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Chapter 7

HEAVY CHARGED PARTICLE BEAM RADIOSURGERY FOR ARTERIOVENOUS MALFORMATIONS OF THE BRAIN

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ABSTRACT

Heavy charged particle beams are successfully used for stereotactic radiation of AVMs. Although a number of particles such as protons, Carbon ions, Helium ions, Neon ions, and negative pi-mesons can be accelerated to form therapeutic beams, clinical experience with charged particle AVM treatments is concentrated around the use of protons and Helium ions. Particle therapy beams are produced by accelerating the relevant particle in a cyclotron or a synchrotron and modern treatment delivery is by way of an isocentric gantry, or a stereotactic positioning device. All heavy charged particles have similar typical dose absorption characteristics with a low entry dose and little to no exit dose distal to the target making them theoretically very suitable for intra cranial stereotactic irradiation. These dose distribution characteristics result in a lower integral dose to the brain, which is of particular importance in the treatment of children and young adults. Treatment delivery is either by beams collimated with beam specific apertures or by a pencil beam scanning method. In addition to their physical advantage, particle beams all have a radiobiological advantage as the Radiobiological Effectiveness (RBE) of these beams is higher than for photon beams used in Gamma knife or linear accelerator stereotactic irradiation. This improved RBE ranges from 1.1 for protons to, 1.3 for Helium ions, and 3 for Carbon ions. This feature combined with the possibility to deliver a high dose in the target volume makes them attractive for AVM radiosurgery where large target volumes and or complex shapes can limit the total dose delivered. In addition

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to this general biological effect charged particle beams show a specific effect on vasculogenesis and endothelial cell migration, whereby low LET particles inhibit the early stages of vasculogenesis and the high LET charged particles affect the endothelial cell migration necessary to form tubules. This is an interesting observation which could explain the very good AVM obliteration results obtained with Helium ion beams.

No direct prospective comparative clinical trials exist to demonstrate the benefit of particle beams over photon therapy. What can be learned from the published data is that particle beams offer an advantage for treating large AVMs with less radiation side effects on the normal surrounding brain.

The results of particle beam therapy for AVM will be discussed as well as future therapeutic use.

Keywords: arteriovenous malformation, proton beam therapy, stereotactic radiosurgery

INTRODUCTION

The discovery of the specific dose absorption characteristics of protons by William Bragg in 1903, called the Bragg peak after its discoverer, attracted the attention for clinical use because of the potential to spare normal tissue (figure 1). The invention of the cyclotron by Ernest Lawrence in 1929 opened up the possibility of producing particle beams of sufficient energy and intensity to explore clinical use [1] and after research by Wilson into the possibilities of clinical applications, the first treatment with protons was done at Berkeley in 1954 [2]. Clinical use of particle beams was initially provided at physics research laboratories such as Berkeley, Los Alamos, TRIUMF (Vancouver), PSI (Switzerland), and the Harvard Cyclotron Laboratories (Boston). A variety of charged particles such as Helium ions, Neon ions, protons, and negative pi-mesons were used. This initial clinical use of charged particles beams at these facilities had limitations in terms of patient treatment logistics and availability of beam time.

Nowadays the majority of particle therapy is provided in dedicated hospital based facilities, using modern delivery techniques with isocentric gantries and robotic controlled patient positioners. Overall the number of patients treated worldwide with charged particles for a variety of clinical indications has reached 122449 by the end of 2013, with 105743 proton, 13119 Carbon, and 2054 Helium ion patients [3]. The number of particle therapy facilities is growing and the majority use protons for their therapy. Therapy with Helium ions, Neon ions, and negative pi-mesons has been stopped as they were dependent on physics research laboratory programs. Presently only protons and Carbon ions are clinically available in dedicated centres, with a growing number of newly proposed facilities planning to offer both proton and Carbon therapy within the same centre.

PRODUCTION AND DELIVERY OF HEAVY CHARGED PARTICLES

1) Production

Heavy charged particles are accelerated in cyclotrons or synchrotrons and reach energies of around 230-250 MeV (Mega electron Volt) for proton beams, and around 400 MeV/ų for

Carbon ion beams. These energies are required for clinical use as they provide sufficient penetration into the body to reach deep seated targets.

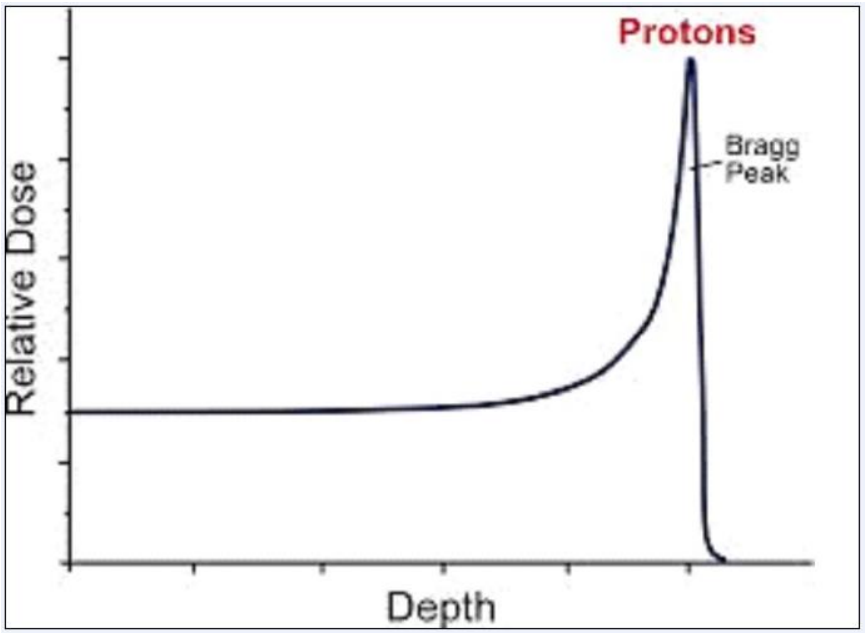

Figure 1. The Bragg peak.

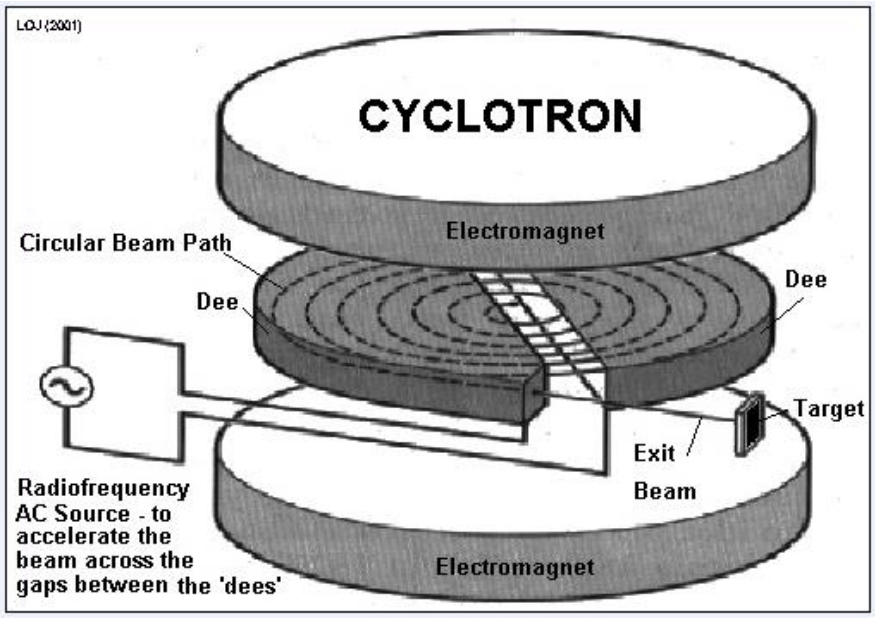

Figure 2. A cyclotron.

a) Cyclotron

In its simplest format a cyclotron consists of dipole magnets designed to produce a region of uniform magnetic field. In between the magnets are 2 D shaped vacuum chambers in which the particles are accelerated by an alternating electric field, produced across the gap by an oscillating voltage. Particles injected into the magnetic field region move on a semicircular path until they reach the gap where they are accelerated (figure 2). As the particles gain energy they follow a semi-circular path with increasing radius before they reach the gap again. At that time the polarity of the electric field reverses and so the particles are accelerated again. As they spiral around more and more the particles gain energy.

The size of the magnets and the strength of the magnetic field limit the particle energy that can be reached by a cyclotron.

Cyclotrons are fixed energy machines and require degraders to reduce the beam energies to what is required for a specific treatment.

b) Synchrotron

A synchrotron is an accelerator ring. Electromagnetic resonant cavities placed at certain positions around the ring accelerate particles during each orbit. A series of magnets along the accelerator ring keep the particles along a fixed orbit. Since the particles move always along the same geometrical~~ly~~ orbit, the strength of the magnetic field must be increased as the particles gain energy in order to keep them on that orbit (figure 3). Because of this synchronization of increasing magnetic field strength with increasing particle energy, these accelerators are called synchrotrons. Synchrotrons are variable energy machines and can change the energy on the fly as required by a specific treatment. The accelerated particles can reach up to 70% of the speed of light.

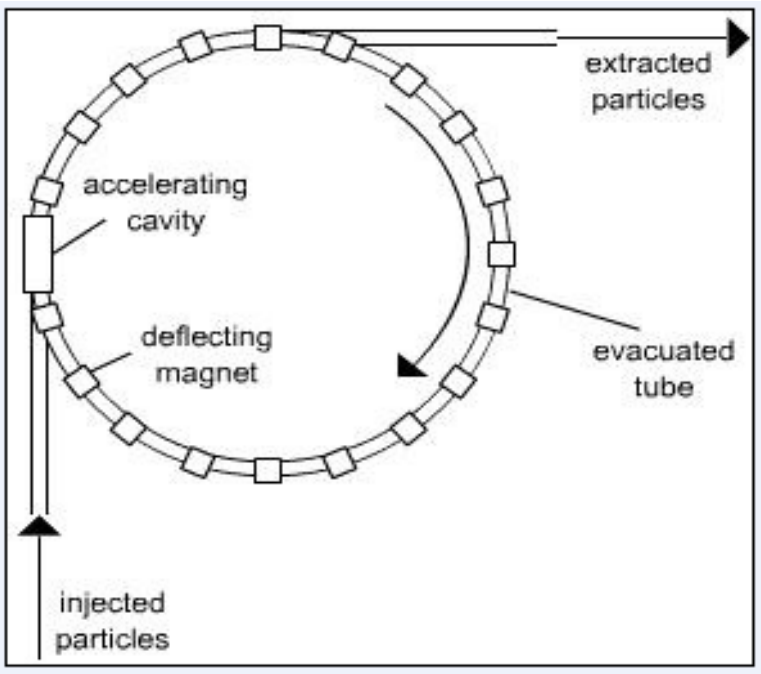

Figure 3. A synchrotron.

2) Beam Transport

Once accelerated the particles are steered into a beam line to transport them to the various treatment vaults. This beam line consists of a vacuum pipe with a number of focusing magnets around it at regular intervals and bending magnets where required to steer the beam into the vault. In modern facilities a single cyclotron or synchrotron can supply the beam to a number of treatment vaults by steering the beam around as required (figure 4).

3) Beam Delivery

The primary beam has a narrow diameter and needs to be modified in order to be able to treat target volumes of clinical relevance. Two basic techniques exist to make the beam clinically useful:

A) Passive Scattering

In this delivery mode the primary beam passes through a scattering system (figure 5). This spreads the beam to clinical useful dimensions and the wider beam is then subsequently collimated to a specific size and shape by metal inserts called apertures (figure 6). Each individual beam needs its own specific aperture as determined by the treatment planning system. The distal target dose shaping is done by compensators. Multiple beams of different shape and energy are used to cover the target volume from a number of angles. The energy of each incoming beam needs to be adjusted to achieve the required range to the target and this practically always means a degrading of the original beam energy if a cyclotron is used. As each individual Bragg peak is very narrow, the dose distribution needs to be widened by a series of beams of slightly lower energy, thereby accumulating the delivered dose from the individual Bragg peaks into a Spread out Bragg Peak (SOPB) that covers the thickness of the target volume along that beam direction (figure 7). The more the Bragg peak is spread out the less favourable becomes the plateau to peak ratio.

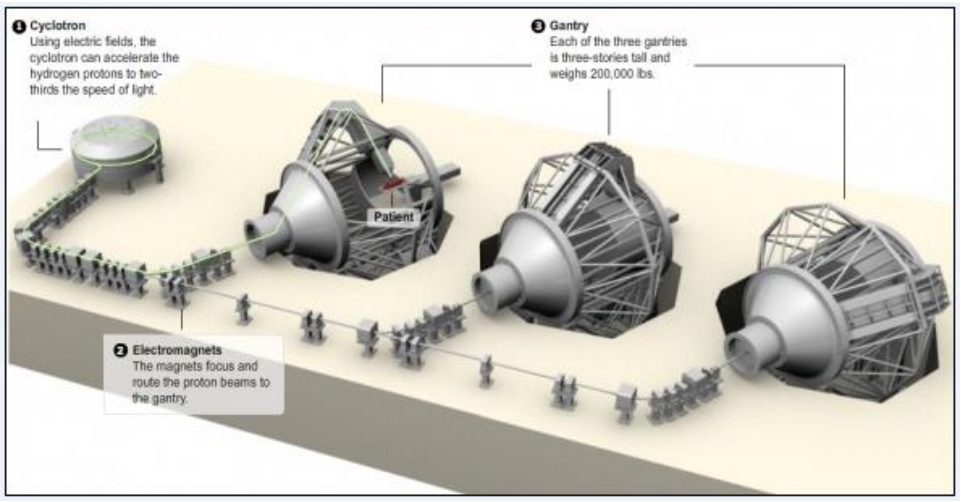

Figure 4. Beam transport.

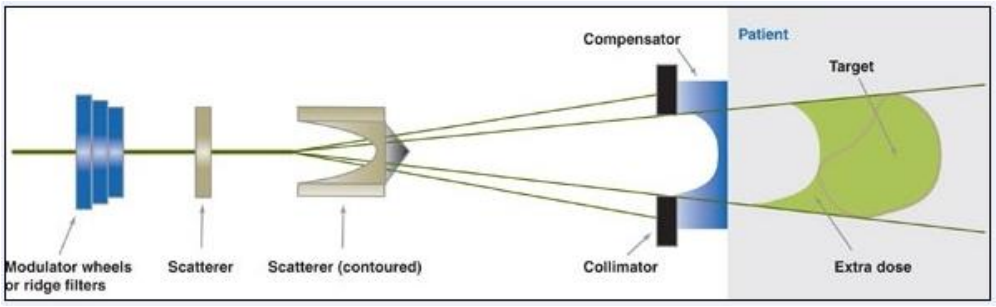

Figure 5. The primary beam passing through a scattering system.

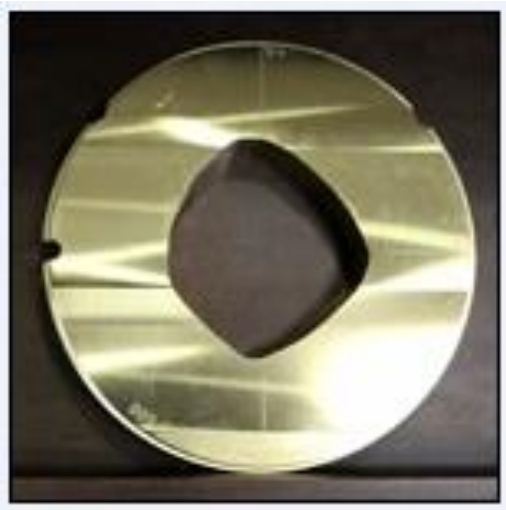

Figure 6. An aperture.

This plateau region of the pristine beam is the main reason for the low entry dose in tissue compared to a photon beam, and hence should be kept as low as possible by choosing a beam direction that needs the least SOBP to cover the target "thickness" from that angle. One problem with the scattering technique is that the Bragg peak effect becomes smaller as the scattered beam diameter becomes smaller and smaller and such small beams are not suitable to treat small diameter targets.

For beam diameters < 1.5-2 cm a shoot through technique, also called transmission technique can be used. With this delivery method only the plateau part of the beam is placed in the patient and the Bragg peak is outside of the patient at the exit side of the beam. With this technique one obviously loses the advantage of the Bragg peak, but the % depth dose is high and the beam penumbra is very sharp especially for high energy beams. Dose distributions for small lesions are however not much better than with radiosurgical photon beams from Gamma knives, Cyber knives, and Linac systems and hence this delivery method carries only some dose distribution advantage over photon systems. Passively scattered beams are simple to dose monitor and the various beam monitoring devices are robust and reliable. Passive beam scattering was the original way of providing a clinical useful beam. This

technique has been used to treat a large number of patients worldwide, and is still in use in a number of facilities.

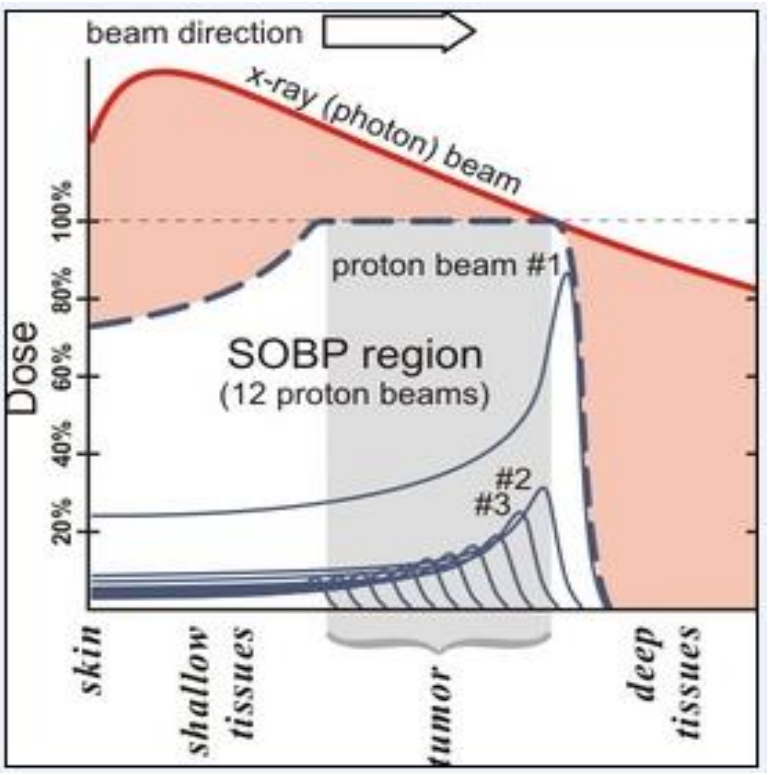

Figure 7. A spread out Bragg peak (SOPB) covers the thickness of the target volume along the beam direction.

B) Dynamic Beam Scanning

Because charged particle beams can be deliberately deflected magnetically, an alternative to the use of a scattered beam is to use the narrow primary "pencil" beam as it comes out of the accelerator and to scan it magnetically across the target volume. Typically the beam is scanned in a linear stepped pattern in the X-Y plane perpendicular to the beam direction (figure 8). The depth scan (Z) is done by means of beam energy variations. This scanning method requires neither a collimator nor a compensator.

The advantage of this technique lies in a better distal dose conformation around the target volume, and a lower dose proximal to the target. A scanning technique also allows for Intensity Modulated Proton Therapy (IMPT), a very valuable technique in the treatment of malignancies, but also with great potential for radiosurgical use [4]. Scanning is becoming more and more the preferred treatment delivery method in various particle therapy centres worldwide. For radiosurgical purposes with strict geometrical dose constraints the size of the spot strongly influences the sharpness of the penumbra around the target volume. The smaller the spot the steeper the dose fall off. Small spots are however less practical for large target volumes such as encountered in oncological indications.

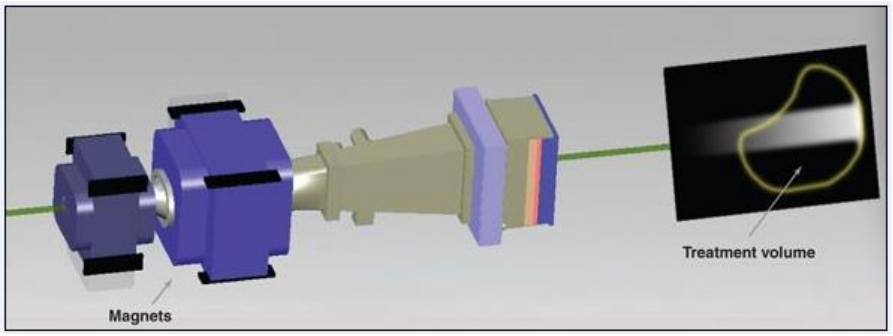

Figure 8. The beam is scanned in a linear stepped pattern in the X-Y plane, perpendicular to the beam direction.

Spot scanning has no limitations in terms of using small diameter beams on condition that the treatment planning system can handle the calculations. The size of the pencil beam spot is primarily determined by the design of the treatment delivery nozzle, but other factors also influence spot size such as beam energy and distance between the nozzle and the isocenter [5]. A small spot is advantageous for radiosurgical applications but a small spot nozzle is not that easily married to a large spot nozzle as used for treatment of larger volume oncological diseases. The dose gradient on the peripheral edges of the beam can be further steepened by adding a metal beam collimation device similar to the aperture used in passive scattering systems.

4) Patient Positioning and Immobilisation

The mechanical isocentric stability of particle delivery systems is equal to Linac based systems, with an accuracy of < 1 mm at the isocenter. The same standards for patient immobilization are used as for photon radiosurgery systems. A number of particle centres doing radiosurgery have developed unique systems to achieve immobilization and position verification during the irradiation procedure.

The proton facility at iThemba LABS in South Africa uses a combination of a fixed horizontal beam combined with a robotic chair controlled by a stereotactic positioning system based on stereophotogrammetric principles [6]. This system allows for both initial patient positioning but also for position monitoring during the actual irradiation time. Other optical tracking systems have been developed for robotic patient couch correction movements for proton therapy [7].The radiosurgical program in Boston, Harvard University, uses a device called “Star” that achieves the required accuracy in immobilization and positioning [8].

RADIOBIOLOGY

1) General Radiobiology of Particle Beams

Two parameters are of importance when discussing the radiobiology of particle beams, one is LET the other RBE. Linear energy transfer, LET, is the function of energy loss per unit

of distance travelled through matter. Particles with a high LET inflict considerable damage along their track through tissue by causing double strand DNA breaks that are difficult to repair by the cell's repair mechanisms. This type of radiation damage show less sensitivity to total dose/fractionation schedules as there is less repair of radiation damage compared to photon irradiation [9].

The relative biological effectiveness (RBE) is a way of comparing radiation modalities in terms of their radiobiological effects on tissue. It is the ratio of biological effectiveness of one type of radiation relative to another for the same amount of absorbed energy. The RBE is an empirical value that varies depending on the type of radiation, energies involved, and which biological effects are under comparison. A radiation modality with a RBE of >1 indicates that this modality is more radiobiologically effective compared to the reference radiation modality. The RBE of particle beams varies for each particle but is always higher than for photons (RBE=1). Protons have the lowest increased RBE which equals 1.1 in the SOBP part, with Carbon ions having the highest RBE of 3 [10].

The RBE of a beam is also not constant along the distance travelled through tissue because as the charged particle loses the last bits of its energy the RBE increases. This is not marked for protons (Max RBE=1.1) but needs to be taken into account in Carbon ion therapy (Max RBE = 3) as the RBE changes significantly along the track and the physical absorbed dose has to be adjusted downward towards the end of the range in order to maintain a constant biological effect across the target volume (figure 9).

RBE has for many years been mainly studied for effects on cell killing and late side effects. However high LET radiation has quite distinct effects on cellular signalling pathways.

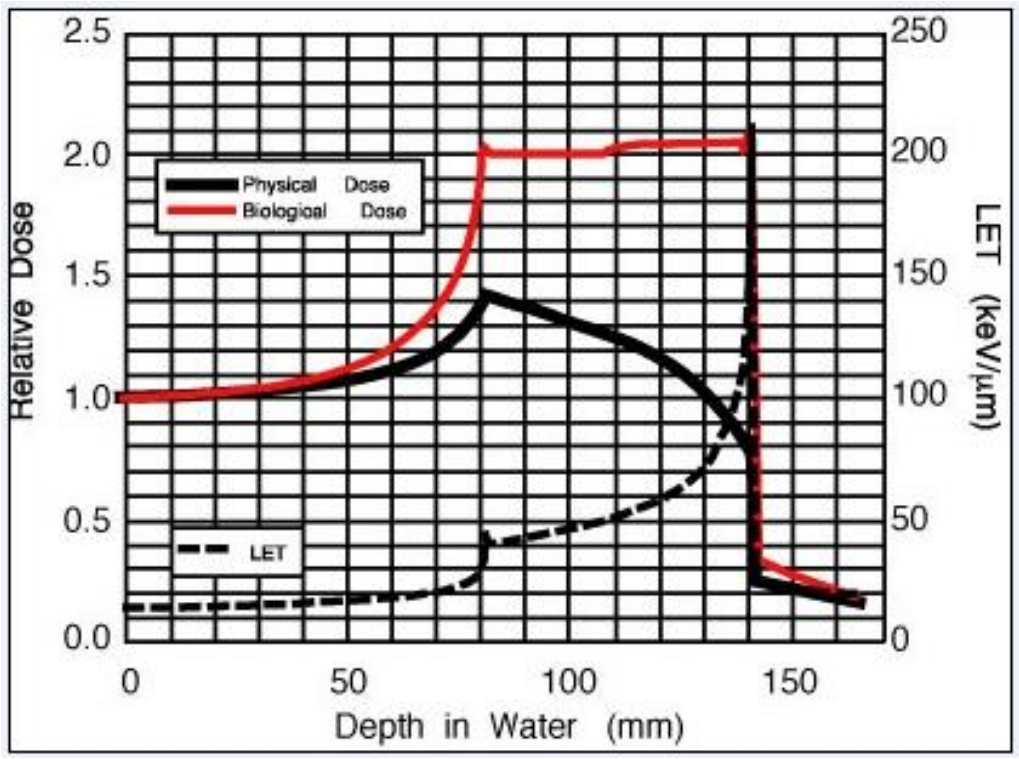

Figure 9. The relative biological effectiveness (RBE) of a beam.

It has become clear that particle radiobiology is not necessarily identical to photon radiobiology and that parameters other than RBE play a role in evaluating the overall biological effect of particle beams [11].

2) Specific Radiobiological Effects Relating to AVMs

Of particular interest for charged particle therapy is that they have specific effects on AVMs. In addition to the favourable general radiobiological effects as described above, charged particles have a specific effect on vasculogenesis, the various cellular components of AVMs and the way they respond to irradiation. Grabham et al. [12] showed that high LET particles are more than four times more effective at disrupting mature vessel tissue models than particles with a low LET. Low LET particles inhibit the early stages of vasculogenesis. High LET particles do not affect this phase but do affect the later stages of endothelial cell migration to form tubes.

The main cellular components of AVMs are endothelial cells and fibroblasts. Their response to stereotactic irradiation is well described and consists basically of an endothelial cell denudation followed by a proliferation of fibroblasts. The magnitude of the denudation influences the fibroblastic response. The proliferation of fibroblasts accounts for luminal narrowing and blood flow disturbances which in turn lead to local thrombosis. If this process is extensive enough it results in complete obliteration of the AVM. There is evidence that AVMs are not necessarily static congenital entities but that they undergo some sort of vascular remodelling based on ongoing angiogenesis [13, 14]. Hence a specific radiobiological effect on both endothelial cells and angiogenesis should incur an additional theoretical therapeutic benefit. Such beneficial effects of particle beams have been described in the literature. For proton beams, Balaiya et al. [15] demonstrated a greater sensitivity of choroidal endothelial cells to proton beam than for the retinal ganglion cells, indicating a therapeutic window for proton beam therapy in the management of age-related macular degeneration. Jang et al. [16] in their work on blood vessel formation in zebra fish embryos demonstrated a significantly increased cell death in human umbilical vein endothelial cells irradiated with protons. Girdhani et al. [17] demonstrated that proton beam irradiation can inhibit expression of pro-angiogenic factors and multiple angiogenesis associated processes including invasion and endothelial cell proliferation. Vascular endothelial growth factor was also significantly down regulated. For Carbon ion beams similar effects have been described. Takahashi Y et al. [18] described a superior suppressive effect on in vitro angiogenesis by Carbon ions compared to photons. Kiyohara et al. [19] used the role of inflammatory cells interaction with endothelial cells as they are considered to play a role in radiation induced late damage. By studying the Intracellular adhesion molecule-1 (ICAM-1) expression on endothelial cells he found that the expression of ICAM-1 by irradiation with Carbon ions was 6.7 fold higher than for non-irradiated cells. For photons this expression was only 2.5 fold higher.

The specific vascular effects have also been studied in carcinomas. In lung carcinoma, Liu et al. [20] demonstrated a significantly suppressed process of angiogenesis in vitro by inhibiting endothelial cell invasion and tube formation. In another study [21] his group demonstrated an inhibition of tumorigenesis and angiogenesis in gliomas with Carbon ion radiation based on a suppression of Vascular Endothelial Growth Factor (VEGF).

These above findings would indicate that there is indeed an additional radiobiological advantage in the use of charged particle beams for AVMs based on the effects on endothelial cells and angiogenesis. The exact interaction of all these factors in the overall process of radiosurgical obliteration remains to be clarified. The physical properties and these particular radiobiological effects makes light-ion beams particularly attractive to treat intracranial AVMs [22] and might also explain the good results achieved with the Helium ion beams for AVMs as reported by Fabrikant [23].

CLINICAL USE

The primary goal of any type of treatment for AVMs is to prevent a hemorrhage, with secondary benefits in terms of reduction or elimination of epilepsy and headaches or other neurological symptoms. The estimated risk of an intracerebral bleed is in the order of 1-5% per year [24- 28]. Intracerebral haemorrhage carries a morbidity risk as high as 80%, with a mortality rate of between 10-30% [26, 28]. Physicians have a number of therapeutic tools at their disposal. These include resection; endovascular embolization; and stereotactic radiosurgery (SRS). The latter can be under the form of photons (Gamma knife, Cyberknife, Linac radiosurgery) or charged particle therapy. Such radiosurgical treatments are done in a single session or more than 1 stage. The various therapeutic tools can also be grouped and given in a short overall time, or can be more spread out over time as sequential treatments or for initial failures. Lastly there is the option of observation in selected cases [27-30].

The goal of SRS, independent of the radiation modality, is to completely obliterate the AVM nidus, while minimising morbidity. There are two caveats to SRS. The first is the risk of hemorrhage during the latency period during which the AVM is not yet completely obliterated. This interval can last up to 4 years. Complete obliteration is amongst others dose dependent [31, 32, 33]. The second is the risk of morbidity to the surrounding normal brain called Adverse Radiation Effects or AREs. Since AREs can be long-term and permanent, they are important parameters in the overall assessment of the therapeutic outcome for the patient, and should always be minimized as much as possible [27, 28].

Based on the above, the observation that all charged particle beams have a physical dose distribution advantage and also for some a radiobiological advantage over photons makes them ideally suited for radiosurgical treatments of AVMs. They have the potential for better obliteration rates based on the possibility to give a higher target dose and for a lower incidence of side effects based on the lower integral dose. The dose distribution advantage has been reported in numerous dose planning studies in which comparisons are made between Intensity Modulated Radiotherapy (IMRT), 3-D conformal radiotherapy, proton beam therapy and intensity modulated proton beam therapy (IMPT) [34-38]. Phillips et al. [39] specifically studied the benefit of charged particles versus Gamma knife and Linac for radiosurgery applications. They studied the effects on Dose Volume Histograms (DVH) and integral doses to the target volume and to normal brain, and demonstrated that charged particle dose distributions were more favourable than those for photon methods. This favourable difference increased with increasing target volume. There was little difference between the various particles (protons, Helium ions, Carbon ions). There were also differences in relation to target shape but these were small. In general what all these dose planning studies have shown is that

particle therapy achieves equally good target dose coverage as for various photon delivery methods but that there is a reduced dose to organs at risk (OAR) and a lower integral dose (figure 10). Proton beams are mainly used for their favourable dose distribution properties seeing that their radiobiological advantage is minimal with an RBE of 1.1 in the SOBP part. There has been a lot of debate on the clinical benefit in oncological situations from this physical dose advantage of protons over photons especially in the light of the high cost of proton facilities. Few prospective comparative clinical results for oncological use have been reported, but a growing number of studies are in progress to elucidate this question.

The use of particle beams for stereotactic radiosurgery falls in a different category. Here one is dealing almost always with histological benign diseases and a normal life expectancy if the disease in question is controlled. This applies also to cerebral AVMs. They occur in eloquent as well as non eloquent areas of the brain, and tend to become clinically manifest mainly in teenagers and young adults.

The brain as an organ is particularly sensitive to the late effects of radiation even more so in children. The basic principal of **ALARA** (**A**s **L**ow **A**s **R**easonably **A**chievable) in radioprotection is one of the cornerstones of minimizing radiation induced side effects. Particle beams are fulfilling this objective very well due to their favourable dose distribution and smaller number of beams required. The demonstrated reduction in integral dose for particle radiosurgery [40] especially with increasing target volumes is a further improvement in adhering to the ALARA principle.

Apart from the effect of radiation on the brain as an organ, reducing the dose to critical parts of the brain close to the target has also been shown to be important. Neurogenic niche sparing during irradiation of paediatric brain tumors lowers the risk of long term neurocognitive sequellae, and this is best achieved by intensity modulated proton therapy [IMPT] [41, 42].

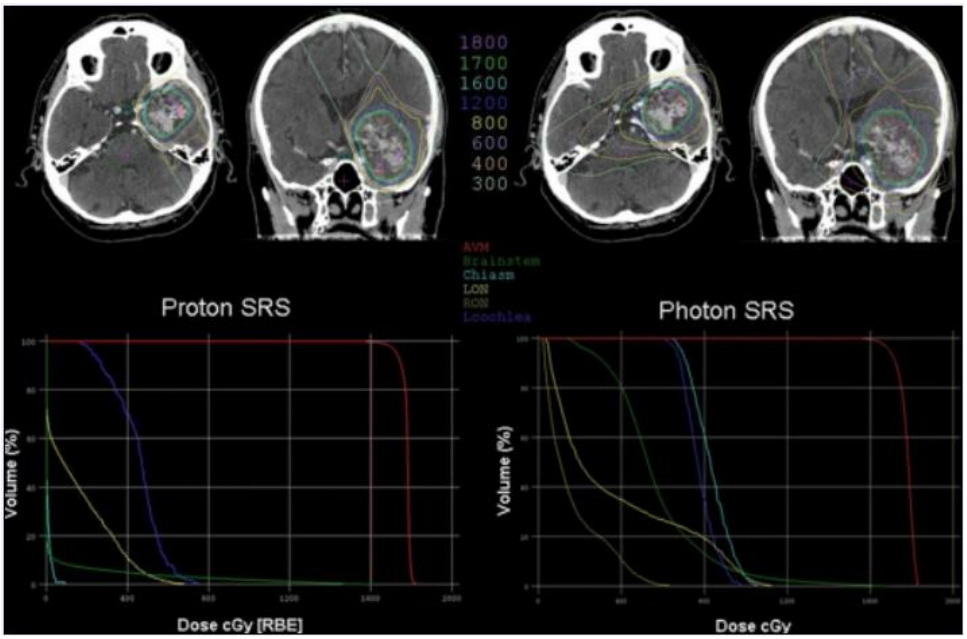

Figure 10. An example dose plan for the treatment of a brain arteriovenous malformation (AVM).

Boehling et al. [34] in comparing various radiation treatments (3dCRT, proton, IMPT, IMRT) in the treatment planning for paediatric craniopharyngiomas found that proton therapy avoided excess integral dose to a variety of normal structures at all dose levels while maintaining equal target coverage. The same benefits as described above should also apply for the irradiation of benign radiosurgical targets. Particle therapy is therefore an ideal method to perform radiosurgery in children and young adults.

Out of the total spectrum of charged particles available for clinical use, Helium ions, Neon ions, and negative pi-mesons have disappeared from the scene due to closure of programs at physics laboratories. The present use of particle beams is heavily influenced by the cost of accelerating and delivering particle beams. Proton beams are the most widely used as they are the "cheapest" to produce. Proton beam facilities are however still markedly more expensive than similar capacity photon facilities. All new particle therapy centres are dedicated cancer treatment centres and the emphasis off their particle therapy program is on the treatment of malignancies.

CLINICAL RESULTS

Negative pi-mesons have not been used for AVM treatments and no published AVM results exist. Although Helium ion beams are no longer in clinical use they warrant mention on the basis of their excellent results for AVM treatments (Table 1).

Steinberg et al. reported the Stanford-Lawrence Berkeley Laboratory Helium experience of 86 AVM patients in which 100% of patients with AVMs smaller than 4 cm^3 obtained complete obliteration. For the entire series, 94% of patients achieved an excellent to good clinical outcome. More impressively was the 70% complete obliteration rate achieved in AVMs larger than 25 cm^3, with 12% of patients developing major neurologic complications [43].

Proton Therapy

Table 1 shows the results from the literature. Early proton experiences revealed low obliteration rates and this did little to encourage AVM proton therapy. Kjellberg et al. reported a 20% complete obliteration rate [44] in the Massachusetts General Hospital series. Seifert et al. reported 15.9% complete obliteration rate of German patients treated in USA [45], with no obliteration in AVMs > 3 cm. Silander et al. reported Uppsala's experience with hypofractionated (2-4 fractions) protons obtaining a 27% obliteration in AVMs < 25 cm^3 and no obliteration in AVMs ≥ 25 cm^3 [46]. Therefore the initial expectation that proton therapy would be the radiosurgical treatment modality of choice for large AVMs did not pan out. These early results should however be seen in the context of the available imaging techniques of those days.

Also no mention was made of dose in the Kjellberg and Seifert series, and Chapman et al. noted that Seifert's "*methods of stereotactic localization and treatment planning are no longer relevant*" [47].

Table 1. Comparison of published series of charged particle radiosurgery series for AVMs

Series (year), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Kjellberg et al. (1983), MGH, USA[44]	74	2-16 years	Protons	7-50 mm beam diameter	NOS	Of 32 patients: Improved 59% Stable 31% Worse 6%	Complete obliteration 20%	8/74 patients (11%): seizures, worsening neurologic deficits
Steinberg et al. (1990), Stanford-Lawrence Berkeley Laboratory, USA[43]	86	Mean 38 months (range 24-72 months)	Helium ions	0.3-70 cc vol treated	Total dose 8.8-34.6 Gy(RBE), mostly single fx, some 2-3 fx	Excellent 58% Good 36%	Complete obliteration 62% 100% < 4 cc (2 cm in diameter) 95% 4-25 cc 70% > 25 cc (3.7 cm in diameter)	10/86 patients (12%) major, including hemiparesis & ataxia 7/86 patients (8%) minor, including visual field deficits, cranial nerve palsies
Seifert et al. (1994), Germany (patients treated in USA)[45]	63	30 months - 12 years	Protons	27% <3 cm 59% 3-6 cm 14% >6 cm	NOS	Improved 44% Stable 27% Worse 29%	Complete obliteration 15.9% (all in AVMs < 3 cm) No obliteration in AVMs > 3 cm	13/63 patients (21%): worsening seizures, neurologic deficits & leukoencephalopathy
Silander et al. (2004), Svedberg Laboratory, Uppsala, Sweden[46]	26	Median 40 months radiological follow-up (range 33-62 months)	Protons	Median vol 13 cc (range 0.3-102 cc)	Hypofractionated 2-4 fx, 20-25 Gy(RBE) total	Improved/stable 54%	Complete obliteration 27% (all in AVMs <25 cc) No obliteration in AVMs ≥ 25 cc	5/26 patients (19%): cerebral edema, resolved with steroids 5/26 patients (19%): transient late effects (headache, paresthesias)
Vernimmen et al. (2005), iThemba LABS, South Africa[48]	64	Median 62 months	Protons	Median vol 16.25 cc (range 1.7-110.6 cc) 70% > 10 cc 41% <14 cc 59% ≥14 cc	Hypofractionated 2-3 fx, Median dose minimum SFE 17.3 Gy Minimum SFE 15.1 Gy(RBE) <14 cc	Excellent to good 49% Fair 2% Stable 34% Worse 9%	Complete obliteration: 67% < 14 cc 43% ≥ 14 cc	15/64 patients (23%): transient late effects, requiring prolonged steroid therapy 4/64 patients (6%): permanent grade 3 or 4 side-effects

Series (year), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
					10.4 Gy(RBE) ≥14 cc			
Ito et al. (2011), University of Tsukuba, Japan[49]	11	Median 138 months	Protons (following embolization)	Mean nidus size 4 cm (range 3-6 cm)	Mean dose 25.3 Gy(RBE)	Excellent 73%	Complete obliteration 82%	1/11 patients (9%): worsening neurologic deficit
Sila et al. (2011), Loma Linda University, USA[50]	29	Minimum 3 years	Protons	Mean vol 6.4 cc (range 1-14.7 cc)	1 or 2 fx to isocenter dose 25 Gy, (marginal dose 20 Gy)	Not reported	Complete obliteration: 100% ≤ 4 cc 55% 4-15 cc	1/29 patients (3%): transient late effect, requiring prolonged steroid therapy 2/29 patients (7%): permanent side-effects
Hattangadi et al. (2012), MGH, USA[53]	59	Median 56.1 months (range 6.6-173 months)	Protons	Median vol 22.9 cc (range 1.5 - 58.1 cc)	Dose prescription 16 Gy(RBE) in 2 fx, to 90% isodose	Not reported	Complete obliteration 15.3%	3/59 patients (5%): controlled seizures, 7/59 patients (12%): grade 1 headaches2/59 patients (3%): minor neurologic changes
Tseytlina et al. (2013), Joint Joint Institute for Nuclear Research Dubna, Russia[51]	56	Median 74 months (range 24-109 months)	Protons	10-24.9 cc 23% ≤ 4.9 cc 32% 5-9.9 cc 30% 10-24.9 cc 14% 25-82 cc	Mean isocenter dose 24.6 Gy(RBE), 70-90% at margin	Not reported	Complete obliteration 50%	4/46 patients (9%): late radiation reactions, resolved with steroids 1/46 patients (2%): grade 4 late side-effect
Hattangadi-Gluth et al. (2014), MGH, USA[52]	248 patients (254 AVMs)	Median 35 months (range 6-198 months)	Protons 6% repeat SRS, median interval 41 months	Median vol 3.5 cc (range 0.1-28.1 cc)	Single fraction, median dose prescription 15 Gy(RBE) to 90% isodose	62% patients presenting with seizures controlled without medication	Complete obliteration: 65% at 35 months	16/248 patients (6%): minor and major neurologic changes 23/248 patients (9%): controlled seizures

Abbreviations: AVM = arteriovenous malformation; Fx = fractions; Gy(RBE) = Gray radiobiologic equivalent; MGH = Massachusetts General Hospital; NOS = not otherwise specified; SFE = single fraction equivalent; SRS = stereotactic radiosurgery; vol = volume.

More recent series, using newer imaging and planning software, have shown an advantage of protons for large AVMs. Vernimmen et al. reported on 64 patients treated with a hypofractionated stereotactic radiotherapy course of 2 to 3 fractions. More than half of this group of patients had an AVM volume of more than 14 cm^3. In this subgroup, 43% of patients achieved complete obliteration. Morbidity was acceptable with 6% of patients demonstrating permanent grade 3 or 4 complications. Excellent to good clinical outcome was achieved in 49% of patients [48].

Very good results, albeit from a small number of patients, were reported by Ito et al. In their group of 11 patients, presenting with a mean nidus size of 4 cm, a complete obliteration rate of 82% was obtained. A combination of proton SRS and embolization was used, whereby all patients had embolization within 2 weeks prior to proton SRS. The mean dose prescribed was 25.3 Gy (RBE) [range 22-27.5 Gy (RBE)] [49]. It is however not possible to determine what the role of each modality is in obtaining this high obliteration rate.

Sila et al. reported the Loma Linda experience of patients with small AVMs (max. 14.7 cm^3) treated with 1 to 2 fractions of protons. The marginal dose was 20 Gy (RBE) and all AVMs $\leq$ 4 cm^3 were completely obliterated. For AVM volumes between 4 and 15 cm^3 a 55% complete obliteration rate was noted. The group as a whole had a 7% permanent complication rate [50].

Similar obliteration rates were seen by Tseytlina et al. who conducted an analysis of 56 patients treated with protons at the Joint Institute for Nuclear Research in Dubna. Overall half of the AVMs achieved complete obliteration, a favourable result considering that 23% of the AVMs had volumes $\leq$ 4.9 cm^3 and that 77% had larger volumes reaching up to 82 cm^3. The mean dose prescribed was 24.6 Gy (RBE) with 70-90% isodose at the margin of the target volume. The incidence of late transient radiation reactions was 9% and one patient (2%) developed a grade 4 complication [51].

Hattangadi-Gluth et al. conducted an extensive study of 248 patients treated at the Massachusetts General Hospital. All patients received a single session SRS to a median dose of 15 Gy (RBE). Although with a relatively short median follow up of 35 months, a complete obliteration rate of 65% was achieved. The median volume of AVMs treated was 3.5 cm^3 with a maximum volume of 28.1 cm^3. It will be interesting to observe if this obliteration rate increases with further follow-up. In terms of the morbidity, 6% of patients developed minor and major neurologic complications and 9% of patients developed seizures but are all controlled with anti-epileptic medication [52]. Hattangadi et al. [53] studied further the outcome of patients with large AVMs. Fifty-nine patients with a median AVM volume of 22.9 cm^3 received hypofractionated stereotactic proton therapy with 16 Gy (RBE) given in 2 fractions. The complete obliteration rate was only 15.3%. This low obliteration rate is not surprising seeing that a single fraction of at least 15 Gy marginal dose is needed for obliteration [27]. The lower dose did correspond with a lower morbidity of 5% of patients developing controlled seizures [53].

Carbon Ion Therapy

No results have been published on the use of Carbon ion therapy for AVMs. Referring to the results of Helium ion beam therapy and taking into account the specific radiobiological

effects of Carbon ion beams, the use of this radiation modality for AVM treatments should be explored.

RADIOSURGERY FOR LARGE AVMS

Comparison of results from the different SRS modalities for large AVMs is complicated by the lack of a standardized volume classification. Table 2 illustrates this. Reviewing the literature discussing " large volume" AVMs a variety of groups was found, ranging from AVM: > 2.5 cm diameter [54], ≥ 9 cm^3 volume [30], > 10 cm^3 volume [55-59], > 3 cm diameter [49, 60, 61, 62], ≥ 14 cm^3 volume [48, 53, 63-66], > 15 cm^3 volume [27, 50], > 4 cm diameter [68, 69], > 25 cm^3 [46, 51], and lastly > 30 cm^3 [70]. Others defined 'extra-large' AVMs as those with a volume > 40 cm^3 [71], while 'giant' AVMs are those having a diameter > 5 cm [72].

With *photon SRS* various treatment combinations have been used to tackle the challenge of treating large AVMs: fractionation, dose staging, volume staging, combined with embolization, and repeat radiosurgery. Table 3 shows the results of such treatment combinations for AVMs with similar definitions of a 'large AVM', but is by no means a reflection on the abundance of data available on photon SRS for AVMs. Fully standard fractionation therapy of 50 Gy given in 2-4 Gy per fraction as an alternative to SRS doses has been abandoned, as it showed significant risks of long-term side-effects with no significant benefit in complete obliteration rates [73, 74].

The complete obliteration rates for Linac and Gamma Knife SRS alone has usually been low: 22% for AVMs ≥ 14 cm^3 [64], 25% for AVMs > 15 cm^3 [58], 33% for AVMs > 2.5 cm [54], improving to 44% for the 'smaller' large AVMs ≥ 10 cm^3 [57]. (Table 3) Favourable results were reported by Engenhart et al. in a large group of 145 Linac SRS patients of which 14% had previous embolization. In a subgroup of patients with AVM volumes 33.5 to 110 cm^3, a 50% complete obliteration was obtained [69].

Combining *embolization and SRS* has also been explored for large AVMs. Blackburn et al. reported this for a group of 21 patients with large AVMs treated at Washington University in St. Louis. Patients had an AVM with mean maximum diameter of ≥ 3 cm, had a mean of 2 embolization procedures each, and 81% of patients obtained a complete obliteration. Since this was a combination approach, the morbidity rates for embolization and SRS were tallied together and were high: 24% demonstrated transient complications and 19% of patients had permanent, albeit minor neurological complications [62].

Combined embolization-SRS remains a debated topic. There is the additional morbidity associated with embolization of between 2 and 7%, and recanalization is known to occur in 12 to 18% of cases [27, 28, 58, 62, 70]. Pre-SRS embolization has been shown to actually reduce the overall obliteration rate [27, 75]. A number of centres have explored an upfront planned *dose staging* technique whereby the entire nidus is treated with a reduced dose per session usually for 2 sessions many months apart. Jaboin et al. reported on 33 patients treated with repeat SRS sessions with a mean interval of 26 months. The median dose for the first treatment was 16 Gy and 14 Gy for the second treatment. A 30% complete obliteration rate was obtained in AVMs > 3 cm [76]. Raza et al. treated 14 patients with a mean dose per treatment of 13 Gy.

Table 2. Published series of comparable SRS treatment modalities for large AVMs

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
AVM ≥ 14 cc								
Steinberg (1990) USA[43]	86	Mean 38 months	Helium ions	0.3-70 cc vol treated	Total dose 8.8-34.6 Gy(RBE), mostly single fx, some 2-3 fx	Excellent 58% Good 36%	Complete obliteration 70% >25cc	12% major complications 8% minor complications
Miyawaki (1999) USA[64]	73	Median 54 months	LINAC	Median vol 8.4 cc	Median minimum dose 16 Gy to 80% isodose	Not reported	Complete obliteration 22% ≥ 14 cc	18% required medical or surgical intervention for treatment related complications 5% developed radiation necrosis requiring surgical resection
Pan (2000) China[58]	240	Median 26 months	Gamma knife	32% > 10 cc	15-18 Gy at margin	67% patients with seizures improved	Complete obliteration 25% > 15 cc	3% transient complications 3% permanent complications
Vernimmen (2005) South Africa[48]	64	Median 62 months	Protons	Median vol 16.25 cc	Hypofractionated 2-3 fx, Median dose minimum SFE 17.3 Gy	Excellent to good 49% Fair 2% Stable 34% Worse 9%	Complete obliteration 43% ≥ 14 cc	23% transient late effects, requiring prolonged steroid therapy 6% permanent grade 3 or 4 complications
Han et al. (2008) South Korea[65]	218	Mean 44 months	Gamma knife Repeat GKS 11%	Median vol 3.4 cc	Median marginal dose 18 Gy	Not reported	Complete obliteration 13% > 14 cc	5% permanent complications

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Yamamoto (2012) Japan[67]	31	Median 99 months	Gamma knife Dose staging, > 36 months interval	Mean vol 16.2 cc (maximum 55.8 cc)	Margin dose 12-16 Gy for 1st session, median 17 Gy for 2nd session	Not reported	Cumulative complete obliteration 76% 22% ≥ 14 cc	6% mild symptomatic side-effects 3% grade 4 complication (secondary to hemorrhage)
AVM > 3 cm diameter								
Jaboin (2005) USA[76]	33	Median 55 months	Gamma knife Repeat GKS mean interval 26 months	61% max diameter > 3cm	1st treatment: median 16 Gy 2nd treatment: median 14 Gy	Not reported	Complete obliteration 30% > 3 cm diameter	6% transient complications
Blackburn (2011) USA[62]	21	Mean 3.6 years	Embolization/ LINAC	Mean max diameter nidus: 4.2 cm (range 3-6cm)	Mean margin dose 17.9 Gy at 50% isodose	Not reported	Complete obliteration 81%	24% transient neurological side-effects (embolization) 19% minor permanent neurologic deficit (combined) 14% minor permanent neurologic deficit (embolization) 5% permanent minor neurological deficit (SRS)
Ito (2011) Japan[49]	11	Median 138 months	Protons (following embolization)	Mean nidus size 4 cm (range 3-6 cm)	Mean dose 25.3 Gy(RBE)	Excellent 73%	Complete obliteration 82%	9% worsening neurologic deficit
AVM mean vol ≥ 25 cc								

Table 2. (Continued)

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Engenhart (1994) Germany[69]	145	Mean 44.5 months	LINAC 28% previous surgery/ Embolization	Median treatment vol 6.1cc	Mean isocenter dose 23.6 Gy	Significantly improved 47% Slightly improved/stable 33%	Complete obliteration 50% 33.5-110 cc	7% transient complications 4% severe late complications
Raza (2007) USA[77]	14	Mean 31 months	LINAC or Gamma knife Repeat SRS, mean interval 41 months	Mean vol 25 cc	Mean 13 Gy per treatment	Not reported	Complete obliteration 36%	14% transient complications
Yang (2009) South Korea[66]	46	Mean 78 months	LINAC and Gamma knife 54% previous embolization 43% repeat SRS, median interval 41 months	Mean vol 29.5 cc (range 14-65 cc)	Mean margin dose 14 Gy for 1st session, median 16 Gy for 2nd session	Not reported	Complete obliteration 38%	0% transient or permanent late complications
Kim (2010) South Korea[70]	44	Median 109 months (range 27-202 months)	Gamma knife Repeat GKS minimum interval 3 years	Mean nidus vol 48.8 cc (range 30.3-109.5 cc)	Mean minimum dose 13.9 Gy	Not reported	Complete obliteration 34%	5% required medical intervention for treatment related complications

Abbreviations: AVM = arteriovenous malformation; Fx = fractions; GKS = Gamma knife session; Gy(RBE) = Gray radiobiologic equivalent; Max = maximum; SFE = single fraction equivalent; SRS = stereotactic radiosurgery; vol = volume.

Table 3. Comparison of published series of Gamma Knife and LINAC radiosurgery series for large AVMs

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Colombo et al. (1994), City Hospital Vicenza, Italy[54]	180	Median 48 months	LINAC	Mean 1.6 cm (range 0.4-4cm)	Mean isocenter dose 28.2 Gy, 70-90% at margin	Not reported	97% < 15 mm diameter 74% 15-25 mm diameter 33% > 25 mm diameter	5/180 patients (3%): transient neurological side-effects 4/180 patients (2%): permanent neurological side-effects
Engenhart et al. (1994), University of Heidelberg, Germany[69]	145	Mean 44.5 months (range 1-9 years)	LINAC 28% previous surgery/ embolization	Median treatment vol 6.1 cc (range 0.38-110 cc) 21% < 1 cc 36% 1-14.2 cc 43% > 14.2 cc	Mean isocenter dose 23.6 Gy	Significantly improved 47% Slightly improved/stable 33%	Complete obliteration 55% 83% 0.4-4.2 cc (< 2 cm in field diameter) 75% 4.2-33.5 cc 50% 33.5-110 cc (> 4 cm in field diameter)	10/138 patients (7%): transient neurological side-effects 6/138 patients (4%): severe late complications
Ellis et al. (1998), University of Florida, USA[57]	108	Not reported	LINAC	32% < 4 cc 26% 4-10 cc 42% ≥ 10 cc	Not reported	Not reported	86% < 4 cc 79% 4-10 cc 44% ≥ 10 cc	Not reported
Miyawaki et al. (1999), UC San Francisco, USA[64]	73	Median 54 months	LINAC	Median vol 8.4 cc 59% ≤14 cc 41% >14 cc	Median minimum dose 16 Gy to 80% isodose	Not reported	Complete obliteration 47% 62% < 14 cc 22% ≥ 14 cc	13/73 patients (18%): required medical or surgical intervention for treatment related complications 4/73 patients (5%): developed radiation necrosis requiring surgical resection
Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Pan et al. (2000), National Yang-Ming and Tam Kang	240	Median 26 months (range 12-73 months)	Gamma knife 14% previous surgery	35% <3 cc 33% 3-10 cc 32% > 10 cc	15-18 Gy at margin	67% patients with seizures improved	Complete obliteration 88% 92% < 3 cc 80% 3-10 cc	7/240 patients (3%): transient neurological side-effects 8/240 patients (3%): permanent neurological side-effects

Table 3. (Continued)

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Universities, Taiwan, China[58]							50% > 10 cc 25% > 15 cc	
Jaboin et al. .(2005), University of Maryland, Baltimore, USA[76]	33	Median 55 months (range 36-137 months)	Gamma knife Repeat GKS, mean interval 26 months Mean SRS sessions: 2 (range 1-3)	61% maximum diameter > 3 cm	1st treatment: median 16 Gy 2nd treatment: median 14 Gy	Not reported	Complete obliteration 35% 30% > 3 cm diameter	2/31 patients (6%): transient late effects
Raza et al. (2007), The John Hopkins Hospital, Baltimore, USA[77]	14	Mean 31 months	LINAC or Gamma knife Repeat SRS Median treatments: 3 mean interval 41 months	Mean vol 25 cc	Mean 13 Gy per treatment	Not reported	Complete obliteration 36%	2/14 patients (14%): transient neurological side-effects
Han et al. (2008), Seoul National University College of Medicine, South Korea[65]	218	Mean 44 months	Gamma knife 11% repeat GKS 1 patient: 3 GKS	Median vol 3.4 cc (range 0.17-35.2 cc)	Median marginal dose 18 Gy	Not reported	Complete obliteration 66% 82% < 4 cc 53% 4-14 cc 13% > 14 cc	5% permanent neurological complications

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Yang et al. (2009), Seoul and Dongguk University College of Medicine, South Korea[66]	46	Mean 78 months	LINAC and Gamma knife 54% previous embolization 43% repeat SRS session: minimum interval 3 years	Mean vol 29.5 cc (range 14-65 cc)	Mean margin dose 14.1 Gy for 1st session, median 16.1 Gy for 2nd session	Not reported	Complete obliteration 38%	No patients experienced transient or permanent late neurological deficits
Kim et al. (2010), Yonsei University Severance Hospital, Seoul, Korea[70]	44	Median 109 months (range 27-202 months)	Gamma knife Repeat GKS, minimum interval 3 years	Mean nidus vol 48.8 cc (range 30.3-109.5 cc)	Mean minimum dose 13.9 Gy	Not reported	Complete obliteration 34%	2/44 patients (5%): required medical intervention for treatment related complications
			Median 2 SRS sessions: (range 1-4)					
Blackburn et al. (2011), Washington University in St. Louis, USA[62]	21	Mean 3.6 years	Embolization /LINAC	Mean max diameter nidus: 4.2 cm (range 3-6 cm) Mean nidus volume: 20.1 cc (range 7.5-60 cc)	Mean margin dose 17.9 Gy at 50% isodose	Not reported	Complete obliteration 81% (13/16 patients)	5/21 patients (24%) transient neurological side-effects (embolization) 4/21 patients (19%) minor permanent neurologic deficit (combined) 3/21 patients (14%) minor permanent neurologic deficit (embolization) 1/21 patients (5%) permanent minor neurological deficit (SRS)

Table 3. (Continued)

Series (year of publication), location	No. of evaluable patients	Follow-up	Treatment modality	Size AVM/ Volume treated	Dose/ fractionation	Clinical outcome	Obliteration rates (%)	Complications
Kano et al. (2012), University of Pittsburg, USA[59]	47	Median 87 months	Gamma knife Volume-staged (2 sessions: interval 3-6 months), followed by repeat SRS in 34% patients 45% previous embolization	Median vol 11.5 cc (range 4-26 cc)	Median margin dose 16 Gy (both stages)	Not reported	Complete obliteration after 2-stage: 36% Complete obliteration after staged & repeat SRS: 56%	6/47 patients (13%): symptomatic ARE
Yamamoto et al. (2012), Tokyo Women's Medical University, Tokyo, Japan[67]	31	Median 99 months	Gamma knife Dose staging technique, > 36 months interval 84% pts – 2nd GKS 6% pts – 3rd GKS	Mean vol 16.2 cc (maximum 55.8 cc) 50% ≥14 cc	Margin dose 12-16 Gy for 1st session, median 17 Gy for 2nd session	Not reported	Cumulative complete obliteration 76% (16/21 patients) 22% ≥ 14 cc	2/31 patients (6%): mild symptomatic side-effects 1/31 patients (3%): grade 4 complication (secondary to hemorrhage)

Abbreviations: ARE = adverse radiation effect; AVM = arteriovenous malformation; GKS = Gamma knife session; Max = maximum; SRS = stereotactic radiosurgery; UC San Francisco = University of California at San Francisco; vol = volume.

The mean interval between SRS sessions was high at 41 months. A 36% complete obliteration rate was achieved, with an AVM hemorrhage occurring in 14% of patients [77].

Kim et al. reported on 44 patients treated with repeat Gamma knife SRS with a minimum interval of 3 years. The mean minimum dose per session was also low at 13.9 Gy. A 34% complete obliteration rate was obtained [70].

Slightly improved obliteration rates of 38% were seen by Yang et al. who followed the same staged treatment protocol as Kim et al. However their AVM volumes were smaller: median AVM volume 29.5 cm^3 (range 14-65 cm^3) compared to Kim et al.'s group with a mean volume of 48.8 cm^3 (range 30.3-109.5 cm^3). In Yang et al. study just over half of the patients also had a previous embolization. Hemorrhage occurred in 17% of patients and no patients experienced transient or permanent late neurological deficits [66]. Yamamoto et al. reported on Gamma knife dose staged SRS in patients with large AVMs. The mean AVM volume was 16.2 cm^3, with a maximum volume of 55.8 cm^3. The interval between the first and second SRS sessions was at least 3 years. The margin dose for the first session varied between 12 and 16 Gy. A higher dose of 17 Gy was possible during the second session due to shrinkage in nidus size after the first SRS session. The overall complete obliteration rate of 76% is impressive, but for the AVMs $\geq$ 14 cm^3 it was only 22%. With the prolonged overall treatment period and hence the prolonged latency period, the haemorrhage rate was high at 23% [67].

An alternative option is the *staged volume* technique, whereby different sub-parts of the nidus volume are each treated to a high dose [27]. The rationale behind the staging technique is to give the normal brain a chance to repair itself and to prevent AREs [27, 28].

Kano et al. reported on 47 patients who received staged volume SRS for a median AVM volume of 11.5 cm^3 (range 4-26 cm^3). Almost half of these patients had previous embolization. Repeat SRS to the remaining nidus volume was also required in 34% of patients after a median interval of 61 months after the initial 2-stage volume procedure. The median margin dose was 16 Gy for all stages of treatment including the repeat SRS. Complete obliteration rate of 36% was obtained for the volume staged SRS and this improved to 56% with the repeat SRS. However 13% of patients sustained symptomatic AREs. In the total group of 47 patients who had the staged treatment as well as those who had repeat additional SRS 13 (28%) post treatment haemorrhages occurred, with a mortality of 61.5% [59].

The improved complete obliteration rates have led to the staged volume approach being advocated in AVM volumes more than 15 cm^3 as stipulated in the International Radiosurgery Association guidelines [78]. Some centres also consider this method if the AVM volume is 10 – 15 cm^3 [27].

The optimum interval between volume stages is unclear and differs between 3-6 months to 3 years [70, 78]. The purpose of the longer time interval is to obtain as much obliteration as possible so that the volume for the second stage is smaller to treat [67].

Because SRS offers only protection against a haemorrhage once complete obliteration has taken place [27], staged treatments with their extended treatment period must be considered a second best approach compared to single stage SRS.

Because of the favourable dose characteristics of charged particle beams as described before, it is more feasible to do particle SRS for "large volume" AVMs in either a single fraction or at least in a hypofractionated (2-3 fractions/1week) manner, thereby avoiding an increased latency period [48-52].

Of note is that although the staged series treated large volumes, they were smaller than those treated by the proton groups [48, 49, 51, 59, 67].

RADIOSURGERY FOR PEDIATRIC AVMS

In this group, the long life expectancy after successful obliteration imparts the risk, albeit small, of the development of radiation induced tumours. It is therefore important to minimize the radiation dose in children. Photon based SRS in this population shows complete obliteration rates of between 34% and 95% [79-85]. For proton SRS there is only one report by Walcott et al. reporting the results of 44 patients younger than 18 years of age. The median follow-up was 52 months and the median target volume was 4.5 cm^3 with the median maximal diameter ranging between 1 and 6 cm. Radiation dose prescribed was 15.5 Gy (RBE) to the 90% isodose. One fraction was given for AVM volumes < 10 cm^3 while larger AVMs and those in eloquent areas were treated in 2 fractions. A 41% complete obliteration rate was found [79].

This obliteration rate fits in the range of results seen with Linac and Gamma-knife radiosurgery. The volumes were however slightly larger than most other pediatric series [80-85].

The advantages of protons over photons in pediatric oncology namely; minimizing the risk of radiation-induced tumours, reducing neurocognitive complications as well as other AREs [79, 86, 87] should make protons beneficial to children needing treatment for their AVMs.

FUTURE DIRECTIONS

A growing number of newly planned facilities are designed to be able to deliver proton as well as Carbon ion beams because of the additional radiobiological advantage of the latter.

By using existing cyclotron and synchrotron technology, but in order to make proton therapy cheaper, a number of small "single room" facilities have been developed by companies such as Mevion^R, IBA^R, and Protom^R and some are already commercially available. ProNova Solutions® is developing a complete proton therapy system employing superconducting technology to reduce the size of the rotating gantry substantially. All these efforts widen the accessibility to proton therapy as these facilities are less expensive than multiple gantry room projects and also take up less space. They are more affordable and easier to integrate into the foot print of existing radiotherapy facilities [88].

In terms of accelerating protons to clinically useful energies other than by cyclotrons and synchrotrons, research is happening with laser plasma acceleration [89] and the Dielectrical Wall Accelerator (DWA) [90], a condensed linear accelerator able to produce a variety of particle beams. Both techniques will allow for a compact machine.

Laser acceleration has the advantage that the laser beam is much easier transported to the treatment vaults as there is no need for heavy focusing magnets along the beam line and heavy radiation protection shielding, resulting in a cheaper facility. Research is also done at modifying the shape of the spot. Single plane magnetically focused narrow proton beams

have an elongated elliptical beam spot. McAuley et al. [91] used Monte Carlo simulations to compare focused beams versus passively scattered collimated beams and demonstrated a 28 to 32% reduction in entrance doses and 26 to 35% smaller integral doses. Such beams may find an application for proton functional radiosurgery and for radiosurgical treatments in and around critical structures. The use of proton mini-beams is also being investigated for radiosurgical purposes. This technique takes advantage of the tissue sparing effects from arrays of parallel thin planes of proton beams of 0.7 mm width and thanks to the spatial fractionation of the dose in the normal tissue higher doses can be deposited in the target volume. With this technique smaller penumbras can be achieved than for Gamma Knife radiosurgery [92]. The same approach with mini beams has also been investigated for Carbon ion beams [93].

Purely experimental is the research on anti-protons [94]. Anti-protons behave in the same way as protons in terms of range in tissue and the formation of a Bragg peak, but when they come to rest they annihilate and give off additional radiation in the SOPB zone which increases the overall dose locally. This increase can be as high as a factor of 4 compared to their counterpart. In terms of their biological effect they are close to Carbon ions, but because of their lower mass they are easier to transport in a beam line than Carbon ions. Their routine clinical production is not yet available however.

CONCLUSION

There is no doubt that SRS, independent of the type of radiation used, is a valuable alternative to surgery in the management of AVMs. Radiosurgery with charged particles has a proven dose distribution advantage over photon irradiation techniques, which becomes greater the larger the target volume gets. Proton SRS has been proven to be effective. Carbon ion therapy has the additional advantages of a higher biological effect, a sharper dose fall-off laterally and distally, and should be investigated for all volume groups and age groups. No results of its use in AVM therapy have been reported yet.

Large AVMs remain a challenge to treat with SRS. For photon SRS the results can be improved by staged dose or staged volume techniques, but at the expense of a higher hemorrhage rate. Single session proton SRS offers equally good results with less morbidity and should be considered as an alternative whenever multi session photon SRS is contemplated. The use of particle SRS should be encouraged in managing AVMs in young people. The number of particle therapy facilities mainly using protons is growing. Their main focus is on treating oncological diseases, but this growing number opens the scope to make proton radiosurgery more and more available.

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