

Video Article

Treatment of Liver Metastases Using an Internal Target Volume Method for Stereotactic Body Radiotherapy

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Abstract

The prognosis of patients with metastatic cancers has improved in the past decades due to effective chemotherapy and oligometastatic surgery. For inoperable patients, local ablation therapies, such as stereotactic body radiotherapy (SBRT), can provide effective local tumor control with minimal toxicity. Because of its high precision and accuracy, SBRT delivers a higher radiation dose per fraction, is more effective, and targets smaller irradiation volumes than does conventional radiotherapy. In addition, steep dose gradients from target lesions to surrounding normal tissues are achieved using SBRT; thus, SBRT provides more effective tumor control and exhibits fewer side effects than conventional radiotherapy. The use of SBRT is prevalent for treating intracranial lesions (known as stereotactic radiosurgery); however, it is now also used for treating spinal and adrenal metastases. Because of advancements in image-guided assistance and respiratory motion management, several studies have investigated the use of SBRT for treating lung or liver tumors, which move as a patient breathes. The results of these studies have suggested that SBRT favorably controls tumors in the case of moving lesions.

Four-dimensional computed tomography (4D-CT) with an abdominal compressor (AC) is clinically convenient for effective respiratory motion management. Because this method is noninvasive and allows free breathing, its use reduces complications. Furthermore, patients consider this method convenient. Moreover, it is considered more efficient than other methods of respiratory motion management by physicians and therapists. The use of 4D-CT with an AC for treating pulmonary lesions has also been widely investigated, and the technique is gaining acceptance for treating hepatic lesions. However, the protocols for using 4D-CT with an AC for treating hepatic lesions are different from those used for treating pulmonary lesions. In this article, we describe a new protocol for SBRT with 4D-CT and an AC for treating liver metastases.

Video Link

The video component of this article can be found at <https://www.jove.com/video/57050/>

Introduction

Conventionally, metastasis is considered the terminal stage of cancer and is associated with poor prognosis and survival. However, Mountain *et al.* in 1984 reported that according to their 20-year experience, complete surgical removal of pulmonary metastasis results in a relatively higher survival rate if the primary tumor site is under systemic control at the time of surgery¹. Hellman and Weichselbaum in 1995 first proposed oligometastases, an intermediate stage between localized lesions and systemic disease with polymetastases, which can be cured using additional local treatment^{2,3}. Over the past decades, early detection of metastasis, novel surgical methods for treating oligometastases (metastasectomy), and effective chemotherapy have improved the prognosis in patients with metastasis. The liver is one of the most common metastatic organs for solid tumors, and surgical resection of hepatic oligometastases can improve survival. Local ablation methods, including radiofrequency ablation, radioembolization, and radiotherapy, for treating liver metastases have been recommended for some inoperable patients to achieve the necessary local tumor control^{3,4,5,6,7}. In past years, several prospective and retrospective studies have reported effective local tumor control of hepatic metastases through stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, with tolerable toxicity^{4,5,8,9}.

Improvements have been made in patient positioning and immobilization methods; image acquisition, integration, and transfer to radiotherapy systems; respiratory motion management; high-dose output and fast radiation delivery; and steep dose gradients from target lesions to surrounding normal tissues. Because of these advances, SBRT achieves highly precise and accurate radiotherapy with minimal serious toxicity^{10,11}. Respiratory motion management is fundamental to SBRT, particularly for hepatic and pulmonary lesions. A respiratory management technique that is noninvasive and clinically convenient would substantially increase the popularity of SBRT as a treatment option. This article

details an SBRT protocol for liver metastases that uses four-dimensional computed tomography (4D-CT) with an abdominal compressor (AC) for image-guided assistance and liver motion management.

Protocol

Taipei Medical University Joint Institutional Review Board approval was obtained for this study.

1. SBRT Consultation

1. Assess patient eligibility for SBRT for the treatment of liver metastases by consulting a multidisciplinary tumor board.
NOTE: The need for local ablation as well as operation and other treatment options must be evaluated by the tumor board. Our selection criteria were as follows: 1) adult patients with a good performance status (Eastern Cooperative Oncology Group 0-1), 2) controlled cancer status through anticancer medication and with only oligometastases in the liver, 3) number of hepatic lesions ≤ 3 and largest tumor ≤ 6 cm in diameter, 4) liver volume (liver excluding gross tumor) greater than 700 cm³, and 5) without acute hepatitis or chronic hepatitis B under stable antiviral control.
2. Discuss SBRT and its associated risks as well as the differences between SBRT and conventional radiotherapy with the patient^{9,19}.

2. CT Simulation

1. **Place the patient in a supine position, head-first on the couch with arms over the head.**
 1. Use a system (e.g., BodyFIX) to immobilize the patient. Position the patient in a personalized, evacuated vacuum bag and cover the patient with a cover sheet.
 2. Apply an abdominal compressor (AC), and mark the depth of the AC.
NOTE: The AC restricts the patient's breathing motion; therefore, some patients may develop dyspnea during this procedure. Oxygen supplementation through the nasal cannula should be provided to relieve their discomfort.
 3. Place the breath-tracking sensor on the chest wall and monitor the respiratory waveform.
2. **Acquire CT images for radiotherapy treatment planning.**
 1. Choose 4D-CT scan mode with a 3 mm slice thickness.
 2. Conduct a survey scan (120 kV, 30 mA) to obtain both anterior-posterior (AP) and lateral view of the patient. Click on "Go" on both the screen and the control panel.
 3. Determine the CT scanning coverage under "Helical scan" pagination and decide the scanning field of 4D-CT under "Pulmonary gating scan" pagination.
NOTE: The coverage of the helical scan should extend from the apex of both the lungs to a distance of at least 5 cm from the caudal border of the liver. The field of pulmonary gating scan, which is smaller than helical scan, should cover the liver with a 3-5 cm extend from both cranial and caudal borders of the liver.
 4. Monitor the respiratory waveform until it remains stable for 3 min.
 5. Inject 100 mL of contrast agent (e.g., Omnipaque), at a rate of 4-5 mL/s, through an 18 G i.v. catheter into antecubital vein.
 6. Conduct a contrasted contiguous helical CT scan (120 kV, 400 mAs/slice), 15 s after the contrast injection.
 7. Subsequently conduct a non-contrasted 4D-CT scan (120 kV, 2,000 mAs/slice) by clicking "Next Series".

3. Radiotherapy Treatment Planning

1. **Import images from the CT simulation and diagnostic scans into the planning system.**
NOTE: Diagnostic images may include positron emission tomography (PET)/PET-CT, magnetic resonance image, or diagnostic helical CT scans.
2. **Contour metastatic tumors into gross tumor volume and adjacent organs at risk (OARs).**
 1. Choose an organ (here, the stomach) and use the brush, pencil, etc. to contour the organ in each slice of the CT image. Circle or define the organ of interest. Use "Up" and "Down" buttons to view each image slice.
NOTE: The OARs include the lungs, stomach, duodenum, spinal cord, liver, small bowel, ribs, and kidneys.
3. **Contour the internal target volume (ITV) of the tumors according to organ motion observed on dynamic tracking images. Add a 5-mm margin to the ITV to obtain the planning target volume (PTV).**
 1. Choose an organ (here, the stomach) and use the brush, pencil, etc. to contour the organ in each slice of the CT image. Circle or define the organ of interest. Use "Up" and "Down" buttons to view each image slice.
4. Prescribe radiation doses of 48 Gy in three fractions or 35 Gy in five fractions to the PTV for relatively large tumors.
NOTE: A treatment plan must consider constraints due to the OARs; a relatively high prescription dose may be acceptable if the radiation dose to the OARs is within the constraints (Table 1).

4. Treatment Delivery

1. Reconfirm the radiation beam data by using daily quality assurance and ensure that the data are within the normal range.
2. Identify the patient using the patient's name, birth date, and ID card. Position the patient in the vacuum bag, place the cover sheet, and fix the AC according to the procedure described in the CT simulation section.

3. **Acquire a 4D cone-beam CT (CBCT) image and adjust the couch to correlate the target location obtained on the 4D-CBCT image to that obtained on the simulation CT images.**
 1. Select 4D CBCT mode and confirm setup data. Click "Go" on the panel.
4. **After 4D CBCT, load the acquired 4D CBCT images into the IGRT system. The upper left and lower right images are from CT simulation as the contouring and treatment planning. The upper right and lower left images are from 4D CBCT, which is performed daily before each fraction.**
 1. Use the software to adjust the set up. Then, manually adjust each parameter on the couch. The couch has only 3 linear motions in X, Y, and Z axes while the system could have adjustment in 6, including rotation, pitch and roll. Therefore, the technicians need to corroborate the adjustment.
 2. Record and print out the parameters for daily adjustment.

NOTE: If the tumor position shifts beyond the tolerance limit of 5 mm on any one of six axes, the patient should be repositioned.
5. Deliver radiation treatment. Confirm treatment plan and the system configuration. Click Go to start the treatment. Monitor the patient using real-time cameras during the entire treatment to ensure patient safety.

Representative Results

SBRT can be implemented by intense-modulated radiotherapy (IMRT) (with ≥ 6 radiation beams) or volumetric arc radiotherapy (VMAT) (with continuous dose delivery and gantry rotation) to cover all targets in a single treatment because a single surgery may not achieve removal of all the tumors. A representative SBRT treatment plan demonstrated successful radiotherapy planning for two hepatic metastatic tumors when surgery was infeasible. The two metastatic tumors were 3cm (from segment 4 to segment 8) and 4.3 cm (in segment 8) in length, and their volume were 13 cm³ and 22 cm³, respectively. The prescribed dose was 50 Gy in 5 fractions and the beams were directed to avoid the OAR (Figure 1A-C). The sophisticated treatment plan consisted of four partial beam arcs namely 180° to 50°, 260° to 50°, 335° to 35°, and 50° to 180° (Figure 1D). Dose-volume histograms show the coverage over both the tumors, with 100% of the volume of the PTVs covered by >95% of the prescribed dose; the radiation doses to the OARs were within the constraints (Figure 2).

	3 fractions	5 fractions
coverage		
PTV	D _{105%} <15%	
	V _{100%} ≥95%	
OAR		
normal liver volume ^{1,2}	>700 cm ³ at <15 Gy	mean <15 Gy
Stomach, duodenum, small bowel	D 3 cm ³ at <21 Gy	D 0.5 cm ³ at <32 Gy
Both kidneys	V 15 Gy at <35%	mean <12Gy
Spinal cord	D 1 cm ³ at <18 Gy	D 0.5 cm ³ at <28 Gy
Heart	D 1 cm ³ at <30 Gy	V 32 Gy at <15 cm ³
Both lungs	V 12.4 Gy at <1,000 cm ³	V 11.4 Gy at <1,000 cm ³
Rib	D 30 cm ³ at <30 Gy	nil

Table 1: Recommended dose constraints for the organ at risk (OARs). PTV: planning target volume. OAR: organ at risk.¹ total liver volume - cumulative gross tumor volume.² The normal liver volume is suggested to be >700 cm³.

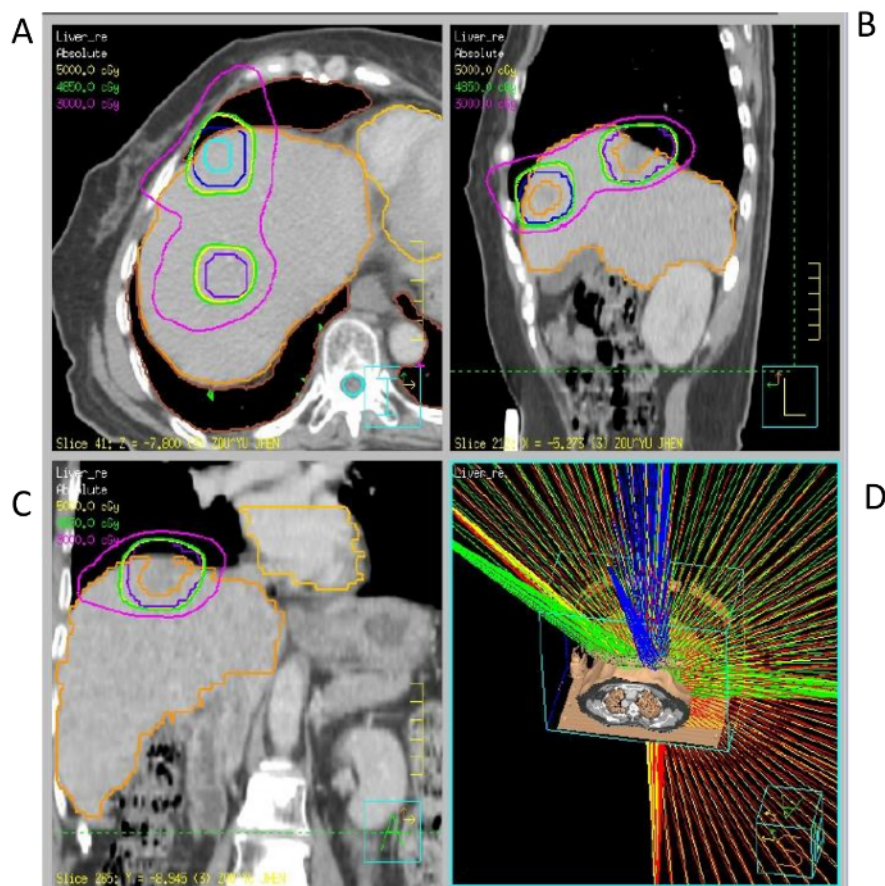


Figure 1: Dose distribution (A-C) and beam direction (D). The purple and light blue lines indicate the planning target volume, whereas the yellow and pink line indicate 50 and 30 Gy, respectively, in (A-C). [Please click here to view a larger version of this figure.](#)

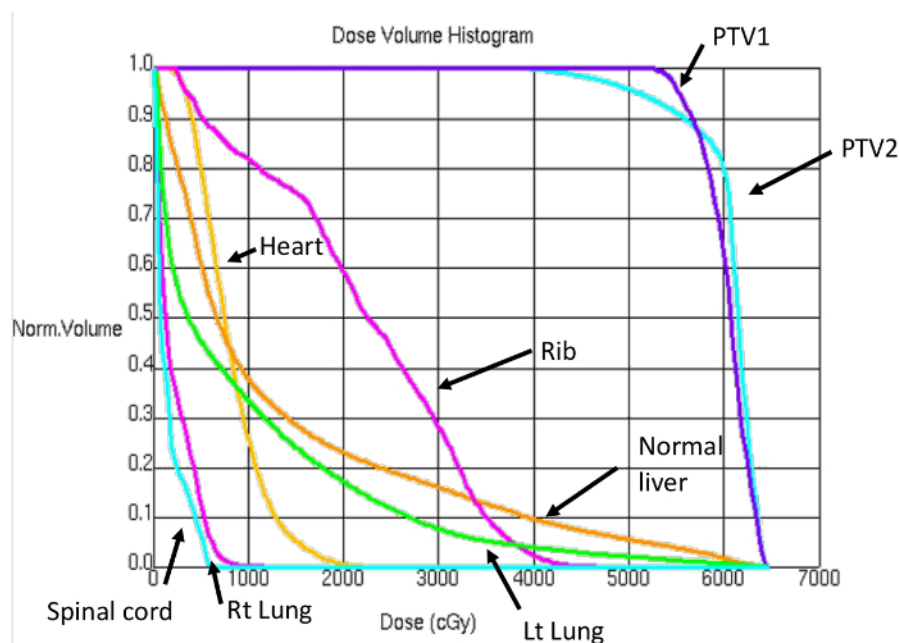


Figure 2: Dose-volume histograms. Planning target volume (PTV)1 and PTV2 are colored in purple and light blue. The organs at risk include the normal liver (orange), rib (light pink), Heart (yellow), left lung (fluorescent green), right lung (pink) and spinal cord (ocean blue). [Please click here to view a larger version of this figure.](#)

Discussion

Respiration-induced liver deformity and organ motion contribute to the difficulties associated with radiation delivery, as well as contouring (target delineation) problems. Improvements in the techniques used for organ motion management have led to improvements in treatment accuracy and precision, which is fundamental to SBRT. Several image-guided techniques and respiratory motion management systems are currently available. Fiducial marker implantation is a common technique for target localization. A fiducial marker is usually a cylindrical gold seed, 2.5 to 5 mm in length with a diameter of 0.8 mm. Implanting a fiducial marker near a lesion enables X-ray-based image-guided systems to localize targets. However, complications associated with using fiducial markers, including internal bleeding, fever, pain, dislocation, and infection, have been reported in >30% of patients. Patients' acceptance of the invasive procedure is another concern¹². Furthermore, the air breath coordination (ABC) and deep inspiration breath-hold (DIBH) technique are regularly used for image-guided radiotherapy; these noninvasive breath-control systems are designed to help patients hold their breath, thus immobilizing the target during radiation therapy. Despite patient training before treatment, however, prolonged treatment time for each fraction, difficulty in breathing, and individual medical conditions have limited the use of ABC and DIBH^{13,14}.

The accuracy of respiration-correlated CT and 4D-CT assisted using an AC for pulmonary SBRT has been widely demonstrated^{15,16}. Several recent studies have discussed the use of this technique for respiration-associated liver motion. Takahashi *et al.* suggested 4D-CT scans with an AC achieve substantial respiratory motion management and reduce the PTV margin to <5 mm¹⁶. In addition, dosimetric evaluation for liver SBRT with 4D-CT integration has been addressed¹⁷. Shimohigashi *et al.* recently reported that 4D-CT with an AC accurately represented tumor motion during SBRT¹⁸. The use of 4D-CT with an AC is more advantageous than that of other respiratory motion management techniques because the technique is noninvasive and allows free breathing. Moreover, patients consider this technique more convenient than other management techniques. Physicians and therapists may also benefit from this technique because it creates a convenient work flow. Some recent studies have reported the use of 4D-CT with an AC as a respiratory management technique during SBRT for liver metastases^{19,20,21}. Patients need not hold their breath when 4D-CT with an AC is used (unlike during patient training when DIBH or ABC is used); hence 4D-CT with an AC is considered convenient and is consequently commonly used in SBRT for the lung and liver. However, it should also be emphasized that the protocol of 4D-CT with an AC in liver motion management is different from that used to treat pulmonary lesions.

First, although the image quality of a planning CT scan is still not as high as that of a diagnostic CT scan, we still suggest that contrasted CT enables accurate tumor contouring. Unlike SBRT for the lungs, pulmonary lesions can be easily distinguished from normal lung tissues on CT images of the lungs. However, in noncontrasted liver images, normal and malignant tissues cannot be easily distinguished. Second, daily 4D-CBCT for verification of tumor positions before treatment is essential for significantly increasing the intrafractional accuracy; 3 mm of the PTV margin was previously considered adequate with daily 4D-CBCT scans (although we still comply with the 5 mm of PTV margin criterion)¹⁸. Third, a slow CT scan or a cine CT scan should be performed under free breathing. The tumor from all phases of the 4D-CT dynamic tracking images can be contoured as the ITV for tumor motion, while the AC limits organ motion to reduce the irradiation volume. Moreover, radiation dose to the lung should be evaluated. Hepatic lesions close to the diaphragm can result in an increased radiation dose to the lungs. Radiation pneumonitis is a common complication; however, grade I radiation pneumonitis is usually asymptomatic. Dose constraints and CT scans of the entire lung should not be neglected.

Historically, conventional radiotherapy for hepatic carcinomas had minimal curative benefit. However, the liver has a relatively low tolerance for radiation doses, and radiation-induced liver disease (RILD) can be lethal. Although some studies have suggested pretreatment evaluation for preventing RILD during irradiation of hepatocellular carcinomas²², the treatment of hepatic lesions using conventional radiotherapy must be administered with caution. SBRT provides improved tumor control with minimal serious complications; however, only a few studies have reported risk evaluation for preventing RILD while using SBRT for treating liver metastases. Moreover, the eligibility criteria of patients for receiving SBRT for liver metastases are not clearly defined, although some common criteria have been reported in some studies^{4,5}. Our selection criteria were as follows: 1) adult patients with a good performance status (Eastern Cooperative Oncology Group 0-1), 2) controlled cancer status through anticancer medication and with only oligometastases in the liver, 3) number of hepatic lesions ≤3 and largest tumor ≤6 cm in diameter, 4) liver volume (liver excluding gross tumor) greater than 700 cm³, and 5) without acute hepatitis or chronic hepatitis B under stable antiviral control. The histopathology of the original cancer did not have to be limited to the colorectum, breasts, and lungs, but these sites were preferred. A multidisciplinary tumor board discussion is required in the proposed protocol, and an operation should be the first option. Other local ablation therapies may be discussed by the tumor board, and final treatment is based upon the patient's decision.

Although local ablation including SBRT can achieve local tumor control and using 4D-CT with an AC can facilitate motion control, survival and progression-free intervals critically rely on the anticancer effects of chemotherapy, target therapy, or other systemic medications. In other words, without proper systemic control, even the most suitable local ablation therapy will not provide any overall benefit. Therefore, reviewing the effects of systemic therapy facilitates the selection of a local ablation therapy. Furthermore, the correlation between control of oligometastases and progression-free survival or overall survival still requires further investigation. Different factors, such as location and number of oligometastases, histopathology of the original cancer, or therapy-naïveté of the patient, may have an effect on outcomes²³. Despite the aforementioned limitations, SBRT, which is noninvasive and is as clinically convenient as 4D-CT with an AC for respiratory motion management, provides a considerable local ablation effect for liver metastases.

Disclosures

The authors have no disclosures.

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References

1. Mountain, C.F., McMurtrey, M.J., Hermes K.E. Surgery for pulmonary metastasis: a 20-year experience. *Ann Thorac Surg.* **38** (4), 323-30 (1984).
2. Hellman, S., Weichselbaum, R.R. Oligometastases. *J Clin Oncol.* **13** (1), 8-10 (1995).
3. Weichselbaum, R.R., Hellman, S. Oligometastases revisited. *Na. Rev Clin Oncol.* **8** (6), 378-82 (2011).
4. Comito, T., Clerici, E., Tozzi, A., and D'Agostino G. Liver metastases and SBRT: A new paradigm? *Rep Pract Oncol Radiother.* **20** (6), 464-471 (2015).
5. Scorsetti, M., Clerici, E., Comito, T. Stereotactic body radiation therapy for liver metastases. *J Gastrointest Oncol.* **5** (3), 190-197 (2014).
6. Shady, W., et al. Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes—A 10-year Experience at a Single Center. *Radiology.* **278**(2), 601-611 (2016).
7. van Hazel, G.A., et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol.* **34**(15), 1723-1731 (2016).
8. Salama, J.K., Milano, M.T. Radical irradiation of extracranial oligometastases. *J Clin Oncol.* **32** (26), 2902-2912 (2014).
9. Rusthoven, K.E., et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol.* **27**(10), 1572-1578 (2009).
10. Ricardi, U., Badellino, S., and Filippi, A.R. Clinical applications of stereotactic radiation therapy for oligometastatic cancer patients: a disease-oriented approach. *J Radiat Res.* **57** (Suppl 1), i58-i68 (2016).
11. Wild, A.T., Yamada, Y. Treatment Options in Oligometastatic Disease: Stereotactic Body Radiation Therapy - Focus on Colorectal Cancer. *Visc Med.* **33** (1), 54-61 (2017).
12. Gill, S., et al. Patient-reported complications from fiducial marker implantation for prostate image-guided radiotherapy. *Br J Radiol.* **85** (1015), 1011-1017. (2012).
13. Eldredge-Hindy, H., et al. Active Breathing Coordinator Reduces Radiation Dose to the Heart and Preserves Local Control in Patients with Left Breast Cancer: Report of a Prospective Trial. *Pract Radiat Oncol.* **5** (1), 4-10 (2015).
14. Swanson, T., et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol.* **36** (1), 24-30 (2013).
15. Sweeney, R.A., et al. Accuracy and inter-observer variability of 3D versus 4D cone-beam CT based image-guidance in SBRT for lung tumors. *Radiat Oncol.* **7**, 81 (2012).
16. Takahashi, W., et al. Verification of Planning Target Volume Settings in Volumetric Modulated Arc Therapy for Stereotactic Body Radiation Therapy by Using In-Treatment 4-Dimensional Cone Beam Computed Tomography. *Int J Radiat Oncol Biol Phys.* **86**(3), 426-431 (2013).
17. Yeo, U.A., et al. Evaluation of dosimetric misrepresentations from 3D conventional planning of liver SBRT using 4D deformable dose integration. *J Appl Clin Med Phys.* **15**(6), 4978 (2014).
18. Shinmohigashi, Y., et al. Tumor motion changes in stereotactic body radiotherapy for liver tumors: an evaluation based on four-dimensional cone-beam computed tomography and fiducial markers. *Radiat Oncol.* **12**, 61 (2017).
19. Goodman, B.D., et al. Long-term safety and efficacy of stereotactic body radiation therapy for hepatic oligometastases. *Pract Radiat Oncol.* **6**(2), 86-95 (2016).
20. Scorsetti, M., et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. *Int J Radiat Oncol Biol Phys.* **86**(2), 336-342 (2013).
21. Andratschke, N.H., et al. Stereotactic radiation therapy for liver metastases: factors affecting local control and survival. *Radiat Oncol.* **10**, 69 (2015).
22. Huang, R., et al. Clinical parameters for predicting radiation-induced liver disease after intrahepatic reirradiation for hepatocellular carcinoma. *Radiat Oncol.* **11** (89) (2016).
23. Huang, F., Wu, G., Yang, K. Oligometastasis and oligo-recurrence: more than a mirage. *Radiat Oncol.* **31** (9), 230 (2014).