Austin Journal of Medical Oncology

Open Access

Austin Publishing Group

Review Article

Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: Procedure of the Salah Azaiez Institute in Tunisia

Kaabia W*; Mousli A; Zarraa S; Ben Zid K; Yousfi A; Gargouri W; Yahyaoui S; Abidi R; Nasr C
Department of Radiation-Oncology, Salah Azaiez Oncology Institute, Tunis-Tunisia

***Corresponding author: Wael Kaabia**
Department of Radiation-Oncology, Salah Azaiez Oncology Institute, Tunis-Tunisia.
Tel: +216 50492029
Email: waelkaabia@gmail.com

Received: September 30, 2023
Accepted: November 06, 2023
Published: November 13, 2023

Abstract

Stereotactic Body Radiation Therapy (SBRT) revolutionizes the management of lung cancer, providing precise and effective treatment. It delivers high doses of radiation to the tumour site while minimizing damage to healthy tissue. Its short treatment duration and high local control rate make it a treatment option for patients with early-stage lung cancer. SBRT is also useful for inoperable tumours and limited metastases. This article provides a brief overview of the use of SBRT in lung cancer treatment at the radiation-oncology department of the Salah Azaiez Institute in Tunisia.

Keywords: Lung cancer; Radiation therapy; Stereotactic radiotherapy; SBRT

Abbreviations: SBRT: Stereotactic Body Radiotherapy; SABR: Stereotactic Ablative Radiotherapy; ISA: Institute Salah Azaiez; NSCLC: Non-Small Cell Lung Cancer; RFA: Radiofrequency Ablation; CRT: Conventional Radiotherapy; CT: Computed Tomography; PET-CT: Positron Emission Tomography Scan; CBCT: Cone-Beam Computed Tomography; ESTRO: Positron Emission Tomography Scan; ACROP: Advisory Committee for Radiation Oncology Practice; BED: Biological Effective Dose; OAR: Organ At Risk; PRV: Planning at Risk Volume; DVH: Dose Volume Histogram; CTCAE: Common Terminology Criteria for Adverse Events

Introduction

Stereotactic Body Radiotherapy (SBRT) is a precise radiation therapy technique used to deliver highly focused and accurate radiation beams to extracranial target localization in 1-8 fractions. It integrates modern imaging, simulation, treatment planning and delivery technologies in order to achieve a high gradient of dose with high conformality with the target volume [1]. It is also referred to as "Stereotactic Ablative Radiotherapy" (SABR) since the convergence of the different beams result in creating a hotspot with a rapid falloff of dose outside of the target, which creates a lethal 'ablative' effect [2]. SBRT is also shown to induce vascular damage and to have an immunological effect, both of which indirectly causing cell death [3].

Since 2018, our patients have started to benefit from this innovative technique in Tunisia at the Salah Azaiez institute (ISA).

The purpose of this document is to present the SBRT procedure for lung lesions, implemented at our radiotherapy department at ISA. We aim to detail the different steps as well as the required equipment for lung SBRT. This procedural document has been elaborated thanks to the tight collaboration between radiotherapists, medical physicists, and technicians.

I. Indications of SBRT in Non-Small Cell Lung Cancer (NSCLC)

Historically, the mainstay in the treatment of early-stage NSCLC has been anatomical surgical resection through lobectomy, segmentectomy or wedge resection [4]. Other treatment options include conventional radiotherapy or Radiofrequency Ablation (RFA). However, during the last decades, there has been a rising interest in SBRT. **Compared to surgery,** SBRT is a non-invasive, organ preserving, outpatient treatment, which typically lasts 1-2 weeks without requiring anaesthesia and allowing for an immediate return to activities. Furthermore, while **segmentectomy** offers a good Local Control (LC) for small lesions less than 20mm reaching 98.1%, this outcome is not maintained for larger lesions falling down to 62.9% [5,6]. **Compared to wedge resection**, there is a trend toward reduced local recurrence with SBRT (4% v 20%; P .07) [7]. SBRT also achieves high rates of LC attaining 97%, regardless of the size of the tumour [8]. **As for RFA,** it yields a significantly lower 5-year local control rate compared to SBRT (42% vs 86% p<.001) [9]. It is noteworthy to highlight the CHISEL trial results, comparing **Conventional Radiotherapy (CRT)** with SBRT, and showing increased local failure

Citation: Kaabia W, Mousli A, Zarraa S, Ben Zid K, Yousfi A, et al. Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: Procedure of the Salah Azaiez Institute in Tunisia. Austin J Med Oncol. 2023; 10(1): 1077.

(31% vs 14%) and decreased survival (median overall survival of 3 years vs 5 years, p=0·027) in the CRT group [10].

1. Primary lung tumour

SBRT is an option for the management of stage I- II (T1-T2a N0) carcinomas, up to 5cm in size, for inoperable patients (major medical comorbidity, severely limited lung function) or patients refusing surgery [11]. It is also indicated for primary lung tumours without histological evidence, especially, those with increasing size on 2 consecutive CT scans (performed in 8-12 weeks interval), hyper-metabolic on the Positron Emission Tomography (PET-CT) and without any other proven aetiology [12]. To note, systematic screening for tuberculosis is needed in our institute to rule it out in case of suspicion.

2. Lung metastases

In light of two randomized phase II trials available, patients with synchronous oligometastatic or oligopersistent cancer can benefit from curative treatment at least once disease has stabilized with initial systemic therapy [13,14]. At our institute, SBRT is indicated for patients presenting with oligometastatic lung disease (1–5 metastatic sites) [15], measuring less than 5cm in size, with slow growth and whose primary tumour is controlled [16].

II. Treatment conditions

Eligibility for SBRT requires a certain set of conditions. A complete and recent radiological workup (≤ 4 weeks) with a thoracic CT and a PET-CT is required for optimum disease staging. Targeted lesions cannot exceed 5 cm in size [12]. While SBRT is feasible for tumours > 5 cm, low quality of evidence limits its use in this case [17]. Patients need to have a KPS (Karnofsky Performance Score) of at least 70, and with no contraindication to supine position. Special considerations are taken into account in the case of patients with cardiac implantable electronic device [18]. In case of altered pulmonary function or pre-existing pulmonary fibrosis, the decision is made during the RT board meeting for a less hypo-fractionated SBRT and adaptation of dosimetric constraints.

III. Prescription dose and fractionation

There is no single standard scheme for all tumour presentations. Published data generally reflect the experience of individual institutions, which to some extent explains inter-institutional differences in total dose, fractionation schedule, total treatment time, and dose delivery technique. These differences make it difficult to standardize dosing regimens and dosimetry specifications when administering SBRT. However, the recommended fractionation regimens are all equivalent to a minimum BED (Biological effective Dose) of 100 Gy. In fact, local control is significantly improved with a BED >100Gy [19] and BED at the peripheral tumour margin was found to be the strongest predictor of local control [20]. As per the ESTRO and ACROP recommendations [11], we aimed to set up *risk-adapted* fractionation regimens according to the location of the tumour, with 48h in-between fractions. Four main locations were defined in Table 1. Some tumours might be “too central” to be safely treated with SBRT when applying a BED10 >100 Gy. These are called ‘hyper-central’ tumours and they extend directly to the bronchial tree or critical mediastinal structures. In this case, an 8-fraction regimen results in high risk of grade 3 to 5 toxicities as well as treatment-related death, and thus a more fractionated schedule is recommended [21].

IV. Positioning and preparation for dosimetric scan

The dosimetric scan should be performed with the presence of the radiation therapist, radiation physicist and radiation technician. The patient is comfortably set on the scanner table, in the supine position, well aligned with the laser at zero. We use a stereotactic body frame (Orfit®) with diaphragmatic compression, to reduce tumour displacement, especially for lower-lobe lesions Figure 1 [23]. Arms are above the head in the upper arm support (if apex tumour, arms’ position is along the body and a 5-strap thermoplastic mask is used). A position report of the stereotaxis equipment is detailed through a checklist. There is usually no need for the injection of a contrast medium. However, it may be useful for central lesions.

On the console, the radiotherapist uses the “Tumour Lock” tool to locate the centre of the tumour. We perform a Four-Dimensional (4D) acquisition on 10 respiratory phases with free breathing with a slice thickness of 2mm.

The scan series are then exported to the Treatment Planning System (TPS) “Varian Eclipse” where we generate of the “average” CT to calculate the radiotherapy dose and MIP (maximum intensity projected) to define the treated volumes.

V. Delineation

1. Target volumes

We use the Eclipse software to import images and to registrate the PET-CT with the planning-CT. The recalibrated images are used for the delineation of the target volumes, but the group of structures must be attached to the planning-CT. Delineated target structures are (Figure 2):

Figure 1: Our immobilization setup consists of a long base plate with cushions for arms, knees and feet, and a mechanical pressure system.

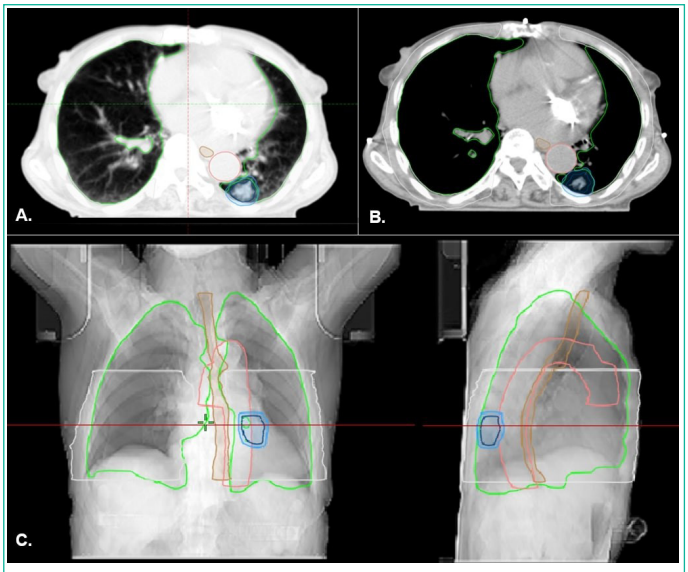

Figure 2: Structures shown on the average CT: ITV in dark blue, PTV in light blue, aorta in pink, lungs in green, oesophagus in brown and thoracic wall in white. **A**. parenchymal window. **B**. Mediastinal window **C**. anterior and lateral reconstruction views.

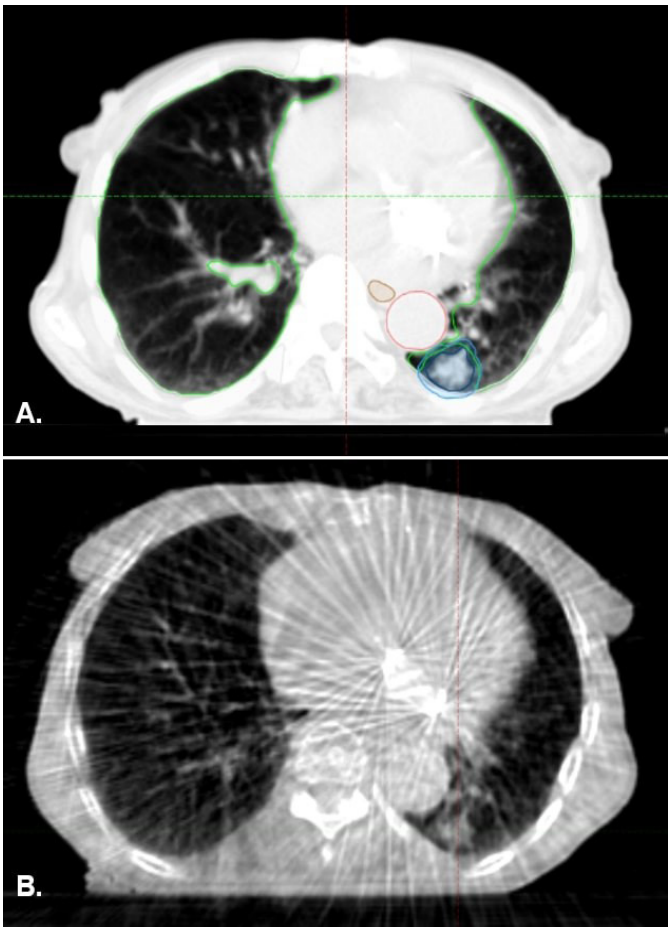

Figure 3: Special care and attention need to be put while matching the planning CT image (A) with the in-treatment Kv CBCT (B) known to be highly sensitive to artifacts, in this case due to a prosthetic heart valve.

1. **GTV** (gross target volume): with the help of the parenchymal window (-600HU ± 1600) for parietal and peripheral lesion, or mediastinal window (20HU ± 400) for central lesions, we contour the GTVs on the 10 phases. All ten GTVs are then transferred to the MIP.

2. **ITV** (internal target volume): union of GTVs of all ten respiratory phases without margin.

3. **CTV** (clinical target volume): No margin from the GTV is made (ITV=CTV). There are no supportive pathological sectional studies, but this decision is well supported by data from trials, and any microscopic disease extending from the tumour would be dealt with by the dose spillage [2,24].

4. **PTV** (planning target volume): is equal to ITV with a 5 mm margin which accounts for set-up variability and tumour motion.

1. Delineation of organs at risk and dose constraints

The Organs At Risk (OAR) are the same as those described for locally advanced bronchial carcinoma. However, given the delivered biological dose, it is necessary to define additional ones (Table 2). Parallel organs must be fully delineated, and their constraints are expressed as dose-volume. A serial organ requires a Planning organ at Risk Volume (PRV) and the reference standard is the maximum dose to one point. OAR are outlined on the *CT-average* according to the Radiation Therapy Oncology Group (RTOG) recommendations [25]. Automatic contouring software can be useful because so many OARs need to be contoured.

VI. Dose objectives and dose constraints

Dose is not prescribed to a reference point, but rather to an isodose line covering the target [26]. Three criteria should be met: The PTV coverage of the prescribed isodose should be between 95% and 100%; the maximum dose in PTV should not exceed 125% of the prescribed dose; and D99% should be at least 90% of the prescribed dose. For example, in case of 4 fractions of 12Gy or 8 fractions of 7.5Gy, D95% = [48-60Gy], D99%= [43.2-54Gy], Dmax= [60-75Gy]. These indicators can be evaluated quantitatively using the Dose Volume Histogram (DVH). During treatment planning, dose inhomogeneity within the PTV is not an issue, it is in fact sought after in the case of SBRT in order to achieve a steep dose profile [26]. Furthermore, because we're dealing with small fields and high doses per fraction, proper dose calculation algorithms need to be used [26]. In our institution, we use the Varian Eclipse TPS provided with the Accuros XB algorithm and a 2mm calculation grid, which accurately considers tissue density heterogeneities known to be predominant in lung SBRT.

Using Volumetric-Modulated Arc-Therapy (VMAT), we use coplanar or non-coplanar arcs enforcing a *conformity index < 1.2 (*prescription isodose volume/PTV ratio) and improving on OAR sparing in complex geometries. Another important dosimetric indicator to consider is insuring a rapid dose falloff.

Table 1: prescription dose and fractionation according to tumour location.

Tumour location	Description	Dose and fractionation
Peripheral	In the pulmonary parenchyma, excluding central and juxta costal lesions (at least 2 cm away from the proximal bronchial tree or critical mediastinal structures).	4 fractions of 12Gy (BED10 = 105.6Gy)
Parietal	In contact with a costal arch.	5 fractions of 11Gy (BED10 = 115Gy)
Central	Within a 2 cm radius of the proximal bronchial tree or critical mediastinal structures, such as the oesophagus, heart, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve [22].	8 fractions of 7.5Gy (BED10 = 105Gy)
Hyper-central	Extend to the mediastinum or hilum, or directly adjacent to the trachea and main bronchi.	10 fractions of 5Gy or 13 fractions of 3Gy

Table 2: Description and Naming of Required Normal Tissue Volumes [25].

lungs	Delineation using the help of automatic segmentation, including small vessels (<1cm)
Lungs-ITV	Combined Left and Right Lungs minus ITV
Spinal Cord	4 cm above and below the PTV
Oesophagus	From cervical oesophagus down to the gastroesophageal junction
Trachea	Starting from the vocal cords and up to 2 cm above the carina
bronchial tree	2 cm above the carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi
Brachial Plexus	According to RTOG delineation atlas.
Chest wall	2 cm outer expansion from the lung (including ribs, intercostal muscles and excluding vertebrae, sternum). Upper and lower limits: 3 cm above and below the PTV.
Great vessels	Ascending and descending aorta, aorta arch, superior and inferior vena cava, pulmonary arteries and veins
Heart	Heart
Skin	Make an internal margin of 5mm from the external contour.
Liver	Liver
Stomach	Stomach
Small bowel	Small Bowel
Spinal cord PRV	Spinal cord + 5mm
Brachial Plexus PRV	Brachial plexus + 5mm
Oesophagus PRV	Oesophagus + 3mm

Table 3: Follow-up after treatment by SBRT for lung tumours.

	2 months	6 months	9 months	12 months	18 months	24 months
Clinical examination	X	X	X	X	X	X
Thoracic CT scan	X	X	X	X	X	X
Respiratory functional exploration		X		X		

Depending on the PTV volume, RTOG metrics for limiting dose spillage are *R50%* (the ratio of 50% isodose volume to the PTV) and *D2cm [%]* (the maximum dose at 2cm from PTV in any direction) [27,28].

Dose-volume limits for OARs are well established for conventional RT (1.8–2.0 Gy per fraction) and moderately fractionated RT. And although dose equivalence can be established using LQ (linear quadratic) models, there is uncertainty about when extreme hypofractionation (≥6 Gy) doses used in SBRT are applied to small volumes, especially to serial OARs.

Therefore, dose–volume constraints specific in different dose-fractionation regimens were systematically defined during prospective clinical trials and correlated with toxicity rates. several guidelines have been published by national and international bodies aiming to standardize the practice of SBRT for early-stage NSCLC. At our practice, we refer to the RTOG, Japan Clininal Oncology Group (JCOG), and the European Organisation for Research and Treatment of Cancer (EORTC) recommendations for dose constraints per number of fractions.

Quality control and Image-guided radiotherapy

There are several important quality assurance steps to be taken prior to placing the patient on the couch.

Our facility uses a C-arm linear accelerator (Linac) equipped with an MLC (multi-leaf collimator) thickness of 5 mm providing a high degree of dose shaping. The main reference point (the *effective* isocentre) is identified through phantom irradiation. This point will be used to monitor the dose accumulation. The positioning fields are created (IP0, IP90/270, kV0, kV270/90, CBCT Full Fan). It is important to check the calculation of monitor units (MU) and MU/Gy/field size. The mechanical accuracy of table rotation must undergo rigorous quality assurance testing and practical issues such as collisions must be considered. Thus, we perform a "dry run" collision risk verification plan. If there are major deviations, the patient is not allowed to be treated until the matter is resolved [29]. Our Linac equipped with image-guidance technology. So, control of positioning is performed using portal imaging, low energy on board two-dimensional imaging (kV orthogonal pair), and three-dimensional repositioning by Cone Beam Computed Tomography (CBCT). A CBCT is performed before each treatment arc under the direct supervision of the radiation oncologist (Figure 3).

VII. Treatment

Treatment ballistics are adapted by the medical physicist to comply with the dose objectives of the planned target volume and the dose constraints defined for the protection of the organs at risk. We use a photonic energy of 6MeV with a flow rate of 600 MU/min. Thanks to VMAT, treatment duration is fast, thereby movements are limited during treatment sessions. First, we emphasize that treatment can only be done after taking care to manually test the recall of all treatment arcs to ensure no collision with the abdominal compression arm. During protocol preparation, technicians verify that all angles of the treatment axes are on the side of the lesion. If an arc is positioned on the opposite side, the table must be shifted with the mobile rulers to avoid a collision, otherwise leave the table at 0°. We set up the positioning equipment by repeating the same procedure as at the preparation for the scanner, and position the patient using the markings taken during the planning-CT. At the first session, we apply the axis off sets determined during the dosimetric planning. Then, we perform the pre-treatment CBCT acquisition with a starting angle opposite to the side of the lesion. The radiotherapist will confirm and finally validate the superposition of the planning PTV with the image of the target on the CBCT. The technician will apply the manual overlay and validate the modifications applied on the isocentre.

VIII. Follow-up

Patients are informed of the risks involved with radiation before starting treatment. Follow-up is crucial for early detection

and treatment of side-effects. When present, side effects are noted with a grading system according to the Common Terminology Criteria for Adverse Events (CTCAE V.5). Acute toxicities can manifest in the form of asthenia, cough, dyspnoea, subacute radiation pneumonitis and esophagitis.

Late toxicity includes pulmonary fibrosis, rib fracture, oesophageal stenosis, radiation plexitis, rarely massive haemorrhage, tracheoesophageal fistula. Risk factors for such toxicities include proximal topography of the tumour or in contact with the chest wall or a BED > 120Gy at the isocentre. It is important to note that radiation-induced fibrotic changes are hardly distinguishable from residual tumour.

In such situations PET-CT is useful.[30] Follow-up for patients at our department, by clinical examination and thoracic CT scan, is done every 3 months for the two year, every 6 months for three years, and then once a year. Respiratory functional exploration is performed at 6 months and 12 months after radiation. Follow-up rhythmicity for patients at our department is detailed in Table 3.

Conclusion

SBRT shows great promise as a non-invasive and transformative approach in the treatment of lung cancer. However, the implementation of SBRT remains challenging in terms of accurate target delineation, motion management, and toxicity mitigation. We emphasize on the importance of implementing local departmental procedures and efficient multidisciplinary communication in order to carry out SBRT in the safest and best conditions possible.

Author Statements

Competing Interests

The authors declare no competing interest.

Authors' Contributions

Conceptualization, W.K. and A.M.; Validation, A.M., S.Z and K.B.Z.; Writing - Original Draft, W.K.; Writing - Review & Editing, A.M., S.Z. and A.Y; Supervision, W.G., S.Y., R.A. and C.N.

All authors had full access to the data in the study and take responsibility for its integrity and accuracy.

References

1. Ricardi U, Badellino S, Filippi AR. Stereotactic body radiotherapy for early stage lung cancer: history and updated role. Lung Cancer. 2015; 90: 388-96.
2. Timmerman R, Galvin J, Michalski J, Straube W, Ibbott G, Martin E, et al. Accreditation and quality assurance for Radiation Therapy Oncology Group: multicenter clinical trials using Stereotactic Body radiation therapy in lung cancer. Acta Oncol. 2006; 45: 779-86.
3. Song CW, Glatstein E, Marks LB, Emami B, Grimm J, Sperduto PW, et al. Biological principles of stereotactic body radiation therapy (SBRT) and stereotactic radiation surgery (SRS): indirect cell death. Int J Radiat Oncol Biol Phys. 2021; 110: 21-34.
4. Asamura H. Treatment of choice for Stage I non-small cell lung cancer: surgery or radiotherapy? J Thorac Oncol. 2006; 1: 766-7.
5. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Effect of tumor size on prognosis in patients with non–small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg. 2005; 129: 87-93.
6. Bando T, Miyahara R, Sakai H, Shoji T, Sonobe M, Sato K, et al. A follow-up report on a new method of segmental resection for small-sized early lung cancer. Lung Cancer. 2009; 63: 58-62.
7. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol. 2010; 28: 928-35.
8. Kestin L, Grills I, Guckenberger M, Belderbos J, Hope AJ, Werner-Wasik M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol. 2014; 110: 499-504.
9. Bi N, Shedden K, Zheng X, Kong F-MS. Comparison of the effectiveness of radiofrequency ablation with stereotactic body radiation therapy in inoperable Stage I non-small cell lung cancer: A systemic review and pooled analysis. Int J Radiat Oncol Biol Phys. 2016; 95: 1378-90.
10. Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019; 20: 494-503.
11. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, 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: 11-7.
12. Khalifa J, Lerouge D, Le Péchoux C, Pourel N, Darréon J, Mornex F, et al. Radiotherapy for primary lung cancer. Cancer Radiother. 2022; 26: 231-43.
13. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A Phase 2 randomized clinical trial. JAMA Oncol. 2018; 4: e173501.
14. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET Phase II randomized trial. J Clin Oncol. 2020; 38: 2830-8.
15. Dingemans A-MC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of synchronous oligometastatic non–small cell lung cancer—A consensus report. J Thorac Oncol. 2019; 14: 2109-19.
16. Lévy A, Darréon J, Mornex F, Giraud P, Thureau S. Lung metastases radiation therapy. Cancer Radiother. 2022; 26: 244-9.
17. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017; 7: 295-301.
18. Escande A, Frey P, Lacornerie T, Mervoyer E, Chargari C, Laurans M, et al. Radiotherapy for patient with cardiac implantable electronic device, consensus from French radiation oncology society. Cancer Radiother. 2022; 26: 404-10.
19. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004; 101: 1623-31.
20. Wulf J, Baier K, Mueller G, Flentje MP. Dose-response in stereotactic irradiation of lung tumors. Radiother Oncol. 2005; 77: 83-7.

21. Lindberg K, Grozman V, Karlsson K, Lindberg S, Lax I, Wersäll P, et al. The HILUS-trial—a prospective Nordic multicenter Phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. J Thorac Oncol. 2021; 16: 1200-10.

22. Chang JY, Bezjak A, Mornex F, IASLC Advanced Radiation Technology Committee. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. J Thorac Oncol. 2015; 10: 577-85.

23. Seppenwoolde Y, Shirato H, Kitamura K, Shimizu S, van Herk M, Lebesque JV, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys. 2002; 53: 822-34.

24. Kilburn JM, Lucas JT, Soike MH, Ayala-Peacock DN, Blackstock AW, Hinson WH, et al. Is a clinical target volume (CTV) necessary in the treatment of lung cancer in the modern era combining 4-D imaging and image-guided radiotherapy (IGRT)? Cureus. 2016; 8: e466.

25. NRG. Oncology. Center for Innovation in radiation oncology [cited May 28 2023]. Available from: https://www.nrgoncology.org/ciro-lung.

26. Wilke L, Andratschke N, Blanck O, Brunner TB, Combs SE, Grosu AL, et al. ICRU report 91 on prescribing, recording, and reporting of stereotactic treatments with small photon beams: statement from the DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. Strahlenther Onkol. 2019; 195: 193-8.

27. Manyam BV, Verdecchia K, Videtic GMM, Zhuang T, Woody NM, Wei W, et al. Validation of RTOG 0813 proximal bronchial tree constraints for pulmonary toxicity with stereotactic body radiation therapy for central non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2020; 107: 72-8.

28. Videtic GMM, Hu C, Singh AK, Chang JY, Parker W, Olivier KR, et al. NRG oncology RTOG 0915 (NCCTG N0927): A randomized Phase II study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperable patients with Stage I peripheral non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2015; 93: 757-64.

29. Trifiletti DM, Chao ST, Sahgal A, Sheehan JP, editors. Stereotactic radiosurgery and stereotactic body radiation therapy: A comprehensive guide. 2019. Cham. Springer International Publishing. 2019.

30. Nagata Y, Matsuo Y, Takayama K, Norihisa Y, Mizowaki T, Mitsumori M, et al. Current status of stereotactic body radiotherapy for lung cancer. Int J Clin Oncol. 2007; 12: 3-7.