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Evaluation of the preventive effect of dexpanthenol in radiation injury by lung perfusion scintigraphy: a preclinical experimental model of radiation injury

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Aim **The aim of this study was to show the preventative effects of dexpanthenol in radiation injuries caused by radiotherapy (RT) through the use of lung perfusion scintigraphy in the pre-RT and post-RT periods.**

Materials and methods **Six male New Zealand rabbits (5–6 months of age and ~ 2.5–3 kg in weight) were the used in this study. The animals were subjected to ^{99m}Tc-macroaggregated albumin lung perfusion scintigraphy in the pre-RT and post-RT (i.e. 2 weeks after treatment) periods. The scintigraphies were performed with the same dose by the same staff and the methodology used the same acquisition parameters. The rabbits were divided into two groups: group I (administered RT only) and group II (also administered intramuscular 500 mg dexpanthenol injections for 14 consecutive days after RT). Quantification was performed to compare the groups and the quantification variables were compared using a paired samples *t*-test, with *P* value less than 0.05 considered to be statistically significant. Histopathological analysis was also carried out.**

Results **The post-RT scintigraphies indicated a decrease in the counts in both lungs, suggesting early post-RT injury. The difference between the counts obtained from both lungs in groups I and II was significantly different and favoured group II. Histopathological results confirmed the scintigraphy results.**

Conclusion **It is possible to estimate post-RT changes in the early period (in contrast to previous data) by lung perfusion scintigraphy. Dexpanthenol may also reduce the effects of RT to a degree. Although this is the first study to report the preventive effects of dexpanthenol on RT injuries, further studies are warranted in this area.** ***Nucl Med Commun*** **00:000–000**

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Introduction

Radiation pneumonitis as a result of radiation injury is a highly mortal and dose-limiting complication of radiation therapy, occurring within 6 months after therapy. The disease is characterized by cough, shortness of breath, fever and reduced lung functions [1]. Among patients receiving radiotherapy (RT), approximately one-third experience radiation pneumonitis [2]. The predisposing factors for the development of radiation pneumonitis are various drugs (such as taxanes) and some diseases (e.g. allergic rhinitis, asthma) [3,4]. Several diagnostic methods are used to investigate radiation pneumonitis, including chest radiography, lung perfusion, ventilation scintigraphy and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET. In addition, ^{67}Ga scintigraphy has been reported to indicate the presence of radiation pneumonitis early in the course of the disease [5], whereas a previous study has suggested that ^{111}In pentetreotide imaging may better delineate the disease [6]. Among these methods, ^{18}F-FDG PET serves as a positive marker (identifying an accumulation of increased activity related to radiation injury) and lung scintigraphy serves as a negative marker (identifying hypoperfusion).

The diagnostic effects of these imaging methods are normally evaluated later on in the course of the disease because the clinical symptoms are generally present in the late phase. However, there has been no study on the presentation of early radiation injury in the lungs as shown by diagnostic tests. In addition, there have been no previous investigations of possible preventative drugs for radiation injury. Dexpanthenol has been shown to be a preventative drug in pulmonary fibrosis in a recent experimental model [7]. Therefore, this study had two aims; first, to investigate the role of lung perfusion scintigraphy in early radiation injury to the lungs following RT and second, to identify the preventative effects of dexpanthenol for radiation injuries using lung perfusion scintigraphy.

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Materials and methods

Rabbits

Six male New Zealand White rabbits, 5–6 months of age and ~2.5–3 kg in weight, were used in this study. The rabbits were divided into two groups: group I ($n=3$, control) and group II ($n=3$, dexpanthenol). Dexpanthenol administration (500 mg/2 ml) was performed in all three rabbits of group II by an intramuscular injection on the day of RT and for 14 consecutive days before the second scintigraphy took place. All animal protocols were approved by the Institutional Animal Care and Use Ethics Committee. The study was carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Helsinki Declaration, revised in 2008.

Radiation therapy

RT was performed using the same dose (6 Gy) on all rabbits in both groups with the same intensity modulated radiation therapy device and methodology (Fig. 1). Before treatment, a dose calculation and simulation was performed.

Sedation

The animals were sedated by an intramuscular administration of 35 mg/kg ketamine and 20 mg xylazine before all imaging and therapeutic procedures were initiated.

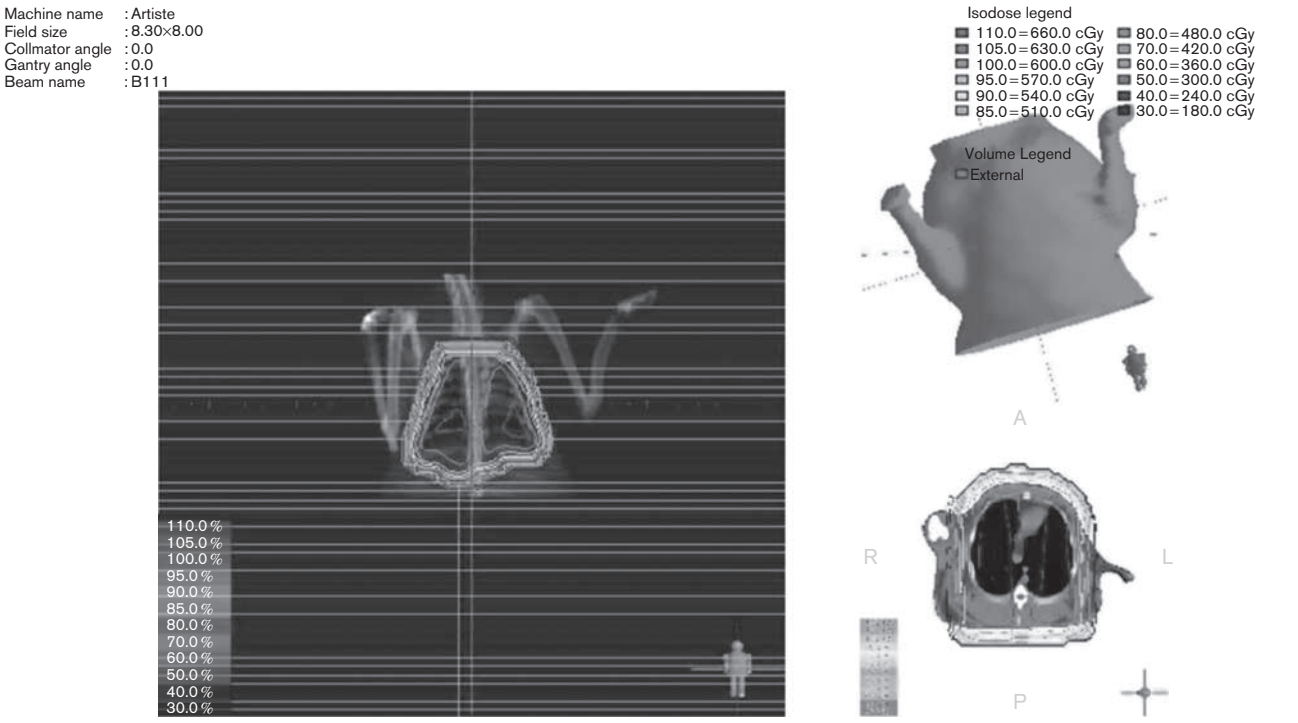
Scintigraphy

Lung perfusion scintigraphy was performed by an intravenous administration of 1 mCi of ^{99m}Tc-macroaggregated albumin through an intravenous line placed in the ear vein, and the imaging of the lung region in anteroposterior projection was performed in the planar mode by a single-photon emission computed tomography (SPECT) gamma camera (Infinia II; GE, Tirat Hacarmel, Israel) under sedation. The images were compared by visual evaluation and quantification by an experienced nuclear medicine physician. The same pixel size rectangular region of interest was generated covering the right and left lobes of the lungs separately and was then compared. In addition, comparison of the upper middle and lower lobes was performed using the quantification program of our Xeleris (GE) workstation.

Statistical analysis

Comparison of the counts (average counts in the lung region of interest) of the lungs of the rabbits in each group was performed using a paired samples *t*-test. A value of P less than 0.05 was considered statistically significant.

Fig. 1



Images of the dose calculation according to simulation (the methodology includes the SAD-100 technique; the distance between the source and target was 100 cm; conformal dose technique).

Pathology

The rabbits were decapitated under high sedation, and the lung tissues of the rabbits were removed and analysed with haematoxylin–eosin staining.

Results

Visual interpretation of the images obtained in the post-treatment scintigraphies showed a significant decrease in the lungs of the rabbits, indicating severe early radiation injury. However, uptake in the lungs of the rabbits in group II was significantly better than that in group I (Fig. 2 and Graph 1).

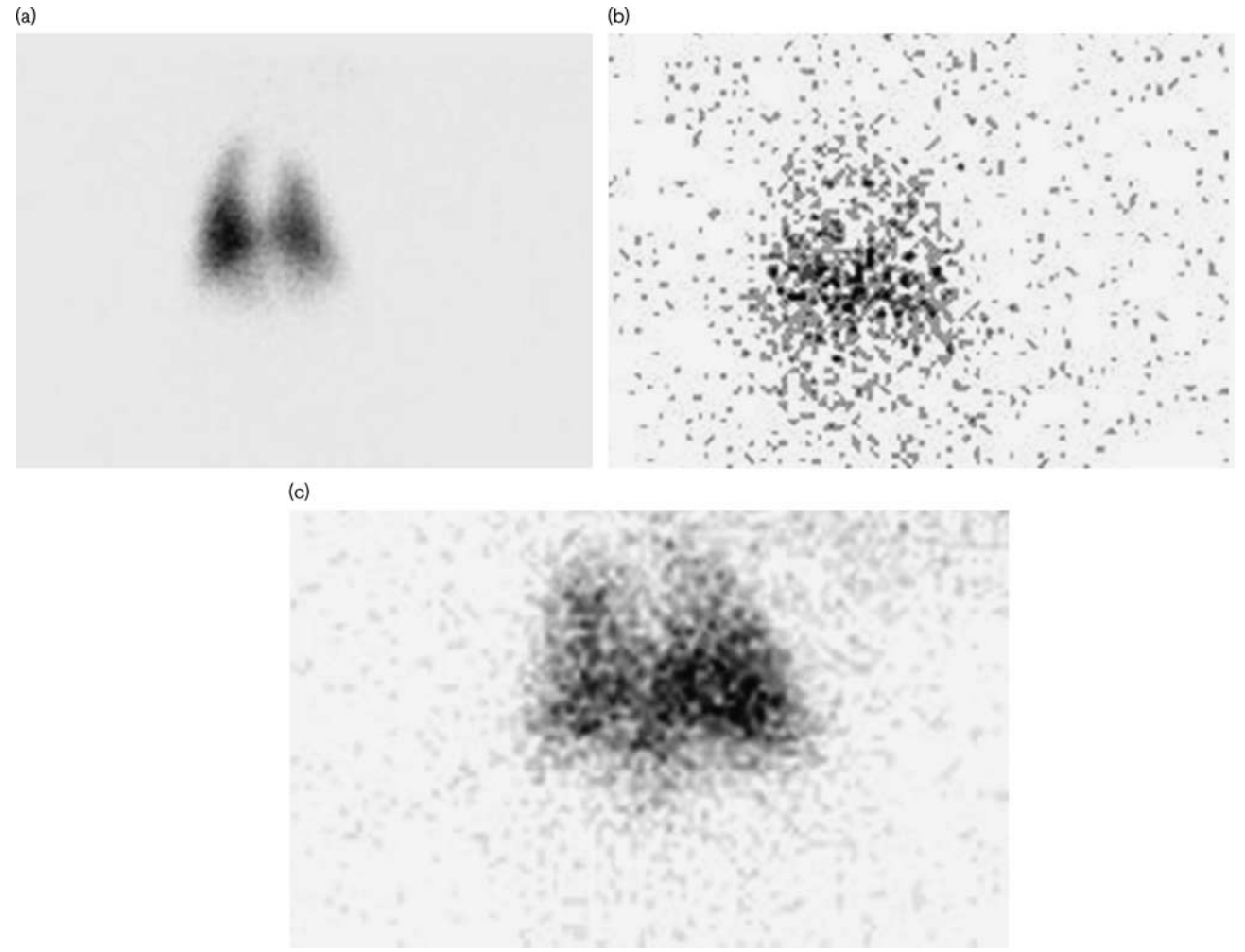
In the histopathological evaluation of the lungs of both groups following RT, pathological changes related to acute radiation injury were observed in the tissues (Fig. 3). In the lungs of group II, the severity of damage related to acute radiation injury was found to be lower compared with group I (Fig. 4).

Discussion

Although the groups were small, our results indicate that lung perfusion scintigraphy might be useful against early radiation injury in the lungs. In addition, dexpanthenol might also exert a protective effect on the lungs in relation to radiation injuries from RT.

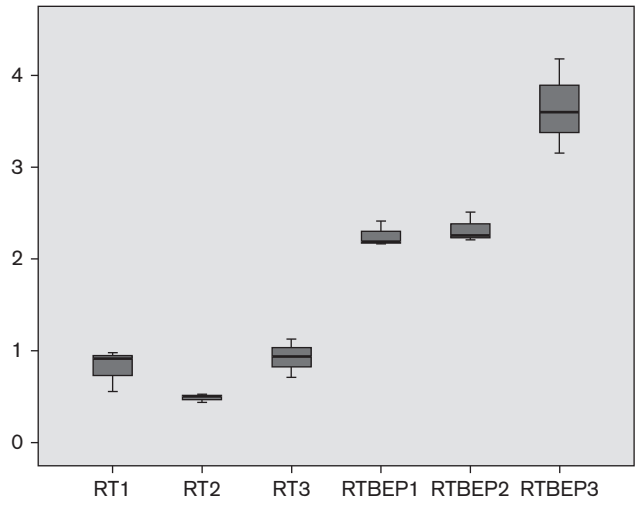
Pulmonary radiation injury is the most common side effect of radiation and is divided into early and late presentation categories. Early presentation involves complaints such as cough and dyspnoea, which can be responsive to steroid treatment; however, late presentation, which is termed fibrotic injury, manifests after 6 months and may lead to mortality [8]. Functional imaging might provide a better and earlier evaluation of

Fig. 2



Anteroposterior ^{99m}Tc-macroaggregated albumin lung perfusion scintigraphy images. (a) Perfusion scintigraphy image of one of the rabbits before radiotherapy (normal). (b) Perfusion scintigraphy image of a rabbit in group I 14 days after radiotherapy. (c) Perfusion scintigraphy image of a rabbit in group II 14 days after radiotherapy.

Graph 1



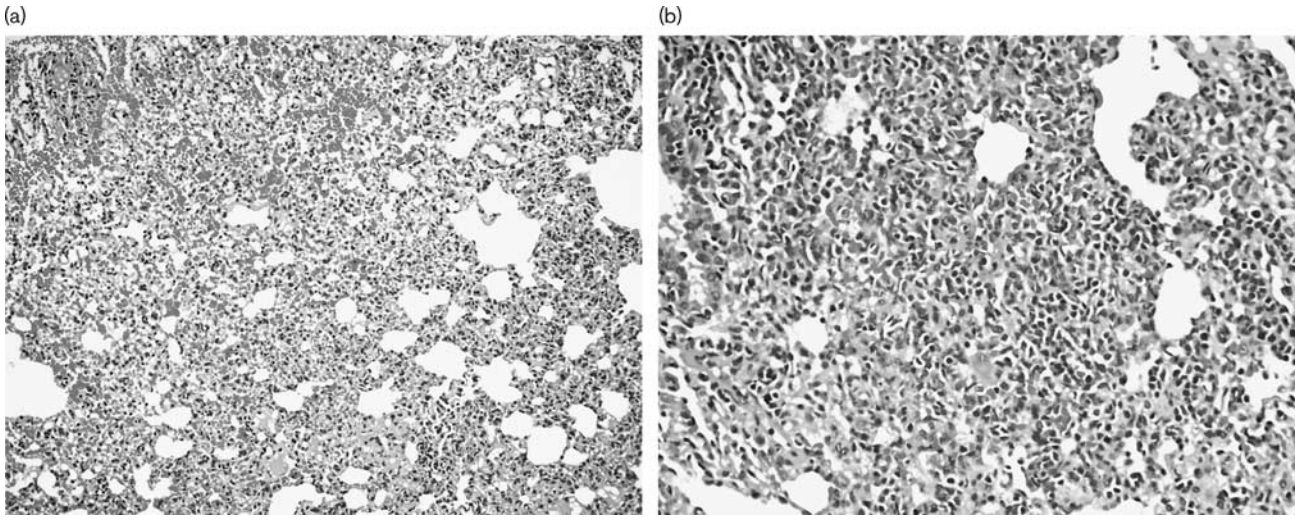
Graphic demonstration of the average counts (mean ± SD) in all rabbits in all groups.

radiation injury in the lungs than morphological imaging methods. In previous studies with rats, it has been shown that hemithoracic irradiation of the lungs leads to perfusion loss within 4–6 weeks of RT [9,10]. Our study indicates that the perfusion changes related to radiation injury begin at an earlier phase after RT, although symptoms also occur in the late phase in humans.

Other imaging modalities have also been used to investigate earlier patterns in the early phase of radiation injury. A previous study with gadolinium-enhanced MRI showed that enhancement patterns may differentiate early radiation pneumonitis and radiation fibrosis according to the pathology results [11]. In a previous review, it was suggested that the earliest indicator of radiation injury is disproportionate perfusion changes [12], and our results confirm this suggestion. In addition, in another previous study, computed tomography (CT) perfusion imaging was shown to be a better tool than CT in the evaluation of early radiation changes [13]. A recent review noted that, with respect to normal tissue injury because of RT, CT imaging shows injury from doses more than 40 Gy; although perfusion scintigraphy was less dose dependent in terms of injury [14] in our study, we used a very minimal dose (6 Gy). To the best of our knowledge, these are the only results in the literature that relate to early radiation injury. Our study includes the earliest evaluation of radiation injury in the lungs and indicates severe impairment of functional tissue in a rabbit model.

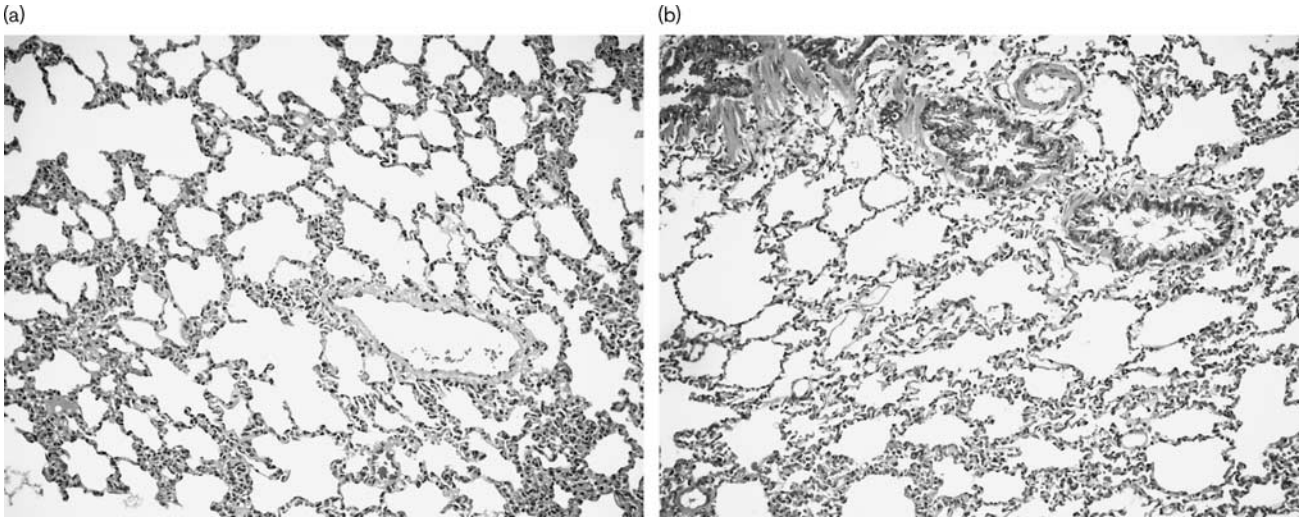
Functional assessment by means of radionuclide imaging aids the diagnosis of radiation injury and helps to predict possible radiation pneumonitis, and there have been suggestions that SPECT-guided intensity modulated radiation therapy applications require dose–volume histogram analysis to decrease the risk of radiation pneumonitis [15–17]. Recent studies have shown that ^{18}F-FDG PET additionally predicts which patients will have a tendency for radiation pneumonitis before RT [18]. We already know that ^{18}F-FDG PET imaging shows early changes related to radiation injury: it is not recommended that ^{18}F-FDG PET imaging be performed early after RT in routine practice. The rationale for this time delay between imaging and therapy is that considerably increased activity, as a consequence of RT, may

Fig. 3



Histopathological findings in group I. (a) Intra-alveolar haemorrhage, alveolar collapse. (b) Interstitial oedema and infiltration of infectious cells. H&E, × 200.

Fig. 4



Histopathological findings in group II. (a) Decrease in intra-alveolar haemorrhage, alveolar collapse. (b) Decrease in interstitial oedema and infiltration of infectious cells compared with group I. H&E, ×200.

obscure other pathologies. Therefore, ^{18}F-FDG PET imaging might reflect early changes related to radiation injury.

A previous study has indicated that recovery following RT is an ongoing process for 4 years after therapy, and it showed that pulmonary functional measurements using lung perfusion and ventilation scintigraphy at month 18 may predict the functional outcome [19]. In addition, a review noted that SPECT imaging may be more efficient than planar imaging in estimating overall pulmonary function [20]. According to a retrospective analysis, upper lung lobes have a higher metabolic radiation response compared with lower lobes when taking into account PET results [18]. This study also suggested 5 Gy radiation as a limiting dose – that is, below this level there may not be enough injury to allow observation. We therefore performed RT with the lowest dose possible (6 Gy) [18]. However, we did not observe differential impairment of lung lobes because of radiation. In addition, the quantitative analysis of the upper, middle and lower lobes showed no significant differences compared with the pretherapy images.

A previous study has shown no significant correlation between the extent of the perfusion defects and radiation pneumonitis [21]. However, many other studies have indicated that perfusion defects correlate with the results of perfusion function tests and the clinical symptoms of patients [22,23]. De Jaeger *et al.* [24] compared pulmonary function tests, SPECT and CT in the evaluation of pulmonary function after RT because of non-small-cell lung cancer and concluded that the mean perfusion-weighted lung dose and predicted perfusion reduction are the best parameters. According to our results, lung perfusion scintigraphy might be among the earliest markers for predicting the functional loss of lung tissue because of radiation injury. This information could be applied to human studies to predict the patients who may go on to develop radiation pneumonitis.

Dexpanthenol has been reported to be an effective antioxidant medication by several previous studies relating to an ischaemia–reperfusion-induced renal injury model, a testicular ischaemia–reperfusion model and reduced oxidative stress because of γ radiation and apoptosis [25–27]. Finally, Ermis *et al.* [7] investigated the effects of dexpanthenol on bleomycin-induced lung injuries. We instead determined the effects of this antioxidant medication on the prevention of radiation injury. As the basic mechanism of RT involves destruction related to oxygen radicals and oxidation because of radiation, this antioxidant molecule might prevent injury. However, it remains to be investigated whether or not this prevention additionally decreases the therapeutic effect of radiation. Dexpanthenol could be used in other types of radiation therapies, but radiation pneumonitis remains the most problematic complication related to radiation therapy.

There are several limitations to this study. First, the groups were small in number and second, the study could have been more informative if it had included a positive marker such as ^{18}F-FDG. However, PET imaging in small objects requires special equipment (e.g. a micro-PET device).

Conclusion

Lung perfusion scintigraphy indicates the earliest signs of radiation injury related to RT and could be performed to

predict the patients who might experience radiation pneumonitis. According to our results, dexpanthenol as an antioxidant agent might prevent radiation injury, but the effects of this vitamin need to be evaluated in much larger prospective studies.

Acknowledgements

Conflicts of interest

AQ5 None declared.

References

1 McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys* 1995; **31**:1187–1203.

2 Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose–volume histogram parameters in lung cancer – a systematic review. *Radiother Oncol* 2004; **71**:127–138.

3 McCurdy M, McAleer MF, Wei W, Ezhil M, Johnson V, Khan M*, et al*. Induction and concurrent taxanes enhance both the pulmonary metabolic radiation response and the radiation pneumonitis response in patients with esophagus cancer. *Int J Radiat Oncol Biol Phys* 2010; **76**:816–823.

4 Frankovich J, Donaldson SS, Lee Y, Wong RM, Amylon M, Verneris MR. High-dose therapy and autologous hematopoietic cell transplantation in children with primary refractory and relapsed Hodgkin's disease: atopy predicts idiopathic diffuse lung injury syndromes. *Biol Blood Marrow Transplant* 2001; **7**:49–57.

5 Valdés Olmos RA, van Zandwijk N, Boersma LJ, Hoefnagel CA, Baas P, Baars JB*, et al*. Radiation pneumonitis imaged with indium-111-pentetreotide. *J Nucl Med* 1996; **37**:584–588.

6 Kataoka M, Kawamura M, Itoh H, Hamamoto K. Ga-67 citrate scintigraphy for the early detection of radiation pneumonitis. *Clin Nucl Med* 1992; **17**:27–31.

7 Ermis H, Parlakpinar H, Gulbas G, Vardi N, Polat A, Cetin A*, et al*. Protective effect of dexpanthenol on bleomycin-induced pulmonary fibrosis in rats. *Naunyn Schmiedebergs Arch Pharmacol* 2013; **386**:1103–1110.

8 Ogasawara N, Suga K, Karino Y, Matsunaga N. Perfusion characteristics of radiation-injured lung on Gd-DTPA-enhanced dynamic magnetic resonance imaging. *Invest Radiol* 2002; **37**:448–457.

9 Robbins ME, Brunso-Bechtold JK, Peiffer AM, Tsien CI, Bailey JE, Marks LB. Imaging radiation-induced normal tissue injury. *Radiat Res* 2012; **177**:449–466.

10 Ward WF. Radiation-induced pulmonary arterial perfusion defects: modification by D-penecillamine. *Radiology* 1981; **139**:201–204.

11 Fleckenstein K, Zgonjanin L, Chen L, Rabbani Z, Jackson IL, Thrasher B*, et al*. Temporal onset of hypoxia and oxidative stress after pulmonary irradiation. *Int J Radiat Oncol Biol Phys* 2007; **68**:196–204.

12 Lull RJ, Anderson JH, Telepak RJ, Brown JM, Utz JA. Radionuclide imaging in the assessment of lung injury. *Semin Nucl Med* 1980; **10**:302–310.

13 Boersma LJ, Damen EM, de Boer RW, Muller SH, Valdés Olmos RA, van Zandwijk N, Lebesque JV. Estimation of overall pulmonary function after irradiation using dose–effect relations for local functional injury. *Radiother Oncol* 1995; **36**:15–23.

14 Evans ES, Hahn CA, Kocak Z, Zhou SM, Marks LB. The role of functional imaging in the diagnosis and management of late normal tissue injury. *Semin Radiat Oncol* 2007; **17**:72–80.

15 McGuire SM, Zhou S, Marks LB, Dewhirst M, Yin FF, Das SK. A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung. *Int J Radiat Oncol Biol Phys* 2006; **66**:1543–1552.

16 Zhao LJ, Zhang WJ, Wang LH, Zheng R, Feng QF, Wang YJ*, et al*. SPECT lung perfusion scans in predicting radiation pneumonitis in lung cancer patients. *Zhonghua Zhong Liu Za Zhi* 2006; **28**:127–129.

17 Hoover DA, Reid RH, Wong E, Stitt L, Sabondjian E, Rodrigues GB*, et al*. SPECT-based functional lung imaging for the prediction of radiation pneumonitis: a clinical and dosimetric correlation. *J Med Imaging Radiat Oncol* 2014; **58**:214–222.

18 Castillo R, Pham N, Ansari S, Meshkov D, Castillo S, Li M*, et al*. Pre-radiotherapy FDG PET predicts radiation pneumonitis in lung cancer. *Radiat Oncol* 2014; **9**:74.

19 Theuws JC, Seppenwoolde Y, Kwa SL, Boersma LJ, Damen EM, Baas P*, et al*. Changes in local pulmonary injury up to 48 months after irradiation for lymphoma and breast cancer. *Int J Radiat Oncol Biol Phys* 2000; **47**:1201–1208.

20 Goethals I, Dierckx R, De Meerleer G, De Sutter J, De Winter O, De Neve W, Van de Wiele C. The role of nuclear medicine in the prediction and detection of radiation-associated normal pulmonary and cardiac damage. *J Nucl Med* 2003; **44**:1531–1539.

21 De Jaeger K, Seppenwoolde Y, Boersma LJ, Muller SH, Baas P, Belderbos JS, Lebesque JV. Pulmonary function following high-dose radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003; **55**:1331–1340.

22 Fan M, Marks LB, Lind P, Hollis D, Woel RT, Bentel GG*, et al*. Relating radiation-induced regional lung injury to changes in pulmonary function tests. *Int J Radiat Oncol Biol Phys* 2001; **51**:311–317.

23 Gopal R, Tucker SL, Komaki R, Liao Z, Forster KM, Stevens C*, et al*. The relation between local dose and loss of function for irradiated lung. *Int J Radiat Oncol Biol Phys* 2003; **56**:106–113.

24 Hu XY, Fang XM, Chen HW, Yao XJ, Qian PY, Zhou JY*, et al*. Early detection of acute radiation-induced lung injury with multi-section CT perfusion imaging: an initial experience. *Clin Radiol* 2014; **69**:853–860.

25 Altintas R, Parlakpinar H, Beytur A, Vardi N, Polat A, Sagir M, Odabas GP. Protective effect of dexpanthenol on ischemia–reperfusion-induced renal injury in rats. *Kidney Blood Press Res* 2012; **36**:220–230.

26 Etensel B, Ozkisacik S, Ozkara E, Karul A, Oztan O, Yazici M, Gürsoy H. Dexpanthenol attenuates lipid peroxidation and testicular damage at experimental ischemia and reperfusion injury. *Pediatr Surg Int* 2007; **23**:177–181.

27 Slyshenkov VS, Omelyanchik SN, Moiseenok AG, Trebukhina RV, Wojtczak L. Pantothenol protects rats against some deleterious effects of gamma radiation. *Free Radic Biol Med* 1998; **24**:894–899.

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