Advances in Radiation Oncology (2024) 9, 101363

advances in radiation oncology

www.advancesradonc.org

Teaching Case

Stereotactic Body Radiation Therapy to the Foot for Bone Metastasis

Pui Lam Yip, FRCR,[a,b] Wan Yan Venus Lee, MPhil,[a] Wing-kin Leung, MSc,[c] Shi Feng Nyaw, FRCR,[a] Ngai Yui Chan, PhD,[a] and Shing Fung Lee, FRCR[a,b,*]

[a]*Department of Clinical Oncology, Tuen Mun Hospital, New Territories West Cluster, Hospital Authority, Hong Kong;*
[b]*Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore; and*
[c]*Auckland Radiation Oncology, Auckland, New Zealand*

Received 22 November 2022; accepted 19 August 2023

Introduction

Stereotactic body radiation therapy (SBRT) delivers high radiation doses, usually in 1 to 5 fractions, to the treatment target in a precise and highly conformed manner. Stereotactic body radiation therapy to oligometastatic lesions represents a new treatment paradigm in oncological care. It was demonstrated to improve overall survival in a proof-of-concept phase 2 randomized study, SABR-COMET.[1] Metastasis-directed therapy has been studied for specific cancer types and reported heterogeneous results. Some phase 2 trials demonstrated that this approach improved progression-free survival in lung and prostate cancer,[2,3] but NRG-BR002 on breast cancer was negative.[4] Furthermore, the efficacy of SBRT in hepatocellular carcinoma (HCC) remains unclear, because this cancer type is underrepresented in the current body of literature.

Stereotactic body radiation therapy is generally safe and well-tolerated.[5] However, distal extremities are known to have poor radiation tolerance.[6] Delivering high radiation dose to a distal extremity has several technical considerations, including the close proximity of complex neurovascular elements and the potential risk of functional and cosmetic complications.[7] Consequently, many clinicians would consider amputation as an alternative.

We report a case of SBRT to the cuboid bone, which will be useful for radiation oncologists who consider treating the distal extremities with SBRT.

Case Presentation

An 83-year-old gentleman had a history of hepatitis B cirrhosis. He was diagnosed with HCC, which was managed with right hepatectomy in 2008. The pathology report showed a 4-cm moderately differentiated HCC with clear margins. The disease was in remission until November 2019, when the patient experienced right foot pain and an elevated alpha-fetoprotein (AFP) level (14 ng/mL). Physical examination revealed a 4-cm bony swelling at the lateral dorsum of the right foot. There was no definite skin involvement. Dual tracer positron emission tomography−computed tomography (PET-CT) with acetate, F-fluorodeoxyglucose (FDG), and iodinated CT contrast in February 2020 showed a lytic bony lesion with intraosseous soft-tissue component and increased acetate (standardized uptake value [SUV] maximum, 5.8) and FDG (SUV maximum, 5.7) activity at the right foot cuboid bone. There was no evidence of disease recurrence elsewhere. A core biopsy showed metastatic carcinoma consistent with HCC.

The patient opted for SBRT in lieu of below-knee amputation. Magnetic resonance imaging (MRI) was arranged for SBRT planning. Magnetic resonance imaging of the right foot (Fig. 1) with T1-weighted (T1W), T2-weighted fat-saturated, and T1W dotarem contrast-

Sources of support: This work had no specific funding.
Research data are not available at this time.
Corresponding author: Shing Fung Lee, FRCR; E-mail: leesf@nuhs.edu.sg

https://doi.org/10.1016/j.adro.2023.101363

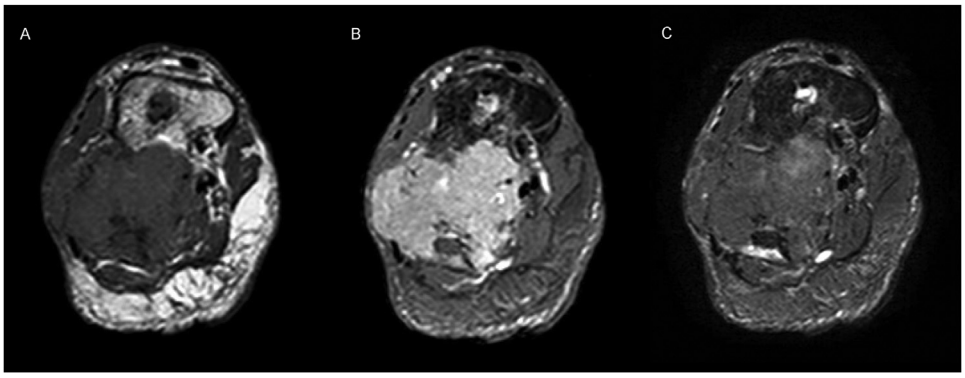

Figure 1 Magnetic resonance imaging of the right cuboid lesion. (A) T1-weighted sequence. (B) T1-weighted dotarem contrast-enhanced fat-saturated sequence. (C) T2-weighted fat-saturated sequence.

enhanced fat-saturated sequences showed a 4.3 × 3.8−cm T1W isointense T2-weighted intermediate enhancing mass with suspicious invasion into the lateral cuneiform bone, peroneus longus tendon, and extensor digitorum longus tendon.

Radiation therapy technique

The right foot was elevated with an alpha-cradle footrest and immobilized with a thermoplastic cast. A 1-cm oil gel bolus was applied for dose build-up (Fig. 2). The previously mentioned MRI images were fused with a plain planning CT. The gross tumor volume was outlined with reference to the clinical finding, CT, and MRI images. A 3-mm clinical target volume margin was trimmed at anatomic barriers, and a 3-mm set-up margin was given. The organ at risk was the skin, which comprised a 2.5-mm rind from the skin surface. The gross tumor volume, clinical target volume, and planning target volume (PTV) were 47.4 cm^3, 77.8 cm^3, and 120.4 cm^3, respectively.

The treatment plan was optimized by the Monaco Treatment Planning System, version 5.11 (Elekta, Stockholm, Sweden) using 6 megavoltage energy and volumetric modulated arc therapy technique. The treatment was delivered using the Versa HD linear accelerator system with agility multileaf collimators (Elekta). Daily kilovoltage cone beam CT and a 6° robotic couch were used for image verification and treatment position correction, respectively. The PTV was prescribed to 32.5 Gray (Gy) in 5 daily fractions to 87.4% isodose line. The dose reports, target volume coverage, and dose-volume histogram are shown in Fig. 3. The homogeneity index was 13.5, and the Paddick conformity index was 0.89. For the skin, D0.5 cm^3 was 36.9 Gy and D10 cm^3 was 28.6 Gy (Table 1). The treatment was completed on June 22, 2020.

Figure 2 Radiation therapy setup.

Follow-up

Two weeks afterward, the patient presented with skin erythema and a blister (Radiation Therapy Oncology Group [RTOG] grade 2[8]), which completely healed after 8 weeks. Subsequently, a mildly painful skin ulcer with serous discharge developed 40 weeks after RT. Wound swabs for bacterial culture were negative. The patient was treated with a course of antibiotics, regular debridement, and dressing. The ulcer (RTOG grade 4[8]) slowly dried up at 80 weeks after RT, with residual hyperpigmentation (RTOG grade 1[8]). Physical examination showed no neurovascular compromise, and the range of motion was maintained. The patient remained ambulatory with minimal assistance from a walking stick, and he could walk unaided 1 year after treatment. Overall, limb preservation was attained (Table 2).

Disease control

Initially, AFP responded to RT. The AFP level dropped from 51.3 ng/mL in April 2020 before RT to 23 ng/mL in August 2020, and it reached the nadir at 22.8 ng/mL in October 2020. However, the AFP slowly rose after December 2020, reaching 139 ng/mL in July 2022.

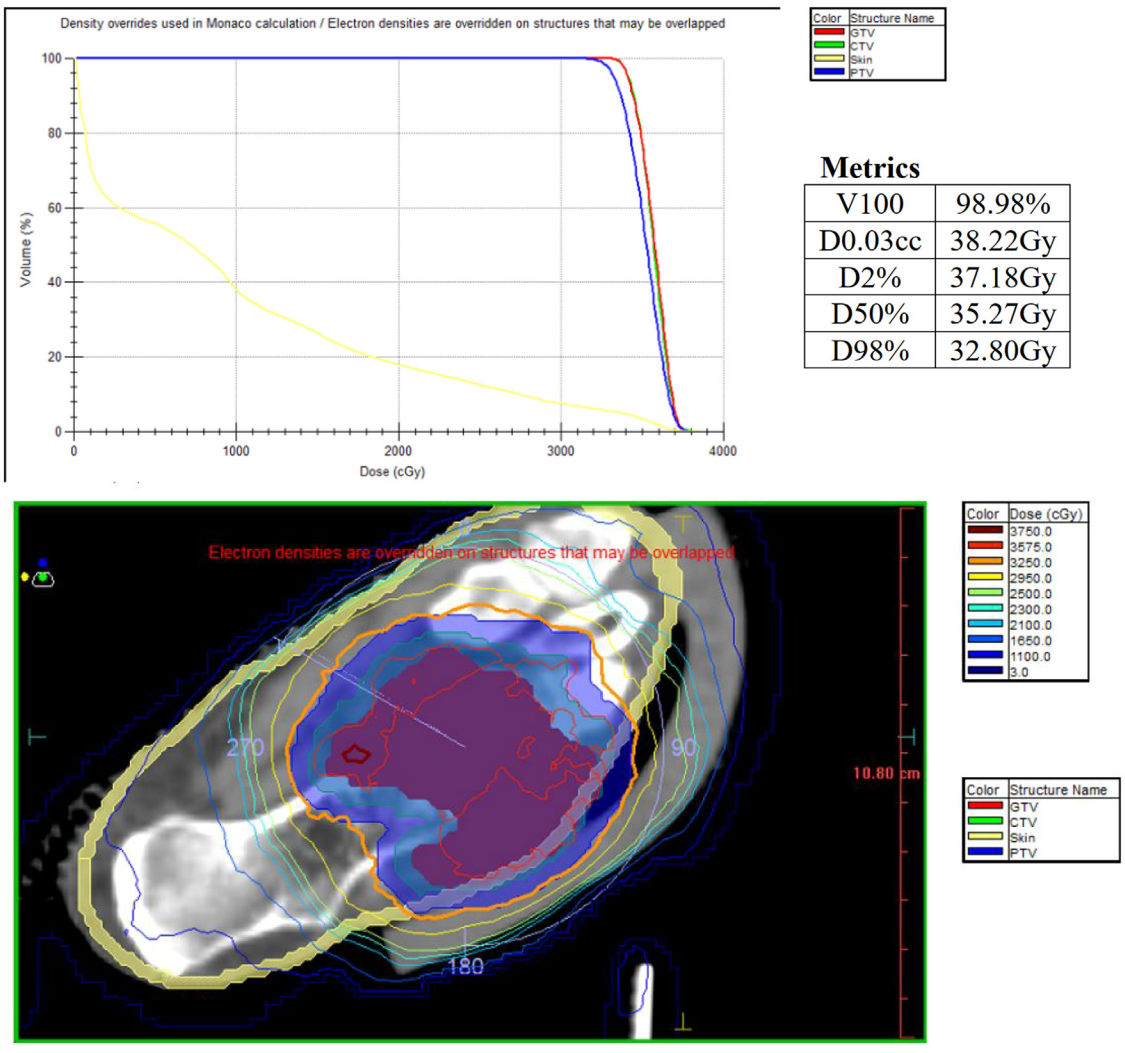

Figure 3 Dose report dose-volume histogram and target volume coverage (planning target volume in blue colorwash).

Table 1 Comparison of skin dose constraints of different guidelines

Literature	Skin	Maximum point, Gy	10 cm^3, Gy
Current study's patient	2.5-mm rind	0.03 cm^3: 37.8 0.035 cm^3: 37.7 0.5 cm^3: 36.9	28.6
	5-mm rind	0.03 cm^3: 38.1 0.035 cm^3: 37.9 0.5 cm^3: 37.2	34.4
TG101[14]	NA	0.035 cm^3: 39.5	36.5
UK SABR Consortium[12]	5-mm rind	0.5 cm^3: 39.5	36.5
RTOG0813[16]	5-mm rind	32	30
Timmerman[17]	NA	32	30
NRG BR-001[15] /002[4]	5-mm rind	0.03 cm^3: 38.5	36.5

Abbreviation: NA = not applicable.

Table 2 Timeline of skin toxicity after radiation therapy

Follow-up	Time interval from radiation therapy completion, wk	Skin condition
June 22, 2020	Radiation therapy completed	
July 2020	2	Erythema and blister
September 2020	10	Skin healed; mild swelling
December 2020	24	Hyperpigmentation
January 2021	40	Right foot ulcer with serous discharge; given antibiotics
April 2021	42	4-cm shallow ulcer; debridement and dressing
June 2021	50	2.5-cm ulcer
July 2021	54	Wound swab showed commensals only
August 2021	58	1.5-cm ulcer
January 2022	80	Skin healed, with hyperpigmentation

Serial MRI in September 2020, May 2021, and October 2021 and whole-body CT in November 2021 showed interval reduction in the size of the right cuboid tumor. A dual tracer PET-CT in February 2022 showed marked improvement in the right cuboid bone that showed subtle acetate (SUV max, 1.6) and mild FDG (SUV max, 2.7) uptake. However, 2 new right popliteal lymph nodes and a new right internal iliac lymph node suspicious for disease progression were noted. In the last follow-up in September 2022, there was no clinical evidence of local failure. The patient opted to continue observation and decided not to receive further SBRT to the metastatic lymph nodes or systemic treatment. In summary, the patient developed radiologic outfield failure 20 months after RT while maintaining local control beyond the 27th month of follow-up.

Discussion

Our case report showed that SBRT to the cuboid bone metastasis showed excellent local control. However, oncologists need to be cautious about acute and chronic skin toxic effects. Most studies on RT to the distal extremity have been on soft-tissue sarcoma using conventional fractionation of 50 to 74 Gy.[9,10] In our literature search, we found only 1 case report[11] on SBRT to the foot. In that report, 30 Gy in 5 fractions was given for glomangiomatosis, which resulted in good symptomatic relief and minimal complications. Thus, the efficacy and toxicity of SBRT to distal extremities for bone metastases remain largely unknown. Our prescription of 32.5 Gy in 5 fractions was mainly a consideration of the skin dose constraint per UK SABR consortium guidance[12] and our institutional practice of a 5-fraction regimen for primary HCC per RTOG 1112.[13] Our plan successfully adhered to the UK SABR[12] and TG 101[14] constraints with skin doses of D0.5 cm^3 36.9 Gy, D0.035 cm^3 37.7 Gy, and D10 cm^3 28.6 Gy, approaching the maximum limits. Any further dose escalation would be challenging.

Our patient experienced both grade 2 acute and grade 4 chronic radiation dermatitis, which gradually healed 18 months after treatment. Dose constraints to the skin were described in the UK SABR Consortium Guidance[12] and TG101,[14] which were adopted in the SBRT-COMET[1] study. Also, a slight variation was adopted in NRG BR-001[15] and BR-002.[4] In contrast, RTOG 0813[16] used more stringent dose constraints adapted from Timmerman.[17] There was no dermatologic safety signal reported from these trials. Of note, these constraints were not validated. During treatment planning, we contoured the skin as a 2.5-mm rind (instead of 3 to 5 mm as described in other references[4,12,15,16]) because the tumor was very close to the skin and a 2.5-mm rind fully encompassed the visualized skin on MRI. Retrospectively, a 5-mm rind from the skin surface was generated to compare with the established guidelines in Table 1. Despite the adherence to the UK SABR Consortium Guidance[12] and TG 101[14] constraints, our patient still experienced significant skin toxicities that necessitated a prolonged period of wound care.

Another technical consideration was the use of bolus. In our case, a bolus was required to provide adequate target coverage and accurate dose calculation at the superficial region. Without using bolus, a lot of inefficient, small multileaf collimator segments will be generated to achieve enough dose to the superficial region, which leads to an increase of monitor unit and quality assurance failure.

To deliver an effective and safe treatment, oncologists should balance the risk and benefit to give a higher dose. To illustrate the tradeoff between the prescription dose, target coverage, and skin dose in our case, we had replanned using more conservative skin dose constraints per RTOG 0813.[17] Using the same prescription dose of 32.5 Gy/5 Fr, the resultant PTV coverage was compromised—V100 dropped from 99.0% to 72.0% and D98% dropped from 32.8 Gy to 27.5 Gy. To achieve better target

Table 3 Alternative radiation therapy plans using RTOG 0813[17] skin constraints

Prescription dose	Replan 1 32.5 Gy in 5 fractions	Replan 2 30 Gy in 5 fractions	Current plan 32.5 Gy in 5 fractions
Prescription isodose level, %	84.9	86.0	87.4
PTV coverage			
V100, %	72.0	90.3	99.0
D98%, Gy	27.5	29.4	32.8
Skin, 5-mm rind			
D0.03 cm^3, Gy	31.8	31.1	38.1
D10 cm^3, Gy	29.6	30.0	34.4

Abbreviation: PTV = planning target volume.

coverage, the prescription dose had to be lowered to 30 Gy/5 Fr, with the resultant V100 and D98% at 90.3% and 29.4 Gy, respectively (Table 3).

To date, dedicated research on SBRT-related skin toxicity is lacking. The occurrence of radiation dermatitis depends on multiple patient-related, treatment-related, and extrinsic factors, including age,[18] dose,[18,19] concurrent chemoradiation,[18,19] pre-existing skin disorder, and so on. We believe that the treatment site and the use of skin bolus might have contributed to the skin toxicities in our patient. In the future, a more stringent dose constraint may be advisable in treating sites with high-risk features including poor blood supply, a tendency for infection, and venous insufficiency.[20] More reports on SBRT-related skin toxicity to inform on the respective dose constraint are advisable.

Conclusion

SBRT to the foot resulted in excellent local control but grade 4 chronic dermatitis. A more stringent skin constraint may be warranted to treat high-risk sites. More reports on SBRT-related dermatitis are awaited.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. 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;38:2830-2838.
2. Phillips R, Shi WY, Deek M, et al. Outcomes of observation versus stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6:650-659.
3. Gomez DR, Blumenschein Jr GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016;17:1672-1682.
4. Chmura SJ, Winter KA, Woodward WA, et al. NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557). *J Clin Oncol*. 2022;40:1007.
5. Lehrer EJ, Singh R, Wang M, et al. Safety and survival rates associated with ablative stereotactic radiotherapy for patients with oligometastatic cancer: A systematic review and meta-analysis. *JAMA Oncol*. 2021;7:92-106.
6. Kim YJ, Song SY, Choi W, et al. Postoperative radiotherapy after limb-sparing surgery for soft-tissue sarcomas of the distal extremities. *Anticancer Res*. 2016;36:4825-4831.
7. Schoenfeld GS, Morris CG, Scarborough MT, Zlotecki RA. Adjuvant radiotherapy in the management of soft tissue sarcoma involving the distal extremities. *Am J Clin Oncol*. 2006;29:62-65.
8. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31:1341-1346.
9. Andrews SF, Anderson PR, Eisenberg BL, Hanlon AL, Pollack A. Soft tissue sarcomas treated with postoperative external beam radiotherapy with and without low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2004;59:475-480.
10. Cammelli S, Cortesi A, Buwenge M, et al. The role of radiotherapy in adult soft tissues sarcoma of the extremities. *Eur J Orthop Surg Traumatol*. 2021;31:1583-1596.
11. Horne ZD, Karam SD, Rashid A, et al. The use of stereotactic body radiation therapy for local control of glomangiomatosis: A case report. *Front Oncol*. 2013;3:26.
12. SABR UK Consortium. *Stereotactic Ablative Body Radiation Therapy (SABR): A Resource*. Version 6.1. January 2019. Available at: https://www.sabr.org.uk/wp-content/uploads/2019/04/SABRconsortium-guidelines-2019-v6.1.0.pdf. Accessed July 29, 2023.
13. Dawson LA, Winter KA, Knox JJ, et al. NRG/RTOG 1112: Randomized phase III study of sorafenib versus stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). *J Clin Oncol*. 2023;41:489.
14. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys*. 2010;37:4078-4101.
15. Chmura S, Winter KA, Robinson C, et al. Evaluation of safety of stereotactic body radiotherapy for the treatment of patients with

multiple metastases: Findings from the NRG-BR001 phase 1 trial. *JAMA Oncol*. 2021;7:845-852.
16. Bezjak A, Paulus R, Gaspar LE, 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;37:1316-1325.
17. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol*. 2008;18:215-222.
18. Teng X, Zhang X, Zhi X, et al. Risk factors of dermatitis during radiation for vulvar carcinoma. *Precision Medical Sciences*. 2022;11:106-110.
19. Collette S, Collette L, Budiharto T, et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: A study based on the EORTC Trial 22881-10882 "boost versus no boost. *Eur J Cancer*. 2008;44:2587-2599.
20. Guo S, Dipietro LA. Factors affecting wound healing. *J Dental Res*. 2010;89:219-229.