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# Can Spatial-Temporal Fractionation Reduce Brain V12 in Linac-based Multi-Mets SRS? A Sanity Check

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**Abstract**
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## Abstract

Objectives:

Stereotactic Radio-Surgery (SRS) represents an alternative treatment option for multiple brain metastases (BM) compared to whole brain radiotherapy (WBRT). SRS administers focused doses to BMs in either a single fraction or very few fractions. In contrast to WBRT, SRS exhibits a higher rate of local control and a lower rate of cognitive function decline due to the higher biologically-equivalent dose (BED) delivered to BMs and the reduced mean brain dose. The primary complication specific to SRS is brain necrosis, which arises from the high fractional dose to normal brain tissue near BMs. The key dosimetry endpoint for preventing brain necrosis is V12Gy for single-fraction SRS. QUANTEC recommends keeping V12 for normal brain tissue below 10cc, while HYTEC offers similar recommendations.

Two studies have explored the potential of spatial-temporal fractionation (STF) to mitigate the toxicity of multi BM SRS using both GammaKnife (GK) and Linac-based SRS. Chen et al. (https://doi.org/10.1002/mp.14722) proposed a method to divide a single-fraction GK treatment into multiple fractions. In each fraction, a subset of BMs is carefully selected to maximize the distance between them and then treated at full prescription dose. This approach offers two distinct advantages. First, it subdivides a 2-5 hour delivery time into multiple manageable fractions, enhancing patient comfort without increasing the total beam-on time. Second, by distributing adjacent BMs to separate sessions, it reduces the overlapping spill dose that would occur if they were treated in a single fraction. The study's conclusion is that STF can reduce V12 by 20% to 50% compared to single-fraction GK SRS.

The other study, conducted by Torelli et al. (https://doi.org/10.1002/mp.16457), investigated the application of STF in Linac-based SRS. Departing from the binary approach employed in the earlier study (where a BM gets full prescription in one fraction and receives no shots in the other fractions), they introduced a more flexible fractionation scheme. In this scheme, a BM received an arbitrary fraction of total dose in each fraction. The fractionation schedule for each BM was optimized, along with optimizing fluence-based plans for each fraction. The baseline of their study was uniform fractionation (UF), which delivers the same dose distributions in each fraction. Specifically, the baseline UF plan delivered 27Gy physical dose (51.3Gy BED10) to the GTV in three fractions. Their optimized STF plans also had three fractions and aimed for same target BED10 in the plan sum. The study reported a reduction of around 10% in the mean dose of normal brain. However, it did not report a reduction in V12.

Given that the mean brain dose in SRS (approximately 6Gy in 3 fractions) is significantly lower than that in WBRT (30Gy in 3), a reduction in mean brain dose is less clinically significant than reducing V12. Since Torelli's study primarily focused on the reducing mean brain dose in its dose reporting and did not provide an explanation for the absence of V12 reduction, we decided to conduct a sanity check for this question: Can STF reduce brain V12 in linac-based Multi-Mets SRS?

Methods:

We optimized a series of benchmark testing plans with simple geometries for this V12Gy sanity check. Each geometry is composed of two spherical PTVs of same size, called them PTV_A and PTV_B. They are separated by a certain distance from boundary to boundary. The volumes of PTV ranges from 1cc to 3.5cc. The distances are 2cm, 1cm, 8mm and 5mm. The field setups are five arcs in HyperArc geometry and 10cmx10cm jaw opening. We turned off jaw tracking to keep the leaf transmission dose similar to clinical plans. The optimization objectives are automatic lower dose objective with a priority of 120 and SRS normal tissue objective with a priority of 100.

Similar to Torelli et.al's work, we set UF as the baseline of our work. All UF plans are 27.4Gy in two fractions, which has the same BED10=65.1Gy as 21Gy in one fraction. The targets in each fraction get 13.7Gy. Other possible spatial fraction schedules are X Gy to PTV_A and Y Gy to PTV_B in the first fraction and swap the dose in the second fraction. The target doses X and Y are constrained by keep BED10 same: [X*(1+X/10) + Y*(1+Y/10) =65.1Gy]. For example, one possible schedule is X=16Gy and Y=11Gy. Denote the dose falloff speed in normal brain tissue around PTV is < k>. Dose falloff < k> is a function of the distance to PTV, < r>, a function of PTV dose < X> and the dose to other PTV < Y>, so < k> = k(r,X;Y). Applying this dose falloff function, the dose at the distance < r> from PTV is X*k(r,X;Y). Summing the dose from two fractions together, BED2 at a distance < r> from PTV is [X*k(r,X;Y)*(1+ X*k(r,X;Y)/2) + Y*k(r,Y;X)*(1+ Y*k(r,Y;X)/2)]

12Gy isodose volume (IDL) the quantity of concern in single fraction SRS. In uniform 2fx SRS, 16.4Gy is equivalent to 12Gy in terms of BED2 for brain. So the isodose of concern in 2fx UF is 16.4/27.4 = 60%. For each PTV, we defined the gradient index as the radius of equivalent sphere of 60% IDV minus the radius of equivalent sphere of 100% IDV, relative the local dose of PTV. For example, the gradient index of 16Gy PTV is calculated by the 9.6Gy IDV and 11Gy PTV calculated by 6.6Gy IDL

Results:

We calculated the gradient index of PTVs in those benchmark plans with difference target sizes, at different target separation distances, and with different fractionation scheme. We found that gradient index is independent of dose to target < X>, the dose to other target < Y> and the distance between two targets, unless the target separation is smaller than 5mm in which case the 60%IDVs will intersect and bridge. For example, the 60%IDV of a 3.5cc PTV is always 9cc, no matter how much dose is prescribed to this PTV (16/13.7/11Gy), the dose to other PTV and how far away the other PTV is (>5mm). As the gradient index is defined such that 60% = k(r=gradient index, XGy; YGy), the dose falloff < k> is also independent of fractionation scheme and target separation, down to 60% falloff. So k(r,Y;X)= k(r,X;Y)=k(r). Subsequently, BED2 at a distance < r>=gradient index from PTV is [X*k*(1+X*k/2) + Y*k*(1+Y*k/2)]. The two variables, X and Y are symmetric. So the BED2 is minimized when X=Y, which implicated uniform fractionation.

Conclusion(s):

The dose of concern for brain necrosis, 12Gy, is a high isodose relative to prescription dose 21Gy. Linac-based SRS plans are essentially non-coplanar VMAT plans which are very good at keeping high isodose conformal. As long as the targets are not too close (< 5mm boundary to boundary), the dose falloff of each target in high dose region is independent of target dose and the presence of another target. UF would achieve the lowest biologically-equivalent V12 in all possible spatial-temporal fractionation schedule. However, the optimal fractionation scheme when 12Gy isodose line bridges between two close targets remains to be investigated. Current strategy used in clinics is dropping the prescription dose locally.