PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A protocol for a randomized controlled trial
AUTHORS	Chen, Cheng; Zeng, Bangwei; Xue, Dan; Cao, Rongxiang; Liao, Siqin; Yang, Yong; Li, Zhihua; Kang, Mingqiang; Chen, Chun; Xu, Benhua

VERSION 1 – REVIEW

REVIEWER	Sathish kumar Ramalingam Lovelace Medical Center, Hospital medicine
REVIEW RETURNED	03-Mar-2022

GENERAL COMMENTS	Can the authors explain in detail how they diagnose the RILI(Radiation pneumonitis /Radiation fibrosis) in CT scan imaging? if there is cancer spread to the lungs, COPD, lung metastasis or other lung abnormalities present during the screening process, are they excluded from the trial? are the patients equally distributed in both groups(sex, age) is there any reported anaphylaxis to Pirfenidone reported? Why do the authors choose 1 year for follow up?

REVIEWER	Gilles Defraene KU Leuven University Hospitals Leuven, Oncology
REVIEW RETURNED	08-Mar-2022

GENERAL COMMENTS	The authors present the study protocol of a randomized phase II trial on the use of pirfenidone versus placebo as prevention of radiation-induced lung injury (RILI) after chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. The study setup, methodological detail and statistics are sound. I have following comments. -Ensuring the radiotherapy delivery quality will be crucial for further analyses involving the lung dosimetry and how it interferes with pirfenidone and the incidence of RILI. Is a QA protocol set up with guidelines on minimal requirements of dose calculation algorithm, uniform daily imaging and setup protocol usage, etc.? Could a 4DCT scan protocol be beneficial for an accurate treatment planning in this group of upper esophageal cancer patients? -It could be described in more detail how the primary endpoint will be scored. RILI grade 2 or more in the first year after treatment is mentioned, meaning both pneumonitis and fibrosis CTCAE 5.0 endpoints will be scored and in the case at least one of both is of grade 2 or more it will be considered a RILI grade 2 event? Will one observer score the patient or is a consensus scoring mandatory (this could increase the consistency by reducing the inevitable inter-

	observer variability in scoring partly subjective endpoints)? Minor comments: -p.11, l.47: '20% dropout rate': Was the expected rate of mortality in the first year taken into account in this number? -p.9, l.29: Did you make an estimate of the number of patients in both strata, i.e., patients not fit for surgery or unresectable cases, in order to avoid one of both strata being too small to draw conclusions? -p.10, l.45: Another interesting secondary endpoint may be the recovery from RILI grade 2 at one year, to study whether a high RILI grade during follow-up normalizes faster in the pirfenidone arm. -p.8, l.24: 'V40<30%' and 'V30<40%'?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for your valuable suggestions. We responded to your questions as best as we can. Please see our point-by-point responses to all your comments below.

Q1：Can the authors explain in detail how they diagnose the RILI (Radiation pneumonitis /Radiation fibrosis) in CT scan imaging?

Answer: The imaging characteristics of RILI on CT scan varies according to the stage and severity of lung injury. In the acute phase that usually appears 4-8 weeks after radiotherapy, CT images may display exudative changes as multiple small patchy or flock-shaped ground glass density shadows in the irradiation field, with fuzzy edge and unclear boundary of surrounding lung tissue. In the consolidatory phase that usually occurs 2-3 months after radiotherapy, CT images may display patchy high-density consolidations in the irradiation field, which is not distributed in the lung lobe and lung segment or partially accompanied by air bronchial signs. In the phase of fibrosis that usually occurs six months after radiotherapy, CT images can present density enhancement shadows of the grid, cord, and patchy shape in the irradiation field with clear boundaries, accompanied by thickened pleura, lung volume reduction, lung hilum reduction, and vascular texture thinning ipsilaterally, with the compensatory increase in contralateral lung volume.[1-5]

Q2：If there is cancer spread to the lungs, COPD, lung metastasis or other lung abnormalities present during the screening process, are they excluded from the trial?

Answer: As this trial focuses on cT3-4N+M0 thoracic esophageal cancer patients (AJCC 8 staging), cancer spread to the lungs and lung metastasis is excluded from the trial. COPD and interstitial lung disease are associated with increasing risk of RILI.[6-9.] Moreover, COPD and ILD patients with RILI might be more symptomatic due to their impaired lung function.[10 11] Therefore, patients with a history

of ILD or non-infectious pneumonia including COPD are excluded from the trial and details were added in the revision.

Q3：Are the patients equally distributed in both groups (sex, age)?

Answer: Specific to age, RP [12] and symptomatic RP[13] were increased in patients over 65-70 years (6% vs. 1%). Older patients may be more likely than younger ones to have a lower general functional status, comorbidities, and reduced lung function, which may explain the high RP risk.[14]However, the cut-off points for defining old patients could produce bias on the estimated effect. Actually, esophageal carcinoma (EC) is more common in men (69%) [15] and in the middle-aged and older individuals with approximately 69.8% of male patients being over 60 year in China[16] According to a retrospective study from the authors' hospital, a large percentage of the patients is supposed to be old males.[17] Therefore, considering the small sample size of the study and the most crucial factor, percentage of lung radiated volume[10 18] for RILI, which may be affected by unplanned conversion surgery, this trail only stratified based on the reasons whether they cannot tolerate surgery or the tumor cannot be removed surgically. The factors including sex and age will be distributed in both groups by randomization.

Q4：is there any reported anaphylaxis to Pirfenidone reported?

Answer: In clinical trials and real-word observational studies, skin reactions, including photosensitivity, are the most reported adverse effects.[19-27] However, little is known about categorization of “rash” and “photosensitivity” reactions, since dermatological assessment has not been thoroughly elaborated in the literatures. Due to its rarity, only 2 cases have been reported as far as we know: 1 case of drug-induced hypersensitivity syndrome (DIHS)[28] and 1 case of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).[29]

Q5：Why do the authors choose 1 year for follow up?

Answer: RILI can be divided into the acute radiation pneumonitis that occurs within 6 months of radiation exposure (most often within 12 weeks) and fibrotic phase that occurs after six months,[5 30-32]while the two stages cannot be clearly separated temporally. Patients may experience with dyspnea, coughing, hypoxemia, and respiratory failure during acute phase while with progressive respiratory insufficiency during the chronic phase.[33] RILI during and after radiation may not only delay or even interrupt radiotherapy, but also result in loss of the quality of life. With both anti-inflammatory and anti-fibrotic properties, pirfenidone is a promising drug in the prevention of radiation pneumonitis and radiation fibrosis.[15 16 18 34]Therefore, we chose 1 year to observe the rate of RP and RF.

Reviewer 2

Thank you for your valuable suggestions. We responded to all your questions as best as we can. Please see our point-by-point responses below.

Q1: Ensuring the radiotherapy delivery quality will be crucial for further analyses involving the lung dosimetry and how it interferes with pirfenidone and the incidence of RILI. Is a QA protocol set up with guidelines on minimal requirements of dose calculation algorithm, uniform daily imaging and setup protocol usage, etc.?

Answer: Thank you for bringing this point up. We added a supplementary explanation to this part of the content.

(Added statement) All patients will be positioned supine on the treatment couch and fixed by a custom-fitted thermoplastic sheet and the setup imaging will be acquired every day before treatment to correct the treatment position by OBI image system. IMRT is recommended when the treatment plans were designed. Because the dose calculation for areas with artifacts generates heterogeneity, leading to high dose deviation. To ensure the quality of radiotherapy delivered, the Acuros XB (version 15.5) dose algorithm which was reported to be as accurate as or close to the Monte Carlo simulation (MC) method will be employed in this present study. The treatment plan for all patients will be verified using phantom named Delta4, and the gamma passing rate at the criteria of 3%/3 mm will be ensured greater than 98%.

Q2: Could a 4DCT scan protocol be beneficial for an accurate treatment planning in this group of upper esophageal cancer patients?

Answer: 4D-PET/CT scan for distal esophageal and EGJ lesions was evaluated in a trial[35] involving 15 patients and adopted by the NCCN Clinical Practice Guidelines.[36] The patients enrolled in this study are thoracic ESCC and the CTVn would cover the whole affected and high-risk lymph node station instead of geometric expansion of nodal GTV. This delineation of CTV included at least a 5-8 mm margin around the GTVn while out-field mediastinal recurrence was relatively uncommon in our center. Therefore, the 4DCT scan has not been planned to use in the present trial.

Q3: It could be described in more detail how the primary endpoint will be scored?

Answer: We now added diagnostic criteria and grading of RILI to improve the relevant content.

(Added statement) RLIL is a diagnosis established by clinical suspicion or radiological findings after excluding other lung pathologies such as pre-existing pathologies and pulmonary infections. It often appears with no specific symptom, vital signs, laboratory profiling or imaging tests. Familiar history of

radiation and recognition of RILI are of utmost importance in the context of regular follow-up. Diagnosis and grading will be confirmed by review by multidisciplinary senior physicians, including a radiation oncologist, a pulmonologist, and a radiologist. History, physical, chest CT, and previous radiotherapy will be evaluated at every follow-up during personal visits when available. RILI will be scored based on the CTCAE version 5.0 classifying symptoms and image findings will be used to classify into five grades.[37] As far as the symptom, dyspnea and dry cough are the most common manifestation in acute lung injury.[33] Occasional fever is usually mild, but high fever is sometimes reflective of co-infectious pneumonitis. The chronic RF is a slowly progressing respiratory disease that can manifest as respiratory insufficiency. In terms of physical symptoms, the physical examination findings may be normal or include pleural rub, moist rales, and signs of consolidation. Chest imaging, particular lung CT at baseline and follow-up are critical in the diagnosis and grading. In acute phase, which usually appears 4-8 weeks after radiotherapy, CT images may display exudative changes such as multiple small patchy or flock-shaped ground glass density shadows in the irradiation field, with fuzzy edge and unclear boundary with surrounding lung tissue. In phase of consolidation, which usually occurs 2-3 months after radiotherapy, CT images may display patchy high-density consolidation in the irradiation field, not distributed according to the lung lobe and lung segment, accompanied by partial air bronchial signs. In the stage of fibrosis, which usually occurs six months after radiotherapy, CT images may show density enhancement shadows of grid, cord, and patchy shape in the irradiation field with clear boundaries, accompanied by thickened pleura, lung volume reduction, lung hilum reduction, ipsilateral vascular texture thinning, and compensatory increase in contralateral lung volume.[1-5]

Q4: RILI grade 2 or more in the first year after treatment is mentioned, meaning both pneumonitis and fibrosis CTCAE 5.0 endpoints will be scored and in the case at least one of both is of grade 2 or more it will be considered a RILI grade 2 event?

Answer: Early acute radiation pneumonia and late chronic radiation pulmonary fibrosis are main manifestations of RILI.[5 30-32] Considering the anti-inflammatory and anti-fibrotic properties, pirfenidone is a promising drug for the prevention of symptomatic RP and RF.[15 16 18 34] The grade will be scored as the maximal level in the case who experiences RP and RF. That is to say, if one case is presented with grade 3 RP and grade 2 RF, it will be recorded as grade 3 for the primary endpoint. Additionally, the time to the occurrence and grade of RP/RF will be reported separately.

Q5: Will one observer score the patient or is a consensus scoring mandatory (this could increase the consistency by reducing the inevitable inter-observer variability in scoring partly subjective endpoints)?

Answer: As you said, observer variability clinically exists in the diagnosis and grading manually. Therefore, the classification will be confirmed by a board-certified radiation oncologist referencing to a joint expert consultation. The multidisciplinary team has a senior radiation oncologist, a pulmonologist, and a radiologist of experience in RILI.

Q6: （p.11, l.47）‘20% dropout rate’: Was the expected rate of mortality in the first year taken into account in this number?

Answer: Due to the anatomical features of esophagus including the lack of serosa and the presence of numerous organs surrounding the esophagus, most of patients in this trial are with cT4N+M0 thoracic esophageal cancer. Even with definitive chemoradiotherapy (CRT) or chemoradiotherapy plus conversional surgery that are currently in use, satisfactory long-term prognosis has not yet been achieved, meaning less than 1 year of survival.[34 38-41] Therefore, we have designed a dropout rate of 20% that includes expected mortality in the first year.

Q7: （p.9, l.29）Did you make an estimate of the number of patients in both strata, i.e., patients not fit for surgery or unresectable cases, in order to avoid one of both strata being too small to draw conclusions?

Answer: The standard treatment for cT4N+M0 thoracic esophageal cancer has not yet been established. Surgery remains to be recommended after down-staging patients following CRT.[42] The major difference between neoadjuvant therapy and definitive CRT is the radiation dose, which is the most crucial factor that influences the development of RILI that is related to the percentage of lung radiated volume. Generally, a radiation dose less than 50 Gy is applied as neoadjuvant treatment. More than 50 Gy is regarded as the definitive dose. For this reason, stratified random cluster sampling is applied for balancing the two groups.

Q8: （p.10, l.45）Another interesting secondary endpoint may be the recovery from RILI grade 2 at one year, to study whether a high RILI grade during follow-up normalizes faster in the pirfenidone arm.

Answer: Quantifiable metrics are presently lacking for diagnosis and grading of RILI. Additionally, no controlled studies have been conducted to evaluate the role of various therapies in treating RILI. Although most experts recommend a long course of systemic glucocorticoids to treat symptomatic RP, the course of starting dose and tapering is not quite clear.[43-45] Therefore, we will observe the recovery time and evaluate the protective effect of pirfenidone by a multidisciplinary team with a considerable experience.

Q8: （p. 8, l.24）‘V40<30%’ and ‘V30<40%?

Answer: The tolerance dose-limit of heart is recommended in the 2018 edition of the Guidelines for Diagnosis and Treatment of esophageal carcinoma[46]authorized by the National Health Commission of the People's Republic of China.

VERSION 2 – REVIEW

REVIEWER	Gilles Defraene KU Leuven University Hospitals Leuven, Oncology
REVIEW RETURNED	11-Jul-2022

GENERAL COMMENTS	The authors have answered all questions and improved the manuscript with sections on physics quality assurance and primary endpoint scoring.