and 5.1 μg/l were stratified into groups A and B. Patients received radiation doses within the margin of the planning target volume. Stereotactic body radiation therapy (SBRT) was used for the treatment of NSCLC and single-photon emission computed tomography pulmonary perfusion imaging was used to assess all patients for the presence of RP. Furthermore, the serum levels of Ape-1, ICAM-1 and IL-17A were examined by ELISA. Prior to SBRT, perfusion images indicated that no RP was present in any of the patients, and 23 patients had high levels of Ape-1, ICAM-1 and IL-17A. After SBRT, 22 out of 23 patients in group A (95.65%) presented with RP and 1 patient (4.35%) had no RP. In group B, 6 out of 23 patients (26.09%) had RP and 17 patients (73.91%) had no RP after SBRT. The difference between the two groups in the incidence of RP was significant ($P=1.66x10^{-12}$ <0.05). In conclusion, high levels of Ape-1, ICAM-1 and IL-17A are associated with an increased risk of RP. A further analysis should be performed in the future to verify whether these factors have significant prognostic value.

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Introduction

Lung cancer is a common type of thoracic malignant tumor and the leading cause of cancer-associated mortality worldwide (1). Radiotherapy is one of the major therapies for the treatment of thoracic malignant tumors, particularly for inoperable tumor patients (2). An increase of the radiotherapy dose delivered to the tumor during the process of radiotherapy may increase the local control rate of the tumor. However, radiotherapy of pulmonary tumors causes damage to the corresponding peripheral tissues and organs, including the lung, heart, esophagus and spinal cord. While radiotherapy is efficient for treating thoracic malignant tumors, it induces certain radiotherapy-associated adverse reactions, including radiation pneumonitis (RP) and radiation esophagitis. RP is one of the most common dose-limiting toxicity syndromes after radiotherapy or concurrent chemoradiotherapy for patients with thoracic malignant tumors (3). Due to RP, the clinical use of higher and more effective radiation doses is not possible, and together with other methods of tumor treatment, it affects the quality of life of patients; severe RP may even endanger the life of affected patients (4,5).

Stereotactic body radiotherapy (SBRT), which has been implemented in the clinic in the late 1950s, is a radio-surgical technology for the treatment of extracranial lesions (6). SBRT features a high repeatability of posture fixation and high conformity of dose distribution, and is able to individually measure tumors during initial image acquisition, treatment and exposure to irradiation; it may be used to formulate and implement targeted plans, and to precisely administer irradiation under the guidance of online and offline images (7). The precise positioning system of SBRT greatly reduces

the radiation dose reaching surrounding normal tissues and organs, while maximising the dose in tumor areas. SBRT has a high efficacy for inoperable patients with early-stage non-small cell lung cancer (NSCLC) (8). RP is one of the most common complications of early-stage NSCLC after the treatment with SBRT. A phase III randomised controlled trial on radiotherapy and chemotherapy of stage-III NSCLC reported that a majority of patients suffered from RP after treatment with SBRT (9).

A previous study indicated that the development of RP is a repair process for injury that involves multiple factors and biomolecular complexes (10). Clinical research showed that some blood cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor-β and platelet-derived growth factor, were associated with the occurrence of RP (11), but their clinical value in treatment is still unclear. At present, no clear biomarker may be used to predict RP. In the course of radiotherapy for lung and breast cancer, healthy lung tissue is also subject to radiation. When lung cancer is treated with radiation, the safe radiation dose is significantly associated with the risk of RP in the surrounding normal lung tissue. This risk is dose-dependent and is commonly predicted by using metrics, including the percentage of volume that received ≥20 Gy (V20), which are usually formulated under the assumption of homogeneous pulmonary function. Because of the uneven distribution of function throughout the lung, the risk of RP may be reduced if high-functioning lung areas are identified in advance and avoided preferentially during treatment (12,13). It is indicated that radiation-induced lung injury can be predicted and avoided to a certain extent (12,13). Therefore, finding a suitable predictor is significant for avoiding the occurrence of RP.

Patients and methods

Patients. NSCLC patients admitted to Henan Province Anti-Cancer Hospital (Zhengzhou, China) between October 2014 and June 2016 were selected for the present study. All patients were diagnosed as stage I NSCLC according to the criteria in the 7th edition of the guidelines of the American Joint Committee on Cancer (14) and TI-4N0M0 by histopathological detection. If lymph nodes with a size of <1 cm in the hilus pulmonis and mediastinum or no abnormal mediastinal lymph nodes on positron emission tomography-computed tomography (PET/CT) were present, the nodal status was considered as N0. The pathological types of the primary lesions were squamous-cell carcinoma, adenocarcinoma, large cell carcinoma, large cell neuroendocrine carcinoma and other unclassified NSCLC. The present study obtained approval from the institutional review board of Henan Province Anti-Cancer Hospital (Zhengzhou, China). All patients provided written informed consent.

The exclusion criteria were as follows: i) Local or distant metastasis confirmed by PET inspection or post-operative pathological staging, or primary cancer or pre-cancerous lesions in the past three years (except disease-free survival and survival time after eradication therapy of aggressive tumors of >3 years, carcinoma *in situ* and early-stage skin cancer through eradication treatment); ii) primary tumor diameter >5 cm; iii) history of chemotherapy, pulmonary lobectomy or pneumonectomy; iv) the same radiation field with that of the present study and previous radiotherapy; v) pure bronchioloalveolar carcinoma; vi) active systemic infection or pulmonary and pericardial infection; vii) women attempting to conceive, during pregnancy or breast feeding, or sexually active, heterosexual men unable or unwilling to use contraception in accordance with the acceptable medical methods (note: This item is required, as the therapeutic methods applied in the present study may lead to sperm cell malformation); viii) unintended weight loss of >10% of body weight over the previous three months; ix) patients with chronic obstructive pulmonary disease and/or heart disease who were inoperable as determined by an experienced thoracic cancer surgeon, patients who refused surgery and those with a performance status score of ≤2.

SBRT schedules. For central lung cancer, a total SBRT dose of 55 Gy was delivered by administration of 5 times within 5-7 days, with a treatment interval of 1-3 days (15). Peripheral lung cancer was treated with a total SBRT dose of 48 Gy administered over 4 times within 5-7 days, with a treatment interval of 1-3 days. These treatments were required to be completed within ten days.

For all patients, the radiation dose was the marginal dose of the planning target volume (PTV). During the calculation of the dose, the heterogeneity of tissues was considered. A requirement during the establishment of the radiotherapy schedule was that the target volume was enclosed by the isodose curve of 95%.

Establishment of radiotherapy schedules and radiation dose

General principles. The treatment aimed to deliver a high dose to the target volume and reduce the dose reaching the surrounding normal tissues. The calculation of radiation dose and the measurement with monitoring device (RadHalo™ RDP and FM Spectroscopic Area Monitors; each, Thermo Fisher, Scientific, Inc., Waltham, MA, USA) was based on the heterogeneity of tissues. Tumors with a shallow depth of <2 cm were treated with gamma rays of 6 MV or below. High-energy gamma ray (16-18 MV) mayoptimize the dose-response curves on the target volume. The calculation of radiation dose excluded the reconstructed images after a breath by using 3-dimensional (3D)-CT. Hot spots in the internal target volume (ITV) were allowed, with the maximum dose being ≤140% of the standard dose. The lung is one of the major dose volume-limiting organs for thoracic radiotherapy. Numerous dosimetric parameters, including the V5, V20, V30 and the mean lung dose, have been reported to be associated with radiation toxicity to the lung. Although no standardization has been performed for delineating the normal lung for dose computation and the dosimetric cut-off is controversial, clinical trials and the National Comprehensive Cancer Network practice guidelines have set the V20 and the mean lung dose as limits on lung dosimetry (16,17).

Criteria of successful treatment plans. i) Normalization: The dose of the treatment plan is normalized to a 100% dose point at the center of the PTV. This point usually coincides with the isocenter (but this is not a requirement). ii) Coverage of isodose curves on the target volume: The dose delivered to 95% of the

PTV, 99% of the ITV and 100% of the gross tumor volume is identical to the prescribed dose, respectively. iii) Dose heterogeneity on the target volume: The dose at the isodose point on the body surface must be >60 and <90% of the dose at the center of PTV (the PTV is equal to that mentioned in the above point i). iv) Maximum dose: Patients are treated with the absolute corresponding maximum dose in the treatment plan, and the dose point must be within the PTV. v) Prescribed isodose: The dose delivered to the prescribed isodose surface must be at least 60% and no more than 90% of the maximum dose. vi) Coverage of prescribed isodose surface: The coverage of the prescribed isodose surface covers 95% of the PTV, or at least 99% of the PTV is treated with 90% of the prescribed dose. vii) High-dose leakage: The total volume of all soft tissues outside the PTV with >105% of the dose <15% of the volume of the PTV. viii) Application of 3D coplanar or non-coplanar beams provides each patient with a highly conformal prescribed dose distribution. In general, when the number of radiation beams is >10, they are applied approximately to the same radiation weight. A larger number of beams is generally used for larger lesions. When static beams are used, application of at least 7 non-penetrated beams is required. When the arc spinning technique is applied, the accumulative angle of all beams is 340 degrees at least. In order to gain an acceptable scope, the size and shape of the aperture on radiation fields is almost the same as the projection on the PTV. The only exception is that when the observed minimum diameter of the radiation fields is 3.5 cm during the treatment of smaller lesions, 60-90% of the PTV is usually covered (maximum dose, 100%). However, higher isodoses (hot spots) must be applied within the target volume, not to the surrounding normal tissues. The isocenter of the treatment or the point setting in stereotactic coordinates depends on systematic data-points, which may be adjusted by location images prior to treatment.

Single-photon emission computed tomography (SPECT) pulmonary perfusion imaging. SPECT (18) and PET (19) are two types of CT technology applied in nuclear medicine. SPECT, which detects photons and PET, which detects the positrons emitted form images that are collectively referred to as ECT. Pulmonary perfusion imaging is able to reflect lung regions with different functional activity, and radiotherapy plans established on the basis of pulmonary perfusion images exhibit high biological conformality, which allows for sparing the most vulnerable non-cancerous tissues from radiation treatment. In addition, the presence of defects or fluid displayed on pulmonary perfusion images was consistent with the pulmonary function, based on which it was possible to estimate the occurrence of lung injury.

Pulmonary perfusion imaging was performed using a dual-head SPECT-CT (Philips, Eindhoven, The Netherlands) at the Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital (Zhengzhou, China). ^{99m}Tc macroaggregated albumin (MAA) was used as a marker. The patient was made to lay flat on the inspection parallel board in the supine position with their elbows held in front of their forehead. The position and placement of the patients was in accordance with that during radiotherapy. A total of 185 MBq ^{99m}Tc-MAA was slowly injected through the brachium vein of the patient. Lung static images were immediately captured from the front, back, left anterior, left posterior, right anterior, right posterior, left lateral and right lateral views. The required acquisition matrix was 128x128 and the acquisition counter in each position was set at $5x10^5$/frame. Cross-sectional images of coronal, cross and sagittal sections were collected for each patient, with one frame for 20 sec every 60 degrees, at double magnification and each probe was rotated 180 degrees.

Cytokine detection. In the morning prior to SBRT, 2 ml fasting blood was collected from each patient in EDTA anti-coagulative tubes. Within the next hour, the blood was centrifuged at 1,000 x g for 10 min at 4˚C. The separated plasma was stored at -20˚C. The cytokines were measured within 2 h after the separated plasma was defrosted at room temperature. The serum levels of apurinic/apyrimidinic endonuclease-1 (Ape-1; cat. no. 65920), intercellular adhesion molecule (ICAM)-1 (cat. no. 70220) and IL-17A (cat. no. 4176AF-50) were detected using ELISA kits (NeoBioscience, Shenzhen, China) according to the manufacturer's protocol. A standard curve was established, from which the concentration of the antigen in the samples was determined. Titer was considered to be present at an optical density greater than that of the blank control well.

Diagnosis and evaluation of RP. All patients were examined at least once a week during the treatment. For follow-up, a routine chest CT scan was performed at 4-6 weeks after radiotherapy and every three months thereafter. If any suspicious RP symptoms (e.g., severe coughing, elevated temperature and choking sensation in the chest) occurred at any time in the process of or after radiotherapy, chest CT examination for confirmation was promptly performed. RP was diagnosed according to patients' clinical symptoms (coughing or dyspnea) and imaging abnormalities, including new ground-glass opacity changes, irregular enhancement or consolidation changes in the radiation field. For the diagnosis of RP, it was required to exclude intrapulmonary infection and the development of pulmonary lesions, and the stage of RP was determined based on the severity of the symptoms.

RP was divided into the following stages according to the standards of acute RP established by the Radiation Therapy Oncology Group (20): 0, no obvious change in symptoms and signs after treatment compared with those prior to treatment; I, mild cough or a cough reflex in response to forceful expiration; II, persistent cough that requires treatment with narcotic antitussive or dyspnea in response to light exercise but no dyspnea in the resting state; III, severe cough for which narcotic antitussive ineffective, dyspnea in the resting state or acute pneumonia confirmed by radiological images, which may be treated with intermittent oxygen inhalation or cortical hormones; IV, severe respiratory insufficiency which requires treatment with continuous oxygen inhalation or assisted ventilation; V, death from RP.

Statistical analysis. SPSS 11.5 statistical software (SPSS, Inc., Chicago, IL, USA) was used for data processing. The Chi-squared test was used to assess differences between groups for categorical/numerical variables. Data of two groups were subjected to normal distribution-homogeneity of variance (homogeneity test of variance) via use of a Student's

Table I. Basic data of patients in the two groups.

Variable	Group A (n=23)	Group B (n=23)	P-value
Age	66.1±11.23	64.2±10.61	0.18
Males/females	17/6	16/7	0.74
Cancer stage (12)			
IA	4 (17.4%)	3 (13.0%)	0.85
IB	3 (13.0%)	4 (17.4%)	
IIA	5 (21.7%)	6 (26.1%)	
IIB	6 (26.1%)	4 (17.4%)	
IIIA	2 (8,7%)	4 (17.4%)	
IIIB	3 (13.0%)	2 (8.7%)	
Histological type			
Squamous cell carcinoma	14 (60.1%)	13 (56.5%)	0.81
Adenocarcinoma	7 (30.4%)	8 (34.8%)	
Large cell carcinoma	2 (8.7%)	2 (8.7%)	
Lung radiation dose			
V5	26.8±0.84	27.4±0.98	0.90
V20	40.6±1.32	48.3±0.93	0.25
V30	48.4±1.09	55.4±1.11	0.46
Smoking history	42.5±2.11	48.7±1.98	0.45
MLD	48.4±2.17	55.4±1.96	0.46

MLD, minimum lethal dose; V5, % total lung volume receiving ≥5 Gy. Values are expressed as the mean ± standard deviation. The cancer staging is according to the 7th edition of the guidelines of the American Joint Committee on Cancer (12).

t-test. If the above conditions were not met, then a rank sum test was performed. Measurement data were expressed as the mean ± standard deviation, and the P-value was used for assessment. P<0.05 was considered to indicate a significant difference.

Results

Basic information. In the present study, patients with high levels of Ape-1, ICAM-1 and IL-17A prior to SBRT were divided into group A, while patients without high levels of Ape-1, ICAM-1 and IL-17A were assigned to group B. The median cut-off values for Ape-1, ICAM-1 and IL-17A were 4.2, 3.0 and 5.1 μg/l. There was no significant difference in age, sex, tumor type and tumor stage distribution between the two groups (P>0.05; Table I).

SPECT imaging. Prior to SBRT, patients were subjected to SPECT, provided a comprehensive information on the condition and function of the lung to establish ideal radiotherapy plans. The images in Fig. 1A and B were captured prior to SBRT and those in Fig. 1C and D were obtained after radiotherapy. No RP occurred in any of the patients with NSCLC prior to SBRT. However, after SBRT, ground-glass opacity changes and irregular enhancement were observed, which demonstrated that the occurrence of RP (21) was ~95.6%. Furthermore, the occurrence of stage II-III RP was ~47.8%.

Basal Ape-1, ICAM-1 and IL-17A levels are associated with the incidence of RP. Prior to SBRT, the Ape-1, ICAM-1 and IL-17A levels in group A were significantly higher than those in group B (P<0.05). There was no significant difference between the two groups in Ape-1, ICAM-1 or IL-17A levels, age, sex, tumor stage or tumor type. After SBRT, the levels of Ape-1, ICAM-1 and IL-17A in group A were still higher than those in group B (Table II).

Table II. Serum levels of Ape-1, ICAM-1 and IL-17A in the patients of the two groups (μg/l).

Group/time-point	Ape-1	ICAM-1	IL-17A
Group A			
Pre-SBRT	16±1.21	19±0.92	14±0.69
Post-SBRT	21	18±0.48	19±1.09
P-value	0.02	0.01	0.02
Group B			
Pre-SBRT	<4.2±0.17	<3.0±0.32	<5.1±0.25
Post-SBRT	<4.1±0.76	<2.1±0.46	<4.2±0.86
P-value	0.06	0.05	0.07

IL, interleukin; ICAM, intercellular adhesion molecule; Ape-1, apurinic/apyrimidinic endonuclease 1; SBRT, stereotactic body radiation therapy. P-value, Post-SBRT vs. Pre-SBRT. The median values 4.2, 3.0 and 5.1 μg/l were selected as cutoff values. Values are expressed as the mean ± standard deviation.

After SBRT, 22 patients in group A suffered from RP, while in group B, 17 were without RP. The difference in

Table III. Incidence of RP after SBRT in groups A and B (n=23 each).

Group	No RP %	RP %	Stage of RP			P-value
			I %	II %	III %	
A	1 (4.3)	22 (95.6)	11 (47.8)	7 (30.4)	4 (17.4)	$1.66x10^{-12}$
B	17 (73.9)	6 (26.1)	3 (13.0)	2 (8.7)	1 (4.3)	

RP, radiation pneumonitis. Values are expressed as n (%).

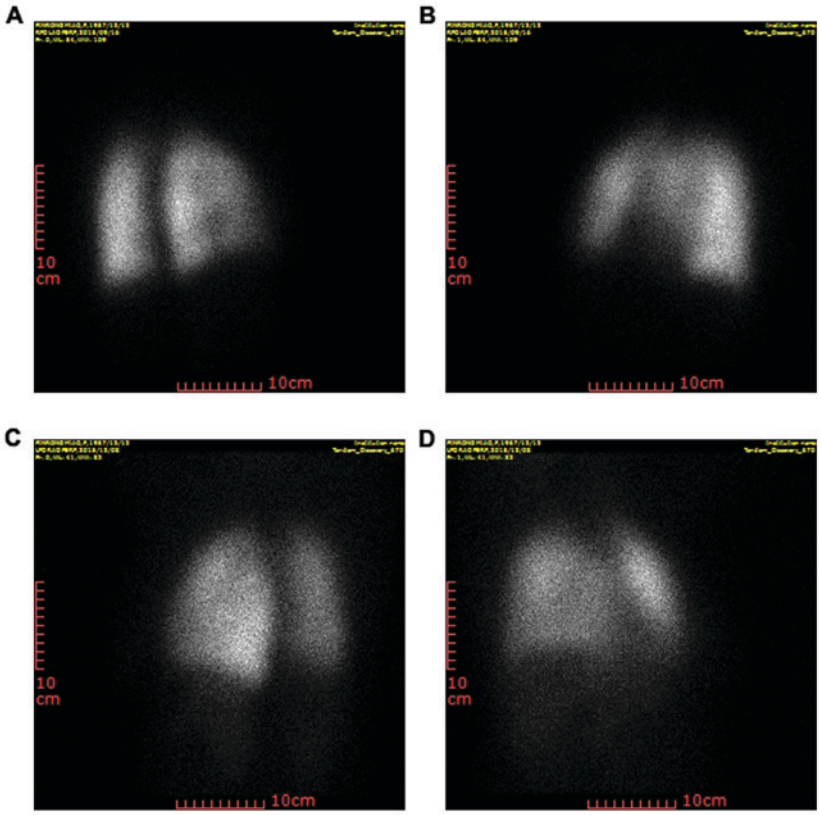

Figure 1. Single-photon emission computed tomography images of patients. (A and B) Representative images of non-small cell lung cancer patients without RP prior to radiotherapy. (C and D) Images obtained after stereotactic body radiation therapy, displaying RP with ground-glass opacity changes and irregular enhancement in the lung (scale bars, 10 cm). All images were obtained from different patients. RP, radiation pneumonitis.

the incidence of RP between the two groups was significant ($P=1.66x10^{-12}$; Table III). Higher Ape-1, ICAM-1 and IL-17A levels were associated with a higher risk of RP. A further analysis should be performed to verify whether these factors have significant prognostic value.

Discussion

RP is a serious adverse effect of SBRT in lung cancer patients. The factors associated with the occurrence of RP have been thoroughly discussed (22). Studies on RP have provided tools for developing improved radiotherapy plans for lung cancer patients, but to the best of our knowledge, no effective factor for the prediction of RP has been provided (23-25). The prognostic value of the cytokines Ape-1, ICAM-1 and IL-17A used in combination should be assessed via multivariate logistic regression analysis.

Ape-1 is a perfect paradigm of the functional complexity of a biological macromolecule (26). It has a crucial role in controlling cellular processes, including apoptosis, proliferation and differentiation. It also inhibits oxidative stress by inhibiting reactive oxygen species generation via the cytoplasmic small guanosine triphosphatase Rac1 (27). The key responsive transcription factor nuclear factor (NF)-κB has a crucial role in regulating the expression of various inflammatory cytokines, and inhibition of NF-κB effectively suppresses the inflammatory response (28,29). Furthermore, inhibition or overexpression of Ape-1 may reduce or activate the DNA binding activity of NF-κB, respectively (30). Therefore, overexpression of Ape-1 may aggravate the inflammatory response after SBRT, which may induce the occurrence of RP. APE1 maintains cellular homeostasis (redox reactions) via the activation of transcription factors that regulate various physiological processes and that crosstalk with redox

balancing agents (for example, thioredoxin, catalase and superoxide dismutase) by controlling levels of reactive oxygen and nitrogen species (31). APE1 expression and/or sub-cellular localization are altered in several metabolic and proliferative disorders, including in tumors and aging (32).

In ICAM-1-knockout mice, no inflammatory response was observed in the lung after exposure to radiation (33). Thoracic irradiation was reported to significantly increase the expression of ICAM-1, which was therefore indicated to be associated with lung injury from radiotherapy (34).

In addition, an animal study has indicated that IL-17A has an important role in processes of lung injury induced by radiotherapy. In the process of radiation-induced lung injury, IL-17A expression exhibited differences in different periods (35). IL-17A expression was appreciable at 1 week, peaked at 4 weeks and subsequently declined at 8 weeks following irradiation. In another study, treatment with IL-17A antibody alleviated RP and subsequent fibrosis and improved post-irradiation survival (36).

In conclusion, while the pathogenesis of RP remains to be fully elucidated at the molecular level, the present study reported an association between increased serum levels of Ape-1, ICAM-1 and IL-17A at baseline and the occurrence of RP. Regarding clinical radiotherapy of NSCLC, high serum levels of the cytokines Ape-1, ICAM-1 and IL-17A at baseline may indicative of an increased vulnerability to RP.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LG and GD made substantial contributions conceiving and designing the current study. WX, YLu, HG and YJ acquired the data. XC and YLi analyzed and interpreted the data. GD, WX, YLu, HG and YJ drafted the manuscript. LG, XC and YLi revised the manuscript critically for important intellectual content. The final version of the manuscript was read and approved by all authors, and each author believes that the manuscript represents honest work.

Ethics approval and consent to participate

The present study obtained approval from the institutional review board of Henan Province Anti-Cancer Hospital. All patients provided written informed consent.

Patient consent for publication

The patients provided written informed consent for the publication of associated data and accompanying images..

Competing interests

The authors declare that they have no competing interests.

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