

Exploring the Current Challenges and Pioneering Clinical Applications of Stereotactic Radiotherapy in Cancer Treatment

Atsuto Katano, MD, PhD¹ 

Abstract

Stereotactic radiotherapy (SRT) has become integral to modern oncology, offering the ability to deliver ablative doses while minimizing damage to surrounding normal tissues. Recent advancements in imaging integration, treatment planning, and dose delivery have expanded their clinical applications across various tumor types. However, challenges such as toxicity in anatomically critical regions, optimal margin determination, and the lack of standardized protocols persist. This review explores key issues in contemporary practice and highlights emerging clinical evidence across lung, liver, prostate, brain, and oligometastatic diseases. Further refinement in patient selection and treatment strategies is essential to maximize therapeutic efficacy and ensure safe implementation in broader clinical settings.

Keywords

radiation oncology, stereotactic body radiation therapy, stereotactic radiotherapy, oncology, radiotherapy

Received: 6 December 2024; revised: 18 March 2025; accepted: 24 March 2025

Introduction

Stereotactic radiotherapy (SRT) has become a pivotal component of precision radiation oncology. Stereotactic body radiotherapy (SBRT), the application of SRT to extracranial sites, has gained widespread clinical recognition as a valuable treatment option for tumors in organs such as the lung, liver, and prostate. As an evolving and innovative treatment approach, SBRT has gained increasing attention through its integration with advanced imaging modalities such as MRI and PET, as well as its potential synergy with immunotherapy.¹ Nevertheless, several key challenges must still be addressed to enable broader clinical adoption, including the establishment of standardized protocols for tumor delineation, irradiation margins, and post-treatment follow-up. Despite its growing utilization, several obstacles remain, including the prevention of severe toxicities, optimization of treatment margins, and establishment of standardized treatment protocols. This review summarizes current challenges and highlights emerging evidence supporting SBRT.

Current Challenges in Stereotactic Radiotherapy

Significant Toxicity of SBRT for Central Thoracic Tumors

For early-stage non-small cell lung cancer (NSCLC), a pooled analysis of two randomized trials comparing surgery to SBRT

demonstrated comparable local control and overall survival rates.² However, treating central lung tumors requires careful patient selection, consideration of severe adverse event occurrence with meticulous radiotherapy planning. A multicenter phase 2 trial evaluating SBRT for thoracic tumors ≤ 1 cm from the proximal bronchial tree used a prescription of 56 Gy in 8 fractions to the 67% isodose encompassing the planning target volume (PTV).³ While the trial reported a 2-year local control rate of 83%, grade 3 to 5 toxicity was observed in 22 of the 65 patients, including 10 treatment-related deaths, primarily due to bronchopulmonary hemorrhage.⁴ A meta-analysis of 27 studies (1 prospective, 26 retrospective) involving 1183 ultra-central NSCLC targets (defined as PTV overlapping the proximal bronchial tree) reported pooled 1- and 2-year local control rates of 92% and 89%, respectively.⁴ However, Grade 3–4 toxicities occurred in 6% of cases, most commonly pneumonitis, while treatment-related deaths, primarily due to hemoptysis, had a pooled incidence of 4%. The LungTech trial demonstrated that SBRT with 60 Gy in 8 fraction for centrally

¹Department of Radiology, The University of Tokyo Hospital, Tokyo, Japan

Corresponding Author:

Atsuto Katano, Department of Radiology, the University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan.
Emails: katanoa-rad@h.u-tokyo.ac.jp; atsuto-katano@umin.ac.jp



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and

distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

located NSCLC achieves acceptable local control (81.5% at 3 years) but is associated with significant late toxicity, with 19.4% experiencing $\geq$ G3 adverse events, including fatal hemoptysis and pneumonitis.⁵ The American Radium Society (ARS) Thoracic Appropriate Use Criteria panel provided consensus guidelines for managing central and ultra-central NSCLC.⁶ Hypofractionated radiotherapy (8-18 fractions) was recommended for ultra-central lesions near critical structures, while five-fraction SBRT was deemed appropriate for other central and ultra-central lesions.

Optimizing Margins in SBRT: Precision, Outcomes, and Challenges

The success of SBRT depends on meticulous treatment planning, especially in determining PTV margins. These margins account for uncertainties such as organ motion, setup variations, and imaging limitations. Balancing sufficiently large margins to ensure tumor coverage against minimizing radiation exposure to organs-at-risk (OARs) is critical for optimizing both oncologic outcomes and patient safety. PTV margins include intrafractional and interfractional errors. Managing intrafractional errors involves addressing spatial uncertainties during radiation delivery. Kang et al investigated the impact of cranial angles on treatment accuracy in CyberKnife radiosurgery. A retrospective analysis of 66 brain tumor patients showed that reducing cranial angles to ≤ 10 degrees enhanced intrafractional stability, with a 1-mm margin providing adequate coverage.⁷ In liver SBRT, the diaphragm is a crucial anatomical structure susceptible to positional and motion variations, which can potentially impact the accuracy of liver tumor targeting. Real-time kilovoltage projection imaging demonstrated consistent diaphragm positional deviations within 1.1 mm during breath-hold treatments, ensuring high precision.^{8,9} Xiong et al evaluated intrafractional prostate motion during gated MRI-guided radiotherapy, demonstrating that prostate motion was minimal, with 95% of shifts within 3.5 mm in anterior-posterior and 3.2 mm in superior-inferior directions.¹⁰

Pioneering Clinical Applications of Stereotactic Radiotherapy

Emerging Evidence of Stereotactic Body Radiotherapy

SBRT is increasingly recognized as a competitive alternative to conventional therapies in early-stage cancers and small tumors. In prostate cancer, the phase 3 PACE-B trial has already shown that SBRT (36.25 Gy in 5 fractions) is non-inferior to conventional fractionated radiotherapy, with 5-year freedom from biochemical or clinical failure rates of 95.8% versus 94.6%, respectively, and comparable toxicity profiles.¹¹ In hepatocellular carcinoma (HCC), a randomized controlled trial by Xi et al compared SBRT to radiofrequency ablation (RFA) in patients with recurrent small HCC.¹² The trial showed that SBRT achieved superior local control, with 2-year local progression-

free survival rates of 92.7% compared to 75.8% with RFA. The difference was statistically significant, with a hazard ratio of 0.45 (95% CI: 0.24-0.87; $P = .014$). In locally advanced HCC, the NRG RTOG 1112 trial showed that adding SBRT to sorafenib improved median overall survival from 12.3 to 15.8 months, though the difference was not statistically significant (HR 0.77, $p = 0.06$).¹³ This result is indicating the expanding role of SBRT in primary liver malignancies and the synergistic potential of combining local and systemic therapies.

Stereotactic Radiotherapy in Brain Metastasis

Brain metastases remain a large problem in oncology, affecting approximately 20% of patients with metastatic cancer during their disease course.¹⁴ Stereotactic radiosurgery (SRS) is a key modality of brain metastases treatment, which treatment outcome was assessed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria.¹⁵ Historically reserved for patients with a limited number of brain metastases (less than 5 lesions), SRS is increasingly being utilized in cases with higher metastatic burdens. JLGK0901 study demonstrated that SRS without whole-brain radiotherapy (WBRT) for patients with five to ten brain metastases is non-inferior to SRS for those with two to four metastases in terms of overall survival.¹⁶ With comparable survival outcomes and low rates of treatment-related adverse events, SRS presents a viable, less invasive alternative to WBRT for patients with up to ten brain metastases. Follow-up intervals are critical for detecting recurrence, managing late-onset toxicities, and ensuring patient well-being. While frequent follow-ups enable early detection of adverse events, they can strain healthcare resources and affect patient compliance. Conversely, less frequent follow-ups risk delayed identification of complications or recurrence. Popov et al investigated the use of MRI for monitoring brain metastases treated with stereotactic radiosurgery.¹⁷ Their findings suggest that routine MRI at one month may be unnecessary unless new neurological symptoms arise, supporting later evaluations based on RANO-BM criteria.

Expanding Horizons: Clinical Indications of SBRT for Oligometastatic Disease

Initially focused on primary cancers such as lung, prostate, and liver, the clinical indications for SBRT have expanded to include oligometastatic and oligoprogressive disease. The SABR-COMET trial demonstrated that adding SBRT to standard care significantly improved 5-year overall survival (42.3% vs 17.7%; $P = .006$) and progression-free survival (17.3% vs 3.2%; $P = .001$) in patients with 1-5 metastases.¹⁸ Chalkidou et al analyzed 1422 National Health Service patients in England with extracranial oligometastases and found that SBRT was associated with high overall survival and low toxicity.¹⁹ Tsai et al conducted a phase 2 trial which demonstrated that adding SBRT to standard care significantly improved progression-free survival in patients with oligoprogressive metastatic NSCLC

(10.0 months vs 2.2 months; HR 0.41, $p = 0.0039$), but not in those with oligoprogressive breast cancer (4.4 months vs 4.2 months; HR 0.78, $p = 0.43$).²⁰ While SBRT shows promise in managing oligoprogressive NSCLC, further research is needed to validate these results and investigate the lack of benefit in breast cancer patients. The NRG BR002 trial, focused on breast cancer patients with 1–4 extracranial metastases, showed limited survival benefit, highlighting the complexity of defining appropriate indications and the need for further clinical evidence.²¹ The expanding indications for SBRT in oligometastatic disease underscore its potential as a transformative treatment modality, highlight the necessity for continued research to refine patient selection criteria, and optimize treatment protocols.

Conclusion

SRT is increasingly being utilized across various cancer types, including early-stage NSCLC, oligometastatic disease, and brain metastases. Expanding its clinical horizons, the ongoing phase III trial NRG Oncology LU008 (NCT05624996) is evaluating SBRT to the primary tumor followed by chemoradiation to involved lymph nodes in patients with inoperable stage II–III NSCLC.²² However, late toxicity remains a critical challenge, particularly in cases involving ultra-central lung cancer or tumors adjacent to vital anatomical structures. While SRT continues to evolve as a novel treatment modality, addressing key issues such as late toxicity, variability in practice, and the need for evidence-based standardized guidelines is essential to further enhance its success. Sustained research and technological advancements are crucial to fully unlocking the potential of this innovative technique.

Statements and Declarations

Ethical Considerations

Ethical approval was not required for this manuscript as it did not involve the use of human or animal samples.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iD

Atsuto Katano  <https://orcid.org/0000-0003-4393-1828>

References

- Katano A, Minamitani M, Ohira S, Yamashita H. Recent advances and challenges in stereotactic body radiotherapy. *Technol Cancer Res Treat*. 2024;23:15330338241229363. doi:10.1177/15330338241229363
- Shinde A, Li R, Kim J, Salgia R, Hurria A, Amini A. Stereotactic body radiation therapy (SBRT) for early-stage lung cancer in the elderly. *Semin Oncol*. 2018;45(4):210–219. doi:10.1053/j.seminoncol.2018.06.002
- Lindberg K, Grozman V, Karlsson K, 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):1200–1210. doi:10.1016/j.jtho.2021.03.019
- Yan M, Louie AV, Kotecha R, et al. Stereotactic body radiotherapy for Ultra-Central lung Tumors: A systematic review and Meta-Analysis and International Stereotactic Radiosurgery Society practice guidelines. *Lung Cancer*. 2023;182:107281. doi:10.1016/j.lungcan.2023.107281
- Levy A, Adebahr S, Hurkmans C, et al. Stereotactic body radiotherapy for centrally located inoperable early-stage NSCLC: EORTC 22113-08113 LungTech phase II trial results. *J Thorac Oncol*. 2024;19(9):1297–1309. doi:10.1016/j.jtho.2024.05.366
- Park HS, Rimner A, Amini A, et al. Appropriate use criteria (AUC) for non-small cell lung cancer in a central/ultra-central location: Executive summary of the American radiation society's systematic review and guidelines. *J Thorac Oncol*. 2024;19(12):1640–1653. doi:10.1016/j.jtho.2024.09.1386
- Kang CL, Huang YY, Chen YR, Tsai SH, Huang CC, Huang YJ. Patient cranial angle and intrafractional stability in CyberKnife robotic radiosurgery: A retrospective analysis. *Technol Cancer Res Treat*. 2024;23:15330338241235058. doi:10.1177/15330338241235058
- Katano A, Nozawa Y, Minamitani M, Yamashita H, Nakagawa K. Novel breath-hold liver target stereotactic ablative radiotherapy using the intrafraction diaphragm registration of kilovoltage projection streaming image with digitally reconstructed radiography of the planning computed tomography. *Tech Innov Patient Support Radiat Oncol*. 2023;27:100217. doi:10.1016/j.tipsro.2023.100217
- Katano A, Nozawa Y, Minamitani M, Ohira S, Nakagawa K. Intrafractional diaphragm variations during breath-hold stereotactic body radiotherapy for a liver tumor based on real-time registration between kilovoltage projection streaming and digitally reconstructed radiograph images: A case report. *Cureus*. 2023;15(11):e48188. doi:10.7759/cureus.48188
- Xiong Y, Rabe M, Nierer L, et al. Assessment of intrafractional prostate motion and its dosimetric impact in MRI-guided online adaptive radiotherapy with gating. *Strahlenther Onkol*. 2023;199(6):544–553. doi:10.1007/s00066-022-02005-1
- van As N, Griffin C, Tree A, et al. Phase 3 trial of stereotactic body radiotherapy in localized prostate cancer. *N Engl J Med*. 2024;391(15):1413–1425. doi:10.1056/NEJMoa2403365
- Xi M, Yang Z, Hu L, et al. Radiofrequency ablation versus stereotactic body radiotherapy for recurrent small hepatocellular carcinoma: A randomized, open-label, controlled trial. *J Clin Oncol*. 2025;43(9):1073–1082. doi:10.1200/jco-24-01532
- Dawson LA, Winter KA, Knox JJ, et al. Stereotactic body radiotherapy vs sorafenib alone in hepatocellular carcinoma: The NRG oncology/RTOG 1112 phase 3 randomized clinical trial. *JAMA Oncol*. 2025;11:136–144. doi:10.1001/jamaoncol.2024.5403
- Katano A, Yamashita H. Brain metastasis: Recent treatment modalities and future-perspectives. *Oncol Lett*. 2022;23(6):191. doi:10.3892/ol.2022.13311
- Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: Proposal from the RANO group.

- Lancet Oncol.* 2015;16(6):e270-e278. doi:10.1016/s1470-2045(15)70057-4
16. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): A multi-institutional prospective observational study. *Lancet Oncol.* 2014; 15(4):387-395. doi:10.1016/s1470-2045(14)70061-0
 17. Popov V, Raycheva G, Graklanov V, Uchikov P, Grudeva-Popova Z. Evaluation of the effect of radiosurgery for target and non-target lesions in patients with brain metastases using RANO-BM criteria. *Technol Cancer Res Treat.* 2024;23: 15330338241273324. doi:10.1177/15330338241273324
 18. Palma DA, Olson R, Harrow S, 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(25):2830-2838. doi:10.1200/JCO.20.00818
 19. Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: A prospective, registry-based, single-arm, observational, evaluation study. *Lancet Oncol.* 2021;22(1):98-106.
 20. Tsai CJ, Yang JT, Shaverdian N, et al. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): An open-label, randomised, controlled, phase 2 study. *Lancet.* 2024;403(10422):171-182.
 21. Burgaleta AM, Burguete AB, Gutiérrez LR, Nuín EB, Felipe GA, de la Vega FA. Local treatment in oligometastasis from breast cancer: An overview. *Clin Transl Oncol.* 2023;25(10):2861-2867.
 22. Heinzerling JH, Pen OV, Robinson M, et al. Full dose SBRT in combination with mediastinal chemoradiation for locally advanced, non-small cell lung cancer: A practical guide for planning, dosimetric results from a phase 2 study, and a treatment planning guide for the phase 3 NRG oncology LU-008 trial. *Pract Radiat Oncol.* 2023;13(6):531-539.