Review Article: Pulmonology

Non-invasive approach to treat primary solid solitary pulmonary nodule: a narrative review by the radiation oncologist perspective

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Objective: The aim of this review is to evaluate the role of stereotactic body radiotherapy (SBRT) in treating solitary lung nodule without pathological confirmation.

Background: Lung cancer is one of the leading causes of cancer death worldwide. Taking into account the increasing number of new diagnoses of solid solitary pulmonary nodules, the issue is to identify when an invasive procedure is needed before planning a radical treatment. The role of SBRT is crucial, particularly in those patients at greater risk of complications after invasive procedures or surgery.

Methods: This review focused on selection criteria of patients submitted to SBRT for solid solitary lung nodules in clinically diagnosed lung cancer. A literature search in Medline was performed until April 2021. Terms used were a combination of "solitary pulmonary nodule", "radiotherapy", "stereotactic body radiotherapy", "pathological confirmation", and "lung". We identified 149 records and 20 studies were selected, analyzed and discussed. All studies but two are retrospective. In 6 studies only patients without pathological confirmation were included, while 14 compared histologically proven and not subgroups. All studies were published between 2009 and 2019. SBRT was used in all except one, even if different doses were administered. SBRT resulted as an efficient treatment with high rates of local control in patients affected by early stage non-small-cell lung cancer (NSCLC), even if overall survival varies greatly depending on different factors (population features, lesion diameter, clinical stage, radiation therapy doses). Three-year local control was higher than 75% in all studies in which it was reported, while 3-year overall survival was different in each one (range, 38.6–90%). Acute and late toxicities were generally low.

Conclusions: Validated probability test together with the use of metabolic imaging may facilitate the clinical diagnosis of cancer in patients with solitary pulmonary nodule. SBRT seems to be a very efficient radical treatment for these subgroups of patients with early stage clinically diagnosed lung cancer, even if more prospective trials are needed.

Keywords: Solitary lung nodule; stereotactic body radiotherapy (SBRT); non-small-cell lung cancer (NSCLC)

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Introduction

Lung cancer is the leading cause of cancer death in men and the second one in women worldwide (1). Recently, lung cancer diagnosis has greatly improved due to the wider use of total body computed tomography scan (CT scan) and metabolic diagnostic tools such as 18-F-fluodososyglucose (18F-FDG) positron emission tomography. Recently, the role of the screening program in high risk patients for lung cancer has been well assessed (2), but concerns on resources, costs, and management of patients with abnormal screening, made its use difficult in the routine. Where the screening program has been correctly applied (3), the use of CT scan seemed to be able to anticipate stage I lung cancer if compared to chest radiography allowing a higher number of surgical radical treatment. This benefit in terms of clinical outcome was also showed in a recent update of the NELSON trial where the lung-cancer mortality for high risk persons was significantly lower among those who underwent volume CT scan screening than among those who did not (4). In the past, the American College of Chest Physicians (ACCP) clinical guidelines tried to identify different categories of lung nodules with different probabilities of malignancy suggesting that transthoracic biopsy or bronchoscopy should be performed even in patients with a high risk of surgical complications (5). However, taking into account the increasing number of new diagnoses of solitary pulmonary nodules, the real issue is to identify when an invasive procedure (such as a biopsy) that could be characterized by severe complications is really needed. Due to age, comorbidities, or poor lung functions, and considering that 2–3.5% of patients refused this procedure, almost 25% of patients with single pulmonary nodule will be deemed medically inoperable and consequently remain without pathological confirmation (6,7). Recently, the role of stereotactic body radiotherapy (SBRT) is becoming crucial, particularly in those patients at greater risk of surgical morbidity/mortality or candidate to sublobar resection. For this reason, the optimal therapeutic option (surgery *vs.* SBRT) should be offered after a multidisciplinary discussion. The role of empirical treatment with SBRT without a pathological confirmation have been increasing in this subset of patients, reaching almost 70% in some studies (8,9). Data from retrospective series showed that SBRT in patients without a histological confirmation have been encouraging (10-12). The aim of this narrative review is to evaluate the existing international literature about the role of ablative SBRT in treating solitary lung nodules without pathological confirmation.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-39/rc).

Methods

A literature search in Medline was performed until April 2021 by one author (ED). Terms used were a combination of "solitary pulmonary nodule", "radiotherapy", "stereotactic body radiotherapy", "pathological confirmation", and "lung". A total of 149 records were identified and screened. English language, full-text articles and presence of data about selection criteria in patients affected by solitary lung nodule not-histologically proven treated with radiation therapy, were inclusion criteria. No time limits were applied. Exclusion criteria were: case reports, abstracts, proceedings from scientific meetings, review and editorials. References listed in the screened articles were also evaluated and cross-referenced to ensure completeness. Studies including sub-cohort of patients treated with and without histological confirmation were included. At the end of the screening procedure, taking into account all the eligibility criteria, 8 studies were selected for the analysis and other 16 were retrieved from references of screened paper. Twenty-four studies were analyzed, and those more relevant will be discussed in our review (*Table 1*).

Results

Characteristics of patients enrolled are reported in *Table 1*. All studies included but two (9,18), are retrospective. In six studies (12-17), only patients without pathological confirmation were included, while other 14 studies compared histologically proven and not populations in terms of clinical outcomes and safety (6,9-11,18,20-27). The studies included in the analysis were published between January 2009 and December 2019. Mean number of patients enrolled in the selected studies was 206 (range, 17–382). In nineteen of the 20 studies, authors declared to perform SBRT. Radiation therapy was delivered using proton or carbon ion just in a single study (22). Conversely, Temming *et al.* (25) and Wang *et al.* (16) delivered SBRT using CyberKnife. The median dimension of not histologically proven lesions was 20 (range, 16–28.4) mm. In all studies 18-F fluorodeoxyglucose CT-PET (18FDG) was used during the initial diagnostic assessment for the vast majority of patients (range,

Table 1 Studies on hystologically proven and not solitary lung nodule

Author	Year	Type	Nr Pts	Median Age	Nr Pts No Histology	Nr Pts Histology	PET (%)	Median Diam (mm)	Tot Dose [Gy] (Nr Fx)	Median BED	RT Techniques	3-yr LC (%)	3-yr OS (%)
No hystologically proven studies													
Inoue (13)	2009	Retrospective	115	77	All	0	62	20	30–70 [2–10]	106	SBRT	–	100
Sakanaka (14)	2014	Retrospective	37	77	All	0	71	20	48 [4]	>100	SBRT, 3DcRT	94	74.2
Harkenrider (15)	2014	Retrospective	34	76	All	0	100	16	30–55 [3–10]	<100	SBRT	–	–
Wang (16)	2017	Retrospective	25	78	All	0	100	16	40–60 [2–5]	136	SBRT	78.8	70.2
Hasan (12)	2018	Retrospective	101	76	All	0	82	16	40–50 [4–5]	72–105.6	SBRT,3DcRT	94	45
Kowalchuk (17)	2020	Retrospective	91	78	All	0	100	20	20–60 [3–5]	132	SBRT, 3DcRT	–	–
Hystologically *vs.* No hystologically proven studies													
Baumann (18)	2009	Phase II	57	75	19	38	14		45–66 [3]	113–211	SBRT	–	60
Verstegen (10)	2011	Retrospective	591	74	382	209	100	31	60 [5–8]	–	SBRT	–	–
Takeda (19)	2012	Retrospective	173	78	58	115	100	27	40 – 50 [5]	–	SBRT	87* 80§	74* 70§
Lagerwaard (9)	2008	Prospective	177	76	117	60	100	26	60 [3–5–8]	–	SBRT	93	84.7
Taremi (6)	2012	Retrospective	108	72	33	80	81	24	48–50–60 [4–10–3]	–	SBRT	–	–
Haidar (20)	2014	Retrospective	55	78	23	32	100	25	48–56 [4–5]	–	SBRT	94*° 91§°	30.2°
Fischer-Valuck (21)	2015	Retrospective	88	73	23	65	100	25	48–60 [10–12]	–	SBRT	–	59.9
Fujii (22)	2015	Retrospective	165	76	54	111	100	29* 19§	–	110* 112§	SBRT Proton	94*° 80§°	90* 73§
Murray (23)	2016	Retrospective	273	74	188	100	100		54–55–60 [3–5–8]	–	SBRT	95.7	38.6
Woody (24)	2017	Retrospective	740	–	223	517	100	22	50–60 [5–3]	105	SBRT	–	43
Temming (25)	2018	Retrospective	106	74	19	87	–	23	–	–	Cyberknife	77	56
Wegner (11)	2018	Retrospective	196	76	100	96	100	16	48–50 [4–5]	100–105	SBRT,3DCRT	94	58
Zehentmayr (26)	2019	Retrospective	163	72	40	123	100	–	–	87–106	SBRT,3DCRT	n.r.	39.4°* 58.6° §
Fernandez (27)	2020	Retrospective	701	75	231	470	95	22	26–60 [1–10]	–	SBRT	–	83.6* 83.8§

*, histologically proven; §, not histologically proven; °, median; n.r., not reached.

62–100%). Main reasons for not proceeding to invasive hystopathological confirmation were: severe COPD, high risk of fatal bleeding, location of the primary tumor, patient' refusal, cardiac comorbidities not suitable for anticoagulant suspension. Furthermore, peripheral lesions were treated more frequently than the central ones. A predictive model for the assessment of cancer probability was used only by Verstegen, Hasan, Sakanaka and Zehentmayr (10,12,14,26), while a combination of clinical and radiological characteristics was used in all the other analyses. Median follow up was 19.7 (range, 13–42) months. Doses delivered were very different, depending on several factors such as tumor dimension and localization, techniques, often also within the same cohort. Radiation therapy doses most frequently delivered were 40–60 Gy in 3–8 fractions using stereotactic techniques. In terms of efficacy, 3-year local control (reported in 55% of studies) was higher than 75%, while reported overall survival was more different ranging between 38.6% and 90% at three years. Overall toxicity reported was generally low, more than G3 were very rarely described (less than 2%) (23).

Discussion

The present review focused on selection criteria in patients addressed to radiation therapy for solitary lung nodules in clinically diagnosed lung cancer.

Patel *et al.* (28) defined the solitary pulmonary nodule as a radiographic opacity up to 30 millimeters in diameter with at least two-thirds of its margins surrounded by lung parenchyma. As underlined in the evidence-based recommendations by the American College of Chest Physicians (ACCP) published in 2013 (5), the management of solitary lung nodules may strongly vary according to its dimension and radiological features. In the absence of a biopsy, performing adequate instrumental exams and collecting clinical information should help to estimate the probability of cancer. Notably, the recommendations stressed the importance of balancing benefits and harms of the different diagnostic procedures. Indeed, major complications appear to be very low after CT-guided transthoracic biopsy, accounting a risk of almost 5.7% (29), but the rate increases up to 40% (30-32) when considering all possible collateral effects. At the same time, the diagnostic yield of biopsies may vary widely (between 64% and 95%), thus exposing some patients to not justified risks without significant benefit.

For patients at high risk for complications (such as pneumothorax in severe COPD patients and fatal bleeding) secondary to diagnostic assessments, some quantitative models for the prediction of cancer probability have been developed. In the Swensen model (33) age, smoking status, history of extrathoracic cancers, nodule diameter, location, and presence of spiculations are combined. Furthermore, the Mayo Clinic model (34) is one of the most extensively validated model in the not-screened population, matching the Swensen model with the use of 18FDG-PET.

The use of those algorithms may help to select patients for SBRT without pathological diagnosis. However, a clear threshold of pre-test probability to treat patients with lung nodules without pathological confirmation using surgery or SBRT is not yet well defined. In the CHEST guidelines the authors stated that an active treatment approach could be reasonable when the pre-test probability of malignancy exceeded 65%. However, this finding is in contrast with the International Association for the Study of Lung Cancer (IALSC) recommendations that suggested a threshold of 85% (35).

Nowadays, merging information from anatomic and metabolic imaging yielded a higher diagnostic value (36). Louie *et al.* (37) and Senan *et al.* (38) added the 18-FDG-PET to the probability test and both identified a threshold of 85%. In our review we included also the study of Verstegen (10) that was the internal validation cohort of Louie model. In their report a comparative outcome analysis between proven and not proven patients was conducted. In patients without a pathological diagnosis the Swensen model for cancer probability assessment (33) was used resulting in a mean probability of malignancy equal to 92.5% (95% CI: 91.8–93.3%); furthermore 93.2% of these patients had a calculated probability of malignancy that exceeded 80%.

An interesting role of 18F-FDG-PET in the follow up was then suggested by Hasan *et al.* (12): indeed, its use may allow a radiologically confirmation of treated lesion, but also it may help the prediction of progression of disease. To date, this approach is not standardized being still under evaluation.

Actually, SBRT is recognized as an efficient and safe alternative to surgery showing high rates of local control in patients affected by early stage non-small cell lung cancer (NSCLC), comparable to surgery, but with a significant inferior morbidity (18).

In 2019, the Empiric Radiotherapy for Lung Cancer Collaborative Group published multi-institutional guidelines for the use of SBRT in patients with lung

nodules without pathological confirmation (39). The authors focused on staging procedures, tools for predicting cancer probabilities and potential benefits of SBRT. They only analyzed the role of SBRT in treating peripheral lesions, because the central ones are usually candidate to surgery because of the high risk of severe toxicities. They suggested a pre-test threshold of 85% to candidate patients for local ablative treatment without having pathologically confirmed cancer; furthermore, they recommended moving for a local treatment based on size, radiological imaging and characteristics of the lesions. Authors also emphasized the need of biopsy prior SBRT whenever possible and strongly highlighted the crucial role of the multidisciplinary team in sharing a therapeutic choice in the context of "tailored" medicine.

The role of the multidisciplinary discussion on patients with suspicious early-lung cancer could be a point of strength requested by the main international guidelines, but the selection criteria are so variable between different Institutions, as observed in the studies collected in this review. Indeed, almost all studies reported not specific inclusion criteria for patients candidate to local "empiric" treatment. Moreover, no pre-test threshold was usually described. Only few authors (10,12,14,26) described the predictive model of cancer probability.

The role of predictive model and guidelines, as previously described, should help clinicians to weighting comorbidities and their life expectancy, in order to identify those patients candidate to invasive procedures for a pathological diagnosis and consequently, to local ablative treatment (surgery or SBRT).

In the comparative studies, patients without histological confirmation had smaller tumor diameter than those with pathological specimen (10,11,22). In Verstegen *et al.* (10), 591 patients were treated with SBRT with significant results in terms of local control (LC). No differences between both cohorts and no factors significantly correlate to overall survival (OS) after multivariate analysis. A subgroup analysis was then performed to assess differences in terms of clinical stage (T1 *vs.* T2) between the two groups, but no difference in OS neither in LC was found. Importantly, Inoue *et al.* found a statically significant difference (P<0.0005) in terms of OS in patients with a tumor size (diameter) of 5–20 mm (n=58) *vs.* 21–45 mm (n=57) (13). Some hypothesis could be made to understand the lack of difference in OS related to dimension, as reported in Verstegen *et al.* and Inoue *et al.* (10,13). In the Japanese cohort, the median follow-up was quite short (14 months), also including 11 patients with a follow up shorter than 4 months. For these reasons, definitive conclusions about OS are difficult, not being possible to completely exclude the option that benign lesions were treated in the group with a median smaller nodule dimension. Similar results were also reported in Sakanaka *et al.* (14), where patients with clinical T1a stage had a significantly higher OS and PFS than those presenting clinical T1b/T2a tumors. On the other hand, no differences in terms of LC were found. The same authors also reported a crude rate of relapse equal to 41%, occurring 36 months after treatment. It should be noted that the vast majority of the studies included in our review reported a median FUP inferior than 24 months, thus probably underestimating the overall incidence of relapse and cancer related death.

Clinical differences are very clear in the inclusion criteria used in the different studies. Hasan *et al.* (12) included patients mostly aged >70 with a smoking history characterized by >50 pack-year, oxygen therapy dependent and with a median predicted forced expiratory volume equal to 42%. This cohort of patients was not suitable for surgery and usually diagnosed by regular CT scan during the management of chronic obstructive pulmonary disease. Conversely, in the series of Verstegen *et al.* (10) patients were mostly defined as operable and diagnosed by the national screening program. These characteristics necessarily reflected the different results in terms of OS and may explain the low rate of OS in the paper published by Hasan *et al.* (12).

In elderly patients, SBRT was evaluated by Wang *et al.* (16). In a small series of 25 patients with more than 75 years and usually not suitable for to surgery (76%) due to comorbidities, 1-, 3- and 5-year local control and cancer specific survival were 100%, 78.8%, 65.7% and 100%, 81.3%, and 67.0%, respectively. Acute and late toxicity was very low. Similar results were reported in most of the studies analyzed (see *Table 1*) where 3-year local control and OS varied between 80–94%, and 54–90%, respectively.

Elderly patients with multiple comorbidities, such as poor pulmonary function, could be at high risk of complications when treated by ablative SBRT, causing an increased and not justified mortality. However, poor pulmonary functions seemed not to be associated to increased mortality or toxicity in patients treated with SBRT for early stage NSCLC (40). Verstegen *et al.* and Takeda *et al.* then confirmed these findings (10,19). As reported in Shaik *et al.* (41), the different results in terms of efficacy could be potentially affected by the presence of benign lesions in the cohorts of patients analyzed,

particularly when nodules' diameter was smaller than 2 cm. At univariate analysis, cancer specific survival and OS were better in patients without histological confirmation as reported in the SEER database series. Regarding these findings, Verstegen *et al.* (10) reported a 3-year local control superior than 90% with local failures observed in only 10 and 18 patients with a pathological or clinical diagnosis, respectively. In the meanwhile, taking into account that benign granulomas were considered unlikely to shrink after SABR, the proportion of patients with stable disease after SBRT in the not pathologically confirmed cohort were 3.5% and 3.7% at 6 and 12 months, very similar to those with pathological confirmation.

Also the presence of previous cancer diagnosis may help in decision-making, but sometimes it could led to confounding results: in Verstegen *et al.*, 34% of total patients presented a previous history of cancer and approximately 50% of them had previously been treated for lung cancer (10).

Other confounding factors could be the presence of lesions other than NSCLC: indeed it is estimated that 4–12% of patients with solid solitary pulmonary nodule may have a SCLC diagnosis (42), so that it could be questionable if a "radical" treatment with SBRT should be used.

When choosing the optimal radiation treatment, the absence of pathological confirmation plays an important role: in Woody *et al.* (24), despite the selection bias, an increased rate of local failure was reported in patients with squamous cell carcinoma treated with SBRT. So, the authors advocate different schedules depending on different histology.

Finally, one of the main limits of all the studies selected was the long time of accrual that may have a crucial impact on the different radiation therapy schedules. Recently, several authors (40,43) supported the important role of biologically equal dose $(BED)_{10}$ >100 Gray (Gy) to improve OS and local control in NSCLC treated with SBRT. However, in the studies analyzed (when reported) median BED_{10} was usually superior to 100 Gy, but many patients received inferior doses. In the cohort of Zehentmayr *et al.* (26) the minimum BED_{10} used was 15% lower, while only 15% of patients had a BED_{10} <100 Gy in Inoue *et al.* (13).

Our review is characterized by several limitations. First, the vast majority of international literature was characterized by a significantly different selection criteria and treatments delivered, probably due to the long period of accrual and the retrospective nature of each study. Second, clinical outcome reported were very different, due to several reasons such as the different populations analyzed in terms of comorbidities and performance status or the different tumor features. Similar limitations were encountered in the comparative studies (*Table 1*), even if the cohorts were apparently more homogenous. Notably, results in terms of efficacy and clinical outcomes were similar between comparative and not-comparative studies, while toxicities were usually very low.

Conclusions

In conclusion, the introduction of validated probability test together with the wider diffusion of metabolic imaging such as 18 FDG PET CT scan may facilitate the clinical diagnosis of cancer in patients with solid solitary pulmonary nodules. Furthermore, clinical outcomes following SBRT seem to be similar in patients either with or without a pathology-proven diagnosis of early stage lung cancer. Prospective well-designed clinical trials are needed in this subset of patients so that stronger recommendations may be proposed in patients with not proven solid solitary pulmonary nodule.

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Footnote

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References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC cancer base no. 11. International Agency for Research on Cancer, Lyon.
2. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013;369:920-31.
3. National Lung Screening Trial Research Team, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013;368:1980-91.
4. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382:503-13.
5. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e93S-e120S.
6. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
7. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. J Clin Oncol 2006;24:413-8.
8. Rutter CE, Corso CD, Park HS, et al. Increase in the use of lung stereotactic body radiotherapy without a preceding biopsy in the United States. Lung Cancer 2014;85:390-4.
9. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
10. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
11. Wegner RE, Ahmed N, Hasan S, et al. SBRT for early stage lung cancer: outcomes from biopsy-proven and empirically treated lesions. Lung Cancer Manag 2018;7:LMT01.
12. Hasan S, Colonias A, Mickus T, et al. Image-based management of empiric lung stereotactic body radiotherapy (SBRT) without biopsy: Predictors from a 10-year single institution experience. Thorac Cancer 2018;9:699-706.
13. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
14. Inoue T, Shimizu S, Onimaru R, et al. Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;75:683-7.
15. Sakanaka K, Matsuo Y, Nagata Y, et al. Safety and effectiveness of stereotactic body radiotherapy for a clinically diagnosed primary stage I lung cancer without pathological confirmation. Int J Clin Oncol 2014;19:814-21.
16. Wang Z, Li AM, Gao J, et al. Clinical outcomes of CyberKnife stereotactic radiosurgery for elderly patients with presumed primary stage I lung cancer. Transl Lung Cancer Res 2017;6:6-13.
17. Harkenrider MM, Bertke MH, Dunlap NE. Stereotactic body radiation therapy for unbiopsied early-stage lung

cancer: a multi-institutional analysis. Am J Clin Oncol 2014;37:337-42.
18. Kowalchuk RO, Waters MR, Baliga S, et al. Stereotactic body radiation therapy for empirically treated hypermetabolic lung lesions: a single-institutional experience identifying the Charlson score as a key prognostic factor. Transl Lung Cancer Res 2020;9:1862-72.
19. Takeda A, Kunieda E, Sanuki N, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. Lung Cancer 2012;77:77-82.
20. Haidar YM, Rahn DA 3rd, Nath S, et al. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. Ther Adv Respir Dis 2014;8:3-12.
21. Fischer-Valuck BW, Boggs H, Katz S, et al. Comparison of stereotactic body radiation therapy for biopsy-proven versus radiographically diagnosed early-stage non-small lung cancer: a single-institution experience. Tumori 2015;101:287-93.
22. Fujii O, Demizu Y, Hashimoto N, et al. Particle therapy for clinically diagnosed stage I lung cancer: comparison with pathologically proven non-small cell lung cancer. Acta Oncol 2015;54:315-21.
23. Murray L, Ramasamy S, Lilley J, et al. Stereotactic Ablative Radiotherapy (SABR) in Patients with Medically Inoperable Peripheral Early Stage Lung Cancer: Outcomes for the First UK SABR Cohort. Clin Oncol (R Coll Radiol) 2016;28:4-12.
24. Woody NM, Stephans KL, Andrews M, et al. A Histologic Basis for the Efficacy of SBRT to the lung. J Thorac Oncol 2017;12:510-9.
25. Temming S, Kocher M, Stoelben E, et al. Risk-adapted robotic stereotactic body radiation therapy for inoperable early-stage non-small-cell lung cancer. Strahlenther Onkol 2018;194:91-7.
26. Zehentmayr F, Sprenger M, Rettenbacher L, et al. Survival in early lung cancer patients treated with high dose radiotherapy is independent of pathological confirmation. Thorac Cancer 2019;10:321-9.
27. Fernandez C, Grills IS, Ye H, et al. Stereotactic Image Guided Lung Radiation Therapy for Clinical Early Stage Non-Small Cell Lung Cancer: A Long-Term Report From a Multi-Institutional Database of Patients Treated With or Without a Pathologic Diagnosis. Pract Radiat Oncol 2020;10:e227-37.
28. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. Chest 2013;143:825-39.
29. Heerink WJ, de Bock GH, de Jonge GJ, et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. Eur Radiol 2017;27:138-48.
30. Boskovic T, Stanic J, Pena-Karan S, et al. Pneumothorax after transthoracic needle biopsy of lung lesions under CT guidance. J Thorac Dis 2014;6 Suppl 1:S99-S107.
31. Wiener RS, Schwartz LM, Woloshin S, et al. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med 2011;155:137-44.
32. Yildirim E, Kirbas I, Harman A, et al. CT-guided cutting needle lung biopsy using modified coaxial technique: factors effecting risk of complications. Eur J Radiol 2009;70:57-60.
33. Swensen SJ, Silverstein MD, Edell ES, et al. Solitary pulmonary nodules: clinical prediction model versus physicians. Mayo Clin Proc 1999;74:319-29.
34. Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest 2005;128:2490-6.
35. Field JK, Smith RA, Aberle DR, et al. International association for the study of lung cancer computed tomography screening workshop 2011 report. J Thorac Oncol 2012;7:10-9.
36. Kim SK, Allen-Auerbach M, Goldin J, et al. Accuracy of PET/CT in characterization of solitary pulmonary lesions. J Nucl Med 2007;48:214-20.
37. Louie AV, Senan S, Patel P, et al. When is a biopsy-proven diagnosis necessary before stereotactic ablative radiotherapy for lung cancer?: A decision analysis. Chest 2014;146:1021-8.
38. Senan S, Paul MA, Lagerwaard FJ. Treatment of early-stage lung cancer detected by screening: surgery or stereotactic ablative radiotherapy? Lancet Oncol 2013;14:e270-4.
39. Berman AT, Jabbour SK, Vachani A, et al. Empiric Radiotherapy for Lung Cancer Collaborative Group multi-institutional evidence-based guidelines for the use of empiric stereotactic body radiation therapy for non-small cell lung cancer without pathologic confirmation. Transl Lung Cancer Res 2019;8:5-14.

40. Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol 2014;190:26-33.
41. Shaikh T, Churilla TM, Murphy CT, et al. Absence of Pathological Proof of Cancer Associated with Improved Outcomes in Early-Stage Lung Cancer. J Thorac Oncol 2016;11:1112-20.
42. Kreisman H, Wolkove N, Quoix E. Small cell lung cancer presenting as a solitary pulmonary nodule. Chest 1992;101:225-31.
43. Moustakis C, Blanck O, Ebrahimi Tazehmahalleh F, et al. Planning benchmark study for SBRT of early stage NSCLC : Results of the DEGRO Working Group Stereotactic Radiotherapy. Strahlenther Onkol 2017;193:780-90.

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