Int J Clin Exp Med 2016;9(2):3247-3264
www.ijcem.com /ISSN:1940-5901/IJCEM0008644

Original Article

Risk factors for radiation pneumonitis after radiotherapy in lung cancer patients: a systematic review and meta-analysis

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Received March 31, 2015; Accepted December 8, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Objective: To study the risk factors for radiation pneumonitis after radiotherapy in lung cancer patients in order to find prognostic parameters and provide reference standard for the best treatment plans. Methods: The database of Pubmed, Embase, Cochrane Library and CNKI were searched from the date of their establishment to Feb. 2015, and other sources as supplied were also retrieved. Meta-analysis on literatures predicting radiation pneumonitis after radiotherapy was conducted by using RevMan 5.2 software. Results: A total of 75 articles were primarily included in systematic review. The exposure factors included demographics (sex, age, chronic lung diseases, pulmonary function, diabetes, tumor site) and treatment factors (operation before radiotherapy, combined radio chemotherapy, using radiotherapy sensitization agent-Amifostine). Meta-analysis results showed that the OR and 95% CI of each were: 0.97 [0.82, 1.15], 0.90 [0.63, 1.28], 2.18 [1.59, 3.00], 0.27 [0.11, 0.65], 2.46 [1.33, 4.58], 0.71 [0.57, 0.90], 0.92 [0.67, 1.25], 1.41 [1.17, 1.71] and 2.38 [1.79, 3.16]. Conclusion: The risk factors for radiation pneumonitis are chronic lung diseases, pulmonary function, diabetes, tumor located in left lower lung, combined radio chemotherapy and using Amifostine. The study results indicate that upper lung cancer patients with strong pulmonary functions and without complications such as diabetes or chronic pulmonary disease have less chance getting radiation pneumonitis after radiotherapy undertaken the simple radiotherapy added with Amifostine.

Keywords: Lung cancer, radiation pneumonitis, radiation lung injury, risk factors, meta-analysis

Introduction

Lung cancer is a kind of malignant tumor with the highest mortality rate in the world and about two-thirds lung cancer patients need to take radiotherapy. With rapidly development of radiotherapy technology, its side-effects, radiation lung injuries are becoming an increasingly severity problems in the world. According to the statistics from abroad, the occurrence rate of acute radiation lung injuries is about 5-36 percent [1, 2]. Meanwhile, radiation lung injuries often lead to respiratory failure, which is the major cause of death for radiation lung injuries. Radiation lung injuries include radiation pneumonitis (RP) in early-stage and radiation pulmonary fibrosis (RPF) in the late-stage. Unfortunately, there has been no satisfactory and effective measure in clinical practice up till now and the patients' treatment effects and quality of life are threatened after the radiation lung injuries occur. So it's essential to make sure the impact factors to predict the radiation lung injuries after radiotherapy. The data were searched from the date of their establishment to Feb. 2013, aimed to find out the risk factors for radiation pneumonitis after radiotherapy in lung cancer patients. This will provide evidence to guide clinical treatments better and reduce the occurrence of radiation pneumonitis.

Methods

Literature search

We undertook computerized literature searches of MEDLINE, PubMed, Cochrane Library, and EMBASE databases, from their inception to Feb. 2013. Search terms were "lung cancer", "radiation pneumonitis" and "radiation lung injury". These terms were used in different combinations with each other. In addition, we reviewed the reference lists of the original articles and reviews on the topic to identify other possible eligible trials.

Study selection

The inclusion criteria for this meta-analysis were as follows: 1) The study objects were patients who were diagnosed with primary lung cancer by cytology or pathology tests and thereby took the lung radiation therapy for the first time; 2) The numbers, percentage or mean ± SD of the possible impact factors to RP were recorded in full texts; 3) When multiple publications from a single institution/author appeared to include duplication of patients, only the study with the largest patient group was included.

The exclusion criteria were as follows: 1) The meeting abstracts could not get its full text; 2) Patients had radiotherapy on other parts of the breast at the same time or had taken thoracic radiation therapy within one year; 3) The outcome of the study was radiation pulmonary fibrosis (RPF); 4) literatures with low grade according to Newcastle score standard; 5) literatures that were duplicate publication.

Data extraction

All the work of literature search was independently reviewed by two authors to identify relevant trials that met the inclusion criteria and checked by an independent reviewer. Disparities were resolved by discussion.

Study quality was assessed using a 3-item questionnaire designed to collect data on random assignment, blinding, and withdrawals/dropouts. All questions were bipolar (yes, 1; or no response, 0). The minimum number of points possible was 0 and the maximum was 5, with a higher number reflecting a greater study quality. Data on trial size, patient characteristics were extracted, using Newcastle score standard to evaluate the quality of outcomes [4]. Study quality was independently assessed by 2 reviewers.

Data analysis

Statistical analyses were performed using Review Manager Software (RevMan 5.2; Cochrane Collaboration. Oxford, United Kingdom). Continuous descriptive data were reported as the mean Continuo deviation (Mean ± SD) and dichotomous data were recorded as the case number (n).

The Mantel-Haenszel Q-statistic was used to assess heterogeneity among the studies and the I^2 statistic was computed to examine the proportion of total variation in the study estimate due to heterogeneity. We considered $P > 0.10$ or $P \leq 0.10$, $I^2 \leq 50\%$ to indicate no significant heterogeneity between the trials and select fixed effect models to analysis. Besides, we considered $P \leq 0.10$, $I^2 > 50\%$ to indicate significant heterogeneity and use random effect models. The integration results regarded $P \leq 0.05$ as the standard of its statistical significance.

Extensive effort was made to remove all duplicated data and to include all studies published to date. Publication bias in outcomes was assessed and treated using standard methodology. Funnel plots were used to visually inspect the relationship between sample size and treatment effects for each of the impact factors. Means, standard deviation, and corresponding 95% (CIs) were computed for continuous demographic factors. Event rates and corresponding standard errors and confidence intervals were computed for the other demographic factors describing proportions of the sample with varying comorbidities.

Results

Search results

A total of 2293 relevant articles were identified in a combined search of MEDLINE, PubMed, Cochrane Library and EMBASE databases, from their inception to Feb 2015, and by a manual approach (search of studies cited in previous reviews and of reference lists from the identified articles). Then 1715 articles were excluded because they were not relevant to the purpose of this meta-analysis through screening Title/Abstract. 150 articles were excluded because there were no full articles or they were repeated articles. Besides, 353 articles were excluded through screening full text for duplication, no relevant results and other reasons. In the end, 75 articles [5-79] were primarily included in systematic review, as shown in **Table 1**.

Table 1. Characteristics of included studies

Author (Ref. #)	Country, year	Age (years), Sex	Study type	N	Predicted factors for radiation pneumonitis
Kong FM et al. [5]	USA, 2006	40-84, M82/F27	Clinical study	109	T stage, primary GTV, total-lung volume, MLD, V20, V13, lung Veff, and NTCP.
Barriger RB et al. [6]	USA, 2009	-	Retrospective review	243	MLD > 18 Gy, treatment with CD.
Shi A et al. [7]	China, 2010	M73/F21	Retrospective study	94	NTCP value and V10.
Line Claude et al. [8]	France, 2004	27-77, M84/F12	Retrospective study	96	MLD, V20, V30, age.
Raymond H. Mak et al. [9]	USA, 2012	67 (37-85), M/F	Retrospective study	136	MTHFR genotype (1298AA vs. AC/CC; rs1801131).
SARA RAMELLA et al. [10]	Italy, 2009	66 (49-82), M86/F11	Retrospective study	97	V20ipsi and V30ipsi.
Jun Dang et al. [11]	China, 2010	63 (19-84), M72/F21	Retrospective study	93	Chemotherapy and DVH parameters.
LI ZHANG et al. [12]	China, 2009	60 (26-83), M207/F46	Retrospective study	253	Genetic polymorphisms of ATM.
Ling Wei Wang et al. [13]	USA, 2000	66 (37-64), M120/F93	Retrospective study	213	ACE inhibitors.
Masaharu Fujino et al. [14]	Japan, 2006	72 (56-86), 76 (49-87); M/F (8/4, 22/9)	Case-control study	12/31	Pre-treatment pulmonary function test (%VC, FEV1.0%), and dose volume statistics (V20, total dose, BED, dose per fraction, peripheral dose).
Bhupesh Parashar et al. [15]	USA, 2011	68 (40-91), M37/F49	Retrospective study	86	Chemotherapy.
Jedidiah M. Monson et al. [16]	USA, 1998	61 (32-86), M47/F36	Retrospective study	83	Low performance status, comorbid lung disase, smoking history, low pulmonary function tests, and the absence of a surgical resection.
Shiva K. Das et al. [17]	USA, 2008	62 (43-83), 64 (27-87); M/F (8/4, 22/9)	Case-control study	34/185	Chemotherapy, EUD for exponent=1.2 to 3; EUD for a=0.5 to 1.2, lung volume receiving 20-30 Gy; female sex; and squamous cell histology.
Falk Roeder et al. [18]	Germany, 2010	63 (42-80), 62 (37-90); M/F (26/7, 145/64)	Case-control study	33/209	V30 and V40.
H. Takahashi et al. [19]	Japan, 2001	65.7; 64.5; M/F (8/4, 11/2)	Case-control study	12/13	Surfactant proteins A and D.
Takashi Uno et al. [20]	Japan, 2006	68 (52-80), M16/F5	Retrospective study	21	A somewhat lower V dose value or MLD.
MICHAEL FAY et al. [21]	Australia, 2004	M73/F21	Retrospective study	156	V30 and MLD.
Tae Hyun Kim et al. [22]	Korea, 2005	60 (35-79), M66/F10	Retrospective study	76	MLD.
MASASHI KOTO et al. [23]	Japan, 2007	72 (47-85), M59/F21	Retrospective study	80	Dosimetric factors.
Songhao et al. [24]	China, 2009	63.5 (41-76), 64.5 (43-78); M/F (41/11, 81/23)	Case-control study	52/104	Diabetes.
Xiao Chun et al. [25]	China, 2010	55.66 (40-71), 59.32 (49-69); M/F (36/6, 39/7)	Case-control study	46/42	-
Tiziana Rancati et al. [26]	Italy, 2003	66 (33-82), M75/F9	Retrospective study	84	Mitomycin or COPD.
Wang Yingjie et al. [27]	China, 2005	64 (20-87), M87/F25	Retrospective study	112	-
THEODORE J. ROBNETT et al. [28]	USA, 2000	63 (30-85), M82/F61	Retrospective study	144	Pretreatment performance status, gender, and FEV1.
Xiao-Jing Zhang et al. [29]	China, 2012	M1091/F4256	Retrospective study	5347	Chronic lung disease, diabetes mellitus, low pre-RT pulmonary function, smoking, tumor located in middle or lower lobe, RT combined with chemotherapy, absence of pre-RT lung tumor surgery, without amifostine combined RT (or RCT), end-RT/preRT TGF-b1 ratio C1 and some dose-volume parameters.
Michelle A. T. Hildebrandt et al. [30]	USA, 2010	63.60 (9.98), M91/F82	Retrospective study	173	Genetic variations among inflammation pathway genes.
ELLEN X. HUANG et al. [31]	USA, 2011	65 (31-94), M105/F104	Retrospective study	209	Heart irradiation.
Alena NJ, et al. [32]	USA, 2004	68.3 (51-89), M37/F11	Clinical trial	48	-
WANG Wei-Hual et al. [33]	China, 2006	52 (33-70), M25/F6	Retrospective study	31	-
YEVGENIY VINOGRADSKIY et al. [34]	USA, 2012		Retrospective study	547	GTV centroid information.

ANDREW J. HOPE et al. [35]	USA, 2006	65.2 (31-94), M108/F111	Retrospective study	219	Inferior tumor position.
SANG-WOOK LEE et al. [36]	Korea, 2003	60 (37-76), M10/F136	Clinical trial	161	Hyperfractionated three-dimensional CRT and concurrent chemotherapy.
Ming Yin et al. [37]	USA, 2011	63 (35-88), M125/F103	Retrospective study	228	HR genetic polymorphisms, particularly RAD51 2135G.C.
George Rodrigues et al. [38]	Canada, 2004		Retrospective study		Dose-volume histogram parameters.
Dongryul Oh et al. [39]	Korea, 2009	71 (32-88), M57/F12	Retrospective study	69	Dosimetric parameters (V20 and MLD).
Hiroki Kobayashi et al. [40]	Japan, 2010	67 (44-75), M33/F4	Retrospective study	37	V5 and V13.
AKIRA INOUE et al. [41]	Japan, 2001	63.9 (36-86), M154/F37	Retrospective study	191	Low PaO2 (<80 torr) before radiotherapy.
mototsugu Yamano et al. [42]	Japan, 2007	64.9 (35-89), M112/F23	Retrospective study	135	Grades.
YOSHIHIKO SEGAWA et al. [43]	Japan, 1997	70 (41-90), M70/F19	Retrospective study	89	Administration of a huge dally dose.
M. Yamada et al. [44]	Japan, 1998	66.6 (43-86), M50/F10	Retrospective study	60	Irradiated site (included lower lung ®eld) and concurrent CRT used with weekly CPT-11.
Luigi De Petris et al. [45]	Sweden, 2005	63 (44-77), M18/F14	Retrospective study	32	GTV, chemoradiotherapy.
Takeyuki Makimoto et al. ([46]	Japan, 1999	70.2 (57-85), 69.0 (44-86); M/F (16/1, 83/11)	Retrospective study	17/94	Pre-existing interstitial changes detected by chest radiography or computed tomography and radiotherapy to the contralateral mediastinum (> 40 Gy).
Yosuke Matsuno et al. [47]	Japan, 2006	73 (45-83), 74 (52-86); M/F (18/1, 19/1)	Retrospective study	19/20	KL-6.
Y. Ishii et al. [48]	Japan, 1999	64.9 (48-73), 66.1 (45-79), M/F (12/0, 17/1)	Retrospective study	12/18/13	Soluble intercellular adhesion molecule-1.
Jing Wang et al. [49]	China, 2009	65 (42-74), M20/F3	Retrospective study	23	Levels of serum TGF-β1.
DANIEL T. CHANG et al. [50]	USA, 2006	66 (34.9-84.9), M42/F26	Retrospective study	68	V20 or MLD.
JINGFANG MAO et al. [51]	USA, 2007	64 (40-87), M47/F44	Retrospective study	91	Pre-RT chemotherapy.
Z. Kocak et al. [52]	USA, 2005	62 (27-84), 65 (37-87), M/F (26/23, 59/69)	Retrospective study	49/128	PORT.
Steven E. Schild et al. [53]	USA, 2003	64 (36-79), M155/F89	Retrospective study	244	Combined-modality therapy.
S. J. Clenton et al. [54]	UK, 2005	64 (36-79), M106/F54	Retrospective study	160	V_{20Gy} value.
Alena Novakova-Jiresova et al. [55]	The netherlands, 2004	62 (45-76), 65 (44-76), M/F (34/1, 10/1)	Retrospective study	35/11	Plasma TGF-b.
Wang Jing et al. [56]	China, 2009	65 (42-81), M91/F24	Retrospective study	115	V5.
Watanabe H et al. [57]	Japan, 1995	63.5 (32-71), M32/F25	Retrospective study	57	Male sex, chronic obstructive lung disease and chemotherapy.
Xie Songxi et al. [58]	China, 2006	62 (38-79), M19/F6	Retrospective study	25	V20.
Zhang Bin, et al. [59]	China, 2010	59 (32-74), M35/F12	Clinical trial	47	Three dimensional conformal radiotherapy, chemotherapy, radiation-induced pulmonary.
E. M. Wilson [60]	UK, 2003	(30-78)	Clinical trial	70	Three-dimensional conformal radiotherapy.
Zhong jun, et al. [61]	China, 2007	(33-79)	Clinical trial	53	TGF-β1.
Yu xian, et al. [62]	China, 2011	(32-83), M52/F10	Clinical trial	62	Radiation pneumonitis was affected by multiple factors. Patients with COPD or abnormal lung function should be treated with optimal plan, and V30<25%.
Cai Yong, et al. [63]	China, 2006	(32-83), M216/F84	Clinical trial	300	Chemotherapy and radiation treatment cycle, the synchronization use ammonia phosphorus set and the radiation dose, M L D radiation factors including lung v10s V 20 and cytokines A CE, have certain correlation with the occurrence of RP.
ELLEN D. YORKE, et al. [64]	USA, 2005	70 (39-84), M49/F29	Clinical trial	78	Correlations between severe pneumonitis and whole lung V13 and with other dose-volume factors of total lung and lower lung are confirmed.

R. BRYAN BARRIGER, et al. [65]	India, 2010	-	Clinical trial	243	Predictive factors for RP were MLD > 18 Gy and treatment with CD.
Ji-Yoon Kim, et al. [66]	Korea, 2009	63 (42-78), M25/F9	Clinical trial	34	Changes of TGF-β1 could be correlated with RP and the incorporation of the biological parameters into the dosimetric data could be useful for predicting symptomatic RP.
Zhang Yong, et al. [67]	China, 2009	63 (39-82), M27/F13	Clinical trial	40	Standardized uptake value (SUV) and the SUV ratio of the irradiated lung tissue to that of the non-irradiated lung tissue (L/B) for FDG PE7r-CT are positively correlated with radiation pneumonitis, and clinicians may use it to predict the occurrence of radiation pneumonitis.
Lujun Zhao, et al. [68]	China, 2007	56 (40-81), M35/F4	Clinical trial	39	Plasma ACE as a predictive factor for radiation pneumonitis deserves further study.
Elizabeth S. Evans, et al. [69]	USA, 2006	65 (33-88), M55/F45	Clinical trial	100	TGF-β1 is generally not predictive for RP except for the group of patients with a high V30.
Feng Ming Kong, et al. [70]	China, 2001	(70-100)	Clinical trial	194	Loss of the *M6P/IGF2R* gene may predispose patients to the development of radiation-induced lung injury .
MITCHELL S. ANSCHER, et al. [71]	USA, 1998	M43/F30	Clinical trial	73	Plasma TGF-β1 levels appear to be a useful means to identify patients at low risk for the development of pneumonitis from thoracic RT.
XIAO-LONG FU et al. [72]	USA, 2001	M60/F43	Clinical trial	103	Combining both physical and biologic risk factors may allow for better identification of patients at risk for the development of symptomatic radiation-induced lung injury.
Ezra E. W. Cohen, et al. [73]	USA, 2001	-	Clinical trial	848	Advances in radiation therapy are triggering a revolution in dose intensity and scheduling that will one day offer superlative local control.
Dosia Antonadou [74]	USA, 2002	M131/F15	Clinical trial	146	Amifostine reduces the incidence of acute and late radiation-induced toxicities.
R. Komaki et al. [75]	USA, 2002	M26/F27	Clinical trial	53	Amifostine significantly reduced acute severe esophagitis and pneumonitis.
DOSIA ANTONADOU, et al. [76]	Greece, 2001	(39-78), M131/F15	Clinical trial	146	Amifostine reduces the incidence of pneumonitis, lung fibrosis, and esophagitis in radiotherapy patients with lung cancer without compromising antitumor efficacy.
RITSUKO KOMAKI et al. [77]	USA, 2003	63.5 (37-80), M33/F29	Clinical trial	62	Conclusion: Amifostine reduced the severity and incidence of acute esophageal, pulmonary, and hematologic toxicity resulting from concurrent cisplatin-based chemotherapy and RT. Amifostine had no apparent effect on survival in these patients with unresectable non-small-cell lung cancer.
YASUHIRO NAKAYAMA, et al. [78]	Japan, 1996	(39-78), M22/F6	Clinical trial	28	Irradiation can induce accumulation of activated T-cells (HLADR and ICAM-I-positive T-cells) in the lung.
Z. VUJASKOVIC, et al. [79]	USA, 2000	62 (44-76)	Clinical trial	27	Elevated TGF-b levels during radio-therapy may not only indicate patients with a higher risk of developing pulmonary toxicity but also patients with a higher risk of treatment failure.

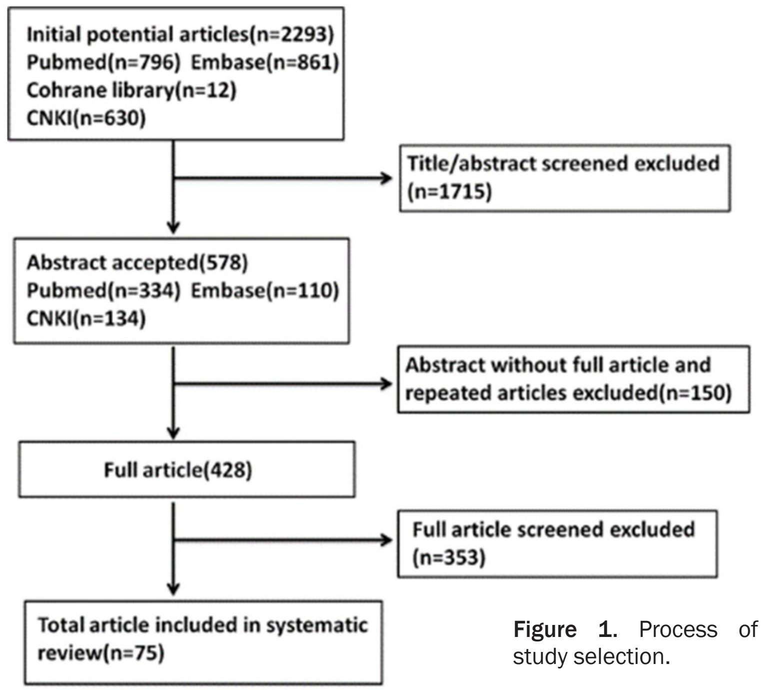


Figure 1. Process of study selection.

Among the 75 included articles, Fu XL's research [73] had two sets of data.6 articles [63, 83-87], which were all randomized controlled trials, focused on the relationship between occurrence of RP and the use of Amifostine, while the other 68 articles were all case-control studies. The exposed factors included 6 demographics (gender, age, chronic lung diseases, pulmonary function, diabetes and tumor site) and 3 treatment factors (operation before radiotherapy, combined radio-chemotherapy treatment, the use of Amifostine). The process of study selection was listed in **Figure 1**.

Associations with demographics

Gender: 18 articles [4, 6, 12, 14, 15, 17, 20, 25-27, 30, 35, 38, 43, 54, 56, 59, 60] including 2178 cases indicated there was no association between gender and the occurrence of RP based on fixed effect model (P=0.73, OR: 0.97, 95% CI: 0.82-1.15), correlated with the result (P=0.45,OR: 1.12, 95% CI: 0.84-1.49) based on random effect model ,which indicated that the result was credible due to its low sensitivity and high stability (**Figure 2A**).

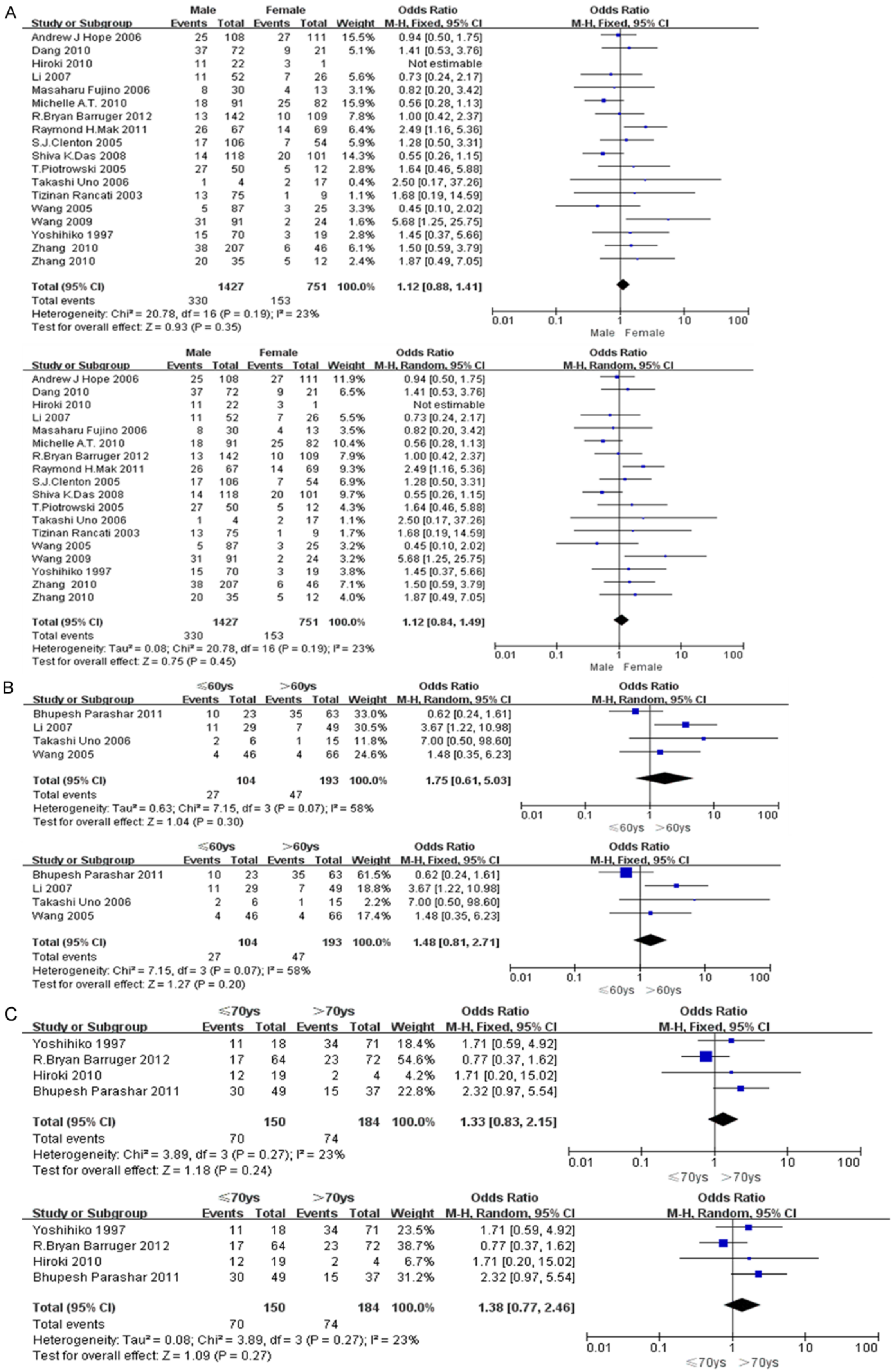
Age: 4 articles [15, 20, 27, 60] including 297 cases analyzed by taking 60 years old as a separatrix (**Figure 2B**). We used random effect model according to P≤0.10, I^2 > 50%, and the results were P=0.30, OR: 1.75, 95% CI: 0.61-5.03, correlated with the result (P=0.20, OR: 1.48, 95% CI: 0.81-2.71) based on fixed effect model, which indicated that the result was credible.

Another 4 articles [6, 15, 43, 49] including 511 cases analyzed by taking 70 years old as a separatrix (**Figure 2C**). We used fixed effect model and the results were P=0.24, OR: 1.33, 95% CI: 0.83-2.15, correlated with the result (P=0.27, OR: 1.38, 95% CI: 0.77-2.46) based on random effect model, which indicated that the result was credible. Through meta-analysis of these two data, it was believed that there was no association between age and RP. Although the former data had large heterogeneity, we could not take subgroup analysis because the article number was small.

Chronic pulmonary diseases: 13 articles [7, 15, 16, 18, 22, 26, 27, 46, 47, 50, 56, 57, 60] including 1409 cases indicated that patients with chronic pulmonary diseases were more liable to have RP based on the result of fixed effect model (P<0.00001, OR: 2.18, 95% CI: 1.59-3.00), correlated with the result (P<0.0001, OR: 2.35, 95% CI: 1.57-3.51) based on random effect model, which indicated that the result was credible (**Figure 2D**).

Pulmonary function before radiotherapy: 3 articles [7, 16, 22] including 237 cases focused on the relationship between forced expiratory volumes in 1 s (FEV1≥2L vs. <2 L) and RP. The data indicated that patients whose FEV1<2 L were more likely to have RP based on the result of fixed effect model (P=0.004, OR: 0.27, 95% CI: 0.11-0.65), correlated with the result (P=0.004, OR: 0.27, 95% CI: 0.11-0.66) based on random effect model, which indicated that the result was credible (**Figure 2E**). But the funnel plot was not completely displayed, considering there were publication bias (**Figure 2F**).

Diabetes: 3 articles [7, 27, 56] including 365 cases indicated that patients with diabetes


A
Male Female Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Andrew J Hope 2006 25 108 27 111 15.5% 0.94 [0.50, 1.75]
Dang 2010 37 72 9 21 5.1% 1.41 [0.53, 3.76]
Hiroki 2010 11 22 3 1 Not estimable
Li 2007 11 52 7 26 5.6% 0.73 [0.24, 2.17]
Masaharu Fujino 2006 8 30 4 13 3.1% 0.82 [0.20, 3.42]
Michelle A.T. 2010 18 91 25 82 15.9% 0.56 [0.28, 1.13]
R.Bryan Barruger 2012 13 142 10 109 7.8% 1.00 [0.42, 2.37]
Raymond H.Mak 2011 26 67 14 69 6.4% 2.49 [1.16, 5.36]
S.J.Clenton 2005 17 106 7 54 5.9% 1.28 [0.50, 3.31]
Shiva K.Das 2008 14 118 20 101 14.3% 0.55 [0.26, 1.15]
T.Piotrowski 2005 27 50 5 12 2.8% 1.64 [0.46, 5.88]
Takashi Uno 2006 1 4 2 17 0.4% 2.50 [0.17, 37.26]
Tizinan Rancati 2003 13 75 1 9 1.1% 1.68 [0.19, 14.59]
Wang 2005 5 87 3 25 3.3% 0.45 [0.10, 2.02]
Wang 2009 31 91 2 24 1.6% 5.68 [1.25, 25.75]
Yoshihiko 1997 15 70 3 19 2.8% 1.45 [0.37, 5.66]
Zhang 2010 38 207 6 46 6.1% 1.50 [0.59, 3.79]
Zhang 2010 20 35 5 12 2.4% 1.87 [0.49, 7.05]
Total (95% CI) 1427 751 100.0% 1.12 [0.88, 1.41]
Total events 330 153
Heterogeneity: Chi² = 20.78, df = 16 (P = 0.19); I² = 23%
Test for overall effect: Z = 0.93 (P = 0.35)
0.01 0.1 1 10 100
Male Female
Male Female Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Andrew J Hope 2006 25 108 27 111 11.9% 0.94 [0.50, 1.75]
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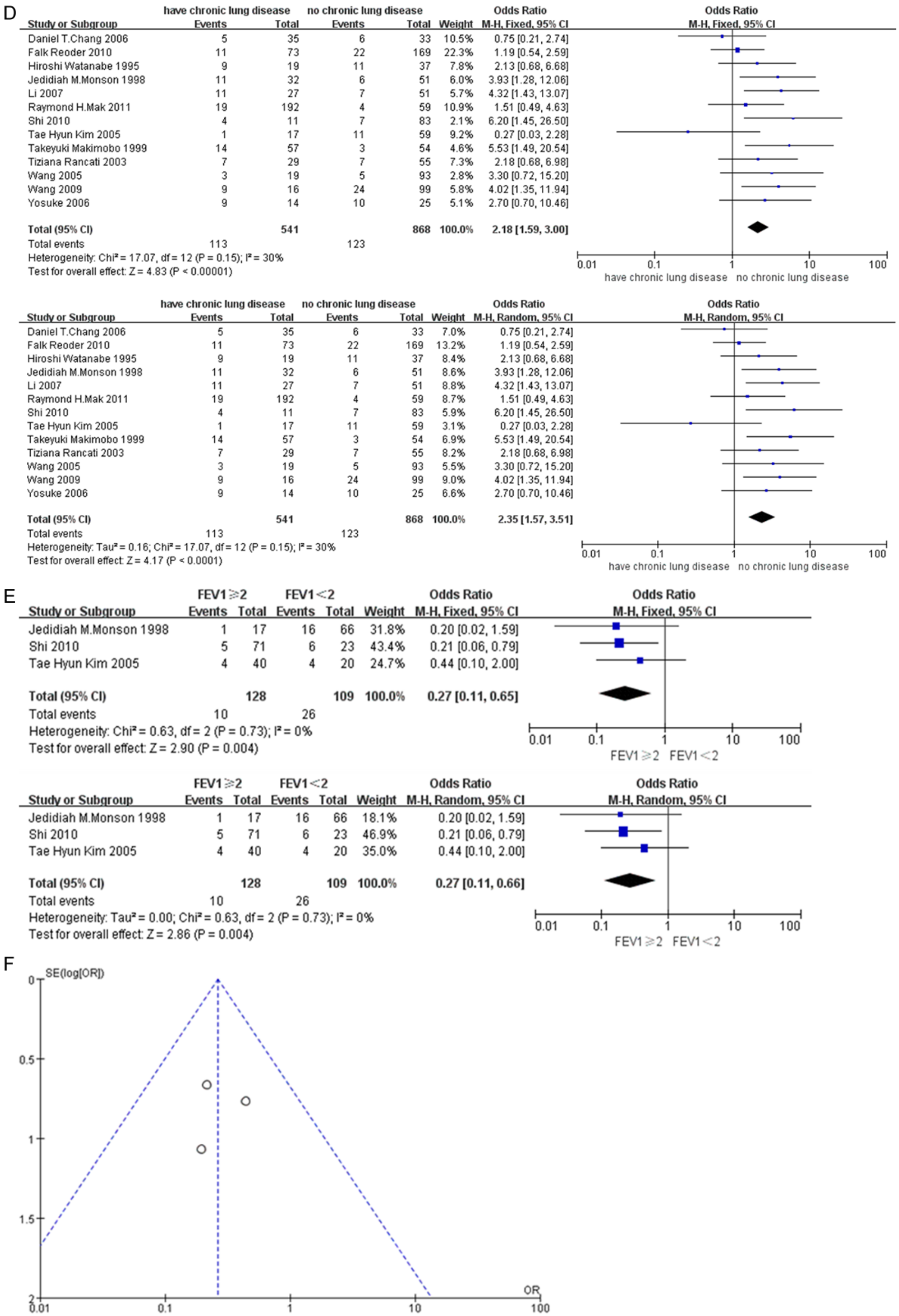
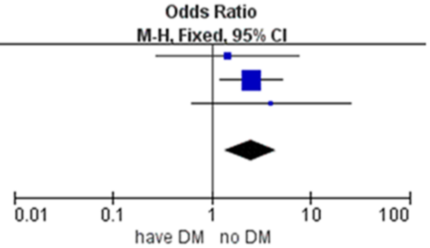
T.Piotrowski 2005 27 50 5 12 4.3% 1.64 [0.46, 5.88]
Takashi Uno 2006 1 4 2 17 1.1% 2.50 [0.17, 37.26]
Tizinan Rancati 2003 13 75 1 9 1.7% 1.68 [0.19, 14.59]
Wang 2005 5 87 3 25 3.2% 0.45 [0.10, 2.02]
Wang 2009 31 91 2 24 3.2% 5.68 [1.25, 25.75]
Yoshihiko 1997 15 70 3 19 3.8% 1.45 [0.37, 5.66]
Zhang 2010 38 207 6 46 7.1% 1.50 [0.59, 3.79]
Zhang 2010 20 35 5 12 4.0% 1.87 [0.49, 7.05]
Total (95% CI) 1427 751 100.0% 1.12 [0.84, 1.49]
Total events 330 153
Heterogeneity: Tau² = 0.08; Chi² = 20.78, df = 16 (P = 0.19); I² = 23%
Test for overall effect: Z = 0.75 (P = 0.45)
0.01 0.1 1 10 100
Male Female
B
≤60ys >60ys Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Bhupesh Parashar 2011 10 23 35 63 33.0% 0.62 [0.24, 1.61]
Li 2007 11 29 7 49 30.5% 3.67 [1.22, 10.98]
Takashi Uno 2006 2 6 1 15 11.8% 7.00 [0.50, 98.60]
Wang 2005 4 46 4 66 24.6% 1.48 [0.35, 6.23]
Total (95% CI) 104 193 100.0% 1.75 [0.61, 5.03]
Total events 27 47
Heterogeneity: Tau² = 0.63; Chi² = 7.15, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 1.04 (P = 0.30)
0.01 0.1 1 10 100
≤60ys >60ys
≤60ys >60ys Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bhupesh Parashar 2011 10 23 35 63 61.5% 0.62 [0.24, 1.61]
Li 2007 11 29 7 49 18.8% 3.67 [1.22, 10.98]
Takashi Uno 2006 2 6 1 15 2.2% 7.00 [0.50, 98.60]
Wang 2005 4 46 4 66 17.4% 1.48 [0.35, 6.23]
Total (95% CI) 104 193 100.0% 1.48 [0.81, 2.71]
Total events 27 47
Heterogeneity: Chi² = 7.15, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 1.27 (P = 0.20)
0.01 0.1 1 10 100
≤60ys >60ys
C
≤70ys >70ys Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Yoshihiko 1997 11 18 34 71 18.4% 1.71 [0.59, 4.92]
R.Bryan Barruger 2012 17 64 23 72 54.6% 0.77 [0.37, 1.62]
Hiroki 2010 12 19 2 4 4.2% 1.71 [0.20, 15.02]
Bhupesh Parashar 2011 30 49 15 37 22.8% 2.32 [0.97, 5.54]
Total (95% CI) 150 184 100.0% 1.33 [0.83, 2.15]
Total events 70 74
Heterogeneity: Chi² = 3.89, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.18 (P = 0.24)
0.01 0.1 1 10 100
≤70ys >70ys
≤70ys >70ys Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Yoshihiko 1997 11 18 34 71 23.5% 1.71 [0.59, 4.92]
R.Bryan Barruger 2012 17 64 23 72 38.7% 0.77 [0.37, 1.62]
Hiroki 2010 12 19 2 4 6.7% 1.71 [0.20, 15.02]
Bhupesh Parashar 2011 30 49 15 37 31.2% 2.32 [0.97, 5.54]
Total (95% CI) 150 184 100.0% 1.38 [0.77, 2.46]
Total events 70 74
Heterogeneity: Tau² = 0.08; Chi² = 3.89, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.09 (P = 0.27)
0.01 0.1 1 10 100
≤70ys >70ys


D
have chronic lung disease
no chronic lung disease
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
Daniel T.Chang 2006 5 35 6 33 10.5% 0.75 [0.21, 2.74]
Falk Reoder 2010 11 73 22 169 22.3% 1.19 [0.54, 2.59]
Hiroshi Watanabe 1995 9 19 11 37 7.8% 2.13 [0.68, 6.68]
Jedidiah M.Monson 1998 11 32 6 51 6.0% 3.93 [1.28, 12.06]
Li 2007 11 27 7 51 5.7% 4.32 [1.43, 13.07]
Raymond H.Mak 2011 19 192 4 59 10.9% 1.51 [0.49, 4.63]
Shi 2010 4 11 7 83 2.1% 6.20 [1.45, 26.50]
Tae Hyun Kim 2005 1 17 11 59 9.2% 0.27 [0.03, 2.28]
Takeyuki Makimobo 1999 14 57 3 54 4.6% 5.53 [1.49, 20.54]
Tiziana Rancati 2003 7 29 7 55 7.3% 2.18 [0.68, 6.98]
Wang 2005 3 19 5 93 2.8% 3.30 [0.72, 15.20]
Wang 2009 9 16 24 99 5.8% 4.02 [1.35, 11.94]
Yosuke 2006 9 14 10 25 5.1% 2.70 [0.70, 10.46]
Total (95% CI) 541 868 100.0% 2.18 [1.59, 3.00]
Total events 113 123
Heterogeneity: Chi² = 17.07, df = 12 (P = 0.15); I² = 30%
Test for overall effect: Z = 4.83 (P < 0.00001)
0.01 0.1 1 10 100
have chronic lung disease no chronic lung disease
have chronic lung disease
no chronic lung disease
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Daniel T.Chang 2006 5 35 6 33 7.0% 0.75 [0.21, 2.74]
Falk Reoder 2010 11 73 22 169 13.2% 1.19 [0.54, 2.59]
Hiroshi Watanabe 1995 9 19 11 37 8.4% 2.13 [0.68, 6.68]
Jedidiah M.Monson 1998 11 32 6 51 8.6% 3.93 [1.28, 12.06]
Li 2007 11 27 7 51 8.8% 4.32 [1.43, 13.07]
Raymond H.Mak 2011 19 192 4 59 8.7% 1.51 [0.49, 4.63]
Shi 2010 4 11 7 83 5.9% 6.20 [1.45, 26.50]
Tae Hyun Kim 2005 1 17 11 59 3.1% 0.27 [0.03, 2.28]
Takeyuki Makimobo 1999 14 57 3 54 6.9% 5.53 [1.49, 20.54]
Tiziana Rancati 2003 7 29 7 55 8.2% 2.18 [0.68, 6.98]
Wang 2005 3 19 5 93 5.5% 3.30 [0.72, 15.20]
Wang 2009 9 16 24 99 9.0% 4.02 [1.35, 11.94]
Yosuke 2006 9 14 10 25 6.6% 2.70 [0.70, 10.46]
Total (95% CI) 541 868 100.0% 2.35 [1.57, 3.51]
Total events 113 123
Heterogeneity: Tau² = 0.16; Chi² = 17.07, df = 12 (P = 0.15); I² = 30%
Test for overall effect: Z = 4.17 (P < 0.0001)
0.01 0.1 1 10 100
have chronic lung disease no chronic lung disease
E
FEV1≥2
FEV1<2
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
Jedidiah M.Monson 1998 1 17 16 66 31.8% 0.20 [0.02, 1.59]
Shi 2010 5 71 6 23 43.4% 0.21 [0.06, 0.79]
Tae Hyun Kim 2005 4 40 4 20 24.7% 0.44 [0.10, 2.00]
Total (95% CI) 128 109 100.0% 0.27 [0.11, 0.65]
Total events 10 26
Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)
0.01 0.1 1 10 100
FEV1≥2 FEV1<2
FEV1≥2
FEV1<2
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Jedidiah M.Monson 1998 1 17 16 66 18.1% 0.20 [0.02, 1.59]
Shi 2010 5 71 6 23 46.9% 0.21 [0.06, 0.79]
Tae Hyun Kim 2005 4 40 4 20 35.0% 0.44 [0.10, 2.00]
Total (95% CI) 128 109 100.0% 0.27 [0.11, 0.66]
Total events 10 26
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)
0.01 0.1 1 10 100
FEV1≥2 FEV1<2
F
SE(log[OR])
0
0.5
1
1.5
2
OR
0.01 0.1 1 10 100

G

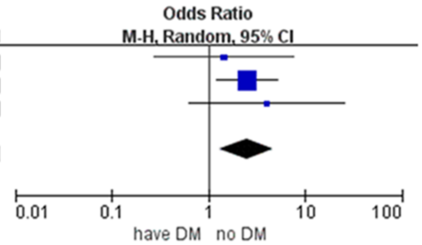
Study or Subgroup	have DM Events	have DM Total	no DM Events	no DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Shi 2010	2	13	9	81	17.7%	1.45 [0.28, 7.64]
Song 2009	21	52	22	104	73.5%	2.52 [1.22, 5.22]
Wang 2009	3	5	30	110	8.8%	4.00 [0.64, 25.13]
Total (95% CI)		**70**		**295**	**100.0%**	**2.46 [1.33, 4.58]**
Total events	26		61			

Heterogeneity: Chi² = 0.66, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



Study or Subgroup	have DM Events	have DM Total	no DM Events	no DM Total	Weight	Odds Ratio M-H, Random, 95% CI
Shi 2010	2	13	9	81	14.2%	1.45 [0.28, 7.64]
Song 2009	21	52	22	104	74.2%	2.52 [1.22, 5.22]
Wang 2009	3	5	30	110	11.6%	4.00 [0.64, 25.13]
Total (95% CI)		**70**		**295**	**100.0%**	**2.46 [1.32, 4.60]**
Total events	26		61			

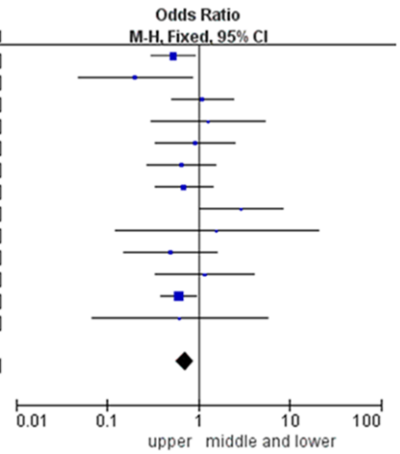
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)



H

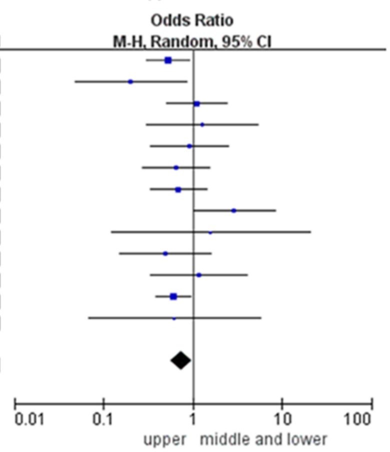
Study or Subgroup	upper Events	upper Total	middle and lower Events	middle and lower Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cai 2011	24	117	60	183	21.9%	0.53 [0.31, 0.91]
Daniel T.Chang 2006	3	40	8	28	5.1%	0.20 [0.05, 0.85]
Falk Reoder 2010	11	76	22	166	7.0%	1.11 [0.51, 2.42]
Hiroki 2010	7	14	7	16	1.9%	1.29 [0.30, 5.43]
Motosugu Yamano 2007	13	90	7	45	4.7%	0.92 [0.34, 2.49]
R.Bryan Barruger 2012	12	155	11	96	7.4%	0.65 [0.27, 1.53]
Shiva K.Das 2008	19	151	15	87	9.8%	0.69 [0.33, 1.44]
T.Piotrowski 2005	23	37	9	25	2.4%	2.92 [1.02, 8.37]
Takashi Uno 2006	2	12	1	9	0.6%	1.60 [0.12, 20.99]
Takeyuki Makimobo 1999	12	90	5	21	4.1%	0.49 [0.15, 1.59]
Theodore J.Robnett 2000	8	91	4	53	2.7%	1.18 [0.34, 4.13]
Yevgenly V. 2011	35	220	78	327	31.1%	0.60 [0.39, 0.94]
Yu 2011	1	8	10	54	1.3%	0.63 [0.07, 5.70]
Total (95% CI)		**1101**		**1110**	**100.0%**	**0.71 [0.57, 0.90]**
Total events	170		237			

Heterogeneity: Chi² = 15.10, df = 12 (P = 0.24); I² = 21%
Test for overall effect: Z = 2.84 (P = 0.005)



Study or Subgroup	upper Events	upper Total	middle and lower Events	middle and lower Total	Weight	Odds Ratio M-H, Random, 95% CI
Cai 2011	24	117	60	183	16.4%	0.53 [0.31, 0.91]
Daniel T.Chang 2006	3	40	8	28	3.6%	0.20 [0.05, 0.85]
Falk Reoder 2010	11	76	22	166	10.1%	1.11 [0.51, 2.42]
Hiroki 2010	7	14	7	16	3.6%	1.29 [0.30, 5.43]
Motosugu Yamano 2007	13	90	7	45	6.9%	0.92 [0.34, 2.49]
R.Bryan Barruger 2012	12	155	11	96	8.7%	0.65 [0.27, 1.53]
Shiva K.Das 2008	19	151	15	87	11.1%	0.69 [0.33, 1.44]
T.Piotrowski 2005	23	37	9	25	6.3%	2.92 [1.02, 8.37]
Takashi Uno 2006	2	12	1	9	1.2%	1.60 [0.12, 20.99]
Takeyuki Makimobo 1999	12	90	5	21	5.2%	0.49 [0.15, 1.59]
Theodore J.Robnett 2000	8	91	4	53	4.7%	1.18 [0.34, 4.13]
Yevgenly V. 2011	35	220	78	327	20.6%	0.60 [0.39, 0.94]
Yu 2011	1	8	10	54	1.6%	0.63 [0.07, 5.70]
Total (95% CI)		**1101**		**1110**	**100.0%**	**0.74 [0.56, 0.99]**
Total events	170		237			

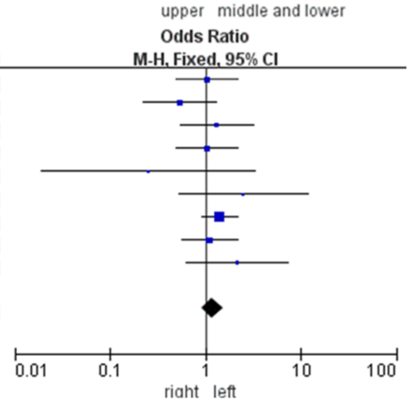
Heterogeneity: Tau² = 0.05; Chi² = 15.10, df = 12 (P = 0.24); I² = 21%
Test for overall effect: Z = 2.02 (P = 0.04)

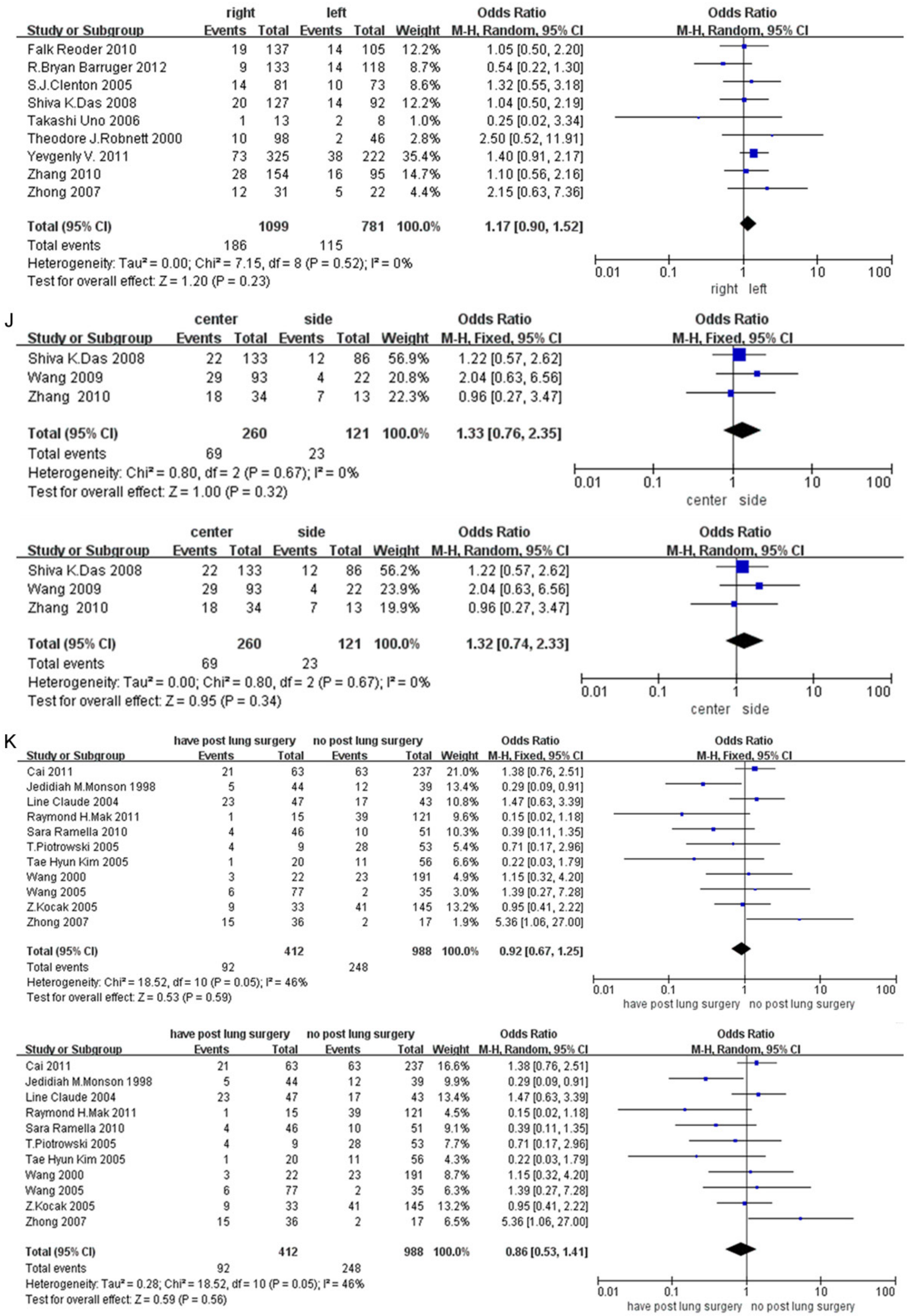


I

Study or Subgroup	right Events	right Total	left Events	left Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Falk Reoder 2010	19	137	14	105	12.5%	1.05 [0.50, 2.20]
R.Bryan Barruger 2012	9	133	14	118	12.6%	0.54 [0.22, 1.30]
S.J.Clenton 2005	14	81	10	73	8.0%	1.32 [0.55, 3.18]
Shiva K.Das 2008	20	127	14	92	12.5%	1.04 [0.50, 2.19]
Takashi Uno 2006	1	13	2	8	2.1%	0.25 [0.02, 3.34]
Theodore J.Robnett 2000	10	98	2	46	2.2%	2.50 [0.52, 11.91]
Yevgenly V. 2011	73	325	38	222	32.0%	1.40 [0.91, 2.17]
Zhang 2010	28	154	16	95	14.8%	1.10 [0.56, 2.16]
Zhong 2007	12	31	5	22	3.3%	2.15 [0.63, 7.36]
Total (95% CI)		**1099**		**781**	**100.0%**	**1.18 [0.91, 1.52]**
Total events	186		115			

Heterogeneity: Chi² = 7.15, df = 8 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)

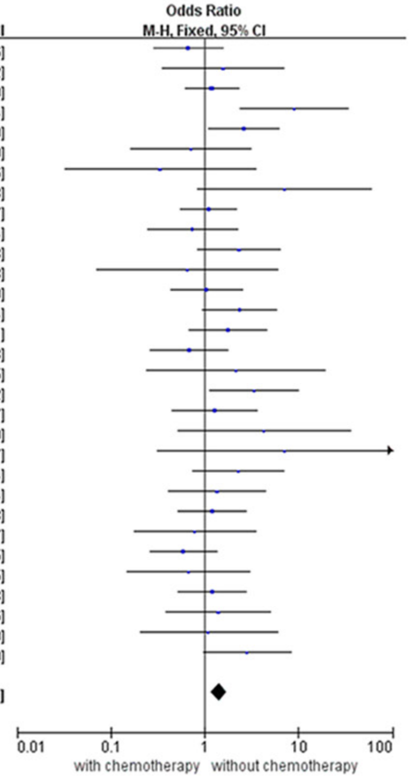



right left
Study or Subgroup Events Total Events Total Weight Odds Ratio M-H, Random, 95% CI
Falk Reoder 2010 19 137 14 105 12.2% 1.05 [0.50, 2.20]
R.Bryan Barruger 2012 9 133 14 118 8.7% 0.54 [0.22, 1.30]
S.J.Clenton 2005 14 81 10 73 8.6% 1.32 [0.55, 3.18]
Shiva K.Das 2008 20 127 14 92 12.2% 1.04 [0.50, 2.19]
Takashi Uno 2006 1 13 2 8 1.0% 0.25 [0.02, 3.34]
Theodore J.Robnett 2000 10 98 2 46 2.8% 2.50 [0.52, 11.91]
Yevgenly V. 2011 73 325 38 222 35.4% 1.40 [0.91, 2.17]
Zhang 2010 28 154 16 95 14.7% 1.10 [0.56, 2.16]
Zhong 2007 12 31 5 22 4.4% 2.15 [0.63, 7.36]
Total (95% CI) 1099 781 100.0% 1.17 [0.90, 1.52]
Total events 186 115
Heterogeneity: Tau² = 0.00; Chi² = 7.15, df = 8 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
0.01 0.1 1 10 100
right left
J
center side
Study or Subgroup Events Total Events Total Weight Odds Ratio M-H, Fixed, 95% CI
Shiva K.Das 2008 22 133 12 86 56.9% 1.22 [0.57, 2.62]
Wang 2009 29 93 4 22 20.8% 2.04 [0.63, 6.56]
Zhang 2010 18 34 7 13 22.3% 0.96 [0.27, 3.47]
Total (95% CI) 260 121 100.0% 1.33 [0.76, 2.35]
Total events 69 23
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
0.01 0.1 1 10 100
center side
center side
Study or Subgroup Events Total Events Total Weight Odds Ratio M-H, Random, 95% CI
Shiva K.Das 2008 22 133 12 86 56.2% 1.22 [0.57, 2.62]
Wang 2009 29 93 4 22 23.9% 2.04 [0.63, 6.56]
Zhang 2010 18 34 7 13 19.9% 0.96 [0.27, 3.47]
Total (95% CI) 260 121 100.0% 1.32 [0.74, 2.33]
Total events 69 23
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
0.01 0.1 1 10 100
center side
K
have post lung surgery no post lung surgery
Study or Subgroup Events Total Events Total Weight Odds Ratio M-H, Fixed, 95% CI
Cai 2011 21 63 63 237 21.0% 1.38 [0.76, 2.51]
Jedidiah M.Monson 1998 5 44 12 39 13.4% 0.29 [0.09, 0.91]
Line Claude 2004 23 47 17 43 10.8% 1.47 [0.63, 3.39]
Raymond H.Mak 2011 1 15 39 121 9.6% 0.15 [0.02, 1.18]
Sara Ramella 2010 4 46 10 51 10.3% 0.39 [0.11, 1.35]
T.Piotrowski 2005 4 9 28 53 5.4% 0.71 [0.17, 2.96]
Tae Hyun Kim 2005 1 20 11 56 6.6% 0.22 [0.03, 1.79]
Wang 2000 3 22 23 191 4.9% 1.15 [0.32, 4.20]
Wang 2005 6 77 2 35 3.0% 1.39 [0.27, 7.28]
Z.Kocak 2005 9 33 41 145 13.2% 0.95 [0.41, 2.22]
Zhong 2007 15 36 2 17 1.9% 5.36 [1.06, 27.00]
Total (95% CI) 412 988 100.0% 0.92 [0.67, 1.25]
Total events 92 248
Heterogeneity: Chi² = 18.52, df = 10 (P = 0.05); I² = 46%
Test for overall effect: Z = 0.53 (P = 0.59)
0.01 0.1 1 10 100
have post lung surgery no post lung surgery
have post lung surgery no post lung surgery
Study or Subgroup Events Total Events Total Weight Odds Ratio M-H, Random, 95% CI
Cai 2011 21 63 63 237 16.6% 1.38 [0.76, 2.51]
Jedidiah M.Monson 1998 5 44 12 39 9.9% 0.29 [0.09, 0.91]
Line Claude 2004 23 47 17 43 13.4% 1.47 [0.63, 3.39]
Raymond H.Mak 2011 1 15 39 121 4.5% 0.15 [0.02, 1.18]
Sara Ramella 2010 4 46 10 51 9.1% 0.39 [0.11, 1.35]
T.Piotrowski 2005 4 9 28 53 7.7% 0.71 [0.17, 2.96]
Tae Hyun Kim 2005 1 20 11 56 4.3% 0.22 [0.03, 1.79]
Wang 2000 3 22 23 191 8.7% 1.15 [0.32, 4.20]
Wang 2005 6 77 2 35 6.3% 1.39 [0.27, 7.28]
Z.Kocak 2005 9 33 41 145 13.2% 0.95 [0.41, 2.22]
Zhong 2007 15 36 2 17 6.5% 5.36 [1.06, 27.00]
Total (95% CI) 412 988 100.0% 0.86 [0.53, 1.41]
Total events 92 248
Heterogeneity: Tau² = 0.28; Chi² = 18.52, df = 10 (P = 0.05); I² = 46%
Test for overall effect: Z = 0.59 (P = 0.56)
0.01 0.1 1 10 100
have post lung surgery no post lung surgery

L

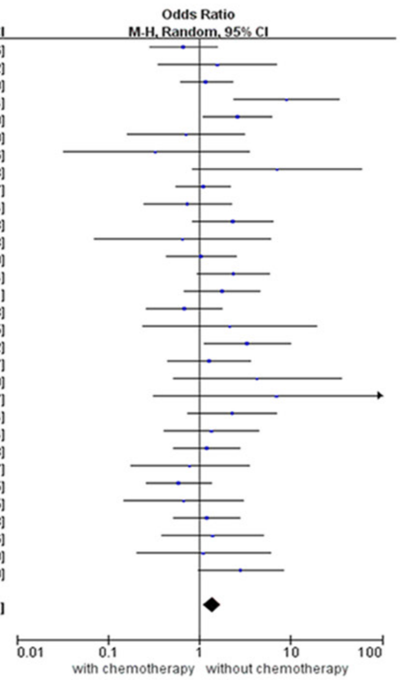
Study or Subgroup	with chemotherapy Events	with chemotherapy Total	without chemotherapy Events	without chemotherapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Akira Inoue 2001	14	123	11	68	6.6%	0.67 [0.28, 1.56]
Alena N.J. 2004	8	30	3	16	1.5%	1.58 [0.35, 7.02]
Andrew J Hope 2006	35	141	17	78	8.7%	1.18 [0.61, 2.29]
Bhupesh Parashar 2011	42	67	3	19	0.9%	8.96 [2.37, 33.84]
Dang 2010	23	36	23	57	3.4%	2.62 [1.10, 6.19]
Daniel T.Chang 2006	8	53	3	15	2.1%	0.71 [0.16, 3.10]
Dirk De Ruysscher 2011	1	4	22	44	1.5%	0.33 [0.03, 3.46]
Hiroshi Watanabe 1995	19	46	1	11	0.5%	7.04 [0.83, 59.68]
Huang 2011	32	136	16	73	8.4%	1.10 [0.55, 2.17]
Jedidiah M.Monson 1998	6	34	11	49	3.9%	0.74 [0.24, 2.24]
Jinyongan 2004	37	69	7	21	2.6%	2.31 [0.83, 6.43]
Li 2007	1	6	17	72	1.2%	0.65 [0.07, 5.93]
Line Claude 2004	26	58	14	32	5.3%	1.04 [0.44, 2.49]
Mao 2007	17	42	11	49	3.2%	2.35 [0.94, 5.84]
Michelle A.T. 2010	37	138	6	35	3.7%	1.77 [0.68, 4.61]
Motosugu Yamano 2007	8	65	12	70	5.4%	0.68 [0.26, 1.78]
Raymond H.Mak 2011	39	130	1	6	0.7%	2.14 [0.24, 18.95]
Shiva K.Das 2008	30	158	4	61	2.5%	3.34 [1.12, 9.92]
T.Piotrowski 2005	21	39	11	23	3.4%	1.27 [0.45, 3.57]
Tae Hyun Kim 2005	11	57	1	19	0.6%	4.30 [0.52, 35.80]
Takashi Uno 2006	3	12	0	9	0.2%	7.00 [0.32, 154.87]
Takeyuki Makimobo 1999	12	60	5	51	2.3%	2.30 [0.75, 7.04]
Tiziana Rancati 2003	9	49	5	35	2.5%	1.35 [0.41, 4.44]
Wang 2000	16	123	10	90	5.3%	1.20 [0.52, 2.78]
Wang 2005	3	48	5	64	2.1%	0.79 [0.18, 3.47]
Wang 2009	18	73	15	42	7.6%	0.59 [0.26, 1.35]
Yin 2011	175	201	20	22	2.5%	0.67 [0.15, 3.05]
Yoshihiko 1997	29	48	23	41	5.2%	1.19 [0.51, 2.78]
Yosuke 2006	12	23	7	16	2.1%	1.40 [0.39, 5.06]
Yu 2011	9	50	2	12	1.4%	1.10 [0.20, 5.89]
Zhang 2010	40	203	4	50	2.7%	2.82 [0.96, 8.30]
Total (95% CI)		**2322**		**1250**	**100.0%**	**1.41 [1.17, 1.71]**
Total events	741		290			

Heterogeneity: Chi² = 37.66, df = 30 (P = 0.16); I² = 20%
Test for overall effect: Z = 3.64 (P = 0.0003)



Study or Subgroup	with chemotherapy Events	with chemotherapy Total	without chemotherapy Events	without chemotherapy Total	Weight	Odds Ratio M-H, Random, 95% CI
Akira Inoue 2001	14	123	11	68	4.9%	0.67 [0.28, 1.56]
Alena N.J. 2004	8	30	3	16	2.0%	1.58 [0.35, 7.02]
Andrew J Hope 2006	35	141	17	78	6.9%	1.18 [0.61, 2.29]
Bhupesh Parashar 2011	42	67	3	19	2.5%	8.96 [2.37, 33.84]
Dang 2010	23	36	23	57	4.9%	2.62 [1.10, 6.19]
Daniel T.Chang 2006	8	53	3	15	2.1%	0.71 [0.16, 3.10]
Dirk De Ruysscher 2011	1	4	22	44	0.9%	0.33 [0.03, 3.46]
Hiroshi Watanabe 1995	19	46	1	11	1.0%	7.04 [0.83, 59.68]
Huang 2011	32	136	16	73	6.6%	1.10 [0.55, 2.17]
Jedidiah M.Monson 1998	6	34	11	49	3.3%	0.74 [0.24, 2.24]
Jinyongan 2004	37	69	7	21	3.8%	2.31 [0.83, 6.43]
Li 2007	1	6	17	72	1.0%	0.65 [0.07, 5.93]
Line Claude 2004	26	58	14	32	4.8%	1.04 [0.44, 2.49]
Mao 2007	17	42	11	49	4.5%	2.35 [0.94, 5.84]
Michelle A.T. 2010	37	138	6	35	4.2%	1.77 [0.68, 4.61]
Motosugu Yamano 2007	8	65	12	70	4.1%	0.68 [0.26, 1.78]
Raymond H.Mak 2011	39	130	1	6	1.0%	2.14 [0.24, 18.95]
Shiva K.Das 2008	30	158	4	61	3.4%	3.34 [1.12, 9.92]
T.Piotrowski 2005	21	39	11	23	3.7%	1.27 [0.45, 3.57]
Tae Hyun Kim 2005	11	57	1	19	1.1%	4.30 [0.52, 35.80]
Takashi Uno 2006	3	12	0	9	0.5%	7.00 [0.32, 154.87]
Takeyuki Makimobo 1999	12	60	5	51	3.3%	2.30 [0.75, 7.04]
Tiziana Rancati 2003	9	49	5	35	2.9%	1.35 [0.41, 4.44]
Wang 2000	16	123	10	90	5.0%	1.20 [0.52, 2.78]
Wang 2005	3	48	5	64	2.0%	0.79 [0.18, 3.47]
Wang 2009	18	73	15	42	5.2%	0.59 [0.26, 1.35]
Yin 2011	175	201	20	22	2.0%	0.67 [0.15, 3.05]
Yoshihiko 1997	29	48	23	41	5.0%	1.19 [0.51, 2.78]
Yosuke 2006	12	23	7	16	2.6%	1.40 [0.39, 5.06]
Yu 2011	9	50	2	12	1.6%	1.10 [0.20, 5.89]
Zhang 2010	40	203	4	50	3.5%	2.82 [0.96, 8.30]
Total (95% CI)		**2322**		**1250**	**100.0%**	**1.38 [1.10, 1.72]**
Total events	741		290			

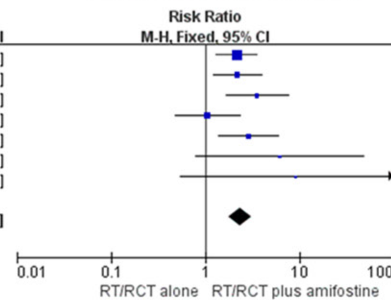
Heterogeneity: Tau² = 0.08; Chi² = 37.66, df = 30 (P = 0.16); I² = 20%
Test for overall effect: Z = 2.78 (P = 0.005)



M

Study or Subgroup	RT/RCT alone Events	RT/RCT alone Total	RT/RCT plus amifostine Events	RT/RCT plus amifostine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cai 2011	69	204	15	96	38.3%	2.16 [1.31, 3.58]
Dosia Antonadou 2003	18	27	10	33	16.9%	2.20 [1.23, 3.94]
Dosia Antonadou 2001	24	36	6	32	11.9%	3.56 [1.67, 7.58]
Dosia Antonadou 2002	15	65	7	32	17.6%	1.05 [0.48, 2.33]
Dosia Antonadou 2003	18	32	7	36	12.4%	2.89 [1.39, 6.01]
R.Komaki 2002	6	26	1	27	1.8%	6.23 [0.80, 48.27]
Rilsuko Komaki 2004	5	31	0	26	1.0%	9.28 [0.54, 160.35]
Total (95% CI)		**421**		**282**	**100.0%**	**2.38 [1.79, 3.16]**
Total events	155		46			

Heterogeneity: Chi² = 7.35, df = 6 (P = 0.29); I² = 18%
Test for overall effect: Z = 5.98 (P < 0.00001)



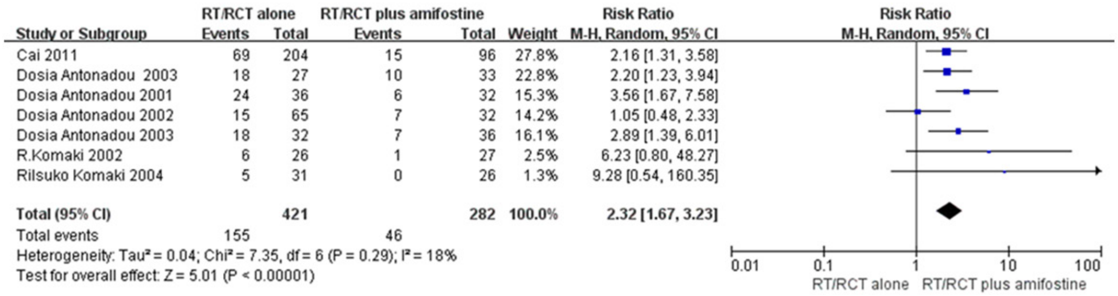


Figure 2. A. Effects estimates and 95% CI of RP odds ratio (OR) associated with Age ≤60 ys or > 60 ys. B. Effects estimates and 95% CI of RP odds ratio (OR) associated with Age ≤70 ys or > 70 ys. C. Effects estimates and 95% CI of RP odds ratio (OR) associated with chronic pulmonary diseases. D. Effects estimate and 95% CI of RP odds ratio (OR) associated with pulmonary function before radiotherapy. E. Funnel plot of RP associated with pulmonary function before radiotherapy. F. Effects estimate and 95% CI of RP odds ratio (OR) associated with diabetes. G. Effects estimate and 95% CI of RP odds ratio (OR) associated with central type vs. peripheral type lung cancer. H. Effects estimates and 95% CI of RP odds ratio (OR) associated with left lung vs. right lung cancer. I. Effects estimates and 95% CI of RP odds ratio (OR) associated with upper lung vs. middle or lower lung cancer. J. Effects estimates and 95% CI of RP odds ratio (OR) associated with operations before radiotherapy. K. Effects estimate and 95% CI of RP odds ratio (OR) associated with radio-chemotherapy treatment. L. Effects estimate and 95% CI of RP odds ratio (OR) associated with sequential chemotherapy. M. Effects estimates and 95% CI of RP odds ratio (OR) associated with operation before.

were more liable to have RP based on the result of fixed effect model (P=0.004, OR: 0.27, 95% CI: 1.33-4.58), correlated with the result (P=0.005, OR: 2.46, 95% CI: 1.32-4.60) based on random effect model, which indicated that the result was credible (**Figure 2G**).

Tumor location: 13 articles [6, 17, 18, 20, 28, 34, 38, 42, 46, 49, 50, 62, 63] including 2211 cases (**Figure 2F**), 9 articles [6, 17, 18, 20, 28, 34, 54, 59, 61] including 1880 cases (**Figure 2H**) and 3 articles [17, 56, 59] including 381 cases (**Figure 2I**) successively focused on upper lung vs. middle or lower lung, left lung vs. right lung and central type vs. peripheral type lung cancer. The OR and 95% CI of each data were 0.71 [0.57, 0.90], 1.18 [0.91, 1.52], 1.33 [0.76, 2.35] based on the fixed effect model and *P*-values each were 0.005, 0.21, 0.32, which indicated that the patients with left lower lung cancer were more likely to have RP. Adjusted into random effect model, the OR and 95% CI of each data were 0.74 [0.56, 0.99], 1.17 [0.90, 1.52], 1.32 [0.74, 2.33] and *P*-values each were 0.04, 0.23, 0.34, correlated with the result based on fixed effect model, which indicated that the result was credible.

Association with treatment factors

Operations before radiotherapy: 11 articles [8, 10, 13, 15, 16, 22, 27, 38, 52, 61, 63] including 412 cases indicated that there was no association between operation before radiotherapy and the occurrence of RP based on fixed effect model (P=0.59, OR: 0.92, 95% CI: 0.67-1.25), correlated with the result (P=0.56, OR: 0.86, 95% CI: 0.53-1.41) based on random effect model, which indicated that the result was credible (**Figure 2J**).

Combined radio-chemotherapy treatment: 31 articles including 3572 cases [8, 9, 11-13, 15-17, 20, 22, 26, 27, 29-31, 32, 35, 37, 38, 41-43, 46, 47, 50, 51, 56, 57, 60, 62] (**Figure 2K**), 18 articles including 1760 cases [9, 12, 15, 17, 27-29, 31, 35, 41, 43, 44, 46, 47, 55, 56, 60, 63] (**Figure 2L**) successively focused on radio-chemotherapy treatment vs. radiotherapy treatment alone and sequential chemotherapy vs. concurrent chemotherapy. The OR and 95% CI of the two series were 1.41 [1.17, 1.71], 0.97 [0.76, 1.25] based on fixed effect model and *P*-values were 0.0003 and 0.83, which indicated that patients with combined radio-chemotherapy treatment were more likely to have RP, Adjusted into random effect model, the OR and 95% CI of the two series were 1.38 [1.10, 1.72], 1.02 [0.71, 1.47], and *P*-values were 0.005 and 0.90, correlated with the result based on fixed effect model, which indicated that the result was credible.

The use of radiotherapy sensitization agent-Amifostine: 7 articles [63, 73-77] including 703 cases indicated that the use of Amifostine was associated with the occurrence of RP based on fixed effect model (P<0.00001, OR: 2.38, 95% CI: 1.79-3.16), correlated with the result based on random effect model (P<0.00001, OR: 2.32, 95% CI: 1.67-3.23), which indicated that the result was credible (**Figure 2M**).

Discussion

Radiation pneumonitis is a restrictive factor to limit the dosage of chest radiation dose, which is also one of the essential risk factors to affect the prognosis of lung cancer patients after radiotherapy [11]. RP often occurs 2-3 months after radiation. If patients at the acute stage were not treated on time, the grade of RP would increase. Conversely, if patients received proper treatment, the RP in some of them would be degraded and some still gradually led to the stage of lung fibrosis. As three-dimensional conformal radiotherapy (3D-CRT) is widely applied, researchers are paying more attention to the relationship between lung dose-volume histogram parameters and RP.

Recent researches suggested that, in clinical factors, gender, age, pulmonary function, tumor sites and treatment factors were related to the occurrence of radiation pneumonitis after radiotherapy. Dang J's research [11] showed that gender had independent effects on the occurrence of RP and the risk of RP morbidity in female was evidently lower than that in male, while more researchers [5, 28] supported that female patients had more opportunities to get this disease. Robnett et al. had analyzed 144 cases of patients with lung cancer, and found that the RP morbidity was higher in female than in male (15% vs. 4%, P=0.01). Their explanation was that the lung volume of female was relatively smaller, and it would be more likely for RP to occur in the same dosage of chest radiation dose. In addition, RP may be a kind of hypersensitivity, similar to autoimmune disease, which was more often in female. The interpretation of this discrepancy is difficult, the possible contributing factors, such as sample size for each gender, difference of living environment, personal smoking history, and genetic background could not be completely ruled out.

Meanwhile, it is widely believed that lung cancer patients who combined with chronic pulmonary diseases [7, 16, 26] and undertook combined radio-chemotherapy treatments [10, 11, 26, 72] had more chances to get RP. However, the influence of cigarette smoking on the development of RP had shown conflicting results in prior studies, with some showing an increase in risk, others no relationship, and still others a protective effect [80-84]. The systematic review of Vogelius I.S. et al. [80] showed that old age, middle or lower lung cancer, combined with complications were risk factors for occurrence of radiation pneumonitis after radiotherapy, and it is interesting to note that in their study current smoking status (defined as active smoking during treatment with or without continued smoking after treatment) was found to be protective against the development of RP because smoking is known to be associated with elevated basal circulating TGF beta levels [85-87]. Also, smoking was known to favor a TH2 immunologic response to noxious stimuli. It is tempting to speculate that the up-regulation of TH2 responses in the lungs of active smokers may be preventing or ameliorating increases in TGF-β during treatment and thereby protecting against the development of subsequent toxicity, but this relationship cannot be proven in this study as we do not have TGF beta levels available for review.

Conclusions

The results of this paper are all convinced by heterogeneity analysis and sensitivity test. We also evaluate the bias effects on final results through sensitivity analysis. Based on the results of our study, we raise a conclusion that the risk factors of radiation pneumonitis are chronic lung diseases, pulmonary function, diabetes, tumor located in left lower lung, combined radio-chemotherapy and using radiotherapy sensitization agent-Amifostine. That is to say, upper lung cancer patients with strong pulmonary function and without complications such as diabetes or chronic pulmonary diseases have less chance getting radiation pneumonitis after the simple radiotherapy added with radiotherapy sensitization agent-Amifostine.

Disclosure of conflict of interest

None.

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References

[1] Medhora M, Gao F, Fish BL, Jacobs ER, Moulder JE, Szabo A. Dose-modifying factor for captopril for mitigation of radiation injury to normal lung. J Radiat Res 2012; 53: 633-640.

[2] Wang D, Sun J, Zhu J, Li X, Zhen Y, Sui S. Functional dosimetric metrics for predicting radiation-induced lung injury in non-small cell lung cancer patients treated with chemoradiotherapy. Radiat Oncol 2012; 7: 69.

[3] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.

[4] Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 2010; 1: 100-107.

[5] Kong FM, Hayman JA, Griffith KA, Kalemkerian GP, Arenberg D, Lyons S, Turrisi A, Lichter A, Fraass B, Eisbruch A, Lawrence TS, Ten Haken RK. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006; 65: 1075-1086.

[6] Barriger RB, Forquer JA, Brabham JG, Andolino DL, Shapiro RH, Henderson MA, Johnstone PA, Fakiris AJ. A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2012; 1: 457-462.

[7] Shi A, Zhu G, Wu H, Yu R, Li F, Xu B. Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy. Radiat Oncol 2010; 5: 35.

[8] Claude L, Pérol D, Ginestet C, Falchero L, Arpin D, Vincent M, Martel I, Hominal S, Cordier JF, Carrie C. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: clinical and dosimetric factors analysis. Radiother Oncol 2004; 71: 175-181.

[9] Mak RH, Alexander BM, Asomaning K, Heist RS, Liu CY, Su L, Zhai R, Ancukiewicz M, Napolitano B, Niemierko A, Willers H, Choi NC, Christiani DC. A single-nucleotide polymorphism in the MTHFR (methylene tetrahydrofolate reductase) gene is associated with risk of radiation pneumonitis in lung cancer patients treated with thoracic radiation therapy. Cancer 2012; 118: 3654-3665.

[10] Ramella S, Trodella L, Mineo TC, Pompeo E, Stimato G, Gaudino D, Valentini V, Cellini F, Ciresa M, Fiore M, Piermattei A, Russo P, Cesario A, D'Angelillo RM. Adding ipsilateral V20 and V30 to conventional dosimetric constraints predicts radiation pneumonitis in stage IIIA-B NSCLC treated with combined-modality therapy. Int J Radiat Oncol Biol Phys 2010; 76: 110-115.

[11] Dang J, Li G, Lu X, Yao L, Zhang S, Yu Z. Analysis of related factors associated with radiation pneumonitis in patients with locally advanced non-small-cell lung cancer treated with three-dimensional conformal radiotherapy. J Cancer Res Clin Oncol 2010; 136: 1169-1178.

[12] Zhang L, Yang M, Bi N, Fang M, Sun T, Ji W, Tan W, Zhao L, Yu D, Lin D, Wang L. ATM polymorphisms are associated with risk of radiation-induced pneumonitis. Int J Radiat Oncol Biol Phys 2010; 77: 1360-1368.

[13] Wang LW, Fu XL, Clough R, Sibley G, Fan M, Bentel GC, Marks LB, Anscher MS. Can angiotensin-converting enzyme inhibitors protect against symptomatic radiation pneumonitis. Radiat Res 2000; 153: 405-410.

[14] Fujino M, Shirato H, Onishi H, Kawamura H, Takayama K, Koto M, Onimaru R, Nagata Y, Hiraoka M. Characteristics of patients who developed radiation pneumonitis requiring steroid therapy after stereotactic irradiation for lung tumors. Cancer J 2006; 12: 41-46.

[15] Parashar B, Edwards A, Mehta R, Pasmantier M, Wernicke AG, Sabbas A, Kerestez RS, Nori D, Chao KS. Chemotherapy significantly increases the risk of radiation pneumonitis in radiation therapy of advanced lung cancer. Am J Clin Oncol 2011; 34: 160-164.

[16] Monson JM, Stark P, Reilly JJ, Sugarbaker DJ, Strauss GM, Swanson SJ, Decamp MM, Mentzer SJ, Baldini EH. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. Cancer 1998; 82: 842-850.

[17] Das SK, Chen S, Deasy JO, Zhou S, Yin FF, Marks LB. Combining multiple models to generate consensus: application to radiation-induced pneumonitis prediction. Med Phys 2008; 35: 5098-5109.

[18] Roeder F, Friedrich J, Timke C, Kappes J, Huber P, Krempien R, Debus J, Bischof M. Correlation of patient-related factors and dose-volume histogram parameters with the onset of radiation pneumonitis in patients with small cell lung cancer. Strahlenther Onkol 2010; 186: 149-156.

[19] Takahashi H, Imai Y, Fujishima T, Shiratori M, Murakami S, Chiba H, Kon H, Kuroki Y, Abe S. Diagnostic significance of surfactant proteins A and D in sera from patients with radiation pneumonitis. Eur Respir J 2001; 17: 481-487.

[20] Uno T, Isobe K, Kawakami H, Ueno N, Kawata T, Yamamoto S, Sekine Y, Iyoda A, Iizasa T, Fujisawa T, Shigematsu N, Ito H. Dose-volume factors predicting radiation pneumonitis in patients receiving salvage radiotherapy for postlobectomy locoregional recurrent non-small-cell lung cancer. Int J Clin Oncol 2006; 11: 55-59.

[21] Fay M, Tan A, Fisher R, Mac Manus M, Wirth A, Ball D. Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2005; 61: 1355-1363.

[22] Kim TH, Cho KH, Pyo HR, Lee JS, Zo JI, Lee DH, Lee JM, Kim HY, Hwangbo B, Park SY, Kim JY, Shin KH, Kim DY. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005; 235: 208-215.

[23] Koto M, Tsujii H, Yamamoto N, Nishimura H, Yamada S, Miyamoto T. Dosimetric factors used for thoracic X-ray radiotherapy are not predictive of the occurrence of radiation pneumonitis after carbon-ion radiotherapy. Tohoku J Exp Med 2007; 213: 149-156.

[24] Song H, Yu JM. Effect of diabetes mellitus on the development of radiation pneumonitis in patients with non-small cell lung cancer. Zhonghua Zhong Liu Za Zhi 2009; 31: 45-47.

[25] Xiao C, Ding HJ, Feng LC, Qu BL, Dou YQ. Efficacy of Liangxue Jiedu Huoxue Decoction in prevention of radiation pneumonitis: a randomized controlled trial. Zhong Xi Yi Jie He Xue Bao 2010; 8: 624-628.

[26] Rancati T, Ceresoli GL, Gagliardi G. Factors predicting radiation pneumonitis in lung cancer patients: A retrospective study. Radiother Oncol 2003; 67: 275-283.

[27] Wang Y, Wang L, Feng Q, Chen D, Zhang H, Xiao Z, Zhou Z, Ou G, Zhao L, Zhang Z, Zhang K, Yin W. Factors predicting radiation toxicity in the treatment of three-dimensional conformal radiotherapy for lung cancer. Zhongguo Fei Ai Za Zhi 2005; 8: 454-458.

[28] Robnett TJ, Machtay M, Vines EF, McKenna MG, Algazy KM, McKenna WG. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000; 48: 89-94.

[29] An JY, Kwon SJ, Lee YS. Factors predicting the development of radiation pneumonitis in the patients receiving radiation therapy for lung cancer. Tuberc Respir Dis 2004; 56: 40-50.

[30] Hildebrandt MA, Komaki R, Liao Z, Gu J, Chang JY, Ye Y, Lu C, Stewart DJ, Minna JD, Roth JA, Lippman SM, Cox JD, Hong WK, Spitz MR, Wu X. Genetic variants in inflammation-related genes are associated with radiation-induced toxicity following treatment for non-small cell lung cancer. PLoS One 2010; 5: e12402.

[31] Huang EX, Hope AJ, Lindsay PE, Trovo M, El Naqa I, Deasy JO, Bradley JD. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol 2011; 50: 51-60.

[32] De Ruysscher D, Wanders R, van Haren E, Hochstenbag M, Geraedts W, Pitz C, Simons J, Boersma L, Verschueren T, Minken A, Bentzen SM, Lambin P. HI-CHART: a phase I/II study on the feasibility of high-dose continuous hyperfractionated accelerated radiotherapy in patients with inoperable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008; 71: 132-138.

[33] Wang WH, Bao Y, Chen M, Zhang L, Li KX, Xu GC, Deng XW, Lu TX, Cui NJ. Initial outcome of induction chemotherapy with weekly paclitaxel followed by three-dimensional conformal radiotherapy and concurrent weekly paclitaxel for stage III non-small cell lung cancer. Ai Zheng 2006; 25: 1279-1283.

[34] Vinogradskiy Y, Tucker SL, Liao Z, Martel MK. Investigation of the relationship between Gross tumor volume location and pneumonitis rates using a large clinical database of non-small-cell lung cancer patients. Int J Radiat Oncol Biol Phys 2011; 82: 1650-1658.

[35] Hope AJ, Lindsay PE, El Naqa I, Alaly JR, Vicic M, Bradley JD, Deasy JO. Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters. Int J Radiat Oncol Biol Phys 2006; 65: 112-124.

[36] Lee SW, Choi EK, Lee JS, Lee SD, Suh C, Kim SW, Kim WS, Ahn SD, Yi BY, Kim JH, Noh YJ, Kim SS, Koh Y, Kim DS, Kim WD. Phase II study of three-dimensional conformal radiotherapy and concurrent mitomycin-C, vinblastine, and cisplatin chemotherapy for Stage III locally advanced, unresectable, non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003; 56: 996-1004.

[37] Yin M, Liao Z, Huang YJ, Liu Z, Yuan X, Gomez D, Wang LE, Wei Q. Polymorphisms of homologous recombination genes and clinical outcomes of non-small cell lung cancer patients treated with definitive radiotherapy. PLoS One 2011; 6: e20055.

[38] Piotrowski T, Matecka-Nowak M, Milecki P. Prediction of radiation pneumonitis: dose-volume histogram analysis in 62 patients with non-small cell lung cancer after three-dimensional conformal radiotherapy. Neoplasma 2005; 52: 56-62.

[39] Oh D, Ahn YC, Park HC, Lim do H, Han Y. Prediction of radiation pneumonitis following high-dose thoracic radiation therapy by 3 Gy/fraction for non-small cell lung cancer: analysis of clinical and dosimetric factors. Jpn J Clin Oncol 2009; 39: 151-157.

[40] Kobayashi H, Uno T, Isobe K, Ueno N, Watanabe M, Harada R, Takiguchi Y, Tatsumi K, Ito H. Radiation pneumonitis following twice-daily radiotherapy with concurrent carboplatin and paclitaxel in patients with stage III non-small-cell lung cancer. Jpn J Clin Oncol 2010; 40: 464-469.
[41] Inoue A, Kunitoh H, Sekine I, Sumi M, Tokuuye K, Saijo N. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001; 49: 649-655.
[42] Yamano M, Ogino H, Shibamoto Y, Horii N. Relationship between radiation pneumonitis and prognosis in patients with primary lung cancer treated by radiotherapy. Kurume Med J 2007; 54: 57-63.
[43] Segawa Y, Takigawa N, Kataoka M, Takata I, Fujimoto N, Ueoka H. Risk factors for development of radiation pneumonitis following radiation therapy with or without chemotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1997; 39: 91-98.
[44] Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. Eur J Cancer 1998; 34: 71-75.
[45] De Petris L, Lax I, Sirzén F, Friesland S. Role of gross tumor volume on outcome and of dose parameters on toxicity of patients undergoing chemoradiotherapy for locally advanced non-small cell lung cancer. Med Oncol 2005; 22: 375-381.
[46] Makimoto T, Tsuchiya S, Hayakawa K, Saitoh R, Mori M. Risk factors for severe radiation pneumonitis in lung cancer. Jpn J Clin Oncol 1999; 29: 192-197.
[47] Matsuno Y, Satoh H, Ishikawa H, Kodama T, Ohtsuka M, Sekizawa K. Simultaneous measurements of KL-6 and SP-D in patients undergoing thoracic radiotherapy. Med Oncol 2006; 23: 75-82.
[48] Ishii Y, Kitamura S. Soluble intercellular adhesion molecule-1 as an early detection marker for radiation pneumonitis. Eur Respir J 1999; 13: 733-738.
[49] Wang J, Qiao XY, Lu FH, Zhou ZG, Song YZ, Huo JJ, Liu X. TGF-beta1 in serum and induced sputum for predicting radiation pneumonitis in patients with non-small cell lung cancer after radiotherapy. Chin J Cancer 2010; 29: 325-329.
[50] Chang DT, Olivier KR, Morris CG, Liu C, Dempsey JF, Benda RK, Palta JR. The impact of heterogeneity correction on dosimetric parameters that predict for radiation pneumonitis. Int J Radiat Oncol Biol Phys 2006; 65: 125-131.
[51] Mao J, Kocak Z, Zhou S, Garst J, Evans ES, Zhang J, Larrier NA, Hollis DR, Folz RJ, Marks LB. The impact of induction chemotherapy and the associated tumor response on subsequent radiation-related changes in lung function and tumor response. Int J Radiat Oncol Biol Phys 2007; 67: 1360-1369.
[52] Kocak Z, Yu X, Zhou SM, D'Amico TA, Hollis D, Kahn D, Tisch A, Shafman TD, Marks LB. The impact of pre-radiotherapy surgery on radiation-induced lung injury. Clin Oncol (R Coll Radiol) 2005; 17: 210-216.
[53] Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, Brindle J, Jatoi A, Jett JR; North Central Cancer Treatment Group. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol 2003; 21: 3201-3206.
[54] Clenton SJ, Fisher PM, Conway J, Kirkbride P, Hatton MQ. The use of lung dose-volume histograms in predicting post-radiation pneumonitis after non-conventionally fractionated radiotherapy for thoracic carcinoma. Clin Oncol (R Coll Radiol) 2005; 17: 599-603.
[55] Novakova-Jiresova A, Van Gameren MM, Coppes RP, Kampinga HH, Groen HJ. Transforming growth factor-beta plasma dynamics and post-irradiation lung injury in lung cancer patients. Radiother Oncol 2004; 71: 183-189.
[56] Wang J, Qiao XY, Cao YK. Analysis of correlated factors of Radiation Pneumonitis after Three-dimens Conformal Radiotherapy for Non-small Cell Lung Cancer. Chinese Journal of Clinical Oncology 2009; 36: 1086-1089.
[57] Watanabe H, Suga A, Tsuchihashi Y, Hori A, Kawakami K, Masaki H, Akiyama M, Ohishi K, Takahashi A, Nagatake T. Clinical study of radiation pneumonitis over 10 years. Nihon Kyobu Shikkan Gakkai Zasshi 1995; 33: 384-388.
[58] Xie SX, Li WX, Lin YR. Segmentation of three-dimensional conformal radiation therapy in non-small cell lung cancer treatment application. China Oncology 2006; 16: 1034-1037.
[59] Zhang B, Qiao TK. Predictors of Pulmonary Lesion Induced by Three Dimensional Conformal Radiotherapy Combined with Chemotherapy of NP for III Stage Non-small Cell Lung Cancer. Cancer Research on Prevention and Treatment 2010; 37: 578-581.
[60] Li Y, Zhu SC, Chi ZF. Three dimensional conformal radiotherapy in patients with lung cancer related factors analysis of radiation pneumonia. Cancer Research on Prevention and Treatment 2007; 34: 586-589.
[61] Zhong J, Liu J, Chen WX. Relationship between the Plasma Transforming Growth Factor-β1 Levels and Radiation-Induced Lung Injury. The Practical Journal of Cancer 2007; 22: 468-471.
[62] Yu X, Yang ZZ, Wang G. Correlative factor analysis of radiation pneumonitis in 62 locally ad-

vanced NSCLC cases treated with 3DCRT. Journal of Modern Oncology 2011; 19: 1120-1122.
[63] Cai Y, Zhou DA. Related factors analysis for Non-small cell lung cancer with radioactive pneumonia. Chinese Journal of Nosocomiology 2011; 21: 3357-3359.
[64] Yorke ED, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. Int J Radiat Oncol Biol Phys 2005; 63: 672-682.
[65] Barriger RB, Fakiris AJ, Hanna N, Yu M, Mantravadi P, McGarry RC. Dose-volume analysis of radiation pneumonitis in non-small-cell lung cancer patients treated with concurrent cisplatinum and etoposide with or without consolidation docetaxel. Int J Radiat Oncol Biol Phys 2010; 78: 1381-1386.
[66] Kim JY, Kim YS, Kim YK, Park HJ, Kim SJ, Kang JH, Wang YP, Jang HS, Lee SN, Yoon SC. The TGF-beta1 dynamics during radiation therapy and its correlation to symptomatic radiation pneumonitis in lung cancer patients. Radiat Oncol 2009; 4: 59.
[67] Zhang Y, Yu YH, Yu JM, He W, Fu Z, Guo SF, Liu XJ, Cong CS. Application of standardized uptake value for FDG PET-CT in predicting radiation pneumonitis. Zhonghua Zhong Liu Za Zhi 2009; 31: 622-625.
[68] Zhao L, Wang L, Ji W, Wang X, Zhu X, Feng Q, Yang W, Yin W. Association between plasma angiotensin-converting enzyme level and radiation pneumonitis. Cytokine 2007; 37: 71-75.
[69] Evans ES, Kocak Z, Zhou SM, Kahn DA, Huang H, Hollis DR, Light KL, Anscher MS, Marks LB. Does transforming growth factor-beta1 predict for radiation-induced pneumonitis in patients treated for lung cancer? Cytokine 2006; 35: 186-192.
[70] Kong FM, Anscher MS, Sporn TA, Washington MK, Clough R, Barcellos-Hoff MH, Jirtle RL. Loss of heterozygosity at the mannose 6-phosphate insulin-like growth factor 2 receptor (M6P/IGF2R) locus predisposes patients to radiation-induced lung injury. Int J Radiat Oncol Biol Phys 2001; 49: 35-41.
[71] Anscher MS, Kong FM, Andrews K, Clough R, Marks LB, Bentel G, Jirtle RL. Plasma transforming growth factor beta1 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 1998; 41: 1029-1035.
[72] Fu XL, Huang H, Bentel G, Clough R, Jirtle RL, Kong FM, Marks LB, Anscher MS. Predicting the risk of symptomatic radiation-induced lung injury using both the physical and biologic parameters V(30) and transforming growth factor beta. Int J Radiat Oncol Biol Phys 2001; 50: 899-908.
[73] Antonadou D, Petridis A, Synodinou M, Throuvalas N, Bolanos N, Veslemes M, Sagriotis A. Amifostine reduces radiochemotherapy-induced toxicities in patients with locally advanced non-small cell lung cancer. Semin Oncol 2003; 30 Suppl 18: 2-9.
[74] Antonadou D. Radiotherapy or chemotherapy followed by radiotherapy with or without amifostine in locally advanced lung cancer. Semin Radiat Oncol 2002; 12 Suppl 1: 50-58.
[75] Komaki R, Lee JS, Kaplan B, Allen P, Kelly JF, Liao Z, Stevens CW, Fossella FV, Zinner R, Papadimitrakopoulou V, Khuri F, Glisson B, Pisters K, Kurie J, Herbst R, Milas L, Ro J, Thames HD, Hong WK, Cox JD. Randomized phase III study of chemoradiation with or without amifostine for patients with favorable performance status inoperable stage II-III non-small cell lung cancer: Preliminary results. Semin Radiat Oncol 2002; 12 Suppl 1: 46-49.
[76] Antonadou D, Coliarakis N, Synordinou M, Athanassiou H, Kouveli A, Verigos C, Georgakopoulos G, Panoussaki K, Karageorgis P, Throuvalas N; Clinical Radiation Oncololgy Hellenic Group. Randomized phase III trial of radiation treatment +/- amifostine in patients with advanced-stage lung cancer. Int J Radiat Oncol Biol Phys 2001; 51: 915-922.
[77] Komaki R, Lee JS, Milas L, Lee HK, Fossella FV, Herbst RS, Allen PK, Liao Z, Stevens CW, Lu C, Zinner RG, Papadimitrakopoulou VA, Kies MS, Blumenschein GR Jr, Pisters KM, Glisson BS, Kurie J, Kaplan B, Garza VP, Mooring D, Tucker SL, Cox JD. Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small cell lung cancer: Report of a randomized comparative trial. Int J Radiat Oncol Biol Phys 2004; 58: 1369-1377.
[78] Nakayama Y, Makino S, Fukuda Y, Min KY, Shimizu A, Ohsawa N. Activation of lavage lymphocytes in lung injuries caused by radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1996; 34: 459-467.
[79] Vujaskovic Z, Groen HJ. TGF-beta, radiation-induced pulmonary injury and lung cancer. Int J Radiat Biol 2000; 76: 511-516.
[80] Vogelius IS, Bentzen S. Clinical factors associated with risk of radiation pneumonitis: A litterature based meta-analysis. Radiotherapy and Oncology 2010; 96: S125-S126.
[81] Johansson S, Bjermer L, Franzen L, Henriksson R. Effects of ongoing smoking on the development of radiation-induced pneumonitis in breast cancer and oesophagus cancer patients. Radiother Oncol 1998; 49: 41-47.
[82] Jin H, Tucker SL, Liu HH, Wei X, Yom SS, Wang S, Komaki R, Chen Y, Martel MK, Mohan R, Cox JD, Liao Z. Dose-volume thresholds and smok-

ing status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol 2009; 91: 427-432.
[83] Nieder C, Bremnes RM. Effects of smoking cessation on hypoxia and its potential impact on radiation treatment effects in lung cancer patients. Strahlenther Onkol 2008; 184: 605-609.
[84] Shurin MR, Shurin GV, Chatta GS. Aging and the dendritic cell cystem: Implications for cancer. Crit Rev Oncol Hematol 2007; 64: 90-105.
[85] Halwani R, Al-Muhsen S, Al-Jahdali H. Role of transforming growth factor-beta in airway remodeling in asthma. Am J Respir Cell Mol Biol 2011; 44: 127-133.
[86] Makinde T, Murphy RF, Agrawal DK. The regulatory role of TGF-beta in airway remodeling in asthma. Immunol Cell Biol 2007; 85: 348-356.
[87] Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: New molecular insights. Respiration 2011; 81: 265-284.