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Image Application in Single Isocenter Multiple Target SRS

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Abstract

Single isocenter multiple target stereotactic radiosurgery (SIMT-SRS) has potentially emerged as a new pillar in radio-immune combination therapy for the management of brain metastasis. Accuracy and efficiency are pushed to a higher level in the era of the linear accelerator-based SIMT-SRS. This short review focuses on patient selection, image preparation, patient simulation, electronic portal imaging device (EPID) QA, and the patient treatment process in the SIMT-SRS treatment only. Image-relevant recommendations and guidelines are presented and contrast application, acquisition efficiency, and alignment accuracy of CT and MRI images are explored. With guidance, the SIMT-SRS can be implemented with high precision and efficiency. 1 mm or 0.5 mm and non-uniform PTV margin expansion for all targets would become possible. It will enhance cancer killing effect in radio-immune combination therapy. General routine daily, monthly, and annual linear accelerator image quality assurances are excluded.

Keywords

SIMT-SRS, Image Application

1. Introduction

Brain metastasis treatment paradigm and technology have advanced in recent decades. From conventional surgical resection, whole brain radiotherapy (WBRT), WBRT adjuvant therapy, stereotactic radiosurgery (SRS), single isocenter multiple target SRS (SIMT-SRS) to target therapy, immunotherapy, radio-immune combination therapy, the overall patient progression-free survival rate has been prolonged [1] from several months to several years. Linac-based SIMT-SRS is an efficient, precise and noninvasive procedure to manage multiple brain metastasis comparing all others above. Recently, as a conventional therapy, the single iso-

center multiple target SIMT-SRS cast some light on the radio-immune combination therapy. The basic assumption of radio-immune combination therapy is derived from the abscopal effect. The abscopal effect is a phenomenon which is early observed in mice in the 1950s. The precision biological mechanism is still not very clear in the medical field but clinicians believe that it is related to the human immune system. The abscopal effect means that one local metastasis treatment can lead to another distant metastasis inside the whole brain shrinking concurrently. The hypothesis is that the radiation kills one local metastasis and thus can release tumor-associated antigens (TAA). These tumor-associated antigens can be recognized and adopted by the antigen-presenting cells. The cytotoxic $CD8^+$ T cells can be primed to attack other cancerous cells inside the primary tumor and distant metastasis. Thus, the radio-immune combination therapy provides the chance for SIMT-SRS with an immunotherapy to boost the abscopal response rate and further enhance radiotherapy killing effect for local and distant metastasis [2]. The SIMT-SRS technique has the potential to play a greater role in future brain metastasis management.

Overviewing the SIMT-SRS provided by all radiation modalities, the Linear accelerator (Linac) based SIMT-SRS is the dominant modality for brain metastases management. Not only because the linear accelerator (Linac) is the most common treatment delivery system in radiation facilities, but also the efficiency and cost of Linac-based SIMT-SRS are much superior to any SIMT-SRS provided by Gamma knife, CyberKnife, ZapKnife and Tomotherapy, Proton therapy. In addition to SIMT-SRS, Linacs provide greater utility of diverse treatment options such as 3D conformal, IMRT, SBRT and electron treatment routine procedures. The accuracy and efficiency of the Linac-based SIMT-SRS needs standard QA protocols and guidelines since the Linac-based SIMT-SRS is the mainstream for the radiation oncologist, neurosurgeon and medical physicist. This review article will exclusively address imaging-specific issues when we implement SIMT-SRS procedures from the physics and treatment aspect. The routine imaging QA for daily, monthly and annual Linac operation, recommended by AAPM TG-142 [3] and AAPM TG-198, [4] will not be discussed. This short review is aimed at the medical physicists who play a major role in SIMT-SRS procedure which includes the patient selection, simulation, complete planning, machine QA, patient specific QA, and patient treatment. We hope it can benefit the above medical physicist to make joint decisions with radiation oncologists and neurosurgeons and complete each task precisely during the SIMT-SRS procedure.

2. Patient Selection

Brain metastasis can be a secondary malignancy of many kinds of cancer cells in the human body. The male patient's brain metastasis is most likely from lung cancer cells while the female patient's brain metastasis is most likely from breast cancer cells. Colon, kidney and melanoma cancer cells can very easily metastasize to the brain as well. Sometimes a single brain metastasis can metastasize to multiple brain metastases.

From physics and imaging aspects, the SIMT-SRS technique is good for patients who have single or multiple brain metastases. The patient's health situation should be in good condition and the patient can tolerate the tight immobilization mask, have no claustrophobia and above average neurocognitive score. The cancer is not at a very late stage. Whether the patient has received whole brain radiation therapy (WBRT) should not be used as a criterion for SIMT-SRS. The SIMT-SRS can be a salvage treatment of WBRT. A very recent MRI image (within two weeks) indicates no severe midline shift, and little seroma. The treatment lesion should be less than 3 cm in diameter (avoiding major radiation necrosis) [5]. A post-surgery SIMT-SRS technique is selected by many neurosurgeons, the pre-surgery SIMT-SRS is also used to "sterilize" tumors before surgery. If the linear accelerator has a cone planning and treatment system, the SIMT-SRS technique can also treat acoustic neuroma, arteriovenous malformations (AVM), trigeminal neuralgia, and arteriovenous fistulas disease sites. It also can treat any other brain tumor which is not surgery accessible or very close to an optical nerve. From a medical aspect, it is upon radiation oncologist and neurosurgeon.

3. Image Preparation

In image-related preparation, the acquisition of clinically meaningful, high quality, and very recent (within two weeks) MRI and CT images are vital steps to create robust, delivery friendly, and precise, efficient treatment plans. To accurately delineate brain metastasis in the whole brain region other than only image Iso center region, the SIMT-SRS procedure demands higher quality images than the regular SRS technique. The MRI image is still the gold standard in the early detection of brain tumors. Medical physicist or dosimetrist who is creating the treatment plan should have good knowledge of the MRI scanner used (T1.5 or T3.0), geographical locations, MRI tech training level, technique, slice thickness, and contrast agent used (not cheapest one) *et al*.; not all poor-quality images are caused by patient motion. The medical physicist should scrutinize and decide if the image quality is adequate to be used in SIMT-SRS procedures. As shown in **Figure 1** from author's clinic, peripheral ring artifacts clearly affect the accuracy of target delineation. In this case the image was rejected and the patient had to be rescanned for a better quality image.

A strategy to avoid poor quality MRI images is that the planner should have more communication with the MRI technologist or imaging physicist, check scanning protocol, and educate them on the difference between therapeutic and diagnostic MRI images. If possible, the planner should be onsite for MRI image acquisition.

The MRI manufacturers market MRI scanners with a variety of features and large prices. Sometimes it can be tempting to limit equipment functionality to lower the price, carefully determine minimum functionality with clinical staff and then determine features and quality needed for the services you wish to offer. A resource to be included in the discussion is the MRI image medical physicist

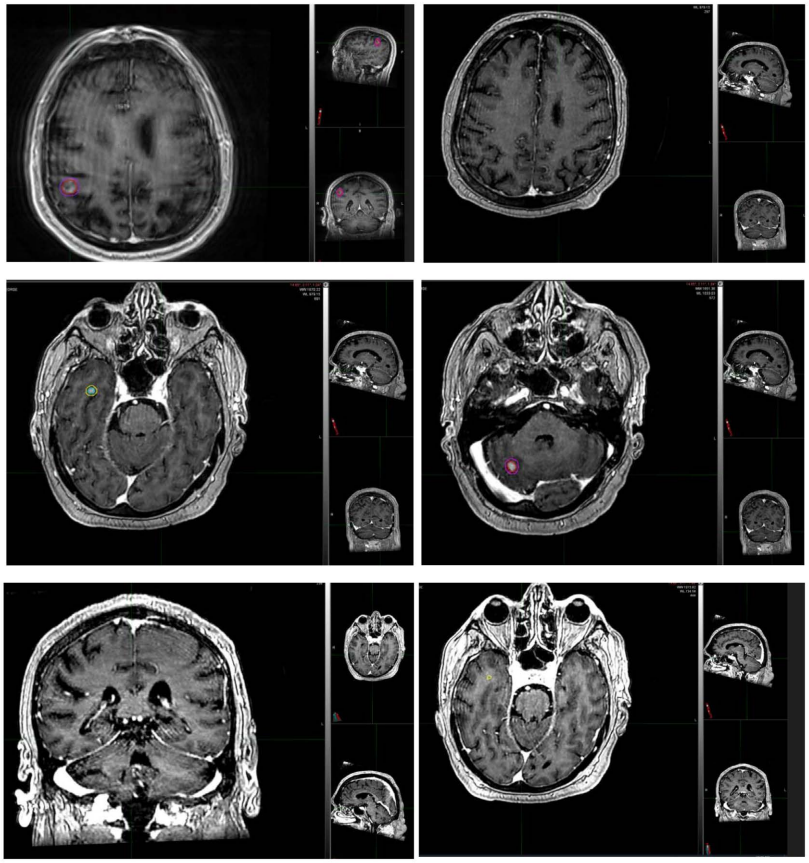

Figure 1. Some poor-quality MRI images were from the author's clinic. These images have to be rejected and we rescanned the patient.

who is familiar with quality assurance guidelines which can change frequently. ACR "MRI Quality Control Manual 2015" [6] is an example of such a guideline. Currently most radiation oncology departments or small cancer centers do not have their own MRI scanners and refer out these imaging services.

From the ACR "MRI Quality Control Manual 2015", the imaging medical physicist or MRI scientist establish the quality control program, test methods and action limits. The quality control is mainly performed by MRI technologist weekly.

The ACR recommendation for weekly quality control protocol for large object is T1-weighted axial series which are: 11 slices, spin-echo, TR = 500 ms, TE = 20 ms, FOV = 25 cm, slice thickness = 5 mm, slice gap = 5 mm, matrix = 256 × 256, NEX = 1.

The recommended sequence for this acquisition for the small phantom is the ACR T1-weighted axial series which are: 7 slices, spin-echo, TR = 500 ms, TE = 20 ms, FOV = 12 cm, slice thickness = 5 mm, slice gap = 3 mm, matrix = 152 × 192, NEX = 1.

MRI artifact is also closely monitored by the MRI technologist.

MRI artifacts include:

- Gross geometric distortion.

- Ghost images.
- Line or pixels with unusually high and/or low intensities.
- Receiver saturation errors.
- Inappropriate image blurring or enhanced truncation artifact.

Gross geometric distortion is caused by inhomogeneities (particularly at low field strengths) which influence image signal uniformity and increase the severity of wrap artifacts and comprise signal noise ratio (SNR) in some fast-imaging sequences. Gross geometric distortion artifacts are especially important in SIMT-SRS image registration and planning processes. L. C. Lu *et al.* [7] has systemically studied the MRI image distortion for 14 MRI scanners whose magnet field strength ranged from 1.5 T to 3.0 T. They concluded that the MRI image distortion increases with the distance from imaging isocenter. For regions of interest with a radius of 10 cm (average of human head radius) centered at the isocenter, the maximum distortion ranged from 0.52 mm to 1.31 mm for some scanners. For an average body size whose region of interest has a radius of 20 cm, centered at the isocenter, the maximum distortion ranged from 1.92 mm to 5.03 mm for some scanners. It is obvious that some scanners are not adequate for SIMT-SRS procedures because the SIMT-SRS tolerance for geometric distortion should be <1 mm.

The slice thickness is also an important image characteristic for the SIMT-SRS technique because ACR recommends MRI weekly QC test using a 5 mm slice thickness rather than a 1 mm slice thickness (which is required for the SIMT-SRS technique). Low slice thickness accuracy can result in the wrong target size, adversely affect the image contrast, and affect image registration accuracy.

Targeted and organ-specific contrast agents [8] should be used in all SIMT-SRS MRI scans. Most MRI contrast agents are chemical compounds using the rare-earth element gadolinium. This element produces an increased signal ("positive contrast") on T1-weighted images (the effect on T2-weighted images is generally negligible). The primary purpose of MRI contrast agent is to identify all brain metastasis withing the brain. The gadolinium contrast agents can be divided into three groups [8] which are extracellular fluid (ECF) agents, blood pool contrast agents (BPCAs) and organ-specific agents. Brain organ-specific agents like Dy-DTPA-BMAb (generic name is Sprodiamide injection) are effective in brain perfusion and therefore effective for early detection of brain metastasis.

Recently one brain tumor imaging protocol for brain metastasis was proposed by Kaufmann *et al.* [9] under multi-institute and multi-national collaboration. It provides a guideline for brain MRI imaging exclusively. This protocol is a good starting point as an SIMT-SRS MRI acquisition protocol. Minimum requirements for both T1.5 and T3.0 MRI scanners are proposed. The MRI used for initial diagnosis at the patient first time console should not be used as SIMT-SRS image fusion and planning in the patient image preparation. Generally, the axial T1 enhanced stealth protocol with image slice thickness of 1 mm is the basic requirement for SIMT-SRS MRI images on T1.5 Scanner. A three-dimensional (3D) T1W MRI sequence is the gold standard for brain metastasis detection [10].

Another image related preparation is reviewing previous biopsy or surgery related CT images. If the brain metastasis is peripheral, far away from optical nerves, and right under the skull, neurosurgeons often perform biopsy and surgical resection. The post-operation SIMT-SRS is also considered standard of care for treating brain metastasis. Pneumocephalus, also known as intracranial aerocele, is not uncommon post stereotactic brain biopsy or surgery. This condition is a result of an induced air cavity during brain biopsy or surgery procedure. The air cavity expands quickly due to the pressure difference between the intracranial and outside atmosphere and is life threatening if not handled promptly and properly. Pneumocephalus changes the brain's anatomy and displaces metastasis resulting in a potential SIMT-SRS geographic miss target. This is considered a catastrophic category error in the AAPM TG-100 [11] failure mode analysis.

In one of the author's clinics, we encountered a pneumocephalus case. It is presented in **Figure 2** in two sets of CT images post biopsy. The upper raw CT images were taken two days after biopsy and bottom raw images were taken nine days after biopsy. The brain metastasis was originally located at the biopsy spot. After seven days the pneumocephalus cavity has been expanded and shifted significantly. It was caught by the Linac CBCT right before the delivery of the SIMT-SRS treatment. The original treatment plan and treatment schema have to be halted. We had to rescan the patient, replan, and re-QA and redo-pretreatment dry run. The medical physicist should review all available images before SIMT-SRS planning and treatment and verifying quality and appropriateness. Image registration is another important step to prepare the images for accurately delineating the treatment target and location. Both rigid and deformable registrations have been heavily investigated in the medical physics field and the commercial software is mature. We will not discuss here.

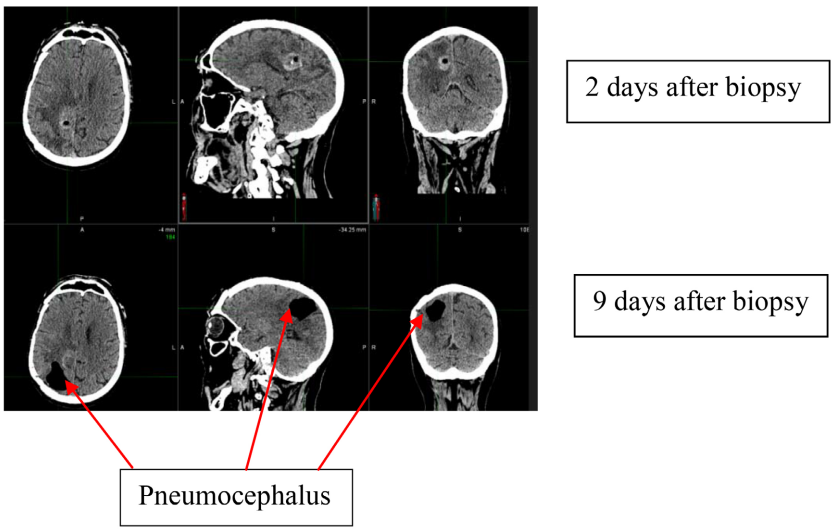

Figure 2. Black cavity is a pneumocephalus post biopsy. Upper row CT images were taken two days after biopsy and the bottom raw CT images were taken nigh days after biopsy.

4. Patient Simulation

CT simulation (including immobilization creation) is a very important starting point for SIMT-SRS procedures however it can be devalued in the process and its importance overlooked. Recently it has been noticed that clinical medical physicists are involved less in patient simulation, treatment plan creation and treatment delivery supervision but focus more on chart checks, and documentation. This can degrade the SIMT-SRS procedure quality. In most clinics, the simulation CT is owned by the radiation oncology department and the quality control is performed by a therapeutic medical physicist. The recently published AAPM TG-233 report [12] provides detailed guidelines for both diagnostic and therapeutic CT scanners. Sections 2.3 and 6.3: "Basic Image Quality Performance" meets SIMT-SRS simulation requirements. Some of the parameters include CT number accuracy, CT number uniformity, Artifact assessment, High contrast resolution, Noise magnitude, Low-contrast contrast-to-noise ratio (CNR), and Slice sensitivity profile. The consistency of these parameters should be closely monitored by the medical physicist every month.

This section will address some contrast enhancements related issues during SIMT-SRS CT simulation. In underserved regions high quality MRI scanners and well-trained MRI technologists can be difficult to find. Insurance authorization can also be a hurdle when requesting additional SIMT-SRS MRI scans for some patients in the United States. Since high quality and recent MRI images are not always available for every SIMT-SRS candidate patient. Thus, good simulation CT images are crucial and become the primary platform for all SIMT-SRS imaging tasks. Brain metastasis on CT images is displayed as solitary or multiple mass lesions with variable surrounding vasogenic edema. Without hemorrhage the brain metastasis can be hypodense, isodense, or hyperdense compared with normal brain tissue density. In the CT simulation, contrast enhancement is vital to the detection of brain metastasis on CT. The use of a contrast agent can enhance the visibility of the brain metastases and is strongly recommended in all SIMT-SRS CT simulations unless the patient has an allergy or other abnormal reaction to the contrast agent. With contrast enhancement, the metastasis is shown as a ring, nodular, or solid enhancement. The metastasis usually does not calcify, and the presence of calcification may complicate diagnosis. The images in **Figure 3** are examples of acceptable simulation CT scans from one of author's worked clinics.

The enhancement contrast agent is usually an iodinated solution. Contrast agents are typically introduced through either intravenous (injected into a vein) or chemotherapy port. The SIMT-SRS image quality requirement is met if the patient-specific trigger delay (the time between post injection and start CT scan) was controlled properly. Contrast circulation inside vascular systems is a dynamic process. If a small amount contrast is injected into a vein in the arm, the contrast will take a few seconds to travel from arm to heart and lung. From the heart it will pass through the aorta, then to the internal carotid arteries, and then

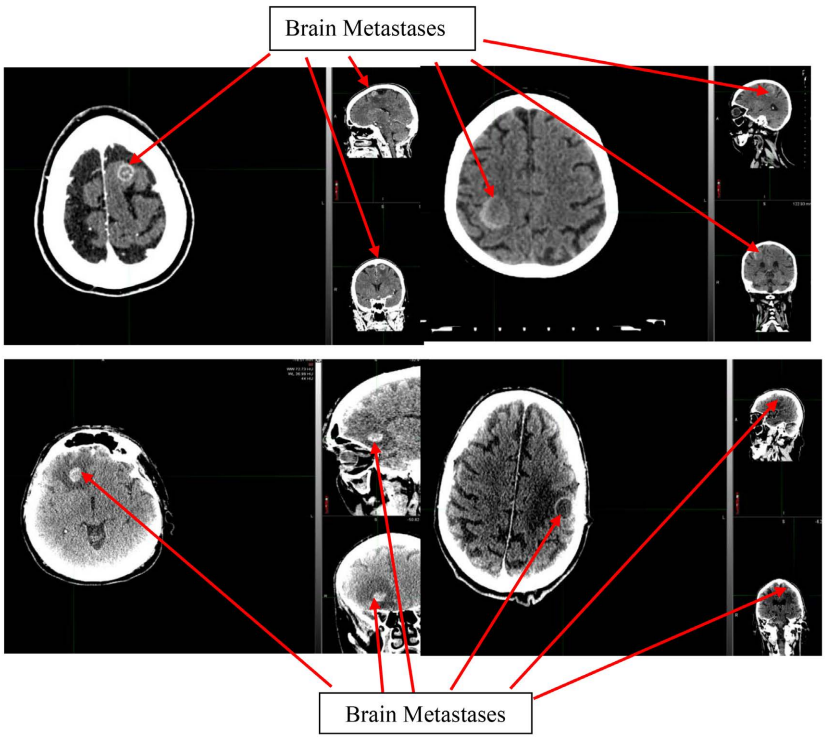

Figure 3. Some simulation CT images with contrast agent acquired from author's clinic by GE 16 slices CT simulator

the vertebral arteries where it travels to the major cerebral arteries (the anterior and middle cerebral arteries) and finally spreads throughout whole brain. The brain has blood-brain barrier (BBB) which filters some substances from peripheral micro circulation and might delay the agent. The most important patient-related factor affecting the timing of contrast enhancement is cardiac output and cardiovascular circulation [13]. For an average size patient it will take about 60 ~120 seconds for contrast to arrive in the brain post injection. Due to patient cardiac output difference, the patient-specific individualized trigger delay time should be used. Practically, if the patient size is large and the head is large, injection from arm, about 120 second post arm injection delay should be propriate. If the patient size is small, head is small, and the injection is from a chemotherapy port, about 90 seconds is typically adequate. If it is a GE scanner and an Omnipaque injection is used, 100 cc contrast agent and 30 second injection time are recommended. Some diagnostic protocols recommend an injection time of 1 - 2 min and a fixed delay time of 5 min for 80 cc contrast [14]. This protocol may not be effective for SIMT-SRS CT simulation since adding another 7 - 8 minutes after approximately 20 minutes of mask making process may be too long for cancer patients to lie on the hard table.

5. EPID QA

The EPID imaging system's comprehensive QA is covered in AAPM's TG-142 and TG-198 and will not be discussed in this article. The SIMT-SRS requires

high accuracy to deliver high doses of radiation to multiple, very small targets. The Winston-Lutz test and Winston-Lutz-Gao test (also called the Off-Iso Winston-Lutz test) ensure the success of this delivery. Nowadays both tests are performed on the EPID for Linac based radiosurgery. The importance of Winston-Lutz-Gao (WLG) test to SIMT-SRS is comparable to the Winston-Lutz test to single ISO SRS. The rationale and test methodology of the WLG test have been elaborated in other publications [15] [16]. Here we only address some QA issues on the EPID which provides the physical platform for a WLG test.

EPID is standard equipment in both Varian and Elekta Linear accelerators. Varian Linacs are equipped with either an aSi1000 or aSi1200 panel. The aSi1000 silicon panel has a resolution of 1024 × 768 pixels with a 40 × 30 cm^2 active detector area. The pixel size projected back to the isocenter is 0.392 mm. The aSi1200 silicon panel has a resolution of 1280 × 1280 pixels with an active detection area of 40 × 40 cm^2. The pixel size projected back to the isocenter is 0.336 mm. The Elekta Linac equipped with the iViewGT system has an EPID with a total field of view of 40 × 40 cm^2 and a resolution of 1024 × 1024 pixels. Each pixel size back projected to the isocenter is 0.25 mm.

The EPID imaging system and Linac treatment coordinate coincidence test is the first essential test for a WLG test. It aims to test if the EPID image isocenter is coincident with the Linac treatment isocenter. The test frequency should be every day of the SIMT-SRS procedure and the tolerance should be <1 mm in any direction. The test is straight forward and easy to be implemented in most clinics. It is performed by placing a cube phantom, which contains a radiopaque marker at the geometrical center inside a phantom and precisely aligning the radiopaque marker to the treatment isocenter with the room lasers or Linac cross hair (which are assumed to represent Linac treatment isocenter though other tests) then using the EPID system to irradiate the phantom from the four cardinal angles (270˚, 0˚, 90˚, and 180˚). In the image analysis windows the deviation between the center of the radiopaque marker and electronic cross hair (which is guaranteed to represent the EPID system isocenter by acceptance and commissioning tests) of each image indicates the difference between EPID imaging system isocenter and Linac treatment isocenter coordinate coincidence. The ideal situation is that the deviation is (0, 0, 0) and the imaging isocenter perfectly matches the Linac treatment isocenter. In reality, there always are some deviations and the tolerance should be less than 1 mm. The ISOCal Calibration (from Varian) is a tool which can be used to perform and correct offsets found in this test.

Another essential test for the WLG test is the uniformity test. Because the SIMT-SRS will treat the targets, potentially spread in 3D space, throughout the whole brain, the WLG test checks the accuracy of the mechanical field and radiation field off-isocenter congruence in 3D space within the whole head volume. Studies show [17] that when the primary beam irradiates the EPID, the energy spectrum of the beam varies from the center of the beam to off-isocenter distance. The EPID exhibits a strong beam energy response difference from center to off-isocenter distance. In the non-flood field corrected EPID image, severe

horn effects are observed at the off-axis distance. These images cannot be used in any WLG tests and any clinical applications directly. These images must be corrected by a "flood field correction algorithm" in the computer. In Varian TrueBeam Lincs, this correction can be done easily by the medical physicist. In the Varian C-series machine, the PotalVision IAS3 calibration procedure is designed to correct for the non-uniform response of the image receptor and non-uniform intensity of the X-ray source. The uniformity test is to test how good the "flood field correction algorithm" is. For Varian TrueBeam Linacs, the standard calibration of EPID uniformity is performed in service mode and is composed of several sub-calibrations: Dark field Calibration, Flood Filed Calibration, Pixel Correction, Beam profile Calibration, Dose Normalization Calibration. The flood field calibration, also known as Gain correction, is used to correct the gain of every pixel to reach a uniform level.

AAPM TG-198 provides the uniformity test detail for medical physicists. It should be performed after a flood-field calibration. We should irradiate the entire EPID sensitive area with 100 MU at the same SID. Measure the mean and standard deviation (SD) of the pixel values within a large region that excludes the detector edges and penumbra (2 cm inside the panel edges and 0.5 cm inside field edges). Calculate the SD as a percentage of the mean. From TG-198, "Image uniformity and noise can be quantified by measuring the average pixel intensity in 1 × 1 cm square regions of interest placed at the image center and 7.5 cm off-center left, right, top, bottom. The measured values of center, left, right, top, and bottom should agree with the baseline values. To quantify image noise, a 5 × 5 cm square ROI is placed at the center of the radiation field. The mean image intensity and the standard deviation of the intensity within the ROI are calculated. Fractional deviation (expressed as the ratio of standard deviation to the mean) should agree with baseline values. The image noise and uniformity calculation processes can be automated using commercially available phantoms and software". SIMT-SRS criteria for the uniformity test is within ±2% (SD as a percentage of the mean).

6. Patient Treatment

During the SIMT-SRS delivery process image acquisition, image registration analysis, and couch shifts are called image alignment in clinical language. The 3D CBCT is strongly recommended in the SIMT-SRS treatment process. 4D CBCT is unnecessary due to the stationary head under an immobilization device. Education and training are needed for all treatment staff due to the procedure's complexity and need for precision with high doses of radiation. CBCT routine QA is not discussed in this section.

In the image acquisition, the first step is to select CBCT mode. The CBCT mode will define how the CBCT will be acquired and reconstructed. Each Linac has a set of predefined CBCT modes where the acquisition parameters or reconstruction methods can't be changed. These predefined modes can be taken as the

default setting for the average patient and averaged head size (about 20 cm of head, 16 cm brain separation). If the patient's anatomy size is different from average, the therapist should consult with a medical physicist to adjust the mode or create a new mode. To acquire a better quality image, the therapist should know how to change kV and mA values for different anatomy structures to acquire high quality CBCT images. Qualified medical physicists should be able to create a new mode from the mode editor in the image computer in the treatment console.

In Varian machines, the predefined modes use 360- or 200-degree gantry rotations. The 360-degree rotation modes use half-fan to enable a large field of view (FOV) (*i.e.* pelvis) while 200-degree rotation modes use full-fan to enable a small FOV (*i.e.* head). Small FOVs can generate high quality images with high spatial resolution and low noise. The 200-degree with full fan mode has no imager offset. This mode can scan the patient more quickly and selectively reduce irradiation of the eyeball and lens. It can also give a better quality image which the SIMT-SRS needs. After the image acquisition, an image registration is performed for analysis.

Image registration is also called image matching. It should be clearly understood that image registration is not just simply two sets of images physically "top each other". There are very complicated algorithms involved in the matching. The nature of the registration is calculating the Registration Metric which is devised to quantify the degree of two image sets are aligned and optimization techniques are used to either minimize or maximize the Registration Metric. There are also geometric-based registrations and intensity-based registrations in the clinical registration software. They are based on the distance and gray scale values respectively between voxels in two set images. More details can be found in AAPM TG-132 [18] and many other publications.

During the treatment operation, we recommend therapists or medical physicists perform a manual match first. A manual match is also called the global alignment of the whole head. It aligns the skull and ventricles preliminarily with a DRR image. Then resize the ROI and focus on small volumes to do the auto match. During the auto match, you can play with parameter sets and intensity ranges to acquire high quality match results. It is recommended that only the head be aligned in image registration as the variation in neck and shoulder angulation can be extremely variable in SIMT-SRS patient setup.

For SIMT-SRS treatments CBCT is strongly recommended as the image alignment modality. The kV X-ray-only imaging modalities (like the CyberKnife, or ExacTrac system) are not good enough to visualize both bony structure and brain soft tissue; it can't capture pneumocephalus as shown in **Figure 4**. These imaging modalities may result in a missed target if brain soft tissue has some anatomy change. If contrast agents are used during SIMT-SRS patient CT simulation, the contrast agent will make the brain soft tissue brighter in the DRR image and reduce the DRR image contrast resolution which will affect the kV X-ray-only modality (like CyberKnife) aliment accuracy.

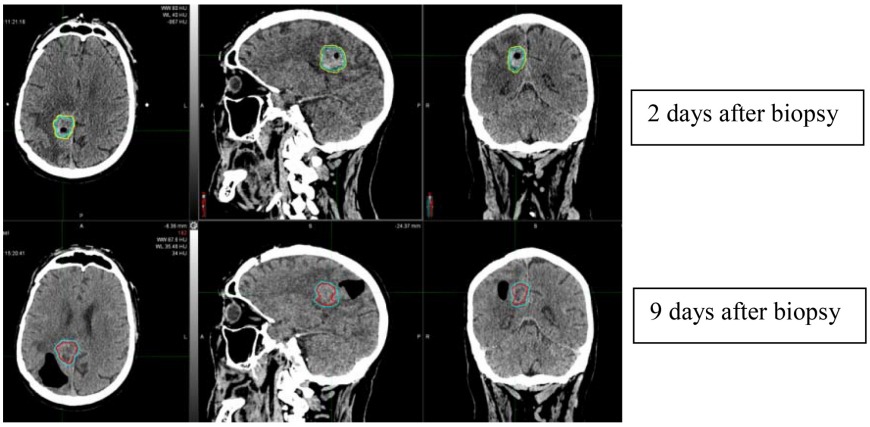

Figure 4. A pneumocephalus CT image example. Upper row is two days after biopsy and bottom row is nigh days after biopsy. The CTV and PTV in upper row are original contours in original plan. The CTV and PTV contoured in bottom raw are new contours in new plan due to the anatomy change.

7. Conclusion

SIMT-SRS image-related practical issues are discussed exclusively and routine. Daily image quality assurance is not included. Through patient selection, image preparation, patient simulation, EPID QA, and patient treatment, each step should be carefully crafted from the physics and treatment aspect. With careful implantation of these recommendations and guidance in the clinic, it is highly possible to achieve 1 mm, or 0.5 mm and non-uniform PTV margin expansion for all targets in SIMT-SRS. Therefore we can boost the abscopal response rate and further enhance the radiotherapy killing effect. Successful SIMT-SRS treatments will light up the pathway to radio-immune combination therapy in brain metastasis management. More studies and clinical trials are expected to be developed to bring this modern therapy into practical clinical application in the future.

Authors Contribution

Dr. Junfang Gao drafted content and initial version. Jeffrey P. Limmer performed editing and revision.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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