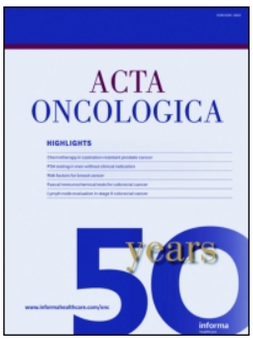

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REVIEW

LINAC based stereotactic radiosurgery for multiple brain metastases: guidance for clinical implementation

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ABSTRACT

Introduction: Stereotactic radiosurgery (SRS) is a promising treatment option for patients with multiple brain metastases (BM). Recent technical advances have made LINAC based SRS a patient friendly technique, allowing for accurate patient positioning and a short treatment time. Since SRS is increasingly being used for patients with multiple BM, it remains essential that SRS be performed with the highest achievable quality in order to prevent unnecessary complications such as radionecrosis. The purpose of this article is to provide guidance for high-quality LINAC based SRS for patients with BM, with a focus on single isocenter non-coplanar volumetric modulated arc therapy (VMAT).

Methods: The article is based on a consensus statement by the study coordinators and medical physicists of four trials which investigated whether patients with multiple BM are better palliated with SRS instead of whole brain radiotherapy (WBRT): A European trial (NCT02353000), two American trials and a Canadian CCTG lead intergroup trial (CE.7). This manuscript summarizes the quality assurance measures concerning imaging, planning and delivery.

Results: To optimize the treatment, the interval between the planning-MRI (gadolinium contrast-enhanced, maximum slice thickness of 1.5 mm) and treatment should be kept as short as possible (< two weeks). The BM are contoured based on the planning-MRI, fused with the planning-CT. GTV-PTV margins are minimized or even avoided when possible. To maximize efficiency, the preferable technique is single isocenter (non-)coplanar VMAT, which delivers high doses to the target with maximal sparing of the organs at risk. The use of flattening filter free photon beams ensures a lower peripheral dose and shortens the treatment time. To bench mark SRS treatment plan quality, it is advisable to compare treatment plans between hospitals.

Conclusion: This paper provides guidance for quality assurance and optimization of treatment delivery for LINAC-based radiosurgery for patients with multiple BM.

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Introduction

Whole brain radiotherapy (WBRT) was traditionally the cornerstone of treatment for patients with multiple brain metastases (BM). WBRT has significant side effects, such as hair loss, fatigue, and cognitive dysfunction which result in a decreased quality of life (QOL) [1,2]. In the last decades, stereotactic radiosurgery (SRS) has become the standard of care for patients with a limited number of BM [3]. Recently, SRS has become a treatment option in patients with 4 or more BM. Yamamoto et al. found a similar overall survival for patients with multiple BM (5–10) compared to limited BM (2–4) when treated with SRS or fractionated stereotactic radiotherapy in low volume BM [4]. For selected patients with a single small brain metastasis, SRS may extend survival and avoid invasive surgery, without compromising local control [5]. There are important advantages of SRS over WBRT, i.e., limiting radiation to the uninvolved brain and obtaining a high probability of local tumor control with a single treatment.

Until recently, linear accelerator (LINAC) based radiosurgery has required each metastasis to be treated using a distinct isocenter, with the patient immobilized in an invasive

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frame. Recent technical advances have made LINAC based SRS significantly more efficient and patient friendly. First of all, cone-beam CT imaging has made it possible to detect translational and rotational set-up errors.

Secondly, robotic couches have made it possible to correct rotational setup errors [6,7]. Combined with the use of proper immobilization masks, this eliminates the need for invasive frames [8]. SRS with immobilization masks and a six-degrees-of-freedom (6-DOF) robotic couch under the guidance of cone beam CT is a widely adopted treatment. Translational and rotational errors can be corrected within 0.3–0.5 mm and 0.3° when using cone beam CT and a 6-DOF couch [9–11]. Another study shows that institutes with real-time tracking capabilities and robotic couches are capable of correcting rotational errors within 0.5° for most patients. With a rotational error of 0.5° the coverage of the target is still $\geq$95% and the risk of a compromised coverage increases due to an increasing rotational error [12].

Thirdly, this improved patient positioning makes it possible to treat multiple BM with one isocenter. Most treatment planning systems can be used to optimize a treatment plan with one isocenter. There are some examples of commercial systems which offer specific forms of automation for the purpose of planning with one isocenter: HyperArc™ (HA) (Varian Medical System, Palo Alto, CA), Monaco HDRS (Elekta AB, Stockholm, Sweden) and MultipleBrainMets™ (MBM) (Brainlab AG, Munchen, Germany). Several studies analyzed the plan quality of such techniques, with promising results [13–16]. Ruggieri et al. compared the plan quality and dosimetric accuracy of MBM and HA. They concluded that both techniques were able to generate high quality plans for patients with multiple BM using SRS [15]. Furthermore, since this a promising and safe treatment option for multiple BM in a single treatment or fractionated treatment, this also has the potential to have a positive impact on the costs of SRS [17].

Lastly, the use of flattening filter free (FFF) beams have further decreased the treatment time. The beam-on time when treating three to twelve brain metastases has been quantified before. It was found that three metastases could be treated in approximately six minutes on a LINAC with FFF and robotic couch, compared to 45–50 minutes on a GammaKnife. This time increased to nine minutes on the LINAC to as much as 2.5 hours on a GammaKnife for twelve metastases [18]. Depending on the chosen number of isocenters and beam configurations, multiple BM can be treated simultaneously within thirty minutes on a LINAC. The risk of an intra-fraction positioning error (>3 mm) is very small when using immobilization masks and a robotic couch. A retrospective study showed that a prolonged treatment time is associated with a greater risk for treatment positioning errors. Therefore, time delays between imaging and delivery should be kept under five minutes to maintain a low risk for positioning deviations. If longer time delays occur, one may decide to verify the patient's position again [19].

When using a non-coplanar LINAC technique, the conformity of the FFF based plans is comparable to GammaKnife treatment plans [16,20]. A detailed analysis of factors affecting LINAC non-coplanar plan quality revealed that low dose spillage can be modulated during the treatment plan optimization process [21].

Other factors that may affect clinical outcome of SRS are the GTV-PTV margin that is used as well as the SRS prescription dose. A randomized trial has shown that 1 mm GTV-PTV margin resulted in equal local control as 3 mm GTV-PTV margin despite physical uncertainties [22]. An explanation for the equal local control in both study arms is the dose penumbra outside the PTV which also sterilizes microscopic disease. Using a 3 mm GTV-PTV margin results in a higher normal tissue complication probability of radionecrosis than 1 mm GTV-PTV margin, due to high dose spillage in the normal brain tissue. Therefore the authors indicate that a 1 mm GTV-PTV margin would be ideal, but possible uncertainties such as patient setup and accuracy, should be considered when choosing the margin. To further lower the risk of radionecrosis, the dose prescription can be adapted. With a risk-adapted approach, a high dose is prescribed for small BM (single fraction of 21 or 24 Gy) and a relatively low dose is prescribed for large BM (e.g., single fraction of 15 or 18 Gy or 3 fractions of 8 Gy). When using this approach in a BM larger than 2 cm in diameter, a relatively high dose is spilled in the normal brain tissue, resulting in an increased risk of radionecrosis as the V12Gy exceeds 10 cm^3. Radiation-induced brain necrosis in patients who are treated with SRS or multifraction stereotactic radiotherapy for BM larger than 2 cm has been investigated. It was concluded that multifraction SRS (27 Gy in 3 fractions) is an effective treatment for large BM and is associated with a reduced risk of radionecrosis, compared to SRS [23]. A relatively new strategy to mitigate the risk of radionecrosis is isotoxic dose prescription. With this approach the tolerance level for radionecrosis is always respected and the dose in the BM is adapted to respect the tolerance level. Clinical studies are needed to validate the promising in-silico results [24,25]. Mitigating the risk of radionecrosis is important to maintain SRS as a treatment option for patients with BM in a multimodality approach.

After SRS, there is a relatively high risk of development of new BM during follow-up, so called Distant Brain Recurrences (DBR). One of the factors that correlates with the risk of DBR development is the number of BM treated initially with SRS, but volume of the initial treated BM, and age play a role as well [26]. Level I evidence for the value of SRS is already available for patients with a limited number of BM, but needs to be determined in patients with four or more BM [5]. Currently, WBRT or primary systemic treatments are frequently being used in patients with four or more BM.

However, the outcome of WBRT is disappointing in the setting of BM [27]. To investigate whether patients are better palliated with SRS than with WBRT, several prospective phase II/III trials are currently being initiated or ongoing: A European trial (NCT02353000), two American trials, and a Canadian CCTG lead intergroup trial (CE.7). The European trial was closed after two years due to poor accrual (NCT02353000) after randomizing 30 patients. Patients, referral physicians, and also some radiation oncologists prefer SRS above WBRT in a multimodality approach in which systemic

therapies are increasingly the cornerstone of the treatment. It is important that SRS is performed with the highest possible quality in the different centers within and outside of randomized trials. In each step of the process, the quality of treatment from patient imaging to planning and delivery, must be assured [28]. This work summarizes the quality assurance measures with the goal to provide guidance for high-quality LINAC based SRS for BM patients. The article is based on a consensus statement of the study coordinators and medical physicists of the four trials and other thought leaders for quality assurance of SRS, with a special focus on single isocenter non-coplanar volumetric modulated arc therapy (VMAT).

Patient selection and endpoints in trials

In general, patients with BM are suitable for SRS if they have a Karnofsky performance status of 70 or more, harbor BM that have a maximum diameter of four cm, and have extracranial treatment options. From an anatomy perspective, BMs need to be separated from the optic apparatus to avoid visual complications. In a large prospective cohort study patients with two to four BM had equal survival as patients with five to ten BM [4,29]. Not only patients with a single BM had a more favorable prognosis, but also long term survivors were observed in patients with five or more BM. In this study, the maximum diameter of the largest BM was three cm, the maximum volume of the largest BM was ten cm^3 and the maximum total volume of the BM was fifteen cm^3. In the four initiated randomized trials there are small discrepancies with respect to inclusion and exclusion criteria, also with respect to SRS on brainstem metastases. All trial protocols respect a maximum number and size of the BM (e.g., maximum diameter of 2.5 cm, a maximum cumulative volume of 30 cm^3, and a maximum of ten or fifteen BM). These inclusion criteria are consensus based, and not evidence based, with a relation to toxicity, such as the risk of radionecrosis. Table 1 visualizes the investigated endpoints to determine the value of SRS for multiple BM.

Diagnostic imaging and planning

Planning-MR, planning-CT, and registration

Based on consensus, the interval between the planning-MRI and actual SRS treatment should be kept as short as possible. A maximum of two weeks (preferably $<$ one week) seems acceptable to avoid a geographical miss at the edge of the BM due to tumor progression [30]. The planning-MR is Gadolinium (Gd) contrast-enhanced with either single, double, or triple dose Gd to visualize the BM. The field strength of the MRI is in the range of 1.0T to 3T with a maximal slice thickness of 1.5 mm. MRI can have geometric distortion and needs to be corrected, especially for the 3T MRI. Quality assurance of the correct execution of the geometric distortion correction is done at least yearly. Using independent phantom measurements which compare cerebral CT images without geometric distortion with the geometric distortion corrected MRI.

A planning-CT with preferably 1 mm, but $\leq$2 mm thick contiguous slices is fused to the contrast-enhanced stereotactic MRI. Preferably the planning-CT is enhanced with Iodine contrast to also visualize the BM on the planning-CT. By default, the planning-CT is 100 kV and combined with dose modulation (mAs) in order to achieve the optimal soft tissue contrast. A dedicated head filtration kernel with beam hardening correction is advised. Ideally, a small collimation is chosen (e.g., 64×0.6 mm). It is recommended that a reproducible methodology is used with a well-defined protocol for image registration of the MRI with the CT. The position of the BM visualized on both the MRI as the CT (if visible) can be used to check the quality of the registration. To minimize the risk of registration errors and to identify unexpected geometric distortion correction errors or artifacts of the MRI, an independent check of the registration has to be performed by a medical physicist and/or radiation oncologist.

Contouring and treatment planning SRS

In general, the BM are contoured based on the contrast enhanced lesions on the planning-MR and fused with the (contrast enhanced) planning-CT. To obtain the maximal therapeutic ratio, e.g., tumor control probability/radionecrosis, while taking into consideration the geometric uncertainties in the treatment chain, GTV-PTV margins are minimized or even avoided [18,22]. Margins should ideally be based on a CTV to PTV margin recipe taking all uncertainties into consideration. However, with a sufficiently high planned prescription dose and median dose to the CTV a satisfactory dose to the CTV might still be obtained. Organs at risk are contoured consensus based [31].

Single isocenter (non-)coplanar VMAT can be used to maximize efficiency with maintenance of a high treatment plan quality. This technique is a highly conformal dynamic intensity modulated technique that delivers high doses of radiation to the target with maximally sparing of OAR [15]. This is done by simultaneously varying the speed of the gantry rotation, the dose rate of the LINAC and the MLC aperture shape. Compared to the conventional multiple isocenter technique, the single isocenter VMAT approach, using one or more gantry arcs, is characterized by a relatively short overall treatment time [10]. For targets that are closely spaced, including couch rotations may lead to a more conformal result (Figures 1–2) [16,32,33]. Other planning and delivery techniques are encouraged to achieve uniform optimized planning quality, such as, knowledge-guided planning using multiple non-coplanar dynamic conformal arcs or VMAT, as well as knowledge-guided planning techniques [34,35].

The use of VMAT for SRS with flattening filter free (FFF) photon beams has demonstrated to shorten treatment time compared with traditional flattening filter (FF) beams [36]. FFF beams potentially have an increased dose rate which can substantially shorten the beam-on time and result in a more favorable dose gradient. Especially with very high single fraction doses, reducing treatment time is an important

Table 1. Measurable endpoints in trials.

Primary endpoints	Difference in quality of life (EQ5D EUROQOL questionnaire) at 3 months post-radiotherapy with respect to baseline Neurocognitive progression-free survival Overall survival
Secondary endpoints	Karnofsky $\geq$ 70, WHO performance status, steroid use (mg), toxicity according CTCAE V4.0 including hair loss, fatigue, brain salvage during follow-up, type of salvage, time to salvage after randomization, and Barthel index, quality of life EORTC QLQ-C30, quality of life EORTC BN20 brain module, and fatigue scale EORTC QLQ-FA13.

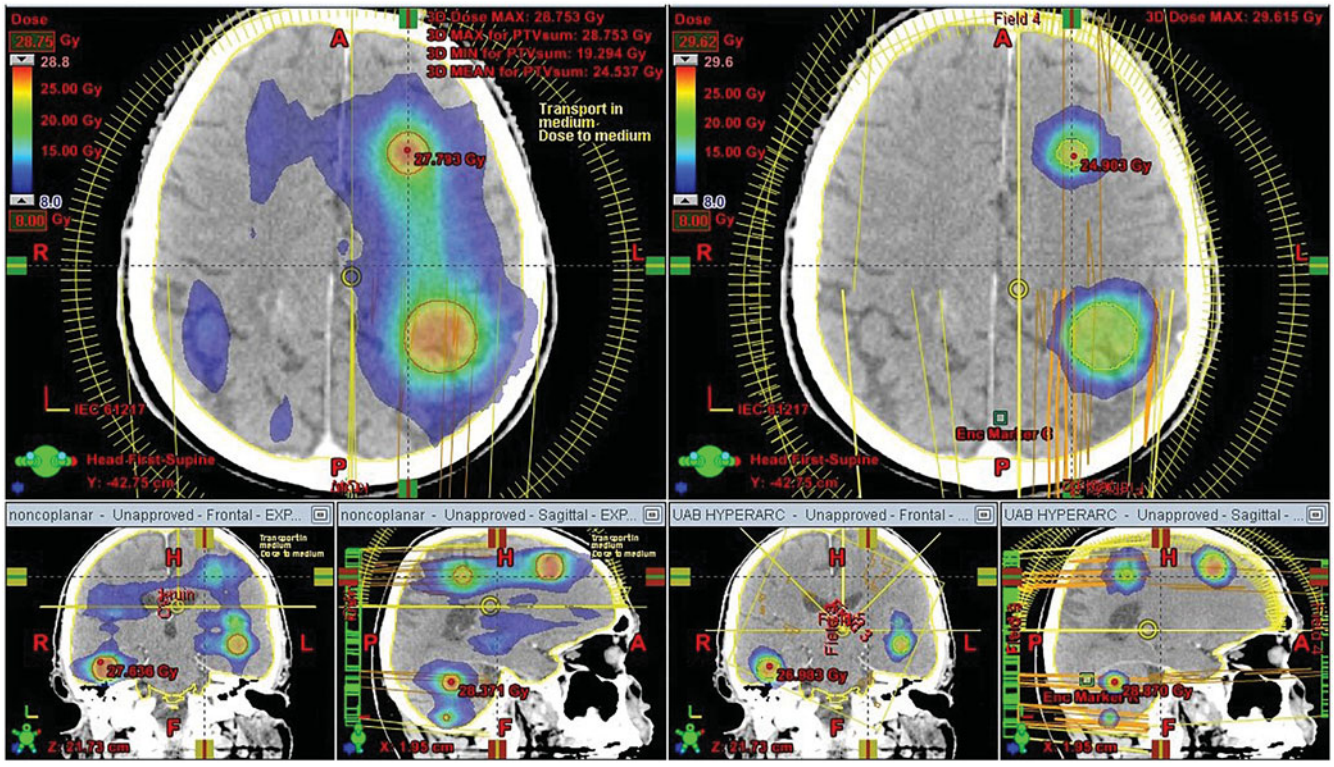

Figure 1. Dose distributions of 2 SRS planning-strategies for a case with 10 brain metastases. Dose distributions are visualized on an anonymized planning-CT of a case with 10 BM treated with 21 Gy SRS on all BM. The planes on the left show the plan made with one coplanar beam and one non-coplanar VMAT beam and the planes on the right show the plan made with four non-coplanar VMAT beams using different couch rotations (HyperArc Varian Medical systems, right transversal CT-image). The planning-CT is demonstrated in transversal (above), sagittal (below right), and coronal (below left) planes. The minimum dose which is demonstrated is the 8 Gy color wash dose (Eclipse, Varian Medical Systems, Palo Alto, USA). With Hyperarc, steeper dose gradients are achieved and brain tissue is much better spared than with a single non-coplanar VMAT beam.

issue in SRS. This improves patient comfort and might reduce intrafraction motion. There is also some clinical experience with FFF VMAT in elderly patients with multiple BM. When treated with a long course radiotherapy, elderly patients often encounter multiple barriers. Therefore, it was concluded that LINAC-based SRS or multifraction stereotactic radiotherapy should be taken into account as a feasible, safe and effective treatment option for elderly patients [37]. Furthermore, a lower peripheral dose is a unique characteristic in FFF beams due to the decrease of photon head scatter, head leakage and leaf transmission [38]. It has been demonstrated that the dose gradients in FFF beams were superior to FF beams and that FFF provides further brain sparing compared to traditional techniques for SRS in single brain metastasis [39,40].

Depending on the treatment planning system used, one will need to prescribe the dose to the PTV or isocenter. To avoid confusion about dose prescription and reporting, it is advised to follow the guidelines of the ICRU [41]. Dose is prescribed depending on size of the BM varying in a single dose of 15 up to 24 Gy or 3 fractions of 8 Gy with this isodose line encompassing the PTV [42]. Commonly used methods of risk adapted SRS dose prescription are shown in Table 2. To optimize the treatment planning- and delivery technique of an institution, it is advisable to compare treatment plans with other institutions, preferably institutions that have broad experience with LINAC based SRS. Plan quality evaluation can be performed using parameters: CTV and PTV D98% for each CTV/PTV, CTV and PTV $D_{V\text{-}35mm3}$ for each CTV/PTV, near maximum dose (D2% or $D_{35\ mm3}$), Median dose D50%, Mean dose (Dmean), RTOG conformity index: Volume (prescribed dose in treatment plan)/V(total PTVs, can only be used if all BM are treated with equal SRS dose), Paddick gradient index: Volume (50% of prescribed dose)/

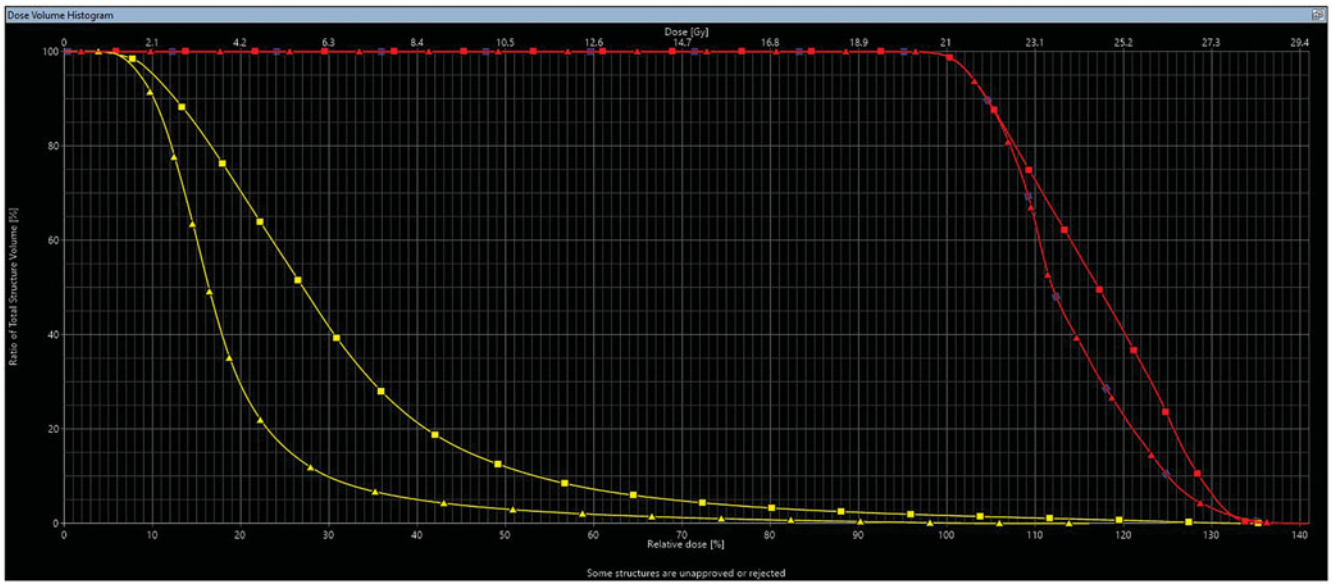

Figure 2. Dose-Volume histograms of 2 treatment planning-strategies for SRS multiple BM: a non-coplanar VMAT beam and multiple non-coplanar beams (HyperArc, Varian Medical Systems). Dose-volume histograms of the planning strategies in Figure 1. With 4 non-coplanar VMAT beams (triangles, HyperArc) normal brain tissue outside the PTV is much better spared than with one one coplanar beam and one non-coplanar VMAT beam (squares). Yellow lines visualize the dose in the brain. Red lines visualize the dose in the PTV. Treatment plans of a SRS fraction of 21 Gy, to 98% of the PTV.

Table 2. Risk adapted SRS dose prescription.

PTV of BM	Dose covering PTV	BM in brainstem
$<1\,cm^3$	20–24 Gy	16–20 Gy
$1–4\,cm^3$	20–24 Gy	16–18 Gy
$4–10\,cm^3$	16–20 Gy	14–16 Gy
$10–20\,cm^3$	16–18 Gy	14–16 Gy
$20–65\,cm^3$	15 Gy or 3×8Gy $=$ 24Gy	No SRS

If the tolerance dose of the brain nearby the largest BM is exceeded, e.g., V12Gy exceeds 10 cm^3, a lower prescribed dose can be used or the fractionation scheme can be adapted into 3 fractions of 8 Gy to avoid the risk of radionecrosis.

Volume(prescribed dose, can only be used if all BM are treated with equal SRS dose), Maximum dose organ at risk (D $0.035\,cm^3$): brain stem, cochlea, chiasm, lens en optic nerves, Total V12 Gy (brain exclusive GTVs), V12 Gy largest BM (so only the surrounding brain exclusive GTV), and the mean brain dose. There are several publications about SRS constraints for organ at risk that can be used to reduce the risk of severe complications [43,44]. It is advisable to use a volume constraint for the maximum dose in an organ at risk, for example an acceptable variation of 0.00–0.03 cm^3.

A commonly used methodology to compare treatment plan quality between institutes, requires that every institute make an anonymized contoured planning-CT available with a FTP-webserver. Subsequently, every institute makes a treatment plan that will then be compared among the institutes. The above mentioned parameters are compared to evaluate the treatment plan quality and to minimize the variation in quality of treatment plans.

Setup, delivery, and quality assurance

There are various SRS modalities available for the treatment of brain metastases, such as Gamma Knife, CyberKnife, Tomotherapy and a standard linear accelerator. LINAC accelerators should have MLC leaves $\leq$5 mm (preferably thinner) and a 6 degree of freedom (6D) robotic couch to correct positional and rotational errors. The patient can be accurately positioned at couch 0 degrees using CBCT online images. If a non-coplanar technique is applied, the LINAC should also have a means of verifying patient position at different couch angles. This can be realized by a surface tracking system and/or a kV based imaging system. It is essential that the couch rotation isocenter be kept as small as possible as correction of errors in this sense is often impossible. One might consider using more stringent values than the ± 1 mm as given in AAPM TG 142 [45]. Patients are immobilized in supine position within a molded immobilization mask or noninvasive frame-based mask, with or without bite block.

Regarding quality assurance, and in particular end-to-end testing of a single isocenter VMAT treatment for multiple BM, the literature is scarce [46,47]. Therefore, the goal of this paper is attempt to formulate a minimum of QA measures and equipment a radiation oncology center needs to set up this state-of-the-art treatment of BM, using the information from the different ongoing trials (Table 3).

Follow-up

Patients treated with SRS as a single modality for BM have a relatively high risk of developing distant brain recurrences during follow-up in the range of 50–84% [19]. Therefore regularly follow-up MRI is justified if the patient is fit enough to undergo salvage treatment of DBR. The optimal frequency of follow-up MRI's in terms of cost efficiency remains to be determined, but a frequency of every two to three months is commonly used [52]. Salvage treatment options for DBRs

Table 3. Examples of the QA measures [48].

Radiation equipment	LINAC equipped with MLC (2.5 mm–5 mm)[a]
Mechanical tests	Winston-Lutz based test to verify the couch rotation[a]
Phantom	Anthropomorphic Rando Alderson phantom Phantom which capability to measure dose distributions with a sub-millimeter resolution[b]
Dosimetry measurement/phantoms	Radiochromic film dosimetry (Figure 2) or Dose Guided RadioTherapy using EPID[a] [49]
	Small field dosimetry detector[b]
	Rotational phantom with small field dosimetry detector[b]
Treatment planning system	A type B dose calculation algorithm.[a][50]
	Knowledge of small field uncertainties of the TPS[b][51]
Analysis method	Gamma analysis and point dose difference.[a] The mm criterion should not be larger than the CTV to PTV margin used unless when a 0 mm margin is used. Then, a 1 mm margin within the gamma evaluation is advised.
Other	Robotic 6DoF couch IGRT (kV-CBCT, kV-kV images)[a]
	Imaging (MV, KV, or surface tracking) during set-up and treatment in case non-coplanar beams are used.[a]
Departmental QM	Quality management system[a] [28]
Patient specific QA	Pre-treatment verification with film dosimetry[a]

[a]Highly recommended.
[b]Optional.

and local failures are SRS, WBRT, neurosurgical resection in case of a large and isolated DBR, and systemic therapy.

Conclusion

In the last decade the management of BM has seen dramatic changes. After publication of the QUARTZ and other trials, the indication of WBRT has become a matter of debate. SRS is an emerging treatment option for patients with a limited number of BM, but recently also for patients with multiple BM.

To deliver high doses to the target, with maximal sparing of the organs at risk, single isocenter (non-)coplanar flattening filter free VMAT is an efficient and therefore attractive delivery technique, with comparable plan quality as Gamma- or CyberKnife. This strategy can potentially lead to a change in the daily practice of BM for healthcare systems making SRS more affordable and feasible in clinical practice. It is essential that SRS be performed with the highest achievable quality to minimize the risk of side effects such as radionecrosis. This paper provides guidance for quality assurance and optimization of treatment delivery for LINAC-based radiosurgery.

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