СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Current Topic / Актуелна тема

Bojana Poparić-Banđur[1], Brankica Milošević-Maračić[1], Aleksandar Stepanović[1,2], Marina Nikitović[1,2], Tatjana Arsenijević[1,2,♣]

Stereotactic radiotherapy in the treatment of lung cancer - current prospective

Стереотаксична радиотерапија у лечењу карцинома плућа – савремене могућности

[1]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Received: July 16, 2024
Revised: August 19, 2024
Accepted: August 26, 2024
Online First: August 30, 2024
DOI: https://doi.org/10.2298/SARH240716070P

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

♣**Correspondence to:**
Tatjana ARSENIJEVIĆ
University of Belgrade, Faculty of Medicine, Belgrade, Serbia
Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia
Email: tatjanaarsenijevic96@gmail.com

Stereotactic radiotherapy in the treatment of lung cancer - current prospective

Стереотаксична радиотерапија у лечењу карцинома плућа – савремене могућности

SUMMARY
Stereotactic body radiotherapy (SBRT) is the standard treatment for early-stage inoperable non-small cell lung cancer. SBRT achieves a high local control rate (74–100%), preserved quality of life, and low treatment toxicity. Different fractionation regimens are used, depending on the localization and size of the tumor, the proximity of the organs at risk, and the general condition of the patient.
The radiobiology behind SBRT is largely unknown, so the precise tumor dose and the number of fractions are still a matter of discussion. Numerous studies are ongoing regarding the standardization of SBRT in lung cancer treatment.
Keywords: stereotactic body radiotherapy; lung cancer; early stage

САЖЕТАК
Стереотаксична радиотерапија (СРТ) је стандардни третман у лечењу раног стадијума, инопарабилног, неситноћелијског карцинома плућа. СРТ постиже високу стопу локалне контроле болести (74–100%) уз очуван квалитет живота и прихватљиву токсичност. У клиничкој пракси користе се различити режими фракционисања у зависности од локализације и величине тумора, близине органа од ризика и општег стања пацијента. Радиобиологија СРТ је још увек недовољно позната, тако да су прецизно дефинисане дозе зрачења као и број фракција и даље предмет расправе. У току су бројне студије стандардизације СРТ у лечењу карцинома плућа.
Кључне речи: стереотаксична радиотерапија; карцином плућа; рани стадијум

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a technique of external beam radiotherapy (EBRT) that accurately delivers a high dose of radiation to an extracranial target in a single or few fractions. Developed in the early 1990s, SBRT has been further adapted and improved and is currently an important component of modern radiotherapy. Nowadays, SBRT represents the standard treatment for patients with early-stage (TNM classification: T1-T2, N0, M0) inoperable, non-small cell lung cancer (NSCLC), with a high local control rate (74-100%), preserved quality of life, and low treatment toxicity [1, 2].

INDICATIONS AND PATIENT SELECTION

Early-stage NSCLC is traditionally managed by lobectomy and systematic hilar and mediastinal lymph node dissection. Overall survival of 60-92% at 5 years after lobectomy, made early-stage NSCLC a curable disease. However, a significant number of patients present

as medically inoperable and thus approached with atypical lung resections, radical radiotherapy (60-66Gy), or best supportive care [2].

Randomized trials that compared the results of operative treatment to SBRT found no difference in the 3-year survival rate (91% in both arms), while 3-year local control was 80% after SBRT and 88% after lobectomy [3]. The ongoing POSTILV study aims to determine whether the SBRT with a precisely defined dose and delivery technique can be more effective than the surgery. The results of this study are expected in 2026. [4].

According to the ESTRO/ACROP consensus in 2017, candidates for SBRT should have pathohistologically confirmed NSCLC, stage I (T1-2 N0 M0), primary tumor of maximum size up to 5 cm, at least 2 cm away from the main bronchus, ECOG performance status (PS) < 3 and minimal life expectancy of one year. There are no absolute contraindications in terms of age, Charlson Comorbidity score, chronic obstructive pulmonary disease, and pre-treatment pulmonary function [5].

Localization of the tumor within the lung parenchyma is crucial in making treatment decisions. Centrally localized lung tumors, defined by the Radiotherapy and Oncology Group (RTOG) as lesions located ≤ 2 cm from the proximal tracheobronchial tree (PBT) represent a challenge both for SBRT and surgical treatment [6]. The implementation of SBRT in this localization is still a matter of debate since it is associated with an increased risk of developing severe radiotherapy-related toxicity (namely esophagitis and bleeding) [7]. Wu et al. indicate that the application of SBRT in tumors localized 2cm from the proximal bronchial tree is a "no-fly zone" due to high toxicity, and that conventionally fractionated RT should be the treatment of choice [8].

Tumors of ultra-central location are defined as tumors located ≤ 1 cm from the PBT. These patients have a particularly high risk of developing severe toxicity (≥ grade 3 according to the National Cancer Institute-Common Terminology Criteria for Adverse Events; NCI

CTCAE). A prospective phase II Nordic study in 2021. established a cut-off at a distance of 1cm from the PBT. The SBRT for (ultra)central tumors ≥ 1 cm from the PTB is associated with an acceptable risk of toxicity (grade 1-2), while in tumors ≤ 1 cm away from the PBT it is unacceptable (≥ grade 3) [9, 10].

Therefore, in everyday practice, patients are assessed multidisciplinary on a "case to case" basis.

SBRT TREATMENT PLANNING

Most of the modern radiotherapy centers are equipped with the necessary devices for the application of SBRT, making it widely adopted. Only four-dimensional computed tomography (4DCT), standard linear accelerator with image guidance and high-resolution multi-lamellar collimator (MLC) < 10 mm are mandatory. All other equipment is optional [5].

To adequately plan and perform SBRT of lung tumors, the positioning, and immobilization of the patient is extremely important. A "wing board" immobilization device with arms overhead is used as standard, while other SBRT-specific immobilization devices are optional and institution-based.

Treatment planning CT of the thorax is performed thereafter, with the previous assessment of the patient's respiratory function and the possibility of applying respiration control procedures (such as deep inspiration breath hold-DIBH). Accordingly, the treatment planning CT is made during free breathing or in a certain phase of respiration (respiratory gating).

For treatment planning, 4DCT is recommended, from the lung apex to the 2nd lumbar vertebra, with 2-3 mm thickness.

Delineation of target volumes is based on ICRU 62 (International Commission on Radiation Units and Measurements) and ICRU 83 recommendations [11].

The tumor volume (GTV-gross tumor volume) is delineated on each CT slice, in the CT lung window, usually without a margin for the potential microscopic spread of the disease (clinical target volume-CTV). In GTV delineation, treatment planning CT and PET-CT fusion is recommended.

After GTV delineation, planning target volume (PTV) is added for set-up errors. Defining PTV depends on the treatment planning CT. If 4DCT is used, it is necessary to delineate the ITV (internal target volume) that corresponds to the position of the target (tumor) during respiration. The PTV is created usually by adding a margin of 5 mm to the ITV in all directions [12]. If the patient is scanned while breathing freely and/or with standard three-dimensional computed tomography (3DCT), the PTV is formed by adding a margin to the GTV of 10 mm in all directions (Figure 1).

Organs at risk (OAR) include the trachea, main bronchi, esophagus, aorta, heart, spinal cord, both lungs and chest wall.

Intensity Modulated Radiotherapy (IMRT) is the most commonly used technique for lung SBRT, using multiple coplanar fields, with 6-10 MV photons. Since 2011, Volumetric, Modulated Arc Radiotherapy (VMAT) became a preferred technique (Figure 2).

Before carrying out each radiation fraction it is mandatory to check the patient and tumor position with cone beam CT, and, if necessary, correct the positioning (Figure 3).

SBRT TREATMENT DOSE

The application of a high radiation dose with each SBRT fraction leads to a high biologically effective dose (BED), and establishes SBRT as a biologically more potent method than the conventional fractionation regimen.

The radiobiology behind SBRT is largely unknown, so the tumor dose and the number of fractions are still a matter of discussion. The administered dose is risk-adapted and depends

on the localization of the tumor within the lung, the proximity of the OAR, tumor volume, and patient's characteristics. Different fractionation regimens are used in practice, but it is recommended BED to be ≥ 100 Gy [13]. In 2019, the Anderson Cancer Center published the results of a retrospective study that high BED (>130 Gy) was associated with longer survival compared to lower BED (100-129 Gy) suggesting the importance of a total dose rather than a fractionation regimen [14].

In the RTOG 0915 trial, two fractionation regimens (34 Gy in 1 fraction vs 48 Gy in 4 fractions, prescription isodose ≥ 60% to < 90%) were compared in patients with peripherally localized tumors. There was no significant difference in the local control, occurrence of late toxicity, and survival between the two regimens [15]. For peripherally localized tumors that are in direct contact with the thoracic wall, Nagata et al. proposed two fractionation regimens: 45 Gy in 3 fractions and 48 Gy in 4 fractions [16].

The RTOG 0813 trial was designed to determine the maximum tolerated dose (MTD) for centrally localized tumors. The MTD was 12 Gy in five fractions, with a local control of 89.4% [17]. According to the GOECP/SEOR radiotherapy guideline and evidence published so far, a safe dose for centrally located tumors is 50-60Gy in 5 fractions, but an 8x7.5Gy regimen can be considered [18].

Ultra-centrally localized tumors represent a special challenge for performing SBRT. HILUS trial in 2022. showed that the fractionation regimen of 8x7Gy for tumors localized < 1 cm from PBT is unacceptable due to the resulting toxicity [9,10]. However, the delineation, treatment planning, and dose delivery vary throughout studies. The novel results of the phase I SUNSET trial in 2024. suggest that a dose of 60 Gy in 8 fractions (precisely planned and delivered) can be considered safe [19].

TREATMENT TOXICITY

The development of acute and late toxicity after lung tumor SBRT is individual, and depends on multiple factors such as patient age, comorbidities, tumor localization in the lungs, the proximity of OAR, and the very method of radiation technique.

The high doses of radiation used during SBRT can cause side effects ranging from mild fatigue to fatal pneumonitis and bleeding.

One of the most frequent side effects following SBRT is radiation pneumonitis. After SBRT, reported rates of symptomatic radiation pneumonitis vary from 9% to 28% [20].

The most common late complications of SBRT for peripherally localized lung cancer are chest wall pain, rib fracture, and pulmonary fibrosis. In about 16% of cases, chest wall pain is symptomatic and usually occurs 6-9 months after treatment. A rib fracture is recorded in 17% of cases, 13-22 months after SBRT [21].

Complications are significantly more frequent and pronounced when performing SBRT of centrally located tumors, namely esophagitis, damage to the mediastinal vascular structures with bleeding, ulceration, and perforation of the esophagus and trachea.

Nguyen et al. reported that the toxicity of grade >2 for ultra-central, central, and peripheral localizations was 57.6%, 14.2%, and 7.1% respectively for the same dose [22]. After the radiation treatment of an ultra-centrally localized tumor, Wang et al. reported 22% of patients with pneumonitis and esophagitis grade ≥3, while tracheobronchial fistula was documented in two patients [23].

Prophylactic administration of corticosteroids during SBRT did not show any benefit. The frequency of acute complications is approximately the same in patients receiving prophylactic Dexamethasone as in those who did not receive corticosteroid therapy [24].

CONCLUSION

Current research indicates that stereotaxic radiotherapy in patients with early-stage, inoperable peripheral lung cancer represents an optimal treatment modality, associated with an acceptable rate of toxicity. The implementation of SBRT in central and ultra-central lung tumors is still a subject of research due to the risk of developing high-grade toxicity. Numerous studies are ongoing regarding the implementation of SBRT in central localization, the results of which are expected soon.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

REFERENCES

1. Heinzerling JH, Hampton CJ, Robinson M, Bright M, Moeller BJ, Ruiz J, et al. Use of surface-guided radiation therapy in combination with IGRT for setup and intrafraction motion monitoring during stereotactic body radiation therapy treatments of the lung and abdomen. J Appl Clin Med Phys. 2020;21(5):48–55. [DOI: 10.1002/acm2.12852] [PMID: 32196944]
2. Vlaskou Badra E, Baumgartl M, Fabiano S, Jongen A, Guckenberger M. Stereotactic radiotherapy for early stage non-small cell lung cancer: current standards and ongoing research. Transl Lung Cancer Res. 2021;10(4):1930–49. [DOI: 10.21037/tlcr-20-860] [PMID: 34012804]
3. Chang JY, Mehran RJ, Feng L, Verma V, Liao Z, Welsh JW, et al. STARS Lung Cancer Trials Group. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol. 2021;22(10):1448–57. [DOI: 10.1016/S1470-2045(21)00401-0] [PMID: 34529930]
4. Csiki E, Simon M, Papp J, Barabás M, Mikáczó J, Gál K, et al. Stereotactic body radiotherapy in lung cancer: a contemporary review. Pathol Oncol Res. 2024;30:1611709. [DOI: 10.3389/pore.2024.1611709] [PMID: 38476352]
5. 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(1):11–17. [DOI: 10.1016/j.radonc.2017.05.012] [PMID: 28687397]
6. Roesch J, Panje C, Sterzing F, Mantel F, Nestle U, Andratschke N, et al. SBRT for centrally localized NSCLC - What is too central? Radiat Oncol. 2016;11(1):157. [DOI: 10.1186/s13014-016-0732-5] [PMID: 27912764]
7. Saito M, Furukawa K, Miura T, Kato H. Evaluation of T factor, surgical method, and prognostic factors in central type lung cancer. Jpn J Thorac Cardiovasc Surg. 2002;50(10):413–7. [DOI: 10.1007/BF02913174] [PMID: 12428380]
8. Wu AJ. Safety of stereotactic ablative body radiation for ultracentral stage I non-small cell lung cancer. Transl Lung Cancer Res. 2019;8(Suppl 2):S135-S138. [DOI: 10.21037/tlcr.2019.08.08] [PMID: 31673517]
9. Rosenberg SA, Mak R, Kotecha R, Loo BW Jr, Senan S. The Nordic-HILUS Trial: Ultracentral Lung Stereotactic Ablative Radiotherapy and a Narrow Therapeutic Window. J Thorac Oncol. 2021;16(10):e79-e80. [DOI: 10.1016/j.jtho.2021.06.030] [PMID: 34561039]
10. 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(7):1200–10. [DOI: 10.1016/j.jtho.2021.03.019] [PMID: 33823286]
11. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). ICRU Report 83. Vol.10, Journal of the ICRU. Oxford University Press; 2010.
12. Inagaki T, Doi H, Ishida N, Ri A, Tatsuno S, Wada Y, et al. Escalated Maximum Dose in the Planning Target Volume Improves Local Control in Stereotactic Body Radiation Therapy for T1-2 Lung Cancer. Cancers (Basel). 2022;14(4):933. [DOI: 10.3390/cancers14040933] [PMID: 35205682]
13. Guckenberger M, Klement RJ, Allgäuer M, Appold S, Dieckmann K, Ernst I, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. Radiother Oncol. 2013;109(1):13–20. [DOI: 10.1016/j.radonc.2013.09.005] [PMID: 24183066]
14. Moreno AC, Fellman B, Hobbs BP, Liao Z, Gomez DR, Chen A, et al. Biologically Effective Dose in Stereotactic Body Radiotherapy and Survival for Patients With Early-Stage NSCLC. J Thorac Oncol. 2020;15(1):101–9. [DOI: 10.1016/j.jtho.2019.08.2505] [PMID: 31479748]
15. Videtic GM, Paulus R, Singh AK, Chang JY, Parker W, Olivier KR, et al. Long-term Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019;103(5):1077–84. [DOI: 10.1016/j.ijrobp.2018.11.051] [PMID: 30513377]
16. Nagata Y, Kimura T. Stereotactic body radiotherapy (SBRT) for Stage I lung cancer. Jpn J Clin Oncol. 2018;48(5):405–9. [DOI: 10.1093/jjco/hyy034] [PMID: 29635536]
17. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37(15):1316–25. [DOI: 10.1200/JCO.18.00622] [PMID: 30943123]
18. Rodríguez De Dios N, Navarro-Martin A, Cigarral C, Chicas-Sett R, García R, Garcia V, et al. GOECP/SEOR radiotherapy guidelines for non-small-cell lung cancer. World J Clin Oncol. 2022;13(4):237–66. [DOI: 10.5306/wjco.v13.i4.237] [PMID: 35582651]

19. Giuliani ME, Filion E, Faria S, Kundapur V, Toni Vu TTT, Lok BH, et al. Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET). Int J Radiat Oncol Biol Phys. 2024:S0360-3016(24)00480-2. [DOI: 10.1016/j.ijrobp.2024.03.050] [PMID: 38614279]
20. Yamashita H, Takahashi W, Haga A, Nakagawa K. Radiation pneumonitis after stereotactic radiation therapy for lung cancer. World J Radiol. 2014;6(9):708–15. [DOI: 10.4329/wjr.v6.i9.708] [PMID: 25276313]
21. Thompson M, Rosenzweig KE. The evolving toxicity profile of SBRT for lung cancer. Transl Lung Cancer Res. 2019;8(1):48–57. [DOI: 10.21037/tlcr.2018.10.06] [PMID: 30788234]
22. Nguyen KNB, Hause DJ, Novak J, Monjazeb AM, Daly ME. Tumor Control and Toxicity after SBRT for Ultracentral, Central, and Paramediastinal Lung Tumors. Pract Radiat Oncol. 2019;9(2):e196-e202. [DOI: 10.1016/j.prro.2018.11.005] [PMID: 30496842]
23. Wang C, Rimner A, Gelblum DY, Dick-Godfrey R, McKnight D, Torres D, et al. Analysis of pneumonitis and esophageal injury after stereotactic body radiation therapy for ultra-central lung tumors. Lung Cancer. 2020;147:45–8. [DOI: 10.1016/j.lungcan.2020.07.009] [PMID: 32663723]
24. Alite F, Shaikh PM, Mahadevan A. Influence of Dexamethasone Premedication on Acute Lung Toxicity in Lung SBRT. Front Oncol. 2022;12:837577. [DOI: 10.3389/fonc.2022.837577] [PMID: 35311107]

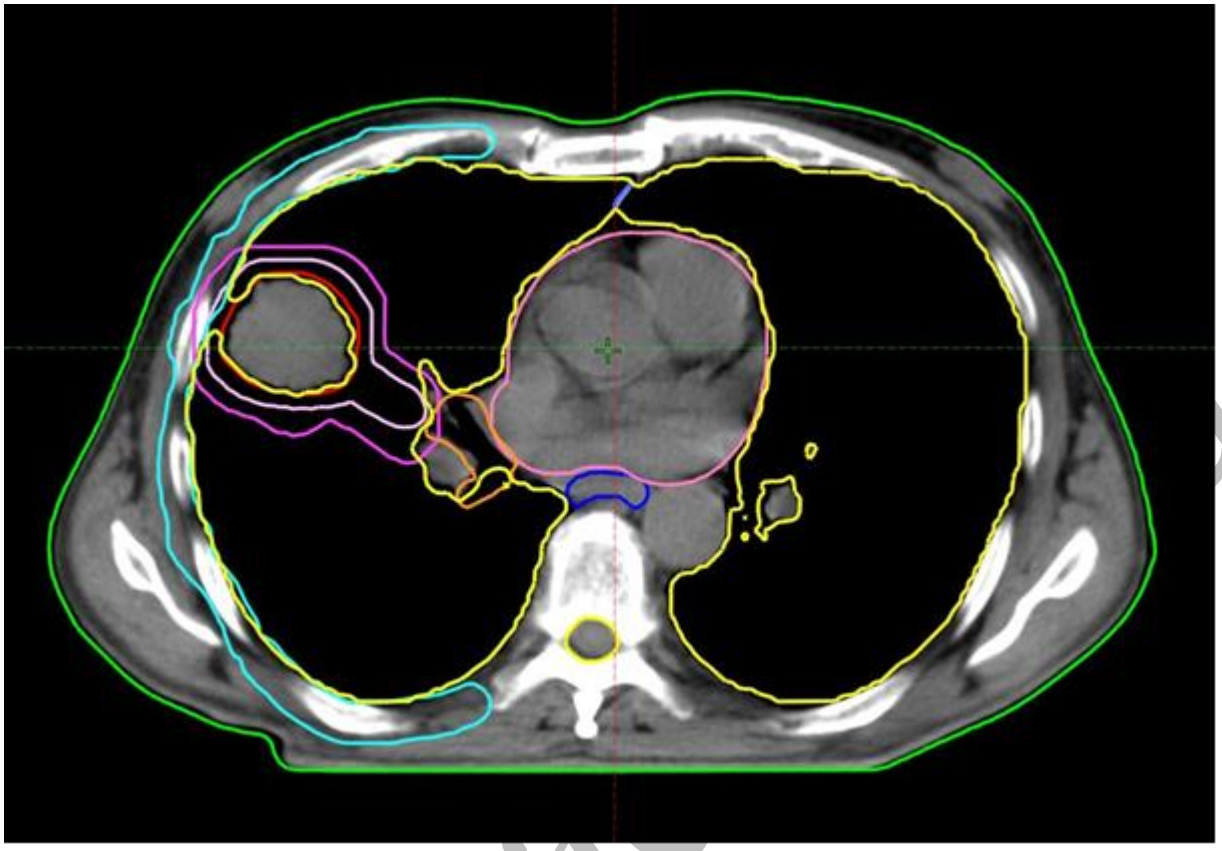

Figure 1. Target volume delineation and organs at risk (Institute for Oncology and Radiology of Serbia)

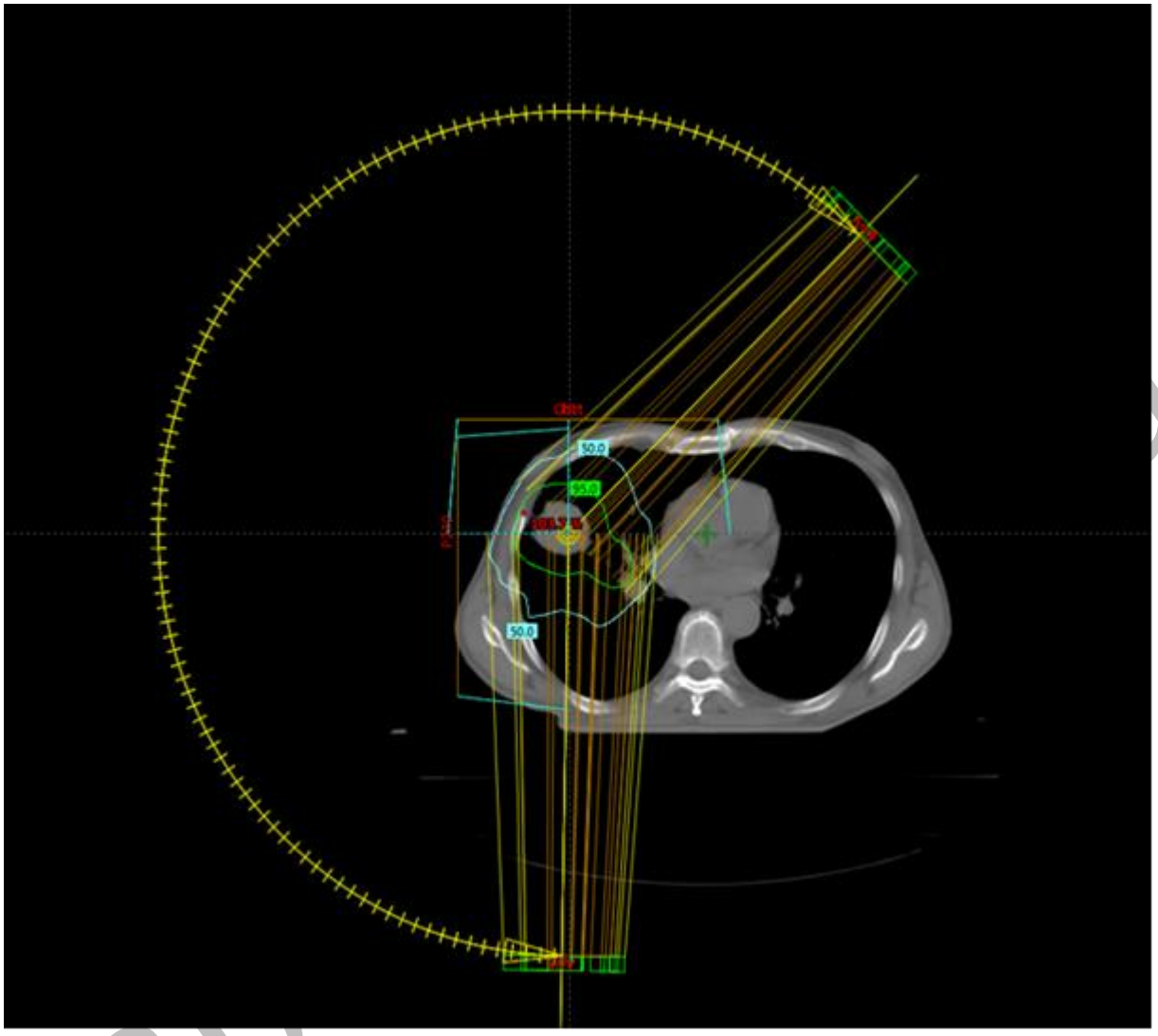

Figure 2. Volumetric modulated arc radiotherapy for lung cancer stereotactic body radiotherapy (Institute for Oncology and Radiology of Serbia)

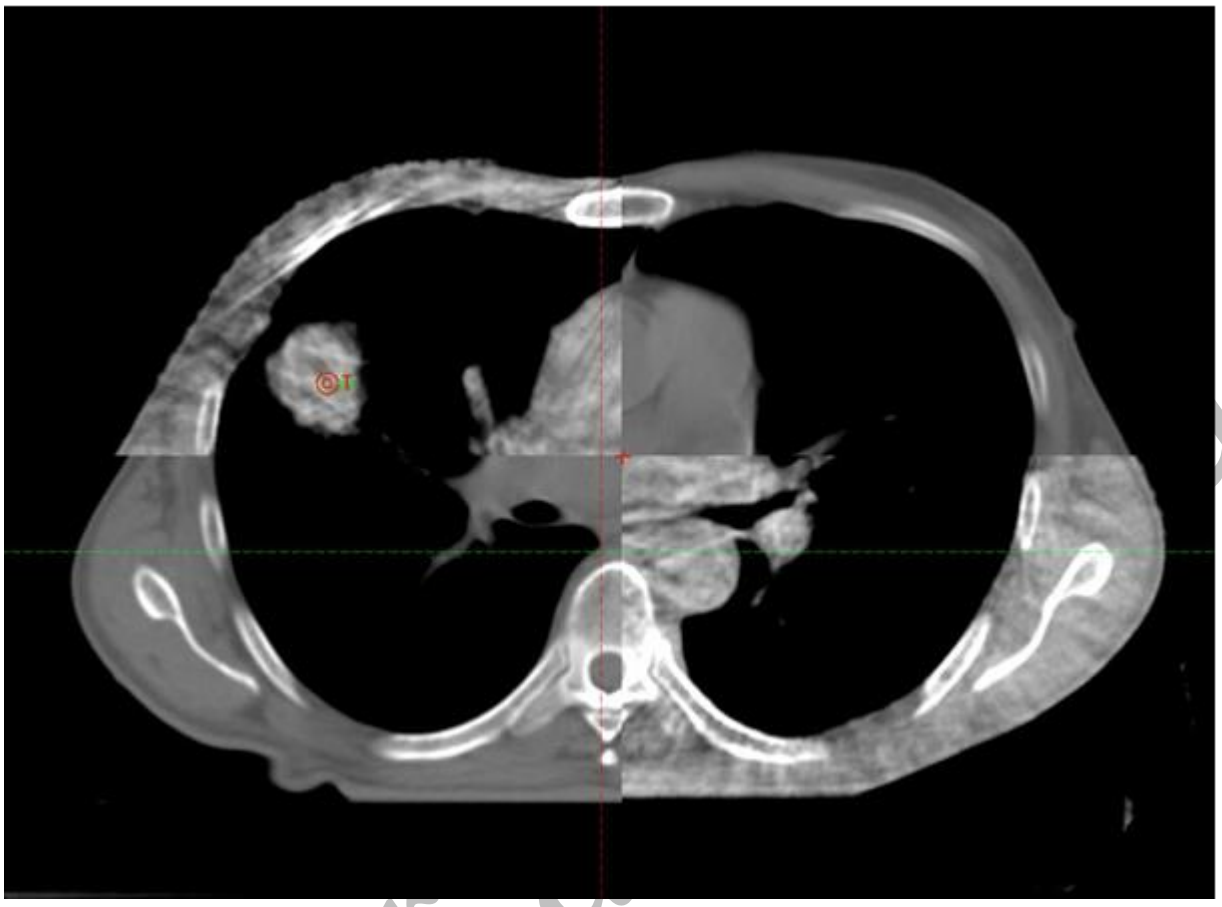

Figure 3. Cone beam computed tomography (Institute for Oncology and Radiology of Serbia)

