BRAINLAB

THE CLINICAL RELEVANCE OF MARGINS IN FRAMELESS RADIOSURGERY FOR BRAIN METASTASES

White Paper

A growing body of literature suggests that the total tumor burden rather than the absolute number of metastases should be considered as a criteria for radiosurgery. This raises questions about the clinical relevance of treatment planning margins that increase the total target volume by including an expansion of normal tissue.

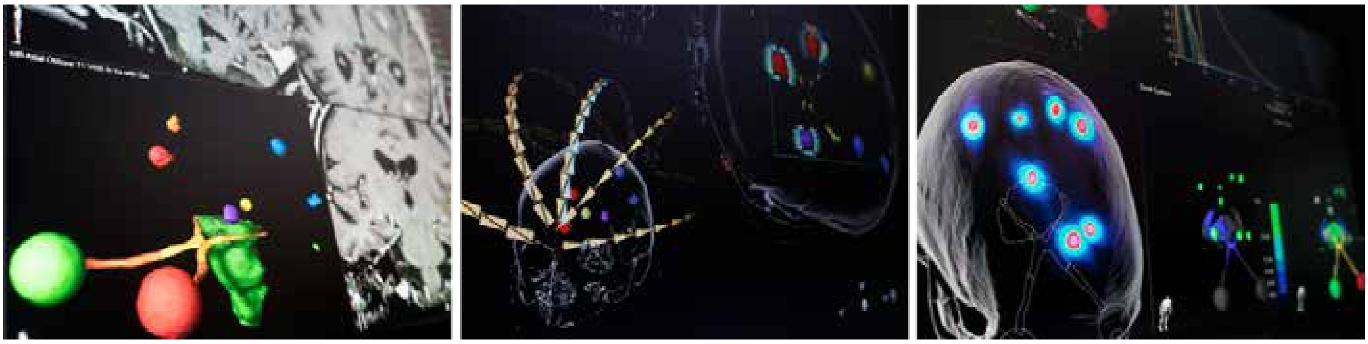

Figure 1: Typical Elements Multiple Brain Mets SRS radiosurgery treatment plans for patients with multiple brain metastases.

Patient eligibility for radiosurgery is based on several prognostic parameters such as performance, age, systemic cancer status and tumor histology. Evidence amassing since 2006 indicates that there is no arbitrary number of brain metastases that restricts the application of radiosurgery. At least six reports from separate research teams have established that total tumor burden is a statistically significant predictor of overall survival[1-6]. Data derived from over 2,500 patients validated that patient survival gradually decreases as a continuous function of increasing total tumor volume[4]. These conclusions are exclusively based on treatments of the gross tumor volume and may not simply apply to tumors expanded with a margin.

The Report 91 of the Journal of the International Commission on Radiation Units and Measurements (ICRU) is dedicated to small field radiosurgery and clearly states how methods for determining margins must be established to ensure that those margins are sufficient but not excessive[7]. Even small treatment planning margins greatly increase the total target volume. The impact of treatment planning margins is inversely proportional to the size of the gross tumor as clearly demonstrated in Fig. 2.

It has long been recognized that the risk of complications after single-fraction radiosurgery increases with treated volume. In 2010, the Quantec guidelines[8] recommended the adoption of the *volume receiving 12 Gy* as the standard method of reporting the dose to the normal brain as toxicity was found to increase rapidly once this volume exceeds 10 cm^3. Since then, five studies confirmed these findings directly and indirectly for brain metastases radiosurgery[9-13].

The impact of treatment planning margins on the total cumulative treatment volume, plan qualifiers and the incidence of adverse radiation effects has been studied in a randomized control trial[11]. Individual lesions were randomized to either 1 mm or 3 mm treatment planning margin before being treated with a single fraction radiosurgery dose of 24, 18 or 15 Gy depending on each lesion's largest diameter. There was a trend toward a higher rate of radionecrosis with the larger expansion given the significantly higher volume receiving 12 Gy in that arm.

Two other independent groups drew similar conclusions based on treatment planning simulation studies. One report found that the volume of brain irradiated by a certain isodose line depends primarily on the sum of the volume of treated lesions, and not on their number, shape, or location[10]. Another group discovered how increasing the margin of perfectly spherical tumors significantly increases the volume of the whole brain around each lesion that receives 12 Gy[14]. The impact of the margin was found to increase with increasing GTV size. All published series clearly indicate that margin reduction is mandatory to deliver a safe radiation dose while maintaining high efficacy.

Typical brain metastases radiosurgery prescriptions are based on the RTOG 90-05 dose escalation study which established maximum tolerated doses as a function of the maximum diameter of each individual lesion[15]. Planning target volume margins increase the maximum diameter triggering lower prescription doses.

Reviewing twelve-month follow-up data for single-fraction treatments demonstrates how reported local control rates vary considerably depending on the prescription dose[16]. Local control rates are higher than 80 % with doses above 20 Gy and higher than 60 % with a dose of 18 Gy. Reported twelve-month local control rates with a dose of 15 Gy are below 50 % in all but one series. Adding generous margins to gross target volumes significantly increase the maximum diameter, thereby lowering the single-fraction dose and local control.

Treatment planning, positioning and monitoring technology combined allow clinicians to confidently reduce margins. Target definition is primarily limited by the accuracy of the multi-modal datasets. The anatomical information presented in CT data is limited, yet precise. In contrast, MRI data presents rich anatomical detail but is subjected to distortions, due to nonlinearity of gradient fields, which may cause incorrect target definition. Further, targeting multiple tumors with a single isocenter challenges patient positioning as the detrimental effects of remaining rotations are magnified when the isocenter shifts outside the volume of the lesion[17].

Brainlab Elements Multiple Brain Mets SRS in combination with **ExacTrac** image-guided patient positioning and monitoring system offers an end-to-end workflow for the automated calculation and precise delivery of conformal radiosurgery treatments. These technologies combined allow treatments of multiple brain metastases with a single isocenter and margins of 1 mm and even less for lesions within a few centimeters of the isocenter[18].

Irrespective of the number of tumors, **Multiple Brain Mets SRS** automatically calculates treatment plans to target multiple brain metastases with a single isocenter, which enables efficient and straightforward planning of complicated multi-target plan scenarios[18-19]. **ExacTrac** enables the verification and realignment of patient position at any couch angle during the treatment, increasing overall treatment accuracy[20]. **ExacTrac** provides precise intra-fraction motion detection and correction, eliminating errors introduced by patient movement during the treatment[21].

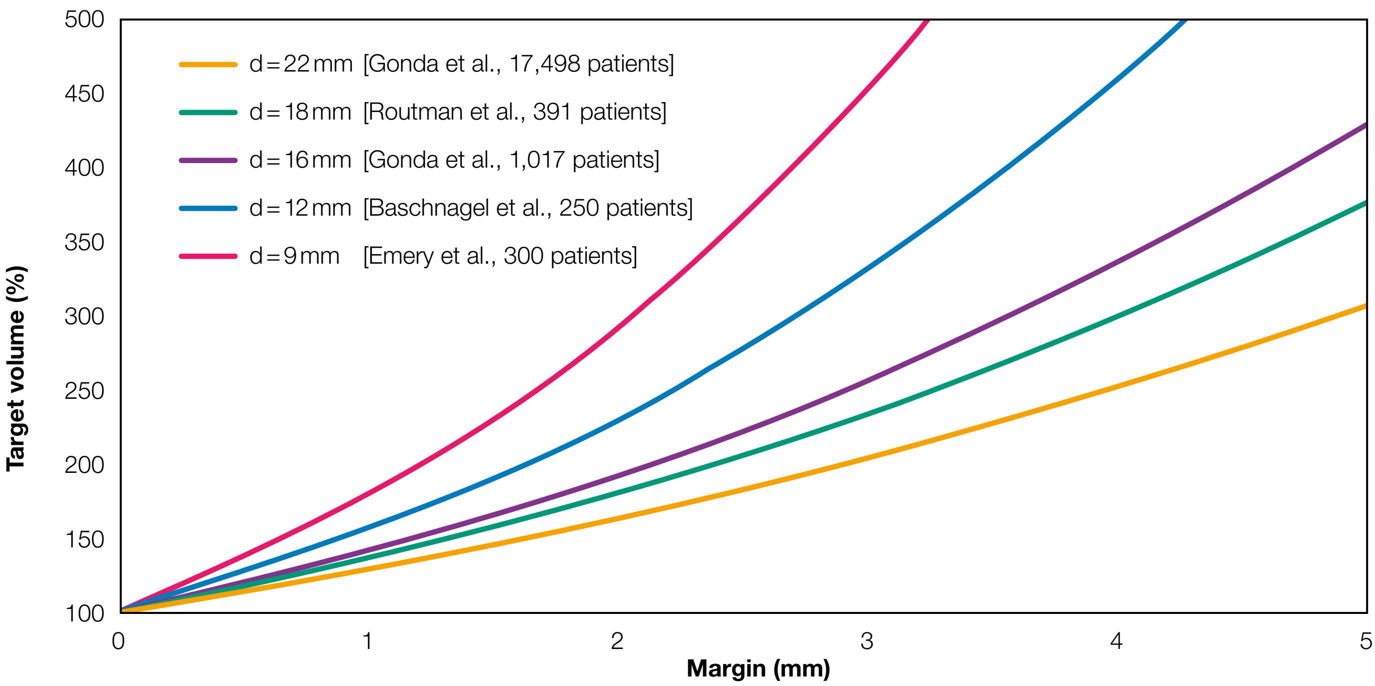

Figure 2: The impact of treatment planning margins on median target sizes from cited publications

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