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REVIEW ARTICLE

Advancements in radiotherapy for lung cancer in China

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Abstract

Lung cancer is the leading cause of death due to cancer in China. In recent years, great progress has been made in radiotherapy for lung cancer patients in China. The main advancements include the following aspects: (1) stereotactic ablative radiotherapy for early stage non-small cell lung cancer (NSCLC), (2) post-operative radiotherapy for NSCLC, (3) combined chemotherapy and radiotherapy for locally advanced NSCLC, (4) improved radiotherapy for advanced NSCLC, and 5) prediction of radiation-induced lung toxicity.

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Lung cancer is the leading cause of death due to cancer in China. The annual mortality rate for lung cancer is approximately 456 deaths per million people [1], which means that approximately 600,000 people die from lung cancer every year in China. Radiotherapy is one of the most important modalities for lung cancer treatment. In recent years, great progress has been made in radiotherapy for lung cancer in China. Since non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, this paper focuses on advancements in radiotherapy for NSCLC patients in China.

Radiotherapy for early stage NSCLC

In early 2006, Xia *et al* [2] published a study on the usage of stereotactic body radiotherapy (SBRT) in patients with early stage NSCLC. Their study included 43 patients with inoperable stage I or II NSCLC treated with a stereotactic gamma-ray whole-body therapeutic system (body gamma-knife radiosurgery). A total dose of 50 Gy was delivered at 5 Gy per fraction to the 50% isodose line covering the planning target volume (PTV), whereas a total dose of 70 Gy was delivered at 7 Gy per fraction to the gross target volume (GTV). The 3-year local control rate was 95%. The 3-year overall survival (OS) rate was 91% for patients with stage I disease and 64% for patients with stage II disease. There was only one patient who developed grade 3 pneumonitis. These promising results, along with other publications [3–5], led to increased interest in stereotactic ablative radiotherapy (SABR) for early stage NSCLC [6–8]. Since then, many more studies of SBRT for early stage NSCLC have been published that have utilized various dose fractions and reported different outcomes [9–10].

A report indicated that a higher dose of radiation led to longer OS5. Based on data from 245 patients, Onishi *et al* [5] found that the local recurrence rate was 8.1% for patients who received a biologically effective dose (BED) ≥ 100 Gy compared to 26.4% for patients who received < 100 Gy ($P < 0.05$). Additionally, the 3-year OS rate was 88.4% for medically operable patients treated with a BED ≥ 100 Gy compared to 69.4% for patients who received <100 Gy ($P < 0.05$). However, Timmerman *et al* [11] reported unacceptable toxicities in cases where high doses were administered to central tumors. An ongoing dose escalation study is seeking to determine the optimal dose for central tumors (RTOG 0813). Zhang *et al* [12] reviewed published data to identify the optimal dose for stage I NSCLC patients. Their analysis included 34 studies with a total of 2,587 patients. Patients were divided into four

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groups based on the BED they received: low (< 83.2 Gy), medium (83.2–106 Gy), medium to high (106–146 Gy), or high (> 146 Gy). Corrected pooled estimates of 2- or 3-year OS were higher in the medium BED (76.1%, 63.5%) and medium to high BED (68.3%, 63.2%) groups than in the low BED (62.3%, 51.9%) and high BED (55.9%, 49.5%) groups, respectively ($P \leq 0.004$). Corrected 3-year cause-specific survival (CSS) was higher in the medium (79.5%), medium to high (80.6%), and high (90.0%) groups than in the low group (70.1%, $P = 0.016$, 0.018, and 0.001, respectively). They concluded that administration of a medium or medium to high BED (range, 83.2–146 Gy) for SBRT may be beneficial and reasonable for stage I NSCLC patients. Larger prospective studies are needed to clarify the optimal dose of SBRT (or SABR) for early stage NSCLC patients.

Robotic stereotactic radiotherapy (the CyberKnife system) integrates a compact, robotically positioned linear accelerator with image-guided stereotactic localization. This system has unique technical characteristics that make it well suited for SABR for early stage lung cancer [13]. In 2007, Brown *et al* [14] reported the use of CyberKnife for the treatment of early stage (stage IA) NSCLC. The study included 19 patients treated with total doses ranging from 24 to 60 Gy delivered in 3 fractions. Real-time target localization was accomplished by radiographic detection of fiducial marker(s) implanted within the tumor combined with respiratory motion tracking. This study found that the CyberKnife system was a safe, minimally invasive, effective modality for treatment of early stage lung cancer. In 2006, the first CyberKnife system was established in Tianjin Medical University Cancer Hospital. In 2008, Yuan *et al* [15] reported preliminary results for 17 early stage NSCLC patients: 8 patients with stage IA disease and 9 patients with stage IB disease. The median PTV was 36 cm^3, with a range of 6 cm^3 to 82 cm^3. The median dose was 50 Gy, with the doses ranging from 45 Gy to 60 Gy in 3 to 5 fractions. The Synchrony Respiratory Tracking System [13] was used for 10 patients, and the X-sight Tracking System [13] was used for 7 patients. All patients were alive during the follow-up period, with the median follow-up being 7 months. Thirteen patients achieved complete responses and 4 had partial responses. Treatment side effects were mild and mainly consisted of fatigue. Using a CyberKnife for the treatment of early stage NSCLC patients appears to be safe and effective. Since these first studies, many more publications have reported the successful use of CyberKnife technology for the treatment of early stage NSCLC [16–20]. Song *et al* [20] reported the safe use of a CyberKnife in elderly patients with early stage NSCLC. In their study, 34 patients with a median age of 78 years were treated with 45 to 60 Gy in 3 to 6 fractions. After a median follow-up duration of 29 months, local control of the primary lesion was achieved in 97.1% of the patients, and the 3-year progression-free survival (PFS) and OS rates were 70.0% and 80.0%, respectively. Robotic stereotactic radiotherapy could be a suitable option for patients with early stage NSCLC.

Post-operative radiotherapy (PORT) in NSCLC patients

Since the PORT meta-analysis was published in 1998 [21], the use of PORT for patients with resected NSCLC has declined worldwide [22–24]. However, improvements in conformal radiotherapy techniques made in the past decade have led to a resurgence of interest in the effects of PORT on stage IIIA-N2 NSCLC [24–30]. Dai *et al* [27] retrospectively analyzed the effects of PORT in patients with resected pathological stage III-N2 NSCLC. The study included 221 consecutive patients treated at Peking Medical College Cancer Hospital. Their results indicated that patients treated with PORT had a significantly longer OS ($P = 0.046$) and disease-free survival ($P = 0.009$), as well as a trend toward longer CSS ($P = 0.062$), compared to the non-PORT group. Patients treated with PORT also had significantly higher rates of locoregional recurrence-free survival ($P = 0.025$) and distant metastasis-free survival ($P = 0.001$). Multivariate analysis showed that PORT was significantly associated with longer OS ($P = 0.000$). The authors concluded that PORT significantly improved the survival of patients with resected pathological stage IIIA-N2 NSCLC. It appears that PORT can be beneficial, but it is important to identify the type of patients who will benefit from PORT. A prospective randomized multicenter clinical trial is ongoing to further validate these findings (NCT00880971).

To select patients suitable for PORT, the prognosis of patients who undergo surgical resection should be extensively studied. Many studies have indicated that the number of lymph nodes dissected and the metastatic lymph node ratio were prognostic factors that impacted disease failure and OS [31–32]. Du *et al* [28] studied the relationship between lymph node metastasis status and the effectiveness of PORT in patients with NSCLC in an effort to select the patients who would benefit most from PORT. Retrospective analysis of clinical data from 359 stage N2 NSCLC patients treated with radical surgery revealed that the 5-year survival rates in the PORT and non-PORT groups were 29% and 24%, respectively ($P = 0.047$). Lymph node metastasis ratio and primary tumor size both significantly correlated with the effectiveness of PORT. Patients were divided into three groups based on the following risk factors: primary tumor > 3 cm and lymph node metastasis ratio > 33%. High-risk group patients had both risk factors, medium-risk group patients had one risk factor, and low-risk group patients had neither or the risk factors. The 5-year OS of the PORT and non-PORT patients in the three groups were as follows: high-risk group, 42%

vs. 16% (P = 0.000); medium-risk group, 26% vs. 22% (P = 0.786); and low-risk group, 22% vs. 50% (P = 0.199). Therefore, only patients in the high-risk group benefited from PORT [33].

In addition to clinical characteristics, molecular biomarkers to predict the prognosis of patients with resected NSCLC were studied. Many biomarkers were found to be correlated with prognosis [30, 34] and may be selected as predictors for PORT. However, larger prospective randomized studies should be performed to validate these findings.

Radiotherapy for locally advanced NSCLC patients

The current standard of care for stage III unresectable NSCLC patients is concurrent chemoradiotherapy, if patients are able to tolerate the combined modality. The etoposide plus cisplatin (EP) regimen is a standard treatment that is combined with radiotherapy for concurrent chemoradiotherapy for NSCLC. However, newly developed drugs are commonly used in the clinic, and many other regimens, such as the paclitaxel plus carboplatin (PC) regimen, are also used concurrently with thoracic radiotherapy. Ren *et al* [35] compared some the regimens commonly used for concurrent chemoradiotherapy for locally advanced NSCLC. Data from 106 patients were retrospectively analyzed. The median survival times (MSTs) of patients treated with paclitaxel-containing, topotecan-containing, and EP regimens were 16.3, 27.3, and 29.1 months, respectively (P < 0.05). Paclitaxel-based regimens were associated with a higher incidence of acute radiation pneumonitis (RP) than the other regimens (10.6% vs. 27.3%, P = 0.03). Based on this retrospective analysis, Wang *et al* [36] conducted a phase II prospective randomized clinical trial to further compare the effects of the EP and PC regimens in patients with unresectable stage III NSCLC. Patients were randomly assigned to receive one of the two regimens. The EP arm received cisplatin (50 mg/m^2) on days 1, 8, 29, and 36, and etoposide (50 mg/m^2) on days 1 through 5 and 29 through 33 as well as 60 Gy of thoracic radiotherapy. The PC arm received weekly concurrent carboplatin (area under the curve = 2) and paclitaxel (45 mg/m^2) plus 60 Gy of radiotherapy. A total of 65 patients were randomized to the treatment arms. The 3-year OS was significantly better in the EP arm than in the PC arm (33.1% vs. 13%, P = 0.04). The rate of grade 2 or greater RP was 25% in the EP arm and 48.5% in the PC arm (P = 0.09). These results suggest that a weekly PC regimen is not recommended, since it did not improve OS or PFS. A recent meta-analysis based on individual patient data showed that concurrent treatment with the PC regimen was associated with a higher risk of RP than concurrent treatment with the EP regimen (odds ratio = 3.33, P < 0.001). The highest risk of RP (>50%) was in patients > 65 years of age who were treated with the PC regimen [37]. These results may partially explain why the EP regimen is associated with more favorable outcomes when administered as part of concurrent radiotherapy.

Many other new drugs have been tested for their efficacy and safety in combination with radiotherapy [38–43]. Along with their clinical use as targeted therapy, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) [44] and angiogenesis inhibitors [45–48] have also been studied in China for their efficacy and safety in combination with concurrent radiotherapy. Jiang *et al* [46] investigated the clinical effects of weekly recombinant human endostatin (RHES) as a hypoxic tumor cell radiosensitizer combined with radiotherapy for NSCLC treatment. Fifty patients with pathologically diagnosed NSCLC (stage I–III) that was confirmed to be hypoxia positive by hypoxia imaging and hypoxia inducible factor-1α immunohistostaining were randomly divided into two groups: a RHES plus radiotherapy group and a radiotherapy only group. The total response rates (complete response plus partial response) in the RHES plus radiotherapy and radiotherapy only groups were 80% and 44%, respectively (P = 0.009). The 2-year local control rates were 63.6% and 43.4%, respectively (P = 0.022), and the median PFS times were 21.1 and 16.5 months, respectively. Further examination showed that the radiosensitizing effect was associated with normalization of the tumor vasculature [47]. Although many kinds of targeted therapy have been studied in combination with radiotherapy for NSCLC treatment, few positive results have been published. There is much enthusiasm for combinations of targeted therapy and radiotherapy in lung cancer, but care should be taken to avoid the negative effects of these combinations. Zhuang *et al* [43] reported preliminary results concerning the incidence of RP in patients treated with concurrent erlotinib and thoracic radiotherapy. In this study, 3 of 24 analyzed patients (12.5%) developed grade 5 RP, which is not acceptable for NSCLC radiotherapy. At the 2012 American Society for Radiation Oncology annual meeting, Santos *et al* [49] presented a meta-analysis of 8 trials (4 phase I, 4 phase II) that included 242 patients and tested 4 different drugs (bevacizumab, cetuximab, erlotinib, and gefitinib). Combining targeted therapy with concurrent radiotherapy significantly increased the rate of severe adverse events in NSCLC patients compared to concurrent radiotherapy alone, whereas no significant differences were observed in survival endpoints. So far, there is no concrete evidence to support the use of targeted therapy in combination with radiotherapy. The EP regimen is still the standard chemotherapy treatment used concurrently with thoracic radiotherapy.

Advancements in radiation techniques may improve radiotherapy outcomes for lung cancer patients [50–52]. Cao *et al* [52] compared treatment outcomes between three-di-

mensional conformal radiotherapy (3D-CRT) and conventional radiotherapy (2D) for patients with locally advanced NSCLC in a study that included 527 patients with stage III NSCLC. The 5-year OS rate and MST were 14.4% and 20.1 months for patients treated with 3D-CRT and 8.0% and 15.6 months for patients treated with 2D radiotherapy ($P = 0.002$), respectively. These results demonstrate that 3D-CRT improves survival compared to 2D radiotherapy, which is consistent with the study by Liao *et al* [53].

In many phase I and II dose escalation studies, and in some retrospective studies, increasing the radiation dose has improved treatment outcomes for patients with locally advanced NSCLC [54–57]. In order to escalate the radiation dose to the target volume, involved-field radiotherapy (IFRT) is used most commonly instead of elective nodal irradiation (ENI). Many clinical studies have evaluated the safety and efficacy of IFRT [58–59]. Yuan *et al* [58] reported the results of a randomized clinical trial that evaluated the effects of IFRT in NSCLC patients treated with increasing radiation doses. In this study, 3D-CRT was delivered in once-daily fractions of 1.8 to 2 Gy for a total of 68 to 74 Gy for IFRT or 60 to 64 Gy for ENI. Patients in the IFRT arm achieved a better overall response rate (90% vs. 79%, $P = 0.032$) and better 5-year local control rate (51% vs. 36%, $P = 0.032$) than patients in the ENI arm. The 5-year OS was 25.1% in the IFRT arm and 18.3% in the ENI arm. Although many studies have suggested that increasing radiation doses may improve survival in patients with locally advanced NSCLC, a randomized clinical trial (RTOG 0617) failed to show a survival advantage with higher radiation doses [60]. Simply increasing the radiation dose is not enough to improve treatment outcomes.

Researchers have attempted many other methods for improving treatment outcomes. Zhu *et al* [61] published the results of a phase II trial of accelerated hypofractionated 3D-CRT in locally advanced NSCLC patients. In this study, all patients received accelerated hypofractionated radiotherapy (initially 50 Gy in 20 fractions, then a fraction dose of 3 Gy) using 3D-CRT, omitting ENI, for a total dose of 65–68 Gy. All patients received two cycles of induction chemotherapy. One to two cycles of consolidation chemotherapy were administered to 31 patients. The study reported that the radiation toxicity was minimal. The median OS and PFS times were 19.0 and 10.0 months, respectively. This study suggested that accelerated hypofractionated radiotherapy using 3D-CRT and omitting ENI can be used in combination with sequential chemotherapy for locally advanced NSCLC. These results were also compared to standard concurrent chemoradiotherapy with a conventional dose fraction schedule [62]. Sequential chemotherapy with accelerated hypofractionated radiotherapy achieved outcomes similar to concurrent chemotherapy with standard radiotherapy; however, there were fewer treatment-associated toxicities in the sequential chemoradiotherapy group.

Liu *et al* [63] tested a different method to increase the probability of tumor control and decrease the risk of treatment-related toxicities. Using intensity-modulated radiotherapy (IMRT), they maintained the radiation dose to the GTV while decreasing the dose to the prophylactic area, thereby increasing the treatment ratio. The prescribed dose was 60 Gy in 30 fractions at 2.0 Gy per fraction to the planning GTV (PGTV, expanding the GTV by 0.5 cm margin), and 54 Gy in 30 fractions at 1.8 Gy per fraction to the PTV. All patients received induction chemotherapy and 25 patients received adjuvant chemotherapy, with 17 of them receiving concurrent chemoradiotherapy. The median OS and PFS for the whole group were 24 and 14 months, respectively. Preliminary results from this study suggest that simultaneous integrated boost-IMRT is safe and effective in patients with stage III NSCLC. All of these studies suggest new directions for the treatment of locally advanced NSCLC.

Prediction of patient prognosis before radiation or early on during the course of treatment could allow for modification of the treatment regimen to further improve outcomes. Many studies have been performed to address this issue [64–72]. In early 1999, Kong *et al* [64] found that pre-radiotherapy plasma transforming growth factor β1 (TGF-β1) levels were significantly higher in patients with lung cancer than in normal controls. TGF-β1 levels were also significantly higher in patients with disease at the last follow-up than in patients with no evidence of disease. Zhao *et al* [65] further examined correlations between dynamic changes in circulating TGF-β1 levels during radiotherapy and the prognosis of 65 patients with locally advanced NSCLC treated with radiotherapy with or without chemotherapy. TGF-β1 levels were measured for each patient within 1 week before radiotherapy (pre-radiotherapy) and in the fourth week of radiotherapy (during-radiotherapy); this information was used to calculate the TGF-β1 ratio (during-radiotherapy level/pre-radiotherapy level). Median OS was 30.7 months for patients with a TGF-β1 ratio ≤ 1 vs. 13.3 months for patients with a TGF-β1 ratio > 1 ($P = 0.0029$); median PFS for these patients was 16.8 months vs. 7.2 months, respectively ($P = 0.010$). This study suggested that decreased TGF-β1 levels during radiotherapy in locally advanced NSCLC patients correlates with favorable prognosis. Xue *et al* [66] studied associations between single nucleotide polymorphisms (SNPs) in the TGF-β1 gene and treatment outcomes in a Chinese population. They found that the TGF-β1 C509T CC genotype was significantly associated with better OS than the CT and TT genotypes. Another clinical study from Japan showed similar results [73]. However, research from MD Anderson Cancer Center yielded different re-

sults [74]; a multivariate analysis found that the TGFB1 rs1800469 (C509T) CT/CC genotype was associated with poor OS, which was different from the Chinese and Japanese findings.

Many other biomarkers have been examined for predictive power in locally advanced NSCLC [67–71]. Bi *et al* [67] extensively studied the association between cyclooxygenase-2 (COX-2) genetic variants and patient survival in unresectable locally advanced NSCLC. In a study that included 136 patients with inoperable stage IIIA or IIIB NSCLC treated with thoracic radiation, the favorable COX-2 -1195GA and GG genotypes significantly correlated with better OS (20.2 months vs. 15.7 months, P = 0.006) and longer PFS (11.9 months vs. 9.5 months, P = 0.034) than the -1195AA genotype. In a multivariate Cox proportional hazards model, the COX-2 -1195G/A polymorphism was independently associated with OS after adjusting for clinicopathologic factors [P = 0.008; hazard ratio (HR), 0.58; 95% confidence interval (CI), 0.39–0.87].

With advances in molecular biology techniques, an increasing number of biomarkers will be identified and validated. In daily clinic practice, higher radiation doses will be administered to patients with biomarkers of radioresistance, and chemotherapy regimens will be tailored accordingly; this will improve treatment outcomes significantly.

Radiotherapy in advanced stage NSCLC patients

Platinum-based doublet chemotherapy is the standard treatment modality for advanced stage NSCLC patients with a good performance status; this therapy may improve survival and quality of life compared to supportive care alone. Thoracic radiotherapy is typically used for palliative purposes [75] as it is an effective way to relieve symptoms. In addition to its palliative effects, recent studies have suggested that adding thoracic radiotherapy to their treatment regimen may improve the survival of patients with stage IV NSCLC [76–79].

Su *et al* [76] examined the efficacy and toxicities of thoracic radiotherapy in advanced NSCLC patients treated with radiotherapy and chemotherapy. The MST in their study was 10.0 months, and the 1-, 2-, and 3-year OS rates were 40.2%, 16.4%, and 9.6%, respectively. The MSTs were 14.0 months for patients who received a total radiation dose ≥ 63 Gy to the primary tumor and 8.0 months for patients who received a total dose < 63 Gy (P = 0.000). Multivariate analysis revealed that a total dose ≥ 63 Gy was an independent prognostic factor for better OS. Treatment-related toxicities were found to be acceptable. This study suggested that radiotherapy should be actively considered, along with systemic chemotherapy, for the treatment of advanced stage NSCLC patients.

Currently, more and more suitable patients are being identified for treatment with EGFR-TKI targeted therapy. However, most patients develop EGFR-TKI resistance and treatment failure, with single-site progression observed in more than 80% of patients [80]. Early administration of radiotherapy may help improve treatment outcomes and prolong survival times [77–79]. Wang *et al* [79] conducted a prospective study to evaluate the safety and efficacy of EGFR-TKIs administered concurrently with radiotherapy in patients with locally advanced or metastatic NSCLC. They studied 26 patients who were treated with EGFR-TKIs and concurrent thoracic radiotherapy. The median thoracic radiation dose was 70 Gy to the GTV. Severe adverse events included neutropenia (grade 4, 4%), thrombocytopenia (grade 4, 8%), esophagitis (grade 3, 4%), and pneumonitis (grade 3, 4%). With a median follow-up period of 10.2 months, a local control rate of 96% was achieved for the thoracic tumors. The median PFS and MST were 10.2 and 21.8 months, respectively. Similar results from other studies also support early intervention with radiotherapy for patients who respond well to EGFR-TKIs or who are resistant to EGFR-TKIs [77, 81], especially in patients with brain metastasis, which may be difficult for the EGFR-TKIs to reach [81–84]. Zhuang *et al* [84] performed a prospective randomized study to explore the efficacy of whole brain radiotherapy (WBRT) concurrent with erlotinib in patients with multiple brain metastases from lung adenocarcinoma. The study included 31 patients treated with WBRT alone and 23 patients treated with the combination of WBRT and erlotinib. The objective response rates were 54.84% and 95.65% in the WBRT alone and the combination arms, respectively (P = 0.001). The median local PFS times were 6.8 and 10.6 months, respectively (P = 0.003), the median PFS times were 5.2 and 6.8 months, respectively (P = 0.009), and the median OS times were 8.9 and 10.7 months, respectively (P = 0.020). No grade 4 or higher toxicities were observed in either group. Multivariate analysis indicated that erlotinib was the most important prognostic factor for prolonged survival.

All of these results support early administration of radiotherapy for advanced NSCLC patients who are able to tolerate the combined therapy. The role of radiotherapy in advanced stage NSCLC patients needs to be evaluated further.

Radiation-induced lung toxicity

Radiation-induced lung toxicity (RILT) is one of the most important obstacles to lung cancer radiotherapy. Many clinical factors have been reported to correlate with RILT, including diabetes mellitus [85–86], poor baseline pulmonary function (PF) [87], thoracic operations [88],

and various chemotherapy regimens [36, 37]. It was generally accepted that poor PF correlated with higher risk of RILT. However, a recently published report found that poor baseline PF did not increase the risk of symptomatic RILT (SRILT). The study, which included 260 patients, found that the risk of SRILT increased with the absence of chronic obstructive pulmonary disease ($P = 0.047$) and with increased forced expiratory volume in 1 s ($P = 0.077$). Therefore, it may not be necessary to exclude definitive radiotherapy as an option for patients with poor PF [87]. For patients who undergo surgery, when dose constraints are applied to normal lung tissue, the risk of RILT for post-operative radiotherapy is acceptable. In these cases, it is recommended that the percentage of the lung that receives > 20 Gy radiation (V20) should be < 25% for patients who underwent lobectomies and < 10% for patients who underwent pneumonectomies [88].

Concurrent chemoradiotherapy is the standard of care for medically suitable patients with locally advanced NSCLC. The various chemotherapy regimens used concurrently with radiotherapy may be associated with different risks of RILT. A phase II study by Wang *et al* compared two chemotherapy regimens and found that patients treated with the PC regimen had a higher risk of RILT than patients treated with the EP regimen; grade 2 or higher RILT occurred in 48.5% and 25% of patients, respectively ($P = 0.09$) [36]. Meta-analysis of individual patient data confirmed these findings by showing that carboplatin and paclitaxel treatment was a significant risk factor for RILT [37].

The relationship between dose-volume parameters to normal lung tissue and the risk of RILT has been extensively studied, and many important parameters that correlate with RILT have been established. The most commonly used parameters for the prediction of RILT are V20 and mean lung dose (MLD). Recently, an increasing amount of data supports the idea that the volume of the lung that receives a relatively low dose of radiation may be important for the development of RILT [89–90]. Using a receiver operating curve method, Wang *et al* [90] found that the V5 and V20 were the most important factors for RILT development ($P = 0.045$ and 0.037, respectively). Another study from Beijing [91] found that V10 ($P = 0.015$) was one of the most significant factors associated with severe acute RP (SARP). The incidence of SARP was 5.7% in patients with V10 ≤ 50%, compared to 29.2% in patients with V10 > 50% ($P < 0.01$). An animal study from Tianjin Medical University Cancer Hospital [92] confirmed the assertion that a low radiation dose spread over a large volume may lead to fatal respiratory dysfunction. Clinically, both the volume and dose of radiation to the normal lung need to be considered.

Many cytokines have been studied for correlations with RILT [93–94]; TGF-β1 is perhaps the most extensively studied. A recently published combined analysis from Beijing and Michigan [94] reported that RILT occurred in 46.2% of patients with elevated plasma TGF-β1 levels during radiotherapy (TGF-β1 ratio > 1) compared to only 7.9% of patients without elevated levels (TGF-β1 ratio ≤ 1; $P < 0.001$). Additionally, the rate of RILT was 42.9% in patients who received a MLD > 20 Gy compared to 17.4% in patients treated with a MLD ≤ 20 Gy ($P = 0.024$). Combining the two risk factors further increased the predictive power. RILT incidence rates were 4.3% in patients with a TGF-β1 ratio ≤ 1 and MLD ≤ 20 Gy; 47.4% in patients with a TGF-β1 ratio > 1 or MLD > 20 Gy; and 66.7% in patients with a TGF-β1 ratio > 1 and MLD > 20 Gy ($P < 0.001$). These results suggest that the combination of TGF- β1 and MLD may help stratify patients according to their risk of RILT.

In addition to circulating cytokines, correlations between genetic variants and RILT risk have recently attracted increased interest. Based on clinical data from MD Anderson Cancer Center, Yuan *et al* [95] found that the CT/CC genotypes of TGFB1 rs1982073:T869C were associated with a statistically significantly lower risk of RP than the TT genotype. However, this association does not appear to exist in Chinese populations [96–97]. Niu *et al* [96] found that the rs1982073 SNP was not associated with RP risk in Chinese patients. However, the novel TGFB1 SNP rs11466345 was found to be associated with RP risk. Further studies are warranted to confirm these findings in populations of different ethnicities.

Many other genetic variations have been evaluated for associations with the risk of RILT [98–100]. Because the ataxia telangiectasia mutated (ATM) protein plays crucial roles in repair of double-stranded DNA breaks, control of cell cycle checkpoints, and radiosensitivity, a study was performed to look for associations between ATM variants and RILT in 253 lung cancer patients [98]. Two ATM variants were found to be independently associated with an increased risk of RILT: the 111G>A polymorphism (HR, 2.49; 95% CI, 1.07–5.80) and the 126713G>A polymorphism (HR, 2.47; 95% CI, 1.16–5.28). Associations between TP53 polymorphisms and RILT risk have also been studied [99]. The TP53 72Arg/Arg genotype was found to be associated with an increased RP risk compared to the 72Pro/Pro genotype. Furthermore, the TP53 Arg72Pro and ATM -111G>A polymorphisms displayed an additive combination effect that intensified the risk of developing RP. A cross-validation test demonstrated that 63.2% of RP cases could be identified by TP53 and ATM genotypes. Adding SNP information to dose-volume parameters can improve the predictive ability [101]. Although these results are promising, a larger prospective study is needed to validate the reliability of SNPs for the prediction of RILT in daily clinical practice.

Disclosure: The authors declare that they have no

competing interests.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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