ORIGINAL ARTICLE

A Comprehensive Survey of Proton Beam Therapy Research and Development in Iran

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Abstract

Purpose: Proton Beam Therapy (PBT) is an emerging radiotherapy technique using beams of proton to treat cancer. As the first report addressing the topic, the principal aim is to highlight the present status of PBT research and development in Iran as a developing country.

Materials and Methods: To do so, the demand for PBT in Iran and Iran National Ion Therapy Center (IRNitc) was investigated and introduced. Then, Scopus and PubMed were searched for studies that dealt with PBT research in Iran and subsequently 6 major subfields of interest were identified. Furthermore, international collaborations were extracted from the bibliographic data. To combine both research and development sides, a SWOT analysis was performed through collecting viewpoints of 48 radiotherapy experts about PBT, and then strengths, weaknesses, opportunities, and threats of it were examined.

Results: Iran contributes to approximately 1% of global PBT sciences. Proton dose calculation using Monte Carlo simulation is the dominant subject of interest for Iranian researchers. Italy is recognized as the major foreign partner in PBT researches. Clinical advantages over conventional radiotherapy modalities are the main strength of PBT development in Iran while the high installation cost remains the most weakness. Finally, 10 general considerations for the launching of a PBT facility in Iran were presented based upon both Iranian experts' viewpoints and IAEA recommendations.

Conclusion: This research reveals that while PBT research and development in Iran are still in their infancy, there are promising trends in both the research and development sides of PBT.

Keywords: Proton Beam Therapy; Iran; Strengths Weaknesses Opportunities and Threats Analysis; Research and Development.

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1. Introduction

Charged-particle accelerators find a major application in radiation therapy such as Proton Beam Therapy (PBT). PBT is recognized as a unique radiotherapy technique with a promising outcome enabling accurate conformal radiation therapy [1-4]. Compared to photon beams showing a high entrance dose and an exponentially decreasing behavior while passing through the body, proton beams deposit most of the initial energy right before the end of beam range, referred to as Bragg peak and followed by a sharp dose fall-off [5-6]. Because of its interesting physical characteristics, PBT outperforms conventional radiotherapy techniques by exhibiting dosimetric advantages. Particularly, where the tumor site is very close to Organ-At-Risks (OARs) (for example in the case of lung, breast, and prostate cancers) [7-8], PBT shows better tumor covering [9] mostly due to a sharp dose gradient [10-11].

Since the introduction of PBT by Wilson in 1946, the number of PBT centers has rapidly increased and its applications were developed worldwide. Thus far, PBT has been served to tens of thousands of patients with different types of cancer [12]. According to the Particle Therapy Co-Operative Group (PTCOG)'s report in May 2020, there are only 98 in operation and 37 under construction PBT facilities around the world [13]. There is, unfortunately, no in-operation PBT facility in Iran.

This work aims at describing the present status of PBT research and development in Iran that is useful for both the researchers and the decision-makers. To this end, the demand for PBT in Iran, the future PBT facility, and a bibliographic study were investigated. Furthermore, Iranian radiotherapy experts' viewpoints about the opportunities and challenges of PBT in Iran were collected through a questionnaire. Then, 10 general considerations for the launching of a PBT facility in Iran, as a developing country, are presented.

2. Materials and Methods

2.1. Literature Survey

To highlight the status of PBT research in Iran, a comprehensive literature survey was conducted. All full-text records-up to the end of 2019-indexed in both Scopus and/or PubMed, as two world leading indexing databases, having the "proton therapy" or "proton beam therapy", "proton therapy", "proton radiotherapy", "ion therapy", "particle therapy", or "hadron therapy" phrases in their keywords with at least one author affiliated to an Iranian organization were considered, as the inclusion criteria of this literature study. However, some identified articles were excluded because they were either duplicated or irrelevant. Finally, a total of 30 full-text articles fulfilled the inclusion criteria. All identification, screening, eligibility, and inclusion steps were based upon the well-known PRISMA guideline. International networking in PBT research was also derived from the literature survey. International networking has the potential to level up the quality of the researches conducted in Iran.

2.2. A SWOT Analysis

To integrate the results of the research and development sides, a field study was then conducted. For this purpose, a dedicated questionnaire was prepared to identify PBT opportunities and challenges in Iran based upon expert staff's viewpoints. A total of 48 (clinical, academic, or both) radiotherapy experts were asked to fill out the questionnaire for Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis, as a tool combining both research and development sides of the PBT in Iran. The SWOT analysis also makes it possible to identify all aspects of PBT for strategic planning by decision-makers. Of the 48 experts who participated in the survey, 31 held a Ph.D. degree in related fields such as Medical Physics, Medical Radiation Engineering, or related disciplines. Additionally, there were 9 radiation oncologists among them. Furthermore, all participants had at least 5 years of experience in radiation oncology research and/or development. Moreover, the reliability and validity of the SWOT questionnaire were also evaluated by calculating Cronbach's alpha and Kaiser-Mayer-Olkin (KMO) indexes, respectively, using SPSS 25.0.

3. Results

3.1. The Unmet Demand for PBT in Iran

There is an increasing trend for the prevalence of various cancers in developed and developing countries. The growth of the cancer rate is more challenging in low-income countries [14-16]. Based upon World Bank classification, Iran falls in the category of developing countries with low- to middle-income located in the Middle East. Cancer as an uncommendable disease is rapidly growing in Iran. Cancer is now responsible for the majority of death and is known as the third cause of death in Iran after heart disease and accidents [17-20]. Several studies showed both aging, growth of the population, alternations in the people's lifestyle, are affecting the distribution and prevalence of the type of cancer in Iran [19, 21]. Figure 1 shows the percentage of death by cancer site for the top 7 cancers in both sexes in Iran. Based on the World Health Organization (WHO) report in 2018 [16], the number of new cancer cases is 110,115 in both sexes (59,077 and 51,038 males and females, respectively).

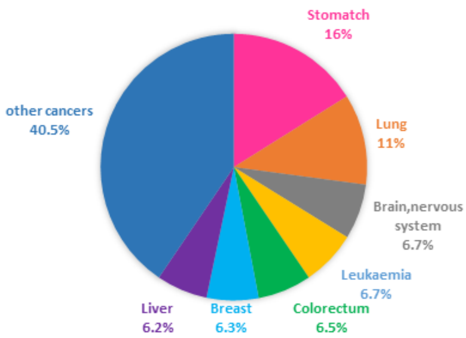

Figure 1. The rate of mortality for top cancer types in Iran in 2018, data taken from [16]

It is evident that cancer is fast growing in Iran and therefore mandates to consider and plan advanced cancer treatment programs. Most of the cancer patients in Iran are eligible to benefit from PBT for cancer treatment or in conjunction with other therapeutic methods, such as chemotherapy or tumor removal surgery [22-23]. Hence, PBT potentially occupies an important niche among the radiotherapy techniques in Iran.

3.2. PBT Development in Iran

3.2.1. PBT Facilities in Iran

There is a report by the Iranian Society of Clinical Oncology in 2018 describing the status of conventional radiotherapy facilities distributed over the country [24] and a similar work for other developing countries [25]. Fortunately, a medical dual-energy linac is also constructed by an Iranian knowledge-based company, Behyar Sanat, addressing a part of national demand [26]. However, the considerable total number of cancer patients mandates to plan for the establishment of new radiotherapy facilities. Hence, PBT potentially plays a key role in such huge demand as an alternative for conventional radiation therapy. Despite the high capabilities and strengths of PBT for cancer treatment, it is currently challenged by a high installation cost. This is the main reason that in comparison with other radiotherapy alternatives there is only a limited number of PBT facilities across the world, and no supply PBT facility in Iran.

Fortunately, Iran National Ion Therapy Center (IRNitc) [27] is a specialized center for ion therapy as an international collaboration between Iran and Austria (MedAustron). The IRNitc facility will be equipped with an 800 MeV proton and 400 MeV/n carbon-ion synchrotron not only for PBT practice, but also for nuclear physics, radiobiology, and high-energy physics researches. The IRNitc is designed to consist of one research and also 3 treatment rooms. The use of a synchrotron (instead of a cyclotron) also enables variable beam energies as well as carbon-ion radiotherapy treatments for a set of cancer types at the IRNitc. The IRNitc is planned to be served for hundreds of patients per year. The IRNitc is under construction in Karaj and it is estimated to be launched in 2023. It is worth noting that due to the unavailability of in-operation PBT machine in the Middle East, the IRNitc can also play a major role in PBT tourism in Iran, as well. In a descriptive-analytical study by Hosseini *et al.* [23], they estimated that at least two particle therapy PBT facilities in Iran are needed (covering northern and southern parts of the country) based upon the number of cancer patients eligible for hadron therapy.

3.3. PBT Research in Iran

3.3.1. A literature Survey

Figure 2 also displays an increasing interest in PBT research in both Iran and the world. As shown in Figure 2, from 2012 a super trend in PBT research is observed in Iran. To speak quantitatively, Iran contributes to approximately 1% of all PBT researches around the world from 2000 to the end of 2019. Referring to Figure 2, the PBT research in Iran started in 2005 with a study on Monte Carlo modeling of PBT. It is evident that due to the lack of a PBT machine in Iran, almost all publications are computer simulation-oriented.

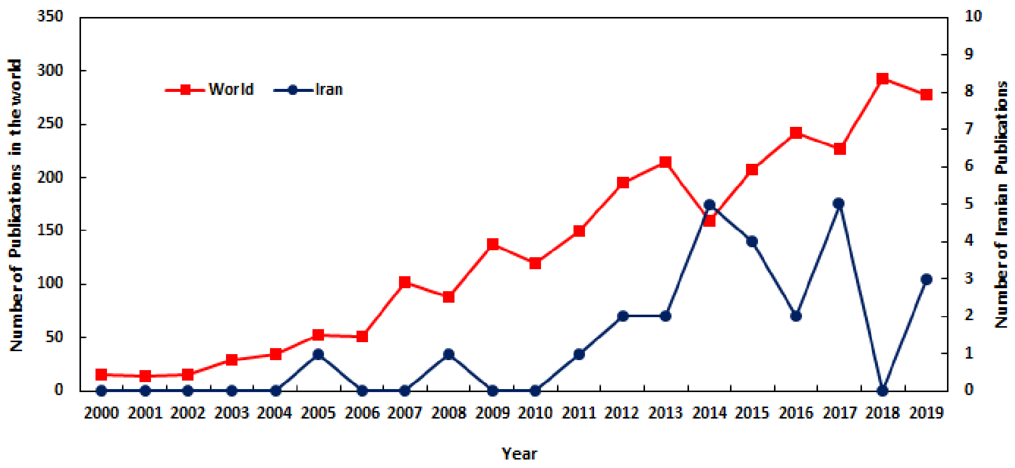

Figure 2. Historic trends of PBT research in Iran and the world as recorded in PubMed and Scopus for the period from 2000-2019

Performing an open-source science mapping tool, VOSviewer [28-29], a science map in PBT research in Iran was obtained (Figure 3), showing more interesting research areas of PBT.

The bibliographic coupling of research areas in PBT is illustrated in Figure 3 via labeled and color-coded circles. The larger the circle, the more interested the field of study. Each color refers to the year of publication of the corresponding article.

Table 1 lists key details of all Scopus- and PubMed-indexed articles fulfilling our inclusion criteria. All articles were then categorized into 6 major subfields of interest as follows:

(1) proton dose calculation, (2) proton range calculation, (3) proton dose enhancement, (4) proton cross-section calculations, (5) secondary particles production, and (6) proton accelerator modeling.

First author, year of publication, main findings, international collaboration, and dedicated simulators used within each article are also presented in Table 1.

In line with Figure 3, Table 1 also indicates that proton dose calculation using Monte Carlo modeling is the dominant research area in the field of interest. It is obvious that because of lacking a PBT machine in Iran, most of the studies are computer simulation-oriented (except those having international collaborations).

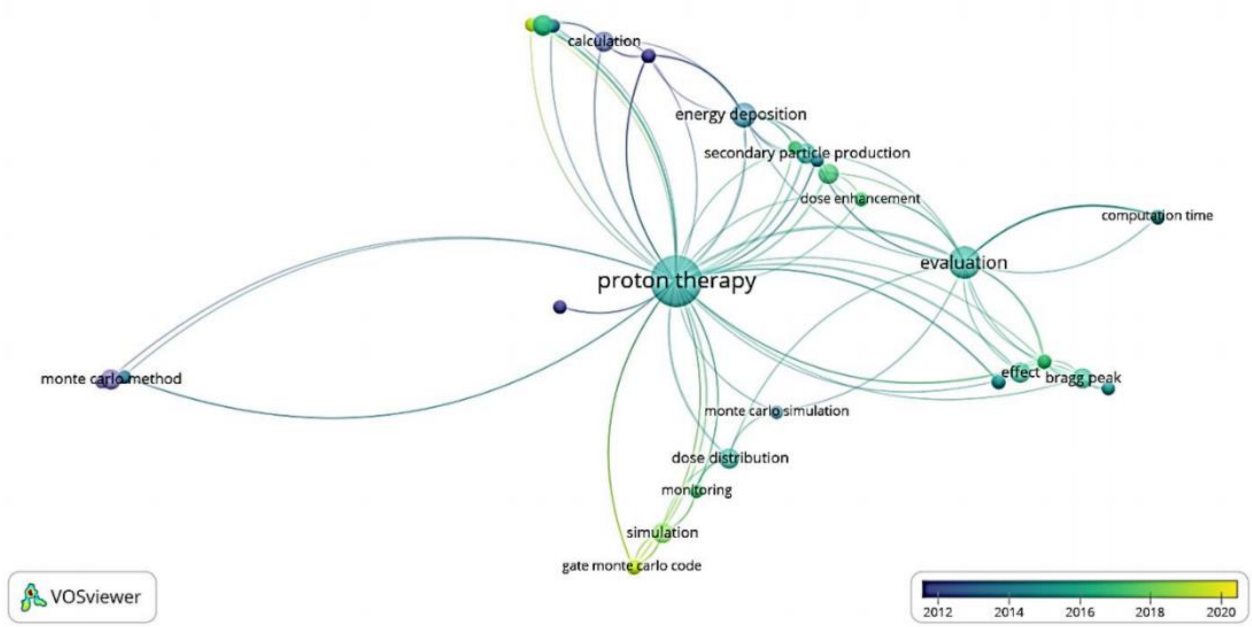

Figure 3. Science map of PBT research in Iran based upon publications indexed in PubMed. The publication years are color-coded

Table 1. Details of all publications in PBT in Iran for the period from 2000 to the end of 2019

Category	First Author	Year of Publications	Main Findings	International Collaboration	Dedicated Simulator(s)
Proton dose Calculation	Bagheri R. [30]	2019	Determination of water equivalent ratio for some dosimetric materials	No	MCNPX
	Rasouli F.S. [31]	2017	Using analytical methods for proton dose calculation	No	-
	Ghorbani. M [32]	2017	Evaluation of the effect of soft tissue composition on dose distribution	Yes	MCNPX
	Jia S.B [33]	2016	Proton dose in passive scattering beam delivery	Yes	GEANT4
	Rasouli F.S [34]	2015	Monte Carlo simulations to simulate a 3D eye model	Yes	-
	Kazemi M [35]	2015	Assessing the advantages of parallelization of Monte Carlo simulations using Message Passing Interface (MPI)	No	GEANT4
	Riazi R. [36]	2015	Literature review	No	-
	Ebrahimi Loushab M. [37]	2015	Impact of Various Beam Parameters on Lateral Scattering	Yes	GEANT4
	Giordanengo. S [38]	2015	Describes the system for the dose delivery system at National Center of Oncological Hadron-therapy (CNAO)	Yes	-
	Rasouli F.S. [39]	2015	Evaluation of the analytical proton dose in compounds and mixtures	Yes	-
	Tavakol M [40]	2014	Calculation of the absorbed dose of the eye and eye tumors	No	-
	Sardari D. [41]	2014	Calculation of dose in proton therapy	No	MCNPX & FLUKA
	Akbari MR [42]	2014	Calculation of water equivalent ratio for different energies	No	FLUKA & SRIM
	Keshazare Sh. [43]	2014	Effects of utilizing an eye media model with ocular media on proton therapy	No	MCNPX
	Jabbari. K [44]	2014	The use of a fast Monte Carlo code for proton transport in radiation therapy	Yes	MCNPX
	Riazi Z. [45]	2012	Simulation of 3D proton dose profile in a homogenous water phantom	No	GEANT4
	Riazi Z. [46]	2011	Introduction of a fast numerical to estimate the proton dose profile inside a water phantom.	No	GEANT4

Category	First Author	Year of Publications	Main Findings	International Collaboration	Dedicated Simulator(s)
Proton range Calculation	Zarifi S. [47]	2019	Bragg peak characteristics of proton beams within the therapeutic energy range	No	GATE
	Zarifi S. [48]	2018	Validation of the GATE Monte Carlo simulation code for various beam energies	No	GATE
Proton dose Enhancement	Malmir S. [49]	2017	Assessment of the dose and its enhancement in a radio-sensitized tumor by Gold Nanoparticles (GNPs)	No	MCNPX
	Malmir S. [50]	2017	Assessment of the pristine Bragg peak and SOBP	No	MCNPX
Proton cross Sections Calculation	Enferadi M. [51]	2017	Calculation of the excitation functions of proton-induced reactions with some relevant materials	Yes	INCL++, TALYS, EMPIRE, & ALICE/ASH
	Mashayekhi.M. [52]	2016	evaluate the positron emitter productions and the actual annihilation points of positrons	Yes	GEANT4
	Jia, S.B [53]	2014	Secondary particles production	No	MCNPX
	Mowlavi, A. [54]	2011	Calculation of the photon and neutron production spectra	Yes	MCNPX
	Noshad H. [55]	2005	Calculation of the proton nuclear cross sections	No	TRIM
Proton Accelerator Modeling	Cirrone G.A.P.[56]	2013	A new hadron therapy concept based on laser driven ion beams	Yes	-
	Giordanengo, S. [57]	2013	Design and characterization of the beam monitor detectors	Yes	-
	Ansarinejad A. [58]	2012	Preliminary characterization tests of detectors of on-line monitor systems	Yes	-
	Hosseinzadeh, M [59]	2008	Modeling a compact model of synchrotron accelerator facility	No	AGILE & MADX

In computer simulation-based works, MCNPX and GEANT4 are the most frequent toolkits. However, a dedicated simulation platform, GATE (based upon GEANT4 package), has been recently introduced for hadron therapy researches for both scattering and scanning proton beam deliveries. It is clear that PBT research is in its infancy in Iran and further works are required to be a mature radiotherapy modality in Iran.

3.3.2. International Networking

Even with few Iranian publications in PBT, notable international networking was observed. Of the total 30 Scopus and PubMed-indexed publications, 17 (i.e., 56%) were in close international collaboration. This study identified three foreign countries having close collaboration with Iran in PBT research, including Italy, the United States, and the Czech Republic

(Figure 4). As seen in Figure 4, Italy stands at the top of the foreign partners' list.

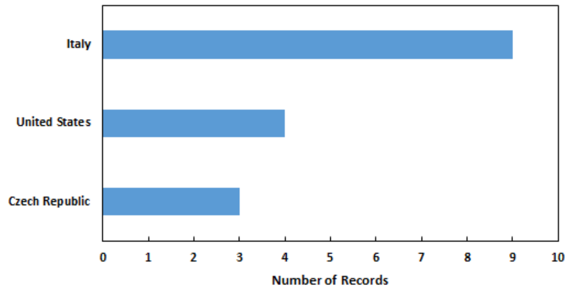

Figure 4. Ranking of active international partners in PBT research in Iran

3.4. A SWOT Analysis

The Cronbach's alpha and KMO indexes of the SWOT questionnaire are 0.87 and 0.81, respectively, indicating a reliable and valid field study. The KMO index is a measure of sampling adequacy of the field study. Similarly, Cronbach's alpha index refers to the internal consistency of the field study. For both, an index of unity is desirable. Table 2, is a description of the SWOT analysis of the current PBT status in Iran. For each 4 SWOT elements, i.e., strengths, weaknesses, opportunities, and threats, five items are listed in order of preference. Considering the limitations listed in Table 2, almost all participants (>90%) agreed to a resultant positive opinion on PBT in Iran. However, being not well-distributed conventional radiotherapy facilities and also the high installation cost remain the two main challenges of a PBT facility in Iran.

Figure 5 summarizes both the research and development sides of PBT in Iran. As indicated in Figure 5, developments in PBT are divided into 2 subbranches: electron and proton accelerators. Although not directly relevant, the experiences in the construction of linacs can be considered as a baseline in PBT. Based on the findings highlighted in the previous section, the research side is also categorized into 6 major subfields of interest, as well.

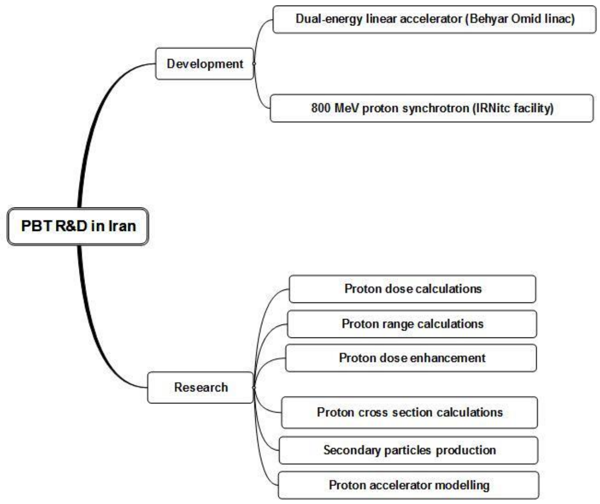

Figure 5. Summary of PBT research and development in Iran

Table 2. SWOT analysis of PBT status in Iran based upon 48 radiotherapy expert's viewpoints

Strengths	Weaknesses	Opportunities	Threats
Clinical advantages in radiotherapy outcome	High installation cost and no insurance coverage	Private/governmental investment	Poor-distribution of current conventional radiotherapy machines
Availability of the IRNitc facility (soon)	Unavailability of after-sales machine services	PBT tourism	Insufficient cancer patient awareness of PBT benefits
Enough internal demand	Lack of enough PBT staff and experts	International corporations (both scientific and financial)	Lack of international finance
Sufficiency of radiotherapy staff and experts	Not applicable to all of the cancer types	IAEA* technical supports	Robust radiotherapy alternatives
The abundance of interest due to the promising outcome of PBT	Complex treatment planning	Experience in electron accelerator design and development	Premature research and development

* International Atomic Energy Agency (IAEA)

3.5. General Considerations for the Launching of a PBT Facility in Iran

As there is no in-operation PBT facility in Iran, it is mandatory to collect and analyze general considerations for the launching of a PBT facility in Iran, as a developing country. Here, 10 key considerations based on both Iranian radiotherapy experts' viewpoints (the SWOT analysis) and IAEA recommendations [60] for the establishment of PBT in Iran are presented:

1. Prior to the establishment of a PBT facility, a more uniform distribution of standard radiotherapy equipment/facilities (with modern linacs) thorough the country has to be followed to make the installation of a proton therapy machine more justifiable.
2. It is recommended that a PBT project should be recognized and shared with 'all' related national investors.
3. It is suggested all related investors and national regulatory authorities with essential management skills should be involved in the beginning step of a PBT project.
4. Availability of major groups such as radiation oncologists, medical physicists, health administrators with multidisciplinary skills, and special experience is necessary.
5. A comprehensive study is recommended before starting a new PBT project (including cancer epidemiology and indications, access issues, connections to an oncology hospital and scientific and specialized society).
6. Prior expertise in conventional radiotherapy (for example Intensity Modulated Radiation Therapy (IMRT)) is mandatory before establishing a new PBT center, as an advanced radiotherapy center.
7. It is strongly recommended training all particle therapy staff, including radiation oncologists, medical physicists, radiobiologists, and radiotherapy nurses. Furthermore, distance learning (e-learning), communication, and practical fellowships are all essential and must be completed with in-house training.
8. It is recommended that all PBT providers, including companies, distributors, and agents consider different training courses regarding the PBT.
9. For developing countries, compact particle accelerators (cyclotrons and synchrotron) are preferred owing to their lower cost.

Finally, whereas in Low and Middle Income Countries (LMICs) the radiotherapy utilization rate will be higher, the number of treatment courses per machine will be higher and the re-treatment rate will be lower, as well. Therefore, it can be predicted that the number of radiotherapy machines should increase to meet the needs of patients.

4. Conclusion

Unfortunately, there is no in-operation PBT facility in Iran despite a large number of cancer patients. This study presents, for the first time, an overview of PBT research and development in Iran which are continuously maturing as high technology radiotherapy modality. Based on this study, there is an acceptable background in particle accelerators (linacs, cyclotrons, and synchrotrons) design and construction in Iran. Since accelerating proton beams towards the therapeutic energy range (up to 250 MeV for protons) is more challenging than electron beams due to their higher rest masses, proton synchrotrons design and construction mandate more technological advances, for example in designing high-power Radio Frequency (RF) cavities. The final cost of a PBT facility remains the main concern. However, emerging technologies such as laser-plasma and linear proton accelerators enable a potentially substantial cost reduction.

PBT machines are not well-distributed around the world and more especially in the Middle East and Central Asia. Referring to the results of the SWOT analysis, cancer patients coming from Iran's neighbors can be potentially served by Iranian PBT facilities the so-called PBT tourism. To be of high quality, this study focused only on full-text articles indexed in both Scopus and PubMed databases. It is important to note, however, there are a number of Persian language PBT researches, including post-graduate thesis/dissertations, and also non-indexed local journals that were not included in this study.

In conclusion, this study is an attempt to draw the science and technology maps of PBT in Iran which is worthy for researchers as well as the decision-makers. Given the increasing demand for PBT facilities, a more uniform distribution of standard radiotherapy machine (modern linacs) is expected to make the installation of PBT facility more justifiable. Recent technological advances in particle accelerators design and development, construction of the IRNitc in near future, considerable unmet demand (local patients and PBT tourists), IAEA supports, and decision-makers interest, offer and then ensure a bright future for PBT in Iran despite the current challenges ahead.

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