ACTA ONCOLOGICA
2020, VOL. 59, NO. 5, 569–573
https://doi.org/10.1080/0284186X.2020.1730002

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Stereotactic ablative radiotherapy in patients with early-stage non-small cell lung cancer and co-existing interstitial lung disease

Tobias Finazzi[a]*, Merle I. Ronden-Kianoush[a]*, Femke O. B. Spoelstra[a], Esther J. Nossent[b], Suzan F. M. Nijman[b], Idris Bahce[b], Chris Dickhoff[c] and Suresh Senan[a]

[a]Department of Radiation Oncology, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [b]Department of Pulmonary Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [c]Department of Surgery and Cardiothoracic Surgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands

ARTICLE HISTORY Received 17 November 2019; accepted 11 February 2020

Introduction

Stereotactic ablative radiotherapy (SABR) is the preferred treatment in medically inoperable patients with early-stage non-small cell lung cancer (NSCLC) [1]. However, there is growing awareness of the risks of SABR in patients with interstitial lung disease (ILD) [2–4], who also have a higher incidence of lung cancer [5]. The term ILD encompasses a large group of parenchymal pulmonary disorders, including idiopathic pulmonary fibrosis (IPF), a form of chronic, progressive fibrosing interstitial pneumonia, characterized by sudden episodes of acute worsening [6]. An accurate diagnosis can be difficult due to the lack of diagnostic molecular markers, and due to overlapping radiographic and histologic patterns with autoimmune and granulomatous lung diseases, as well as other idiopathic interstitial pneumonias [7–9]. Tumor boards often face a major challenge when assessing patients with an early-stage NSCLC and radiological findings of interstitial fibrosis, particularly in patients for whom a definitive ILD diagnosis has not been established [10].

Both lung surgery and SABR are associated with increased toxicity in patients with ILD [2,11]. A systematic review reported a SABR-related mortality rate of 16%, and suggested that toxicity may be minimized by limiting lung doses [2]. With this in mind, we modified our SABR planning and delivery approach for this patient group. An expert ILD panel evaluation was incorporated, aiming for improved classification of the subtypes and stages of ILD treated at our center. This brief report summarizes our institutional experience with SABR in patients with early-stage NSCLC and co-existing ILD, which may allow for future pooled analyses of the limited literature on SABR outcomes in this cohort [2–4].

Material and methods

Institutional ethics approval was obtained to establish a database of all patients with ILD who were treated for a lung tumor in our institution since 2007. The initial patients included in our database were those in whom the presence of ILD was revealed after a retrospective review of pretreatment imaging in patients undergoing SABR for a moderately central, ultracentral, or >5 cm measuring tumor [10,12,13]. The second group included patients that were routinely screened and referred for ILD review once awareness of this risk factor became widespread within the institutional tumor board after 2015. Reports of the institutional tumor board meetings were screened to identify missing cases. In addition, clinical notes of a dedicated ILD-lung cancer team, which was established in 2015 to provide expert review of possible ILD cases, were reviewed. Using this information, we identified patients with co-existing ILD that had undergone SABR for early-stage NSCLC. We defined SABR as involving use of $\leq$12 fractions, delivered in fraction sizes of $\geq$5 Gy. Initially, all SABR was delivered on a linear accelerator with image-guided radiation therapy (RT) using daily cone-beam computed tomography (CT) imaging (Varian Medical Systems, USA). We used a motion-encompassing internal target volume (ITV) approach, with delivery of volumetric modulated arc therapy (VMAT) treatment plans. Since 2016, patients were preferably treated using magnetic resonance (MR-)guided SABR (ViewRay Inc., USA), which uses real-time MR imaging to deliver gated SABR to smaller target volumes, an thus reduced lung doses [14,15].

The database included information on the ILD subtype based on clinical, radiological, and histopathological data. ILD-related prognosis was scored using the ILD-gender age physiology (GAP) index [16]. Follow-up data were collected from medical records and from referring institutions, if necessary. Local control and overall survival (OS) were estimated using the Kaplan–Meier (KM) method, calculated from the start of RT. Median follow-up was defined using the reverse KM method [17]. Patients were censored for local control at last CT or positron emission tomography (PET-)CT imaging. Reported toxicities were scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [18], and verified by at least two radiation oncologists. Lung

CONTACT Tobias Finazzi t.finazzi@amsterdamumc.nl Department of Radiation Oncology, Amsterdam University Medical Centers, location VUmc, Postbox 7057, 1007 MB Amsterdam, The Netherlands
*These authors contributed equally to this work.

doses were defined based on lungs minus the planning target volume (PTV). Comparative statistics were performed using Wilcoxon rank sum test, and a p value $<.05$ was considered to be statistically significant. All analyses were carried out using RStudio v1.1.456 (RStudio, USA).

Results

As of October 2019, our database comprised 50 patients with ILD who were treated for a lung tumor at our institution over a 12-year period from 2007 to 2019. Nineteen patients had undergone SABR with curative intent for an early-stage NSCLC (stage IA–IIB, TNM 8th edition). The remaining patients with co-existing ILD underwent surgery with or without adjuvant treatment ($n = 11$), chemoradiation ($n = 7$), conventional RT ($n = 5$), SABR for lung metastases ($n = 3$), palliative chemotherapy ($n = 4$), or best supportive care ($n = 1$).

Characteristics of the 19 patients with early-stage NSCLC are summarized in Table 1. The median age was 78 years (range, 61–91) at time of SABR, with a median Eastern Cooperative Oncology Group (ECOG) performance status of 2 (range, 0–3). The commonest ILD subtype scored was IPF, followed by unclassifiable ILD. The median ILD-GAP score was 4 (range, 0–6) [16]. Biopsy confirmation of NSCLC was obtained in 8 patients, and 11 patients were diagnosed after multidisciplinary review of clinical and radiological features [1].

Details of SABR are summarized in Table 2. SABR was delivered using either conventional (ITV-based) SABR ($n = 12$) or MR-guided SABR ($n = 7$), in a median of eight fractions and to a median biologically effective dose (BED_{10Gy}) of 105.0 Gy (range, 90.0–151.2). The median GTV and PTV were 21.5 cm^3 (range, 1.2–66.0) and 76.4 cm^3 (3.1–140.8), respectively. The respiration-gated PTVs used for MR-SABR were smaller than the ITV-based PTVs (mean 38.8 versus 88.2 cm^3, $p = .03$), but GTVs in the latter group also appeared larger (mean 20.8 versus 31.0 cm^3; $p = .23$).

Median follow-up was 25.0 months (95%CI, 23.2-NR). The 12-month rate of OS was 68.4% (95%CI, 50.4–92.9), and median OS was 16.6 months (95%CI, 12.3-NR). Five patients developed recurrent disease, with distant metastases and second lung primaries as the first site of recurrence in two patients each, and a regional lymph node recurrence in another patient. No local tumor recurrence has been observed, although follow-up imaging was limited in this cohort, with CT or PET-CT scans at 6, 12 and 18 months available in only 12, 8 and 5 patients, respectively.

Grade $\geq$2 lung toxicity was observed in 6 (32%) patients, with 4 (21%) cases classified as a possible, probable or definite grade 5 radiation pneumonitis (RP). Although based on a low number of observations, patients developing symptomatic (grade $\geq$2) RP had larger PTVs (mean 95.7 versus 58.2 cm^3; $p = .04$) than those who did not, and also received higher total (mean 4.5 versus 3.2 Gy; $p = .04$) and ipsilateral (mean 10.0 versus 6.5 Gy; $p = .03$) mean lung doses (MLD_{EQD2}). In three patients, fatal RP developed at 1.5, 3 and 6 months after SABR, following hospitalization for progressive dyspnea. Another patient was a 74-year-old man with advanced IPF (ILD-GAP 6), who developed signs of accelerated ILD and/or RP during the first month following SABR. Following symptomatic improvement under steroids, the patient's health gradually declined and he ultimately died at home 13 months after SABR, which we scored as a probable grade 5 RP. Non-SABR-related causes of death were metastatic disease ($n = 4$), cerebral or cardiovascular events ($n = 2$), infections ($n = 2$), Parkinson's disease ($n = 1$), acute

Table 1. Patient characteristics.

Nr.	Sex	Age at RT	ECOG	ILD subtype	ILD-GAP	FVC %pred	DLCO %pred	ILD therapy	NSCLC histology	Lobe	AJCC stage (8th Ed)
1	M	78	2	IPF (probable UIP)	4	66	69	None	SCC	RLL	IIB
2	M	74	1	NSIP	2	73	60	None	SCC	RLL	IB
3	M	67	1	CT-ILD (SLE)	3	97	29	Prednisone	SCC	RUL	IB
4	M	72	2	IPF (UIP)	4	59	93	None	No biopsy	RUL	IA
5	M	89	0	Unclassifiable ILD	4	84	51	None	No biopsy	RLL	IB
6	M	68	1	NSIP	4	57	33	None	SCC	LLL	IA
7	M	86	2	Unclassifiable ILD	3	133	94	None	No biopsy	LLL	IB
8	M	72	3	IPF (probable UIP)	6	78	Not possible	None	AC	LUL	IB
9	M	79	3	IPF (UIP)	5	111	31	None	No biopsy	LLL	IA
10	F	76	2	CPFE (probable UIP)	3	122	40	None	No biopsy	LUL	IA
11	F	68	2	DIP	4	83	27	Prednisone	No biopsy	LLL	IA
12	M	81	1	Unclassifiable ILD	5	58	44	None	No biopsy	RML	IA
13	M	61	2	Unclassifiable ILD	2	86	56	None	No biopsy	LUL	IA
14	M	88	2	IPF (probable UIP)	4	86	47	None	No biopsy	RLL	IA
15	M	74	2	IPF (UIP)	6	54	21	Nintedanib	SCC	LUL	IB
16	M	86	1	IPF (probable UIP)	4	86	39	Nintedanib	No biopsy	RUL	IA
17	F	81	1	CHP	0	92	70	None	NOS	LUL	IA
18	F	80	0	IPF (probable UIP)	3	102	40	Pirfenidone	SCC	RLL	IB
19	M	91	1	Unclassifiable ILD	5	99	38	None	No biopsy	RLL	IB

Characteristics of 19 patients with early-stage NSCLC and co-existing ILD who underwent SABR (listed in chronological order of treatment).
AC: adenocarcinoma; AJCC: American Joint Committee on Cancer; CT-ILD: chronic tissue disease-associated ILD; CPFE: combined pulmonary fibrosis and emphysema; CHP: chronic hypersensitivity pneumonitis; DIP: desquamative interstitial pneumonia; DLCO: diffusion capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FVC: forced vital capacity; F: female; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; LUL: left upper lobe; LLL: left lower lobe; M: male; NSCLC: non-small cell lung cancer; NSIP: nonspecific interstitial pneumonia; SLE: systemic lupus erythematosus; %pred: percentage of predicted; NOS: not otherwise specified; SABR: stereotactic ablative radiotherapy; SCC: squamous cell carcinoma; UIP: usual interstitial pneumonia; RT: radiation therapy; RLL: right lower lobe; RUL: right upper lobe; RML: right middle lobe.

Table 2. SABR in patients with early-stage NSCLC and co-existing ILD.

Nr.	Technique	Fractionation	GTV (cc)	PTV (cc)	Ipsilateral lung MLD_{EQD2} (Gy)	Total lung MLD_{EQD2} (Gy)	Total lung V20Gy (%)	Total lung V5Gy (%)	Lung toxicity	Survival after SABR (months)
1	SABR	5 × 12 Gy	61.4	139.1	16.3	5.7	11	32	Grade 5 RP	7
2	SABR	8 × 7.5 Gy	46.4	110.0	11.4	5.0	11	27	None	70
3	SABR	8 × 7.5 Gy	23.4	52.8	5.9	2.9	7	16	None	12
4	SABR	8 × 7.5 Gy	11.3	41.9	6.6	3.4	9	16	Grade 5 RP	2
5	SABR	5 × 11 Gy	41.8	108.0	8.1	4.5	9	24	None	27
6	SABR	8 × 7.5 Gy	14.7	53.8	11.4	5.0	11	24	Grade 2 RP	46
7	SABR	8 × 7.5 Gy	40.9	95.8	10.3	4.5	11	23	None	13
8	SABR	8 × 7.5 Gy	40.2	114.3	12.2	5.8	10	32	Grade 3 RP	17
9	SABR	8 × 7.5 Gy	21.5	140.8	6.5	3.3	7	18	None	1
10	MR-SABR	8 × 7.5 Gy	10.4	18.3	5.2	2.8	7	17	None	23
11	MR-SABR	5 × 11 Gy	5.9	12.0	6.7	3.1	5	21	None	22
12	SABR	8 × 7.5 Gy	17.4	76.4	8.5	3.9	9	19	None	3
13	MR-SABR	5 × 11 Gy	2.2	5.2	3.0	1.5	3	11	None	25+ (alive)
14	SABR	3 × 18 Gy	1.4	21.8	4.3	2.2	3	12	None	23+ (alive)
15	SABR	12 × 5 Gy	51.2	103.6	6.7	2.8	6	17	Grade 5 RP	13
16	MR-SABR	5 × 11 Gy	1.2	3.1	2.3	1.2	2	9	None	19+ (alive)
17	MR-SABR	5 × 11 Gy	2.1	8.6	4.0	1.6	3	11	None	14+ (alive)
18	MR-SABR	8 × 7.5 Gy	66.0	121.4	6.8	4.4	6	34	Grade 5 RP	3
19	MR-SABR	5 × 11 Gy	57.7	103.2	8.3	4.5	7	25	None	5

Characteristics of lung SABR delivery, and survival outcomes, in 19 patients with early-stage NSCLC and co-existing ILD. Lung doses were defined based on lungs minus the PTV.

EQD2: equivalent dose in 2 Gy fractions; GTV: gross tumor volume; MR: magnetic resonance; NSCLC: non-small cell lung cancer; MLD: mean lung dose; PTV: planning target volume; SABR: stereotactic ablative radiotherapy; RP: radiation pneumonitis.

leukemia ($n = 1$), and unknown ($n = 1$; a 79-year-old male who died 6 years after SABR). Four patients are alive and undergoing follow-up at the time of this report.

Discussion

Patients with early-stage NSCLC and co-existing ILD pose a particular challenge for clinicians, who need to weigh the prognosis of underlying ILD and risks of toxicity of curative treatments, against the poor outcome of untreated lung cancer. For patients who are operable or inoperable, the median survival after presenting with an untreated stage I NSCLC is in the range of 16.6 and 7.6 months, respectively [19]. Consequently, pursuing an active treatment strategy would appear warranted in many cases, and a study using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database has suggested that most IPF patients with early-stage NSCLC do receive stage-appropriate therapy [20].

Our experience with delivering SABR in patients with early-stage NSCLC and co-existing ILD confirms an increased risk of severe lung toxicity, consistent with previous reports [2–4]. The survival outcomes in our elderly cohort were poor, a finding which was predicted by a high ILD-GAP score of $\geq$4 in 63% of patients. European radiotherapy guidelines recommend performing SABR in patients with early-stage NSCLC if the estimated life expectancy is at least 1 year [21], and the present analysis reveals that approximately 30% of our patients survived for a shorter period. We suggest that use of the ILD-GAP index [16], or modifications thereof [22], may aid in identifying patients with poor prognosis, who may not benefit from active cancer treatment. For patients who elect to undergo SABR, limiting the irradiated lung volumes may reduce the risk of ILD exacerbation and severe RP [2], a finding which has led us to the use of MR-guided breath-hold SABR for such patients [15]. However, we acknowledge that the evidence to support a resource-intensive approach such as MR guidance is currently lacking.

Tumor board expertise plays an essential role in the assessment of lung cancer patients with a co-existing ILD. The diagnostic challenges are reflected in substantial interobserver variability for diagnosing IPF among expert radiologists [23], and the revision of prior ILD diagnoses in nearly 42% of cases after multidisciplinary expert review [24]. Misclassification of patients with ILD may also lead to tumor boards advising against SABR for early-stage NSCLC [3]. In 2017, we established a dedicated ILD lung tumor board at our institution, with the aim of facilitating diagnosis and improving treatment of patients presenting with suspicion of an ILD. The board establishes and/or revises a diagnosis of ILD, determines whether antifibrotic therapy is indicated, and estimates the risk of disease exacerbation following lung cancer therapy. Our early experience suggests that the ILD board allowed for timely assessment of patients, and resulted in re-classification of ILD subtypes in a majority of cases [25]. However, the broader application of such an approach, and its feasibility particularly in smaller centers, has not been studied.

The limitations of this brief report deserve attention, especially its completeness. Patients with ILD undergoing SABR before introduction of our structured ILD panel review in 2015 may not have been identified. In addition, not all CT images from patients with lung cancer treated with SABR were systematically screened. Consequently, we assume that some patients with mild forms of ILD may have been missed, including those with (asymptomatic) interstitial lung abnormalities, who also appear to have a poorer prognosis [26–28]. Another limitation is that not all patients were prospectively followed up by an expert ILD team, which is desirable given the difficulty in differentiating ILD exacerbations

from radiation pneumonitis and tumor progression. We now encourage (additional) expert clinical follow-up within our ILD clinic whenever feasible, in consideration of patient age, general condition, and commute to our center.

Further progress may require collaborative efforts to pool the small cohorts treated at centers such as ours [2–4], using information on ILD subtypes and characteristics of SABR delivery. This collaboration may also involve registry-based studies, which are already established in general ILD populations [29], and which may enable a better understanding of the optimal management of such patients. This may include the evaluation of antifibrotic agents, which are effective in reducing disease progression in fibrosing ILDs [30–33], but have not been studied in patients undergoing SABR. Whether antifibrotic therapy should cease or be continued during radiotherapy, is also unclear at present.

In conclusion, our findings confirm that patients with ILD treated for an early-stage NSCLC have a poor prognosis, despite curative-intent SABR, and are at increased risk for developing severe RP. Patients with a poor underlying prognosis, as predicted by ILD-GAP scores, could be counseled to refrain from therapy. In patients eligible for treatment, careful attention must be given to limiting lung doses during SABR. Future collaborative studies are needed to differentiate outcomes in ILD subtypes, to evaluate the efficacy of combined approaches, as well as to identify patients who may not benefit from curative cancer treatment.

Disclosure statement

The Department of Radiation Oncology at the Amsterdam University Medical Center (location VUmc) has funded research agreements with ViewRay Inc. and Varian Medical Systems. S.S. reports personal fees from Varian Medical Systems, outside the submitted work. All other authors have nothing to disclose.

Funding

No industry funding was received for the planning or conduct of this study. T.F. reports grants from the Swiss Cancer Research Foundation (bursary grant; BIL KFS-4380-02-2018), the Swiss Cancer League section Basel (cancer research grant; KlbB-4468-03-2018), and the University Hospital Basel, Clinic of Radiotherapy and Radiation Oncology (departmental research support), in support of the research project.

ORCID

Tobias Finazzi http://orcid.org/0000-0002-4118-4171
Merle I. Ronden-Kianoush http://orcid.org/0000-0003-4267-3396

References

[1] Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv1–iv21.
[2] Chen H, Senan S, Nossent EJ, et al. Treatment-related toxicity in patients with early-stage non-small cell lung cancer and coexisting interstitial lung disease: a systematic review. Int J Radiat Oncol Biol Phys. 2017;98(3):622–631.
[3] Glick D, Lyen S, Kandel S, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival in patients treated with lung stereotactic body radiation therapy (SBRT). Clin Lung Cancer. 2018;19(2):e219–e226.
[4] Bahig H, Filion E, Vu T, et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol. 2016;6(5):367–374.
[5] Naccache JM, Gibiot Q, Monnet I, et al. Lung cancer and interstitial lung disease: a literature review. J Thorac Dis. 2018;10(6):3829–3844.
[6] Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68.
[7] Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27: 180076.
[8] Goldberg HJ. Understanding progressive fibrosing interstitial lung disease through therapeutic trials. N Engl J Med. 2019;381(18):1775–1777.
[9] Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–1823.
[10] Tekatli H, van 'T Hof S, Nossent EJ, et al. Use of stereotactic ablative radiotherapy (SABR) in non–small cell lung cancer measuring more than 5 cm. J Thorac Oncol. 2017;12(6):974–982.
[11] Kolb M, Shargall Y. Lung surgery in interstitial lung disease-a safe and useful procedure? J Thorac Dis. 2013;5(4):375–377.
[12] Tekatli H, Senan S, Dahele M, et al. Stereotactic ablative radiotherapy (SABR) for central lung tumors: plan quality and long-term clinical outcomes. Radiother Oncol. 2015;117(1):64–70.
[13] Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "Ultracentral Non-Small Cell Lung Cancer". J Thorac Oncol. 2016;11(7):1081–1089.
[14] Finazzi T, Palacios MA, Spoelstra FOB, et al. Role of on-table plan adaptation in MR-guided ablative radiation therapy for central lung tumors. Int J Radiat Oncol Biol Phys. 2019;104(4):933–941.
[15] Finazzi T, Palacios MA, Haasbeek CJA, et al. Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. Radiother Oncol. 2019;144:46–52.
[16] Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: The ILD-GAP model. Chest. 2014;145(4):723–728.
[17] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17(4):343–346.
[18] U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. [cited 2019 Jan 6]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
[19] Rosen JE, Keshava HB, Yao X, et al. The natural history of operable non-small cell lung cancer in the National Cancer Database. Ann Thorac Surg. 2016;101(5):1850–1855.
[20] Whittaker Brown S, Padilla M, Mhango G, et al. Outcomes of older patients with pulmonary fibrosis and non-small cell lung cancer. Annals Ats. 2019;16(8):1034–1040.
[21] Guckenberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017;124(1):11–17.
[22] Kobayashi H, Naito T, Omae K, et al. ILD-NSCLC-GAP index scoring and staging system for patients with non-small cell lung cancer and interstitial lung disease. Lung Cancer. 2018;121:48–53.
[23] Walsh SLF, Calandriello L, Sverzellati N, et al. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax. 2016;71(1):45–51.
[24] De Sadeleer LJ, Meert C, Yserbyt J, et al. Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases. Chest. 2018;153(6):1416–1423.

[25] Ronden-Kianoush MI, Nossent EJ, Dickhoff C, et al. 58P Evaluation of a care path for patients with lung tumors and co-existing interstitial lung disease. Ann. Oncol. 2019;30:mdz066.003.
[26] Whittaker Brown S-A, Padilla M, Mhango G, et al. Interstitial lung abnormalities and lung cancer risk in the national lung screening trial. Chest. 2019;156(6):1195–1203.
[27] Li F, Zhou Z, Wu A, et al. Preexisting radiological interstitial lung abnormalities are a risk factor for severe radiation pneumonitis in patients with small-cell lung cancer after thoracic radiation therapy. Radiat Oncol. 2018;13:1–9.
[28] Putman RK, Gudmundsson G, Axelsson GT, et al. Imaging patterns are associated with interstitial lung abnormality progression and mortality. Am J Respir Crit Care Med. 2019;200: 175–183.
[29] Culver DA, Behr J, Belperio JA, et al. Patient registries in idiopathic pulmonary fibrosis (IPF). Am J Respir Crit Care Med. 2019; 200(2):160–167.
[30] Richeldi L, Cottin V, Du Bois RM, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS® trials. Respir Med. 2016;113:74–79.
[31] King TE, Bradford WZ, Castro-Bernardini S, ASCEND Study Group, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–2092.
[32] Iwata T, Yoshida S, Fujiwara T, et al. Effect of perioperative pirfenidone treatment in lung cancer patients with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2016;102(6):1905–1910.
[33] Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381(18): 1718–1727.