Proton Therapy in Neurosurgery: A Historical Review and Future Perspective Based on Currently Available New Generation Systems

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ABSTRACT

Purpose: To evaluate of Proton therapy (PT) for neurosurgery patients and is also to explain the need for this system in Iran.
Methods: A literature review was conducted (1984–2016). The strategy included a combination of keywords including proton therapy, neck, neurosurgery, brain, head, tumor, spine, arteriovenous malformation (AVMs), cervical and spine in database of PubMed. New generation PT systems were assessed. Findings are summarized, with a focus on the application of PT in neurosurgery. Finally, the future of PT is discussed.
Results: A total of 1329 citations were screened. In all, 60 articles were included. The synthesis of the data showed two applications of PT in neurosurgery, including: (a) the use in head disease such as AVMs, acromegaly, medulloblastoma, primitive neuroectodermal tumors, papillary tumors of the pineal region, low-grade astrocytoma, head and neck adenoid cystic carcinoma, meningioma, mesenchymal tumors, pediatric cranial tumors, squamous cell carcinoma of the head, craniospinal, and skull base chordomas and chondrosarcomas; (b) the apply in the spinal disease as chordoma or chondrosarcoma of the cervical, sacrum, thoracic and lumbar spine, ependymomas, tumor locations included cervical, thoracic, lumbar, S1-S2, and S3 or below. In addition, the combination of a gantry and cyclotron with new proton therapy systems, results in a lower cost.
Conclusion: PT may be associated with better outcomes for selected patients with malignant diseases of the head and spine. The findings suggest that there exists a need for at least one center to treat the patient demand in Iran.

Keywords: Proton therapy; Neurosurgery; Review; Iran

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INTRODUCTION

Approximately 60% of all cancer patients receive radiation as part of their treatment program. However conventional beams also deliver damaging radiation to healthy tissues surrounding the tumor site [1]. Proton therapy (PT) is one of precise method of radiotherapy such as stereotactic radio surgery that uses a high-energy proton beams for cancer treatment. These protons damage the DNA of cancer cells, ultimately inducing cell death. The observation that energetic protons could be an effective treatment method was made by Robert R. Wilson in 1946. The first treatments were performed with particle accelerators built for physics research in 1957. In 1961, collaborative efforts began to pursue PT. Over the next 52 years, this program refined and expanded these techniques while treating 93,452 patients until January 1, 2013 [2]. PT is used today to treat many cancers and is particularly appropriate in sites where treatment options are limited and conventional radiotherapy presents unacceptable risks to patients. Because PT targets tumors better than traditional treatments, it is ideal for the treatment of tumors that are located near a vital organ. These sites include brain cancers, tumors close to the brain stem or spinal cord, head and neck cancers, eyes, inner ears, prostate cancers, and pediatric cancers. Recent studies have also shown the key impact PT can have on lung tumors, a medical condition that is today poorly treated with conventional radiation therapy. Today there are 39 PT facilities in operation worldwide and 20 more under construction or planned, representing merely 0.8% of all conventional radiotherapy systems. This is now an important tool to treat cancerous tumors [2]. The technology is still advancing, with a number of research groups developing new ways of delivering protons more effectively and economically. By 2017 there will be 255 operational PT treatment rooms [1].

PT is a precise form of radiotherapy which is currently unavailable in the Iran. The aim of this literature review is to evaluate of PT for brain tumors and spinal disease and is also to explain the need for this system in Iran based on cost-effective new generation, and medical excellence.

METHODS

A brief introduction to physics of proton therapy

PT employs a cyclotron; which is a nuclear reactor that can smash atoms to release proton, neutron, and helium ion beams. Protons are accelerated in a cyclotron to a speed equal to approximately half the speed of light. This also determines their energies, between 60 and 250 MeV, and enables them to damage tumors up to a depth of about 30 cm. The protons are then targeted with a strong magnetic field into a very narrow beam - a pencil beam - and transferred with a high degree of accuracy via a 3D image to a target, such as a malignant tumor. The energy is released during deceleration in the tumor tissue with subsequent ionization and damage of the DNA of the affected cell. If the damage is sufficient, the cell stops dividing and growing or dies immediately [3].

Physics of proton therapy compared to photon therapy

Similar to conventional radiotherapy, PT is an external-beam radiation therapy technique. It is one of the most precise modalities of external radiation therapy. Unlike a photon beam which has a high entrance dose and decreases gradually while passing through the body, a proton beam can penetrate through tissues and deposit most of its energy near the end of its track, known as the Bragg peak (Figure 1) [4]. The energy from proton beam is released during deceleration in the tumor tissue with subsequent ionization and damage of the DNA of the affected cell [4]. In clinics, a spread-out Bragg peak (SOBP) field can be generated by using protons of multiple energies [5]. The rationale of using protons is based on the favorable depth–dose distribution, so that the targets can be located on a SOBP while the normal tissue is exposed in the plateau region [6]. Compared to the conventional photon therapy, PT has a much lower entrance dose and no dose beyond the target volume. Because of this unique depth-dose characteristic, proton therapy is able to deliver highly conformal radiation fields to target volumes. Therefore, it is preferred for tumors with irregular shapes and/or around critical structure. Also, because of its much lower integral dose (approximately 60% lower than in photon therapy) [5], PT may provide some advantage for the treatment of pediatric patients, when the probability of secondary tumor caused by radiation dose to the normal tissue is a concern. For these reasons, the number of proton therapy centers is growing rapidly worldwide despite the high capital cost. Several companies are currently developing compact proton treatment equipment, which is expected to greatly reduce the cost of proton therapy. There are currently 37 proton therapy centers in operation and over 25 in development. Worldwide development of proton therapy centers is rapidly increasing to meet patient demand (Figure 2) [7]. In addition, PT was suitable for large-field radiotherapy, compared to traditional radiotherapy based on the relative biological effectiveness (RBE) [8]. PT has become a trusted method for accurately targeting tumors and minimizing damage to healthy tissues, thus having

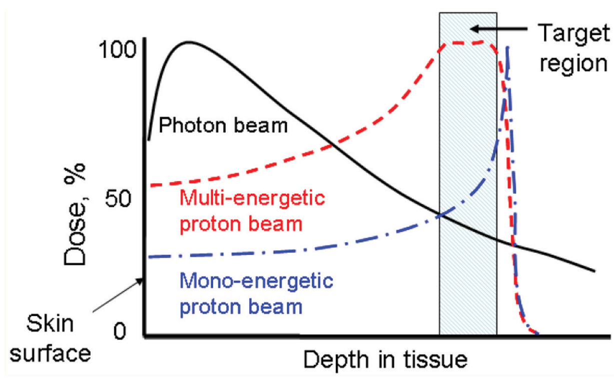

Figure 1. The comparison of dose-depth profiles for photon and proton therapies, which was derived from reference 5.

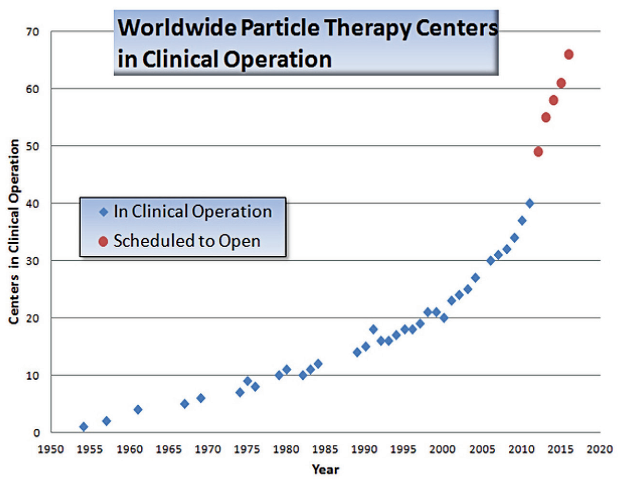

Figure 2. Proton radiotherapy centers in the world, which was derived from reference 7.

a positive impact on reduced side effects and improved quality of life [9].

Search strategy

A literature search was performed using PubMed. The intention was to review all full publications that appeared in the English language biomedical journals. The search strategy included a combination of keywords including proton therapy, neck, neurosurgery, brain, head, spine, arteriovenous malformation (AVMs), tumor, and cervical in titles/abstract of publications. Since the first study of proton therapy in neurosurgery was published in 1984, time interval was set from 1984 to present (2016). The initial search was carried out in early 2013 and updated two times in 2015 (September, and November) and in 2016 (February).

Inclusion and exclusion criteria

All research articles using the PT in neurosurgery were included. Papers were excluded if the topic was about other disease conditions or the manuscript dealt with animal studies.

Data synthesis

The data obtained from each study were synthesized by providing descriptive tables reporting authors' names, publication year, study setting, study sample, disease conditions (where relevant data were available), and the main findings or conclusions. The findings were then sorted and presented chronologically.

RESULTS

Statistics

A total of 1329 citations were identified and screened. Overall, 1269 papers were found irrelevant (other disease conditions or physical assessment). Thus, 60 were included in this review (Figure 3). In general,

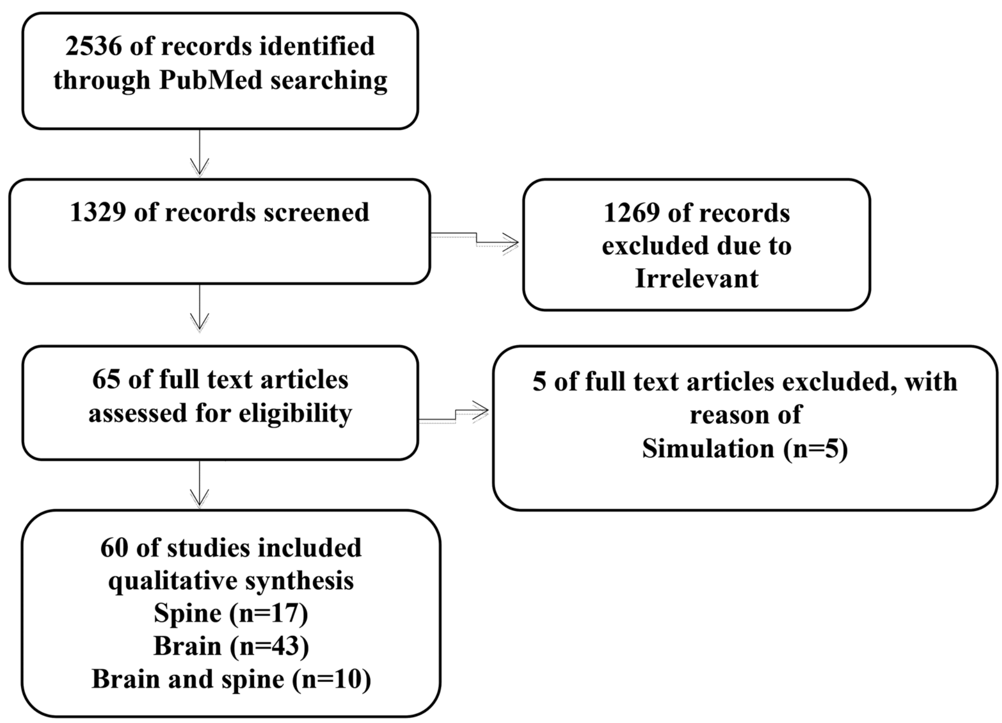

Figure 3. Relevant manuscript selection process.

factors of "Indications of proton therapy", "How many proton therapy systems are needed in Iran?" and "Cost-effectiveness of proton beam therapy new generation" were assessed. In addition the application of PT in neurosurgery can be divided into two major groups: the brain and the spine assessments. The major findings are summarized and presented under the following headings.

Indications for proton therapy

Clinical indications for PT continue to expand. Listed below are currently accepted indications. Indications included: a) Head, neck and spine, as meningiomas, chondrosarcomas, chordomas, isolated brain metastases, acoustic neuromas, anaplastic ependymoma, pituitary tumors and paranasal sinus/nasopharynx; b) Pediatric oncology, as astrocytoma, craniopharyngioma, ependymoma, medulloblastoma, rhabdomyosarcoma, Ewing's sarcoma and Wilm's tumor; c) Prostate; d) Eye and Orbit, as ocular melanomas and subfoveal neovascularization; e) Abdomen; f) Colon and rectum; g) Pancreas and liver h) Extra-Cranial radiosurgery, as non-small cell lung cancer, soft tissue sarcomas, osteosarcoma and Hodgkins disease; i) Breast, as partial breast irradiation and left-side breast.[9]

How many proton therapy systems are needed in Iran?

Sixty percent of cancer patients will receive radiotherapy and 20% of patients are candidates for proton therapy [10]. With more than 74,067 people to be diagnosed with cancer in Iran at 2009, 14,814 of whom will be potential candidates for proton therapy per year. Hence, about 18 treatment rooms are needed (800 patient per system per years) [10]. however, Gamma Knife or stereotactic radiosurgery – both of which are more precise and less toxic also can be considered in Iran.

Cost-effectiveness of new generation proton therapy

New generation PT systems were assessed [9,11]. They combine the gantry and the cyclotron in the new technology PT systems. They maintain the full functionality of today's PT solutions, at a smaller size, weight and power, without sacrificing today's most important clinical capabilities, ultimately leading to a lower cost. Once the cost of proton facilities comes down, the cost of treatment may be similar to Intensity-Modulated Radiation Therapy (IMRT). In addition, a systematic review reported that PT for brain and spine could be cost-effective if appropriate risk groups were chosen as targets for the therapy [12]. Although, clinical results documenting proton radiosurgery to have comparable effectiveness to other modalities have been published, randomized trials have never been conducted.[13] Brief comparisons of PT systems are shown in Table 1[9, 11, 14-21].

Proton therapy for brain tumor

In neurosurgery, PT has been successfully used for treatment of cerebral arteriovenous malformation (AVMs) [22-26], acromegaly [27], recurrent medulloblastoma [28], medulloblastoma [29-34], primitive neuroectodermal tumors [33], papillary tumors of the pineal region [35], progressive or recurrent low-grade astrocytoma [36], head and neck adenoid cystic carcinoma [37-39], benign intracranial meningioma [40], intracranial benign or malignant tumors [41-42], brain tumor [43-44], mesenchymal tumors [45], pediatric cranial tumors [46], squamous cell carcinoma of the head and neck [39, 47-48], head-and-neck cancer [49], craniospinal localized intracranial, or parameningeal [50], skull base and cervical canal primary bony malignancies [51], and skull base chordomas and chondrosarcomas[52-66]. A list of papers on proton therapy used in the brain tumor is shown in Table 2.

Proton therapy of spinal disease

The PT has also been successfully used for the treatment of chordoma and chondrosarcoma of the cervical spine [60-70], chondrosarcoma of the sacrum [66], chordoma of thoracic spine [70], chordoma of the lumbar spine and sacrum [70], chondrosarcoma of thoracic

Table 1. Brief comparisons of different generation technologies of proton therapy.

Manufacturer	Max Energy (MeV)	No. of Units: (Single-room and Multi-room)	Cost	Considerations
IBA (Proteus)	250	39	High	-
Mevion (S250)	250	8	Medium-High	-
Varian (Probeam)	250	8	High	-
Hitachi (Probeat)	250	8	High	-
Misubishi	250	11	High	Ion & Proton Beam
ProNova (SC360)	250	0	Medium-High	Have not been cleared yet by FDA
Elekta	-	-	-	Provides software

*Some other unique systems are developed by different institutions. Specifically, synchrotron-based proton-therapy systems are very high cost.

Table 2. Studies on proton therapy used in the brain disease.

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Weber et al.[52]	2016	Switzerland	Paul Scherrer Institute, Villigen,	77	Skull-base chondrosarcoma (ChSa)	Long-term local control (LC) results, overall survival (OS), and prognostic factors of ChSa of the skull base	NR	Mean follow-up of 69.2 months, 6 local (7.8%) failures were observed, 2 of which were late failures. Five (6.5%) patients died. The actuarial 8-year LC and OS were 89.7% and 93.5%, respectively. This was the largest PT series reported the outcome of patients with low-grade ChSa of the skull base treated with PT only. Our data indicated that protons were both safe and effective. Tumor volume, brainstem/optic apparatus compression, and age were prognosticators of local failures.
Stromberger et al.[47]	2016	Germany	Charité-Universitätsmedizin Berlin	20	Squamous cell carcinoma of the head and neck	To compare intensity-modulated proton therapy (IMPT), helical tomotherapy (HT), and RapidArc therapy (RA) for patients with head and neck cancer.	NR	All methods satisfied modern standards regarding toxicity and excellent target coverage for unilateral and bilateral treatment of head and neck cancer at the planning level.
Munck Af RP et al.[50]	2016	Denmark	Rigshospitalet, Copenhagen	24	Craniospinal (CSI, n = 10), localized intracranial (IC, n = 7), head/neck (HN, n = 4) or parameningeal (PM, n = 3)	Dosimetry, estimated growth hormone deficiency, and neurocognitive dysfunction risks were compared for PT and XT.	To compare proton and photon therapy	PT clearly benefitted the patients studied, except for IC disease where differences between PT and XT were modes.
Eaton et al.[30]	2016	USA	Winship Cancer Institute of Emory University and Massachusetts General Hospital	Proton (n=45), photon (n=43) and overall (n=88)	medulloblastoma.	To compare long-term disease control and overall survival between children treated with proton and photon radiation therapy (RT) for standard-risk medulloblastoma.	To compare proton and photon therapy	Median (range) age was 6 years old at diagnosis (3-21 years) for proton patients versus 8 years (3-19 years) for photon patients. Cohorts were similar. Median follow-up time was 6.2 years for proton patients versus 7.0 years for photon patients. There was no significant difference in RFS or OS between patients treated with proton versus photon RT. Disease control with proton and photon radiation therapy was appeared equivalent for standard risk medulloblastoma.
Bhattasali et al.[37]	2015	USA	Kaiser Permanente Medical Center, Los Angeles	9	Unresectable node-negative, nonmetastatic head and neck adenoid cystic carcinoma (ACC)	To assess clinical outcomes	NR	Median follow-up was 27 months. Four patients achieved complete response at the primary site, and an additional 4 patients achieved stabilization of local disease. Only 1 patient developed local disease progression. The results suggested that proton RT and concurrent chemotherapy was a definitive treatment option for select patients with head and neck ACC
Feuvret et al.[53]	2015	France	Groupe Hospitalier La Pitié-Salpêtrière-Charles Foix	159	Chondrosarcoma of the Skull Base	To assess the effect of the quality of surgery and radiation therapy parameters on local control (LC) and overall survival (OS).	Patients were treated with either protons alone or a combination of protons and photons	Median follow-up was 77 months, 5 tumors relapsed based on the initial gross tumor volume. The 5- and 10-year LC rates were 96.4% and 93.5%, respectively, and the 5- and 10-year OS rates were 94.9% and 87%, respectively. Systematic high-dose postoperative proton therapy for skull base chondrosarcoma was achieved a high LC rate with a low toxicity profile. Maximal safe surgery, followed by high-dose conformal proton therapy, was recommended.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Linton et al.[38]	2015	USA	Indiana University School of Medicine	26	Head and neck adenoid cystic carcinoma.	To report outcomes of proton therapy	NR	Twenty patients (77%) had base of skull involvement; 19 (73%) were treated for initial disease and 7 (27%) for recurrent disease. Median follow-up was 25 months. The 2-year overall survival was 93% for initial disease course and 57% for recurrent disease. Initial outcomes of proton therapy were encouraging.
Barten et al.[49]	2015	Netherlands	VU University Medical Center, De Boelelaan	10	Head-and-neck cancer	To assess organ-at-risk (OAR) sparing and plan robustness for spot-scanning proton planning techniques and compared these with volumetric modulated arc therapy (VMAT) photon plans.	NR	Single-field Optimization (SFO) plans were significantly more robust than Multifield Optimization (MFO) plans. VMAT plans were the most robust. MFO plans had improved OAR sparing but were less robust than SFO and VMAT plans, while SFO plans were more robust than MFO plans but resulted in less OAR sparing. Robustness of the MFO plans did not increase with more fields.
Jakobi et al.[48]	2015	Germany	University Hospital Carl Gustav Carus	45	Head and neck squamous cell carcinoma (HNSCC)	Physical dose distributions were evaluated as well as the resulting normal tissue complication probability (NTCP) values, using modern models for acute mucositis, xerostomia, aspiration, dysphagia, laryngeal edema, and trismus. Patient subgroups were defined based on primary tumor location.	Intensity modulated radiation therapy (IMRT) was compared to intensity modulated proton therapy (IMPT)	Generally, IMPT reduced the NTCP values. Subgroup analyses revealed a higher individual reduction of swallowing-related side effects by IMPT for patients with tumors in the upper head and neck area. Subgrouping could help to identify patients who may benefit more than others from the use of IMPT and, thus, could be a useful tool for a pre-selection of patients in the clinic where there were limited PT resources.
Giantsoudi et al.[31]	2015	USA	Massachusetts General Hospital, Boston, Massachusetts	111	Medulloblastoma.	To assess CNS injury in medulloblastoma patients treated with PT	NR	The 5-year cumulative incidence of CNS injury was 3.6% for any grade and 2.7% for grade 3. Central nervous system and brainstem injury incidence for PT in this series was similar to that reported for PT. The risk of CNS injury was higher for whole posterior fossa boost than for involved field.
Walcott et al.[24]	2014	USA	Massachusetts General Hospital	44	Cerebral arteriovenous malformations (AVMs)	To determine the outcomes of pediatric patients with AVMs	NR	The median target volume was 4.5 ± 5.9 mL (range, 0.3-29.0 mL). Median follow-up was 52 ± 25 months. Median time to obliteration was 49 ± 26 months, including 17 patients who underwent repeat proton radiosurgery. High-risk AVMs can be safely treated with proton radiosurgery in the pediatric population.
Orecchia et al.[66]	2014	Italy	Strada Privata Campeggi	10	Chordoma (of the skull base in three cases, the cervical spine in one case and the sacrum in three cases) and three chondrosarcoma (skull base).	The clinical and technical characteristics of the first ten PT treatments were reported.	NR	Treatment was well tolerated without toxicity-related interruptions. The analysis of the first ten patients treated with proton therapy showed that this treatment was feasible and safe.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Frank et al.[39]	2014	USA	University of Texas MD Anderson Cancer Center	15	Ten patients presented with squamous cell carcinoma (SCC) and 5 with adenoid cystic carcinoma	To report clinical and toxicity of multifield optimization (MFO) intensity modulated proton therapy (IMPT)	NR	All 15 patients were able to complete treatment with MFO-IMPT, with no need for treatment breaks and no hospitalizations. There were no treatment-related deaths, and with a median follow-up time of 28 months. Mucositis within the planning target volumes was seen during the treatment of all patients: grade 1 in 1 patient, grade 2 in 8 patients, and grade 3 in 6 patients. No patient experienced grade 2 or higher anterior oral mucositis. Early clinical outcomes were encouraging
Stokkevåg et al.[34]	2014	Norway.	Haukeland University Hospital, Bergen,	6	Pediatric medulloblastoma	To assess secondary cancer risk following cranio-spinal irradiation (CSI), using either: 1) electrons and photons combined; 2) conformal photons; 3) double-scattering (DS) protons; or 4) intensity-modulated proton therapy (IMPT).	The objective of the study was to compare the secondary cancer risk of these modalities.	Regardless of technique, using protons decreased the estimated risk of secondary cancer following paediatric CSI compared to conventional photon and electron techniques.
Carabe et al.[43]	2013	USA	University of Pennsylvania, Philadelphia	15	Five brain tumors, five prostate tumors and five liver tumors	Clinical consequences of relative biological effectiveness variations in proton radiotherapy	This study showed that the consideration of RBE variations could influence the comparison of proton and photon treatments in clinical trials	The RBE variations were clinically significant in particular for the prostate GTV and the critical structures in the brain
Abela et al.[35]	2013	Switzerland.	University Children's Hospital of Zurich,	1 (3-year-old)	Papillary tumors of the pineal region (PTPR)	Clinical outcomes of surgical resection combined with proton-beam radiation	NR	Recurrent tumor was irradiated with proton radiotherapy. Three months later, the tumor showed near-complete remission.
Tseĭtlina et al.[23]	2013	Russia	Russia	65	Arteriovenous malformation (AVMs) of the brain	To report outcome	NR	The volumes of brain AVMs varied from 0.92 to 82 cc. There was full obliteration in 46.6% of patients with volume of AVM 10-24.9 cc. There was radiation necrosis in one patient, and it was relieved in 12 months after several courses of dehydration and corticosteroid therapy. So, proton beam therapy was effective and safe modality for treatment of inoperable brain AVM, especially of middle- and large size.
Hattangadi et al.[25]	2012	USA	Harvard Radiation Oncology Program	59	High-risk cerebral arteriovenous malformations (AVMs),	To report outcome	NR	Median follow-up was 56.1 months, 9 patients (15%) had total and 20 patients (34%) had partial obliteration. Median time to total obliteration was 62 months. High-risk AVMs can be safely treated with two-fraction, although total obliteration rate is low and patients remain at risk for future hemorrhage.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Nakia et al.[26]	2012	Japan	University of Tsukuba	29	Cerebral arteriovenous malformations (AVMs),	To report outcome	NR	AVMs larger than 2.5 cm were embolized to achieve reduction in size, to enhance the safety of the surgery, and to render the AVM amenable to GK radiosurgery. For larger AVMs located in deep or eloquent areas, PB was offered with/without embolization. Fractionated PT for cerebral AVMs seems to be useful for the treatment of large AVMs, but careful long-term follow up is required to establish the efficacy and safety.
Kuhlthau et al.[44]	2012	USA	Harvard Medical School	142 pediatric patients (age 2 to 18 years)	Brain tumors	quality of life (QoL) of cases treated with proton	NR	Overall reports of QoL during treatment were 74.8 and 78.1 for child self-report and 67.0 and 74.8 for parent proxy report for the core and brain tumor modules, respectively. This study demonstrated that the effect of disease type and intensity of treatment on QoL
Arvold et al.[40]	2012	USA	Harvard Medical School	10	Benign intracranial meningioma	To calculated projected second tumor rates and dose to organs at risk.	Proton therapy better than photon radiotherapy.	Compared with photon radiotherapy, proton therapy for benign intracranial meningioma decreases the risk of RT-associated second tumors by half and delivers significantly lower doses to neurocognitive and critical structures of vision and hearing.
Yasuda et al.[63]	2012	France	Lariboisiere Hospital (AP-HP), Paris,	30	Chordomas of the skull base and cervical spine	Clinical outcomes of surgical resection combined with proton-beam radiation	NR	Permanent neurological morbidity was seen in 3.8%. The mean dose was 68.9 cobalt gray equivalents. The median follow-up was 56.5 months. The 5-year PFS and OS rates were 70% and 83.4%, respectively. The tumor location at the cranio-cervical junction (CCJ) was associated with a lower PFS ($P = 0.007$). The CCJ location was also related to a lower OS ($P = 0.043$). Multimodal surgery and proton therapy thus were improved the chordoma treatment. The CCJ location and a younger age were risks for disease progression.
Moeller et al.[32]	2011	USA	University of Texas MD Anderson Cancer Center, Houston	23 children	Medulloblastoma	Audiometric outcomes of proton-beam radiation	Compared to photons, proton radiotherapy reduces radiation dose to the cochlea for these patients.	Hearing sensitivity significantly declined following radiotherapy across all frequencies analyzed ($P < 0.05$). Rates of high-grade early post-radiation ototoxicity following proton radiotherapy for these patients were low. Preservation of hearing in the audible speech range, as observed here, may improve both quality of life and cognitive functioning for these cases.
Engelsman et al.[64]	2011	USA	Harvard Medical School	Biological modeling	The skull base/ cervical spine chordoma group	The biological effect of treating alternating subsets of fields for different treatment fractions.	NR	For the skull base/cervical spine chordoma group, the largest effect is a 4-Gy increase in the generalized equivalent uniform dose of the chiasm when treating only a subset of fields on any day. The effects of field set of the day treatment delivery were depending on the tumor site and number of fields treated each day.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Habrand et al.[51]	2008	France	Centre de Protonthérapie d'Orsay	13	Skull base and cervical canal primary bony malignancies in children	To evaluate outcomes and tolerance of high-dose photon and proton therapy	High-dose combined fractionated photon-proton therapy.	Twenty-six patients had chordomas (CH), 3 had low-grade chondrosarcomas (CS), and 1 had an aggressive chondroma (AC). The mean age was 12.8 years. The 5-year overall survival/progression-free survival rates for CS and CH were 100%/100% and 81%/77%, respectively. High-dose combined fractionated photon-proton therapy was well tolerated in children and allowed excellent local control with minimal long-term toxicity.
Petit et al.[27]	2007	USA	Massachusetts General Hospital and Harvard Medical School	22	Persistent acromegaly	To evaluate outcomes	NR	Median follow-up was 6.3 years. A response to PT was observed in 21 of 22 patients (95%). No visual complications, seizures, clinical evidence of brain injury, or secondary tumors were noted on regular magnetic resonance imaging scans. These results demonstrate that PT was effective for persistent acromegaly, with 59% of patients attaining normal insulinlike growth factor-I levels without use of any medication after a median of 6.3 years.
Timmermann et al.[29]	2005	Switzerland	Paul Scherrer Institute, Villigen,	1	Recurrent medulloblastoma	To assess the feasibility and the potential advantage of spot-scanning proton therapy for craniospinal irradiation (CSI).	NR	During treatment, grade 1 skin reaction and grade 2 central nervous system toxicity were observed. After 2 months, the boy presented with a transitory fatigue. After 24 months, he was alive and free of disease. Growth hormones and thyroid hormones were reduced. Spot-scanning proton therapy for craniospinal treatment was feasible and safe.
Mu et al.[28]	2005	Sweden.	Umeå University.	5	Medulloblastoma	To explore different spinal irradiation techniques with respect to the risk of late side-effects, particularly radiation-induced cancer.	The radiotherapy techniques compared were conventional photon therapy, intensity modulated x-ray therapy (IMXT), conventional electron therapy, intensity/energy modulated electron therapy (IMET) and proton therapy (IMPT).	This model study showed that spinal irradiation of young children with photon and electron techniques resulted in a substantial risk of radiation-induced secondary cancers. Multiple beam IMXT seemed to be associated with a particularly high risk of secondary cancer induction. To minimize this risk, IMPT should be the treatment of choice. If proton therapy was not available, advanced electron therapy may provide a better alternative.
Noel et al.[41]	2003	France	Centre de Protonthérapie d'Orsay	17	Intracranial benign (6 cases) or malignant (11 cases) tumors	To evaluate clinical results and complications of a combination of proton and photon irradiation	Combined photon-proton therapy.	Mean follow-up was 27 months. Two patients recurred locally (one marginal and one in situ). Fifteen patients are alive and doing well. Overall, 12, 24, and 36-month local control rate was 92 +/- 8% and, 12, 24, and 36-month overall survival rates were 93 +/- 6%, 83 +/- 11%, and 83 +/- 11%, respectively. Proton therapy was well tolerated with an excellent local control rate.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Noel et al.[60]	2003	France	Centre de Protonthérapie d'Orsay	67	Chordoma or chondrosarcoma of the base of the skull and the cervical spine	Analysis of local tumor control, survival and treatment complications	Combined photon-proton therapy.	Median age and follow-up were 52 years and 29 months, respectively. he 3-year local control rates were 71% and 85% for chordomas and chondrosarcomas, respectively, and the 3-year overall survival rates 88% and 75%, respectively. In chordomas and chondrosarcomas of the skull base and cervical spine, combined photon and proton radiation therapy offered excellent chances of cure.
HUG et al.[36]	2002	USA	Loma Linda	27	Progressive or recurrent low-grade astrocytoma	To evaluate the safety and efficacy of proton radiation therapy	NR	At a mean follow-up period of 3.3 years (0.6-6.8 years), 6/27 patients experienced local failure (all located within the irradiated field), and 4/27 patients had died. This report on pediatric low-grade astrocytomas confirmed proton radiation therapy as a safe and efficacious 3-D conformal treatment modality.
Hug et al.[45]	2002	USA	Loma Linda	29	Mesenchymal tumors	To assess treatment efficacy and safety	NR	Local tumor control was maintained in 6 (60%) of 10 patients with chordoma, 3 (100%) of 3 with chondrosarcoma, 4 (100%) of 4 with rhabdomyosarcoma, and 2 (66%) of 3 with other sarcomas. The actuarial 5-year local control and overall survival rate was 72% and 56%, respectively. Proton RT for children with aggressively recurring tumors after major skull base surgery can offer a considerable prospect of tumor control and survival.
Habrand et al.[42]	1999	France	Centre de Protonthérapie d'Orsay	9	Intra-cranial malignancies	To assess treatment efficacy and safety	NR	With a follow-up of seven to 49 months, three patients died (grade 2 to 4 gliomas), one was living with a persistent disease. Four children had treatment-related toxicity (one cataract, two hormonal failures and two seizures). The other children were doing well. In this experience, such rare tumors seemed to behave in children like in adults.
Hug et al.[55]	1999	USA	Loma Linda	58	Chordomas (n= 25) and chondrosarcomas (n=33) of the base of the skull	Local tumor control, patient survival, and treatment failure outcomes were analyzed to assess treatment efficacy	NR	Mean follow up was 33 months. In 10 patients (17%) the treatment failed locally, resulting in local control rates of 92% (23 of 25 patients) for chondrosarcomas and 76% (25 of 33 patients) for chordomas. Tumor volume and brainstem involvement influenced control rates. All tumors with volumes of 25 ml or less remained locally controlled. Actuarial 5-year survival rates were 100% for patients with chondrosarcoma and 79% for patients with chordoma. High-dose proton RT offers excellent chances of lasting tumor control and survival, with acceptable risks.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Santoni Ret al.[56]	1998	USA	Massachusetts General Hospital	96	Chordomas and chondrosarcomas of the base of the skull	To determine the temporal lobe (TL) damage rate	Combined photon-proton therapy.	Of the patients, 10 developed TL damage, with bilateral injury in 2 and unilateral injury in 8. The cumulative TL damage incidence at 2 and 5 years was 7.6 and 13.2%, respectively. Despite the different TL damage rates related to age, tumor volume, number of surgical procedures prior to radiation therapy, and prescribed doses to the tumor, only gender was a significant predictor of damage.
McAllister et al.[46]	1997	USA	Loma Linda	28	Pediatric cranial tumors	To assess treatment efficacy	NR	Median Follow-up was 25 months. Four instances of treatment-related morbidity were identified. Forty-one instances of site-specific, disease-related morbidity were identified: 15 improved or resolved and 26 remained unchanged after treatment. Four patients had radiographic evidence of local failure. Three of these patients, including two with high-grade glioma, have died. Early treatment-related morbidity associated with proton therapy was low.
Miralbell et al.[35]	1997	Switzerland	University Hospital, Geneva	NR	Pediatric medulloblastoma/ primitive neuroectodermal tumors	The dose distribution was evaluated with dose-volume histograms to examine the coverage of the targets as well as the dose to the non-target brain and optical structures	To compare proton and photon therapy	Proton beams succeeded better in reducing the dose to the brain hemispheres and eye than any of the photon plans.
Debus et al.[57]	1997	USA	Massachusetts General Hospital	367	Chordomas (n = 195) and chondrosarcomas (n = 172) of the base of skull	To analyze the long-term incidence of brainstem toxicity in patients treated for skull base tumors with high dose conformal radiotherapy	Combined photon-proton therapy.	Mean follow-up time was 42.5 months. Brainstem toxicity was observed in 17 of 367 patients attributable to treatment, resulting in death of three patients. Actuarial rates of 5 and 10-year high-grade toxicity-free survival were 94 and 88%, respectively. Increased risk of brainstem toxicity was significantly associated with maximum dose to brainstem. Tolerance of brainstem to fractionated radiotherapy appears to be a steep function of tissue volume included in high dose regions rather than the maximum dose of brainstem alone
Benk et al.[61]	1995	USA	Massachusetts General Hospital	18	Base of skull or cervical spine chordomas in pediatric	To evaluate the outcome	Mixed photon and 160 MeV proton beams	The median follow-up was 72 months. The 5-year actuarial survival was 68% and the 5-year disease-free survival was 63%. Chordomas in children behave similarly to those in adults: children can receive the same high-dose irradiation as adults with acceptable morbidity.

Table 2. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Fagundes et al.[62]	1995	USA	Massachusetts General Hospital	204	Chordoma of the base of skull or cervical spine	To determine the patterns of failure and outcome following relapse of chordomas of the base of skull and cervical spine.	NR	Sixty-three of the 204 patients treated (31%) had treatment failure. Among the 63 patients who relapsed, 60 (95%) experienced local recurrence, and in 49 patients (78%), this was the only site of failure. Two of 63 patients (3%) developed regional lymph node relapse and 3 of 63 (5%) developed surgical pathway recurrence (1 left neck, 1 palate and 1 nasal cavity). Thirteen of 204 patients relapsed in distant sites, accounting for 20% (13 of 63) of all patients with recurrence in this series. Local relapse was the predominant type of treatment failure for chordomas of the base of skull and cervical spine.
Austin-Seymour et al.[58]	1990	USA	Massachusetts General Hospital	110	Chordomas or low-grade chondrosarcomas of the base of skull	To evaluate the outcome	NR	Actuarial 5-year local control rate is 82%, and the disease-free survival rate is 76%
Austin-Seymour et al.[59]	1989	USA	Massachusetts General Hospital	68	Chordomas or low-grade chondrosarcomas of the base of skull	To evaluate the outcome	NR	The 5-year actuarial local control rate is 82% and disease-free survival rate is 76%. The incidence of treatment-related morbidity has been acceptable.
Munzenrider et al.[65]	1985	USA	Harvard Medical School	846	Uveal melanomas, and chordomas and chondrosarcomas involving the skull base and cervical spine	To assess proton treatment in general, in major patient categories	NR	Generally, local control rates have been good.

spine [71], spinal sarcoma [72-73], recurrent ependymoma [74], ependymomas [75], leptomeningeal spinal metastases such as medulloblastoma, atypical teratoid/rhabdoid tumor (AT/RT) ependymoma, and primitive neuroectodermal tumour (PNET) [76], primary or locally recurrent thoracic, lumbar, and/or sacral spine/paraspinal chordomas or sarcomas [77]. Tumor locations included cervical, thoracic, lumbar, S1-S2, and S3 or below [78], intracranial and cervical spine [79], and craniospinal [80-83]. A list of papers on PT used in the spinal disease is shown in Table 3.

DISCUSSION

Based on this literature review, PT for brain and spine is safe and can avoid large volumes of normal tissue due to unique characteristics of the beam's distal edge [22-83]. However, the evidence on clinical efficacy of proton therapy in brain and spine disease relies to a large extent on non-controlled studies, and thus is associated with a low level of evidence. Long-term clinical data are forthcoming. The results from the present study suggest that the need for at least one center in Iran to treat the anticipated patient demand.

Most brain tumors are not cured by surgery alone and may require radiation therapy to eradicate the remaining cancer cells. In cases where surgery and radiation are combined, PT can be used with fewer side effects [3]. Tumors of the brain, calvarium, and some base of skull histologies such as chordoma and chondrosarcoma are of special interest to proton therapy as well because required doses are often 70 to 79.2 Gy [84]. In addition, this high dose cannot be delivered with standard radiation therapy due to the proximity of, the brainstem posteriorly, the optic apparatus anteriorly, and the hippocampi and cochleae laterally [84]. Notably, in early studies, local control of PT for the treatment of intracranial or skull base tumors as pituitary gland adenoma, para-CNS sarcomas, osteogenic and chondrogenic tumors, chordomas, and meningiomas was achieved in 71% to 100% of patients. Complications were radiation dose/volume and site dependent, and were mild to severe [85-92]. A systematic review concluded that there was evidence for a benefit of PT over photon approaches in treating chordomas [93]. In addition, a

Table 3. A list of papers on proton therapy used in the spinal disease

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Matsumoto et al.[72]	2015	Japan	Graduate School of Medical Sciences, Kyushu University, Fukuoka	6	Spinal Sarcoma	Carbon ion radiotherapy (CIRT), proton therapy (PT) and intensity-modulated radiotherapy (IMRT) were radiation modalities suitable for treatment of spinal sarcomas.	The objective of the study was to compare the treatment planning of these modalities.	CIRT achieved better homogeneity of dose distribution and coverage of target than PT independently of tumor extent around the spinal cord. In IMRT plans, the spinal cord dose was higher than that under CIRT and PT and coverage of the target deteriorated depending on the tumor extension. CIRT was most appropriate for the treatment of advanced spinal sarcomas.
Hill-Kayser et al.[74]	2015	USA	Perelman School of Medicine at the University of Pennsylvania	1	Recurrent ependymoma	Delivery of craniospinal irradiation (CSI) was a curative approach to recurrent ependymoma, but was associated with risks from re-irradiation, particularly of the brainstem.	NR	Brainstem-sparing CSI that resulted in excellent coverage of the craniospinal axis with minimal radiation to brainstem
Holliday et al.[69]	2015	USA	Anderson Cancer Center	19	Chordoma and chondrosarcoma of the spine	Results of proton radiotherapy	NR	For the entire cohort, 2-year local control, relapse-free survival, and overall survival were 58%, 51.9%, and 93.3%, respectively. Patients referred early for primary adjuvant radiation therapy after surgery had higher rates of disease control than those referred for salvage treatment of recurrent disease. Recurrence rates in this cohort were higher overall than other published series, indicated that even higher radiation doses may be helpful for further improving local control in the presence of gross or recurrent disease.
Stoker et al.[82]	2014	USA	Anderson Cancer Center	10	Craniospinal irradiation	To compare field junction robustness and sparing of organs at risk (OARs) during craniospinal irradiation (CSI) using intensity modulated proton therapy (IMPT) to conventional passively scattered proton. therapy (PSPT).	NR	Field junction robustness along the spine was improved using the staged IMPT planning technique. IMPT lowered maximum spinal cord dose, improved spinal dose homogeneity, and reduced exposure to other OARs. IMPT had the potential to improved CSI plan quality and the homogeneity of intrafractional dose at match lines. The IMPT approach developed may also simplify treatments and reduce workload per patient relative to PSPT.
Delaney et al.[77]	2014	USA	Harvard Medical School	50	Primary or locally recurrent thoracic, lumbar, and/or sacral spine/paraspinal chordomas or sarcomas	Adjuvant radiotherapy (RT) may be recommended but tumor dose may be constrained by spinal cord, nerve, and viscera tolerance.	Prospective clinical study incorporating high dose pre- and/ or post-operative photon/proton RT ± radical resection.	No myelopathies were seen. No late neurologic toxicities noted with radiation doses ≤72.0 GyRBE while three sacral neuropathies appeared after doses of 76.6-77.4 GyRBE. A local control rate with this treatment was high in patients with primary tumors. Late morbidity was appeared to be acceptable.

Table 3. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Delaney et al.[76]	2013	USA	Indiana, Bloomington	22	Leptomeningeal spinal metastases as medulloblastoma, ATRT, ependymoma, and PNET	Particulars of therapy, including, toxicities, and outcomes were reported.	NR	Fifteen (68%) children continued to have local control at last follow-up visit. Median dose was 37.8 Gy (range 21.6-54 Gy). The 12-month overall survival was 68% with grade 1 skin erythema as the most frequent toxicity. Durable response was possible for these children in over two-thirds of cases. Significant toxicity was infrequent using proton radiotherapy and these fractionation schemes.
Chen et al.[78]	2013	USA	Harvard Medical School	24	Tumor locations included cervical, thoracic, lumbar, S1-S2, and S3 or below.	Results of high-dose proton radiotherapy for unresected spinal chordomas.	NR	Median tumor volume was 198.3 cm. Median total dose was 77.4 GyRBE. Analysis at median follow-up of 56 months showed overall survival of 91.7% and 78.1%. Tumor volume more than 500 cm was correlated with worse overall survival. Long-term side effects included 8 sacral insufficiency fractures (none required surgical stabilization), 1 secondary malignancy, 1 foot drop, 1 erectile dysfunction, 1 perineal numbness, 2 worsening urinary/fecal incontinence, and 4 grade-2 rectal bleeding. These results were supported the use of high-dose definitive radiotherapy for patients with medically inoperable or otherwise unresected, mobile spine or sacrococcygeal chordomas.
Yadav et al.[71]	2013	USA	Wisconsin, Madison	1	Chondrosarcoma of thoracic spine	Dosimetric comparison of photon and proton treatment techniques	Tomotherapy plans were comparable to proton plans and produce superior results compared with other photon modalities.	Tomotherapy was an attractive alternative to proton radiotherapy for delivering high doses to lesions in the thoracic spine.
Amsbaugh et al.[75]	2012	USA	Anderson Cancer Center, Houston,	8	Ependymomas of the spine	To assess acute toxicities, and preliminary outcomes	Treatment planning of photon and proton therapy evaluated.	All patients had surgical resection of the tumor before irradiation. Mean radiation dose was 51.1 cobalt gray equivalents. The most common toxicities during treatment were Grade 1 or 2 erythema (75%) and Grade 1 fatigue (38%). PT dramatically reduced dose to all normal tissues anterior to the vertebral bodies in comparison to photon therapy. Preliminary outcomes showed the expected control rates with favorable acute toxicity profiles.
Staab et al.[70]	2011	Switzerland	Paul Scherrer Institute, Villigen,	40	Chordoma of cervical, thoracic, and lumbar spine and sacrum	Clinical outcomes	NR	Mean total dose was 72.5 Gy(RBE).5-year local control rates were 62%, disease-free survival rates were 57%, and overall survival rates were 80%. PT was safe and highly effective in these patients

Table 3. Continued

Author(s) Ref.	Year	Country	Institution	Sample size	Conditions	Main focus	Comparison with other radiotherapy	Results/Conclusion(s)
Knopf et al.[79]	2011	USA	Harvard Medical School	23	Intracranial and cervical spine	An off-line PET and a CT-scan after proton radiotherapy to assess in vivo treatment verification	NR	They showed that intracranial and cervical spine patients can greatly benefit from PET and CT-scan range verification. In addition, patients with arteriovenous malformations or metal implants represent groups that could especially benefit from the approach.
Choi et al.[67]	2010	Korea.	Yonsei University, Seoul	2	Pediatric cervical chordoma	Clinical outcomes of surgical resection combined with proton-beam radiation	NR	The tumors were subtotally removed in an attempt to improve the success of adjuvant proton beam radiotherapy. They reported that postoperative adjuvant radiotherapy as proton radiotherapy should be considered in such cases
Newhauser et al.[80]	2009	USA	University of Texas, Houston	Simulations were used by Monte Carlo method	Craniospinal	Comparing of the risk of developing a second cancer after craniospinal irradiation using photon versus proton radiotherapy	Proton therapies were better than photon therapies	Simulations revealed that proton therapies confer significantly lower risks of second cancers than 6 MV conventional and intensity-modulated photon therapies.
DeLaney et al.[40]	2009	USA	Harvard Medical School	50	Spine sarcomas	Clinical outcomes of high-dose photon/proton radiotherapy in the management of spine sarcomas	NR	5-year actuarial local control, recurrence-free survival, and overall survival were: 78%, 63%, and 87% respectively. Local control with this treatment was high in patients radiated at the time of primary presentation. Sacral nerves receiving 77.12-77.4 Gy RBE were at risk for late toxicity
de Ribaupierre et al.[68]	2007	Switzerland	Lausanne,	1	Pediatric cervical chordoma	Clinical outcomes of surgical resection combined with chemotherapy and proton-beam radiation	NR	The child died, 6 years after diagnosis. They reported that early recognition of this rare entity compared to its more benign differential diagnosis was crucial, and as an aggressive management was needed.
Parodi et al.[83]	2007	USA	Harvard Medical School	9	The clivus (n=2), spine (n=4), sella, orbit, and ocular globe	To investigate the feasibility of positron emission tomography and computed tomography (PET/CT) for treatment verification after proton radiotherapy	NR	This study demonstrated the feasibility of post-radiation PET/CT for in vivo treatment verification. It also indicated some technological and methodological improvements needed for optimal clinical application.
Krejcarek et al.[81]	2007	USA	Harvard Medical School	13	Children craniospinal	To illustrate of the distal edge of the proton beam in craniospinal irradiation	NR	This study showed that evidence for a sharp fall-off in radiation dose and supported the premise that proton radiotherapy spares normal tissues unnecessary irradiation.

GyRBE: proton dose unit, gray relative biological effectiveness; NR: Not reported

systematic review of concluded that PT showed better results in comparison to conventional photon irradiation, resulting in the best long-term (10 years) outcome for skull-based chordomas with relatively few significant complications [94]. The use of PT to treat chondrosarcoma of the skull base after surgery was widely accepted. In a systematic review, reported that studies of PT for skull-based chondrosarcoma resulted in local control ranging from 75% to 99% at 5 years. The authors concluded that PT following surgical resection showed a very high probability of medium- and long-term cure with a relatively low risk of significant complications [95]. Petit et al. showed that proton radiotherapy was effective for acromegaly that was refractory to surgical treatment and medication [27]. Meanwhile, National Comprehensive Cancer Network (NCCN) suggests considering protons over photons for craniospinal irradiation in adults with medulloblastoma [96]. On the other hand, PT plays a key role for re-irradiation of patients with recurrent or progressive head and spine cancer. Recently, McDonald et al., reported a series treated with protons for progressive or recurrent chordoma [97]. Although, the initial results were promising, but additional follow-up was required to assess true rates of late toxicity in these patients.

Radiation therapy has played an important role in the treatment of children diagnosed with malignant tumors; given that around 70% of children with malignancies can now expect to be treated, the late effects of cure have now become a major focus [98]. PT is associated with a decrease in acute and long-term toxicities, as well as lower rates of radiation-induced second malignancies, and potentially less acute and long-term damage to developing organs in pediatric and adolescent patients with cancer [98-100]. Thus, the benefits of PT are potentially the greatest in this population. Although limited, published reports of pediatric and adolescent patients cured with proton beam radiotherapy have mostly addressed tumors arising on or near critical structures, as well as tumors where organs in the exit path of photon radiotherapy present significant secondary malignancy risk or risk of impaired development and function; such tumours as medulloblastomas, gliomas, ependymomas, retinoblastomas, rhabdomyosarcomas, and pelvic sarcomas [98, 101]. Recently, a literature review was conducted to assess clinical outcome of the PT in benign and low-grade pediatric central nervous system tumors such as craniopharyngioma, low-grade glioma and ependymoma. They were reported that treatment with PT was important for cognitive development, endocrine function, and hearing preservation and to reduce the total body dose associated with second malignancy risk [102], however, long-term research results are lacking in this issues, leading to some uncertainty among pediatric specialists with regard to indications and require to refer cases for this limited resource and expensive form of radiation therapy [103].

Radiosurgery of small size (up to 10 cm^3) AVMs using photon emitters (Gamma Knife and linear accelerator) has demonstrated excellent results: complete obliteration in 70–80% cases [104-105]. However, radiosurgery these results diminish as AVM size increases. For AVMs with the volume of more than 15 cm^3, complete obliteration by 40 months can be achieved only in 20–36% cases [22]. However, Tseĭtlina et al. reported that PT was the effective and safe technique for treatment of inoperable brain AVMs, especially those of medium and large size [23]. They showed that irradiation of AVMs with the volume of more than 10 cm^3 with protons has a definite advantage over photon radiation. Meanwhile, Walcott et al. reported that high-risk AVMs can be safely treated with PT in the pediatric population [24], and adolescent patients [25]. Because protons deposit energy more selectively than photons, there is the potential benefit of protons to lower the probability of damage to healthy tissue in the developing brain [15]. Nakai et al. were also reported that fractionated PT can to be useful for the treatment of large cerebral AVMs [26].

Spine tumors are uncommon for patients of all ages. With advances in proton therapy equipment such as intensity modulated proton therapy (IMPT), high-dose proton radiation can be delivered with better precision and prescribed to highly conformal structures. The anatomical juxtaposition of the spine and normal structures that poorly tolerate high doses of radiation make protons a superior option for radiation therapy of spine, especially in children [106]. Orecchia et al. analyzed the first 10 patients with the skull base, the cervical spine, and the sacrum in treated with PT and showed that this treatment was feasible and safe [66]. Amsbaugh et al. showed that the acute toxicities and preliminary outcomes were acceptable for 8 pediatric patients with ependymomas of the spine who treated with PT [75].

The studies above mentioned showed that PT is safe for brain and spine. However, several systematic reviews reported the lack of evidence supporting PT and the need for well-designed prospective studies comparing PT to other forms of radiation therapy [107-110].

Due to increase in cancer treatment, there was concern that conventional PT centers might lack some stable future [111-112]. On the other hand, compared with data for photons, clinical and toxicity data for PBT were incomplete, so, truly assess the cost-effectiveness of PBT was difficult [113-114]. Until now, PT has been limited to only a few institutions, because of the high-cost, large space requirements, and operation complexities of legacy proton therapy systems. Powered by a TriNiobium Core™, new generation system such as the Mevion S250 is a unique proton therapy system that provides the same precise, non-invasive treatment capabilities and advantages of conventional systems but with significantly reduced size, improved reliability, efficient clinical workflow, and lower implementation and operational costs. With a footprint similar to an X-ray radiation therapy device, this system can be easily integrated into any existing radiation therapy department.[11]Rrecently a systematic review was conducted on the cost and cost-effectiveness of proton radiotherapy by Verma et al, They were reported that PT offered promising cost-effectiveness for pediatric brain tumors, and high-risk head/neck cancers [12]. In addition, careful patient selection was absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly [12]. Meanwhile, Vega et al. reported that PT was a cost-effective strategy for the management of pediatric patients with medulloblastoma compared to standard of care photon therapy.[115] Moreover, recent advances in radiation technology such as image guidance and proton therapy have led to a new era of highly precise beams of protons with significantly less exposure to healthy tissues. These developments, along with the promise of molecular classification of tumors and targeted therapies point to an optimistic future for neuro-oncology patients [116]. Future studies must incorporate health economic endpoints to assess the value of proton therapy.

According to some reports, PT is expected to ultimately replace the traditional systems of radiotherapy in the future. The problem with protons has been the cost of building the facility. Once the cost of proton facilities comes down, the cost of cure will may be similar to IMRT. At that point, there will be no doubt what treatment people would chose and that is treatment in the form of the PT [1]. Recently, to quantitatively assess the effectiveness of proton therapy for individual patients, Cheng et al. compared photon and proton treatments on dose metric, toxicity and cost-effectiveness levels with 23 head and neck cancer datasets. They were reported that a) on the toxicity level, proton therapy significantly reduced all toxicities. b) On the dosimetric level, proton therapy significantly lowered doses to the organs at risk. c) On the cost-effectiveness level, they were observed an increase in quality-adjusted life years for all the patients in their proton therapy plans, although it was also significantly more expensive [117]. In addition, protons are an exciting aspect of pediatric radiation therapy especially in head and spine that will ultimately become more available geographically as machine costs decrease [118]. Trends are moving toward emphasizing cost-effectiveness, compactness, ease of use, safety, good mechanical alignment, high reliability, and precise dose delivery. Although, clinical results documenting PT to have comparable effectiveness to other modalities have been published, randomized trials have never been conducted [13].

Nevertheless, there are no current providers of PT in the Iran. As previously mentioned, the PT has suggested interventions for a number of Iranian patients, focusing on pediatric patients and two types of adult cancer in particular: chondrosarcomas and chordomas affecting the base of the skull and the upper part of the spine respectively. In other countries, most notably the USA, many patients with prostate cancer and eye disease have been treated with proton therapy. A limited number of Iranian patients were treated by proton therapy in other countries. However, there are no a list of indications considered appropriate for overseas treatment

Finally, in recent years, the advantage of protons over photons in providing a highly conformal and uniform dose to a tumor has been largely diminished by advances in photon therapies, such as intensity-modulated photon therapy and volumetric arc therapies. However, the relative advantage of the PT in sparing normal tissues has never been more apparent or important; in the United States, approximately 65% of adults and 80% of children survive 5 years after their cancer diagnosis. About half of cancer patients receive radiotherapy as part of their treatment. Recent studies discussed the incidence of treatment-related morbidity, including second cancers, cardiovascular disease, fertility complications, and other late effects, is alarmingly high in long-term survivors of cancer. Presently, about 3% of the US populations are cancer survivors, corresponding to 11 million people, a figure projected to grow to 18 million by 2022. For these reasons, there is increasing interest in exploiting the tissue-sparing capabilities inherent to the PT to reduce the burden of treatment-related complications on patients and the healthcare system [120]. Nonetheless; controversies remain regarding the ultimate role of the PT in radiation oncology. Especially in the last few years discuss seems to focus on cost-effectiveness and cost-competitiveness. Basically, the argument goes, the cost and value of proton therapy has not been proven with evidence of improved patient outcomes, which are presumed to offset some or all of the higher costs of proton therapy systems. If the price differential between proton and photon therapies were to substantially shrink or disappear, e.g. due to economies of scale, many clinics would replace at least some photon treatment units with proton units [119].

This study has several limitations. First, despite the very significant costs involved, proton therapy centers are opening up all over the world. However, is the fact that some public insurance does not pay for particle therapy [120]. Second, yet no clinical trials have been performed to reveal that proton therapy is superior to much less expensive photon therapy [120-121]. Although, it is claimed that such trials are not needed because it is obvious that protons are better. Third, it seems that cost-effectiveness of proton beam therapy is higher than the traditional treatment. However, very little data were available for assessing of the indirect medical costs associated with each form of treatment for brain and spine diseases (i.e. the costs of treating acute and late complications). In the future, these data should be collected prospectively to produce robust cost-effectiveness evidence to improve decision making process.

CONCLUSION

Compared with photon therapy, PT may be associated with better outcomes for patients with malignant diseases. The findings showed that clear need for developing PT services in the Iran in order to expand its access to all patients for whom this treatment has been identified as the most clinically appropriate.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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