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Review Article

Radiotherapy in the Management of Schwannomas

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Abstract

Schwannomas being benign tumours of the nerve sheath are usually treated with surgery. For intracranial schwannomas, especially acoustic neuromas, the role of stereotactic radiotherapy is well established as a viable alternative. For other sites the role of stereotactic irradiation is less well established, however based on experience in the successful use of dose/fractionation schedules in the management of acoustic neuromas there may be merit in their application to extracranial sites when lesions are deemed irresectable. Given the carcinogenic nature of radiation, care must be applied, when treating benign conditions, where the ultimate goal is to maintain a normal life expectancy. This risk of a secondary malignancy is low and can be further reduced by the use of proton therapy which has a lower integral dose. The increasing number of proton therapy facilities worldwide should allow better access to this advantageous radiation modality.

ABBREVIATIONS

SRS: Stereotactic Radio Surgery; HSRT: Hypofractionated Stereotactic Radiotherapy; FSRT: Fractionated Stereotactic Radiotherapy; LINAC: Linear Accelerators; AN: Acoustic Neuroma; PBS: Pencil Beam Scanning; IMPT: Intensity Modulated Proton Therapy; SOBP: Spread Out Bragg Peak

INTRODUCTION

Schwannomas are benign tumors of the Schwann cells covering the peripheral nerves, and they can occur on any nerve in the body. Most frequently they are managed with surgery. If they grow on the 8th cranial nerve they are commonly called Acoustic Neuromas (vestibular schwannomas) and account for 6-8% of all intracranial neoplasms [1]. Other cranial nerves are less frequently affected [2]. For intracranial locations radiotherapy is an established alternative to microsurgery especially in the management of acoustic neuromas [3-5]. Radiotherapy can be given in a number of ways, either by various dose/fractionation schedules, or by using different radiation modalities such as photons or particle therapy (protons), also called Hadron therapy. When the total radiation dose is given in a single session under stereotactic conditions this is called stereotactic radiosurgery (SRS). The total radiation dose can also be given in a small number of fractions and this is called hypofractionated stereotactic radiotherapy (HSRT), or even in a standard number of fractions (n=25-30) called fractionated stereotactic radiotherapy (FSRT). Both radiation modalities can be used to deliver these fractionation schedules. For intracranial locations radiosurgery is less invasive, more cost effective and causes less cranial nerve damage than microsurgery [4,6]. In terms of radiosurgical modalities, dose comparative studies have demonstrated the superiority of proton over photon radiosurgery [7-10].

RADIATION MODALITIES

Photon therapy

Photon therapy is the most commonly used form of radiation if schwannomas are to be managed by radiotherapy. Figure 1 shows the dose distribution of photons compared to protons. A variety of radiation delivery techniques are available such as Linear accelerators (Linacs), Gamma knife®, and robotic beam delivery systems such as the Cyberknife®. As mentioned above the total dose can be delivered in a variable number of sessions (fractions), although for the Gamma knife traditionally 1 session has been given (SRS).All these photon treatments are given under stereotactic conditions in order to spare normal surrounding tissues.

Proton therapy

Hadron therapy is not new as the first charged particle treatment was done with protons at Berkeley in 1954.The main attraction of proton therapy comes from the specific dose distribution profile called the Bragg peak (Figure 1) which allows for highly conformal radiotherapy as there is a lower entry dose, and no dose distal to the charged particle's range. Normal structures adjacent to the target are thus spared while the target receives a high dose [9,10]. This is ideal for treating tumors in close proximity to critical structures.

Clinical Hadron therapy was initially provided at physics research laboratories like Berkeley, Los Alamos, TRIUMF (Vancouver), PSI (Switzerland), the Harvard Cyclotron

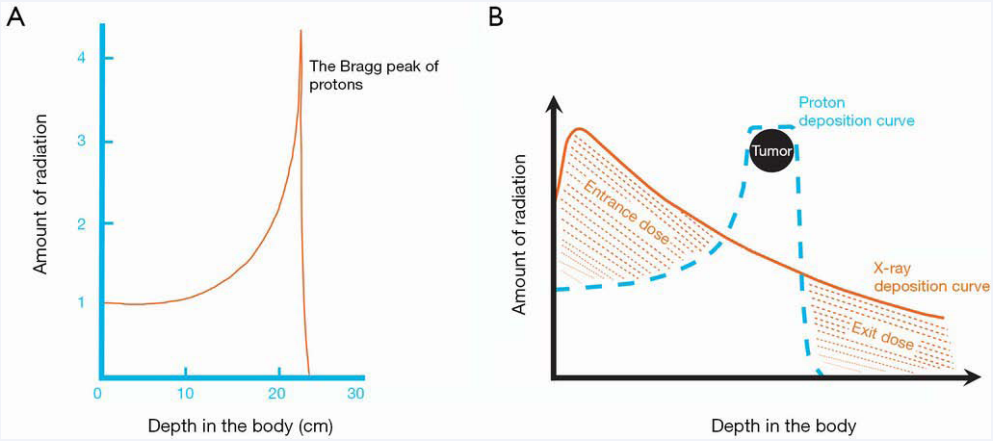

Figure 1 A) Mono energetic single Bragg peak dose absorption in tissue
B) Spread out Bragg Peak (SOBP) to cover a target volume at depth. Photon dose distribution superimposed for comparison
Source: Bragg peak, Picture courtesy of Advanced Oncotherapyc

Laboratories (Boston), and iThemba LABS (Cape Town) [11]. A variety of charged particles such as Helium ions, Neon ions, protons, and negative Pi-mesons were used. The medical use of particle beams at these facilities had limitations in terms of patient logistics and beam time availability, but generated the first series of publications on their clinical use. Over time the spectrum of charged particles has diminished as Helium ions, Neon ions, and negative pi-mesons have disappeared from the scene and only protons and Carbon ions are presently in use. Nowadays particle therapy is provided in dedicated hospital based facilities, and the number of such facilities is growing with the majority of them using protons. Due to high investment costs of particle therapy centres, patient preference, and referral patterns, the emphasis of most of the therapy programs in these facilities is on treating malignancies, with a few centres offering radiosurgery for benign intracranial pathologies.

DISCUSSION

Acoustic neuromas

Although schwannomas can occur on any nerve in the body the vast majority of the literature deals with acoustic neuromas and their management for which good guidelines exist [12]. Most acoustic neuromas (AN) are diagnosed between the ages of 30 and 60, and are these days discovered when they are still small. Various epidemiologic studies have revealed incidences of acoustic neuromas of between 0.7 and 1.74 per 100 000 persons annually [13]. In Denmark, Tos *et al*. [14], described an annual increase in the number of patients diagnosed with acoustic neuroma as well as a decrease in the size of tumors seen over a 5-year period. This is ascribed to a greater awareness among patients and health professionals as well as advances in imaging of acoustic neuromas. There is a vast amount of photon literature reporting on dose, results, and hearing preservation. In contrast there is almost no proton literature on the subject (Table 1). Over time doses required for local control have come down and nowadays 12-13GySRS is recommended. This makes achieving "dose to the target" easy for any radiation modality. Volume and integral dose are therefore not decisive parameters for selecting the form of radiation for small ANs. The radiation side effect profile relates mainly to hearing preservation, but other local structures at risk have been identified, such as the intratemporal facial nerve, the stria vascularis, and the sensory neuroepithelium of the inner ear organs or their ganglia. These structures are related to the development of tinnitus, dizziness, vertigo, and imbalance. For large lesions proton therapy based on its favorable dose characteristics should be of particular value. Phillips *et al*. [9], using dose-volume histograms, showed that charged particles gave a better dose distribution than photons. For protons the integral dose increased from 4.6cm^3.Gy for a 1 cm diameter target volume to 53.5 cm^3.Gy for a 5 cm diameter volume. For photons this increase was from 4.99 cm^3.Gy to 76.6 cm^3.Gy for the same respective diameters. The difference between protons and photons increases with increasing target volumes. Verhey *et al.* [8], found that protons demonstrated a more conformal and homogenous dose distribution than photons, independent of target size. In a companion study Smith *et al.* [7], found that protons gave the lowest complication rate for larger and more peripheral targets. These clinical results were achieved by using passively scattered proton beams. Nowadays most proton centers are using pencil beam scanning (PBS) allowing to deliver intensity modulated proton therapy (IMPT) and this technique can even better spare the normal surrounding structures, especially for increasing target volumes.

Growth control: There is still debate concerning the superiority of surgery versus radiosurgery, with gamma knife and linac radiosurgery giving a better functional outcome than microsurgery [5,15]. Radiosurgery is however associated with less facial and trigeminal nerve neuropathy [5] and is more cost-effective than microsurgery [6]. For large lesions, combining surgery and photon radiosurgery has been suggested [16,17]. For such large lesions and for non-resectable ANs, IMPT on its own could be a valuable alternative although there is no recent IMPT literature on this subject.

Cranial nerves: Cranial nerve preservation becomes a decisive factor in a situation whereby various treatment modalities offer similar long-term disease control. Urie *et al*. [18],

Table 1: Comparison of radiation therapy for acoustic neuromas.

Author	RT modality	Dose prescribed	Fractions (no of patients)	Mean tumor volume (cm^3)	Growth control (%) (years)	Nerve Preservation			Mean follow-up (months)
						Hearing (%) (years)	Facial (%) (years)	Fifth (%) (years)	
Harsh *et al.* [13]	Proton therapy	12 CGyE (margin)	Single (n = 64)	2.49	84 (5yrs)	30	95	91	44
Weber *et al.* [42]	Proton therapy	12 CGyE	Single (n = 88)	(1.4 median)	95 (5 yrs) actuarial CR	79 (2 yrs) 22 (5 yrs)	91 (5 yrs)	89 (5 yrs)	38.7 (median)
Williams [15]	Linac-based	25 Gy	5 fractions (n = 111)	1.4	100	64	100	100	21.6 (median)
		30 Gy	10 fractions (n = 14)	8.1					
Meijer *et al.* [43]	Linac-based	10- 12.5 Gy	Single (n = 49)	2.6	100 (5 yrs)	75 (5 yrs)	93 (5 years)	92 (5 yrs)	33
		20- 25 Gy	5 fractions (n = 80)	2.5	94 (5 yrs)	61 (5 yrs)	97 (5 yrs)	98 (5 yrs)	33
Iwai *et al.* [44]	Gamma knife	12 Gy (margin)	Single (n = 51)	(3.6 median)	92 (5 yrs)	56 (5 yrs)	100 (5 yrs)	96 (5 yrs)	60 (median)
Unger *et al.* [16]	Gamma knife	13 Gy (margin)	Single (n = 86)	(3.4 median)	96	55	98	95	75 (median)
Bush *et al.* [45]	Proton therapy	54- 60 CGyE	30- 33 fractions (n = 30)	4.3	100	31	100	100	34
Fuss *et al.* [22]	IMRT	54 Gy	30 fractions (n = 8)	5.09 (2.48 median)	100	100	100	100	17 (18.5 median)
Lunsford *et al.* [20]	Gamma knife	13 Gy (margin)	Single (n=829}	2.5	97 (10 yrs)	50-77	99	97	120
Flickinger *et al.* [46]	Gamma knife	13 Gy (margin)	Single (n=313)	1.1	98.6 (6 yrs)	78.6 (6 yrs)	100 (6 yrs)	95.6 (6 yrs)	24 (median)
Vernimmen et al. [47]	Proton therapy	21.9 CGyE (margin) (13.5 CGyE single fract. equivalent)	3 fractions (n = 42)	7.0	100 (2yrs) 93 (5yrs)	77 (2yrs) 62 (5 yrs)	91 (2 yrs) 87 (5 yrs)	97 (2 yrs) 91 (5yrs)	66 (62 median)

discovered no relationship between dose and time to developing a cranial nerve injury. Injuries were seen on average at 22 months extending to a maximum of 60 months post radiosurgery (Table 1).

Regis *et al.* [19], and Lunsford *et al.* [20], in their studies of a large number of patients (1000 and 829) with long-term follow-up reported a hearing preservation in the order of 50% to 78%.

Facial and trigeminal nerve: Table 1 shows that the VIIth nerve can be preserved in 91%-100% of patients and the Vth nerve in 89%-100% of patients. Cranial nerve damage generally develops slowly from about 22 to 60 months after therapy [18], with the majority happening in the first 2 years.

Fractionation: When confronted with large lesions and/or to preserve cranial nerve function, fractionation has been used in an attempt to improve the therapeutic ratio [13,16,21]. Outcomes have been similar independent of the fractionation schedule [22-24].

Non-acoustic intracranial schwannomas

Non-acoustic intracranial schwannomas are much rarer and the literature contains mainly reports on small numbers of schwannomas in specific sites, and hence their management is therefore more case by case based [25-29]. However due to the difficulties in obtaining complete resections radiotherapy has also been used for intracranial schwannomas based on the vast experience with AN using the same total dose/fractionation schedules [30-33].

Extra cranial schwannomas

The usual initial management for extracranial schwannomas, mainly brachial and retroperitoneal, is surgery [25,30]. The role of upfront radiation for these locations has been poorly explored but reports are coming out indicating that this could be a viable treatment option. The ideal total dose/fractionation schedule is unknown [34], but based on the acoustic neuroma experience single fraction doses in the order of 12-13 Gy should give equivalent local control. However it is worth noting that acoustic lesions were originally treated with higher doses (16-18 Gy SRS) but these dose levels were abandoned not because of a lack of disease control, but in order to reduce the side effects on the hearing/trigeminal nerve/facial nerve function. For extracranial locations the risk of side effects could be smaller depending on the exact location and hence doses of 16-18 Gy SRS or biological equivalent doses given in a hypofractionated way could be considered.

For extracranial schwannomas that are managed with radiotherapy because of irresectability or patient desire, proton beam IMPT with its advantageous dose distribution would be an ideal modality to maintain the higher target dose levels from the past with fewer side effects on the normal surrounding tissue [35,36]. IMPT with proton arc therapy further improves the dose conformality and offer even better sparing of normal tissue [37]. This benefit could be explored maximally for paraspinal/dumbbell lesions or for retroperitoneal lesions using stereotactic body radiotherapy techniques similar to those used for photon therapy.

Whenever radiation is used to treat a benign condition the risk of secondary malignancies, although low, has to be taken into account [38,39], because local disease control incurs a normal life expectancy. The basic principal of ALARA (As Low as Reasonably Achievable) in radioprotection is one of the corner stones of minimizing radiation induced side effects. The demonstrated reduction in integral dose [13,40,41] and dose to organs at risk (OAR), especially with increasing target volumes, allows particle beams to fulfil the ALARA objective very well.

CONCLUSION

Based on the evidence of efficacy of stereotactic irradiation for acoustic neuromas and to certain extend for other cranial nerve schwannomas it is reasonable to consider the same dose/fractionation schedules for extracranial schwannomas deemed irresectable due to technical factors or patient desires. In such a scenario proton therapy with its advantageous dose distribution and lower risk for side effects and carcinogenesis should be considered as an option. The growing number of proton therapy facilities worldwide increases the availability of this particular option.

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