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REVIEW ARTICLE

Proton Therapy: Malaysian Perspective

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ABSTRACT

Proton therapy is an advanced type of radiotherapy and the use of charged particle proton instead of high energy X-rays to treat cancer has been increasing in recent years, as it offers superior dose distribution and more effectively spares healthy tissues compared to conventional radiotherapy. Proton therapy has potential clinical advantages for some types of tumours that are difficult to treat by conventional radiotherapy, it also has the added benefits of no exit dose beyond tumour. Many countries that established cancer treatment facilities in the last decade chose proton therapy because of its lower capital cost and higher cost-effectiveness compared to carbon ions therapy. This review first describes the physical characteristics of proton beam for radiotherapy, followed by potential clinical benefits of proton beam therapy in Malaysia. The paper also discusses the challenges of implementing the first proton centre in Malaysia.

Keywords: Charged particle therapy, Proton therapy, Radiotherapy, Cancer treatment

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INTRODUCTION

Charged particle therapy is an advanced technique that uses positively charged subatomic particles (i.e., protons) to kill cancerous tumours. Due to the natural properties of charged particles, protons offer better conformality to the tumour target, superior dose distribution, and better ability to spare healthy tissues compared to conventional radiotherapy. Proton therapy deposits the major part of protons' energy at the end of their range (i.e., at the Bragg peak), which provides a greater dose to the tumour in the meantime minimal the residual doses to nearby healthy tissues. For this reason, proton beams are particularly suitable for treating cancerous tumours situated near to the organs at risk (e.g., spinal cord, central nervous system, optic nerve).

Over the last decade, many proton centres have been set up throughout the world. Most of these centres use only protons, although some combine proton and carbon ion beam. Currently, most countries, including the United States, offer only proton beam beams (1). However, carbon ion beams are currently available in Japan, Germany and China.

The advantages of proton beams over conventional radiotherapy have been well established for some types of cancers, including paediatric cancers, uveal melanoma, head and neck cancer and others (2-7). However, almost all clinical studies of proton therapy are conducted in Western countries and Japan instead of Southeast Asian countries, and the cancer incidence patterns in these countries may differ from those of Southeast Asian countries and Malaysia. Therefore, the potential clinical benefits of proton therapy described in this review are based on the latest published Malaysia National Cancer Registry Report, 2012-2016 (8) and the Malaysia Study on Cancer Survival, 2018 (9).

Cost-effectiveness of proton therapy is another major issue that must be considered (10-11). The investment cost of setting up a proton centre and cost per treatment of proton beams are higher than those of conventional radiation therapy, thus most existing proton centres are located in high-income or developed countries. Over the last decade, although the capital costs to establish proton centres have been reduced with the development of compact, single-room proton centres, but still, the cost of a facility is at least US$ 20 million, and the cost of a multi-room facility can reach US$ 200 million (7).

The techniques used in conventional radiotherapy, which is based on high energy X-rays, have improved significantly over the last two decades (e.g., image-guided radiotherapy, volumetric modulated arc therapy, as well as the latest magnetic resonance imaging-linear accelerator). Those new advanced X-ray radiotherapy techniques can also increase the therapeutic effects, minimise residual doses to the patients remarkably.

Therefore, when evaluating whether proton therapy should be pursued in Malaysia, the two most important questions that must be answered are i) is proton therapy superior to the new advanced X-ray radiation therapies for cancer treatment, and ii) is the effective treatment modality of proton therapy suited to the cancers that are prevalent in Malaysia. Apart from the two questions mentioned above, the cost-effectiveness of proton therapy also needs to be considered because the cost of establishing and operating proton centres are higher than those conventional radiotherapy centres. This review describes and evaluates the incidence of cancers in Malaysia for which proton therapy is appropriate.

PHYSICAL CHARACTERISTICS OF PROTON BEAMS AND DEVELOPMENT OF PROTON THERAPY

Physical Characteristics of proton beams

Conventional radiation therapy using X-rays exposes patients to high ionisation radiation because X-rays deliver a high entrance dose before penetrating to the tumour and remarkable exit doses after tumour localisation. The extra ionisation radiation can damage the surrounding healthy tissues, causing side-effects and second malignancy is also always a concern. No technological advances in X-ray radiotherapy can change the natural physical properties of X-rays when passing through a medium. Thus, extra ionisation radiation to the surrounding normal tissues is unavoidable when using high energy X-rays.

Proton therapy is the next level of advanced radiotherapy, it uses positively charged protons to destroy cancerous tumours instead of high energy X-rays. Compared to X-rays, protons deliver a lower entrance dose in front of the tumour and deliver most of the energy to the tumour, and almost zero doses to the normal tissues after tumour localisation. The physical characteristic of protons called the Bragg peak is the main reason why protons are superior to conventional X-rays for cancer therapy (Fig. 1).

A single Bragg peak is not wide enough to cover a whole tumour, thus the Bragg peak needs to be spread out by summation of multiple peaks, and the superimposition of multiple peaks of different depths can be obtained via an appropriate selection of energies. The extended Bragg peak, called the Spread-out Bragg peak is used to make sure the beams are delivered to the full size of the tumour. As shown in Fig. 1, protons deposit most of their energies in the tumour location while minimising the residual doses to the nearby normal tissues, thereby delivering zero exit doses beyond the tumour.

Protons and X-rays have similar clinical relative biological effectiveness (RBE). X-rays have an RBE value of 1 and protons have an RBE of 1.1. At the same dose, protons provide 10% more biological damage than X-rays delivers to the tumour (12).

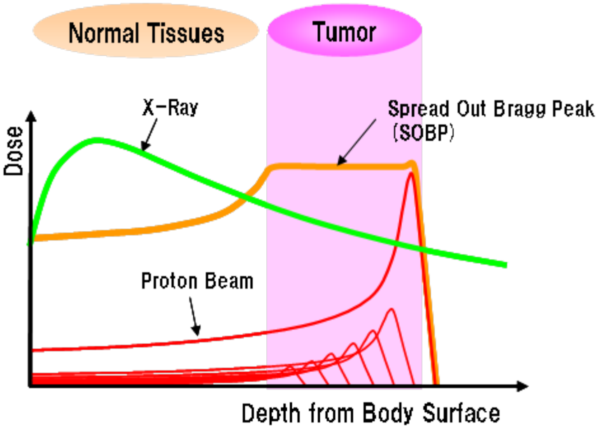

Figure 1: Dose distributions of a X-ray (green line) and a proton beam (red line) as a function of penetration depth in the tumour (Source: https://www.shi.co.jp/quantum/eng/product/proton/proton.html)

Development of proton therapy

Robert Wilson first suggested that charged particles, protons, can be applied in radiation oncology in 1946 based on his measurements of the depth dose profiles of proton beams at the Berkeley cyclotron. He found the dose at the end of the particle range increases significantly, this is the properties of the charged particle when passing through the water medium, called the Bragg peak (13-14). Eight years later in 1954, the first cancer patient was treated with proton therapy at the Berkeley Radiation Laboratory. Additional pioneering research in proton radiation therapy was conducted at the Harvard Cyclotron Laboratory in Cambridge, Massachusetts, where patient treatment commenced in 1961 (15-16). Both the Berkeley and Harvard cyclotrons had a great impact on the early development of proton therapy. In 1990, the first hospital-based proton centre was established at Loma Linda University in Loma Linda, California. By the end of 2018, more than 77 proton centres throughout the world were equipped with multiple treatment rooms and high energy proton beams to treat many types of cancerous tumours, and more than 190,000 cancer patients were treated by proton beams (1).

The source of the proton beams are hydrogen and separating the hydrogen's electron from proton using an electric field, the beams can be accelerated to therapeutic energies by using an accelerator up to 70% speed of light, from 70 to 250 MeV to reach the maximum depth of deep-seated tumours. The two main options for the accelerator designed are the cyclotron and the synchrotron. Most existing proton centres use cyclotrons to deliver proton beams. The cyclotron is a compact accelerator consisting of dipole magnets to produce a region of a uniform magnetic field, delivering continuous monoenergetic proton beams. The extraction of energy and particle species of the cyclotron is fixed, the beam energy needs to be adjusted according to the maximum tumour depth since the extracted energy cannot be changed, the required lower energies can be achieved by inserting energy degraders through the path of proton beams.

On the other hand, synchrotron can accelerate different particle species, but the size is much larger and also more complex, a synchrotron is a circular accelerator ring, allows the change of the extraction energy to the desired energy, then transmitted to the treatment room. The advantage of synchrotrons is that they have greater energy flexibility, being able to extract different types of ion species, not only restricted to protons. A synchrotron is ideally suited for using fully active beam delivery techniques. In general, when planning a particle therapy centre featuring different types of ion species including protons, the synchrotron is the better of choice.

The extracted monoenergetic proton beams are guided through the beamline to the rotating gantry in the treatment room using dipole magnets, the function of the gantry is used to direct the beam to the target. In general, a proton accelerator can serve multiple treatment rooms, the beam can be switched from one room to another. Due to the high capital cost and operation cost for multi-room proton centres, more affordable compact single treatment room proton centres are also becoming more popular to meet the growing demand for proton therapy. The proton therapy technique has improved over the last decade, the most advanced technique now uses active beam shaping method instead of the passive beam shaping method. Active beam shaping also called spot scanning proton therapy (SSPT), intensity-modulated proton therapy (IMPT) or pencil beam scanning sending a narrow proton beam directly to the tumours by scanning, provides even more promising therapeutic effects than the older technique.

Nowadays, proton therapy has become more accessible and growing numbers of proton facilities around the world, and it is developing quickly. There were only 10 proton centres worldwide before 2000, and most of the centres were in the United States and Europeans countries. Between 2000 and 2009, 13 centres were opened, totally 23 centres. However, a dramatic increase to 96 proton centres from 2010 to 2019 (i.e., 300 % more than in the previous decade. Fig. 2 shows the distribution of current proton centres by nation (1). In the past, the majority of proton centres and charged particle centres have been located in the United States, Japan and Europeans countries because proton centre centres have very high capital costs, high operation costs, and more advanced technology. Therefore, only a few developed countries can afford to have proton centres. However, since 2010, more and more Asian countries have been establishing proton centres, majority of them are in China, followed by Taiwan and India due to the declining cost and fast technological developments occurring in these countries.

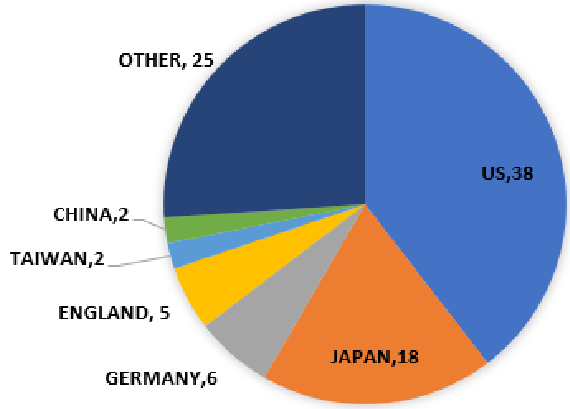

Figure 2: Number of proton centres by nation

Fig. 3 shows the proton centres currently under construction. In total, 30 new proton centres are currently under construction, and most of these centres will be completed between 2020 and 2021. Most proton centres are located in China (7) and United States (6). Malaysia's neighbouring countries - Singapore and Thailand, will begin treating the first patient with proton therapy in 2 years (17-18). On top of that, an additional 26 proton centres are currently in the planning stage. Global demand and the use of proton therapy are expected to increase.

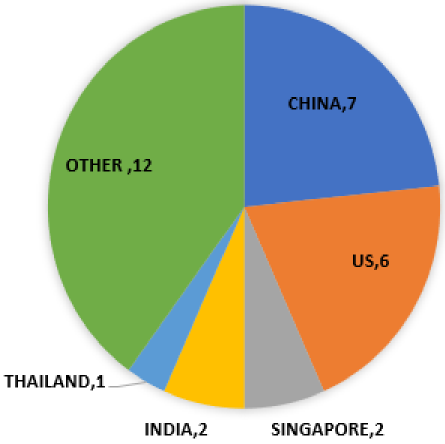

Figure 3: Proton centres currently under construction

POTENTIAL CLINICAL BENEFITS OF PROTON THERAPY IN MALAYSIA

Cancer is a leading cause of death in Malaysia today, the lifetime risk for males is 1 in 10 and for females, it is 1 in 9 (8). Radiotherapy plays a pivotal role in treating many types of cancerous tumours, especially those that develop in a crucial part of the body. For some cancer patients, radiotherapy is the first treatment approach when the tumour is situated near the organ at risk (OAR) or not suitable for surgery. Fig. 4 shows the percentages of the 10 most common cancers in Malaysia for 2012-2016 based on the Malaysia National Cancer Registry

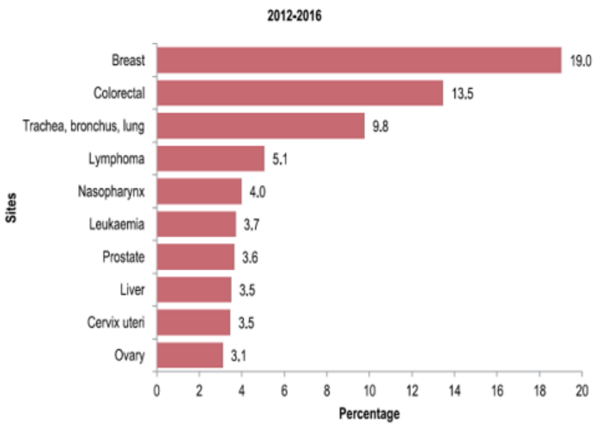

Figure 4: Percentages of 10 most common cancers in Malaysia

Report (8). The three most common cancers in Malaysia are breast cancer, followed by colorectal cancer and lung cancer for both male and female patients. In the following sections, several of the cancers common in Malaysia are reviewed, and the suitability and potential clinical benefits of their treatment with proton therapy are discussed.

Nasopharyngeal cancer (NPC)

NPC is the fifth most common cancer in Malaysia, with 4597 cases reported between 2012 and 2016. Most NPC cases in males were detected at the III and IV stages, and the 5year survival rate is 46 % for both male and female patients (8-9). Intensity Modulated Radiation Therapy (IMRT) is the first approach to treat NPC. The complications of radiotherapy in NPC are always a major concern, as the high energy of residual doses to OARs can cause many side effects, including dry mouth, swallowing difficulty, taste loss and hearing impairment, all of which reduce a patient's quality of life after treatment.

Some studies (19-20) show that OARs' toxicities can be substantially reduced with proton beams compared with high energy X-ray beams. The more advanced SSPT or Intensive IMPT shows more promising results compared to IMRT (21-22). In a treatment planning study by Taheri Kadkhoda et al. (23) compared the potential advantages of IMPT with IMRT in NPC. The IMPT treatment plan has greater potential than IMRT plans with respect to tumour coverage and conformation and substantially spares doses to OARs and non-specific normal tissues, the authors suggested further clinical trials needed to be carried out to verified the actual benefits of IMPT (p.11). Another similar dosimetry study by Kandulas et at. (24) to evaluate the feasibility of SSPT for head and neck malignancies and compared with IMRT. The authors reported that SSPT can reduce the integral dose to head and neck critical structures, significantly lower residual dose than IMRT in the contralateral submandibular, parotid gland, oral cavity, spinal cord and brainstem (p.390).

Radiotherapy currently is the main treatment of NPC, the potential benefits of proton therapy in head and neck cancer mainly are due to sparing OARs from the residual dose, most cancer patients with head and neck tumours (including NPC) might benefit from proton therapy because it would reduce treatment complications translates to improved quality of life.

Primary liver tumour

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Liver cancer is the fifth most common cancer worldwide (25) and the second leading cause of cancer-related death (26). It also is the eighth most common cancer in Malaysia, with more than 4033 newly diagnosed cases between 2012 and 2016. For most of the patients, it was detected at the last stage, resulting in high mortality and a 12.8% overall 5-year survival rate (8-9). Surgery is always the first consideration for the treatment of a primary liver tumour. However, some tumours are not suitable for surgery due to many reasons. Other approaches such as radiofrequency ablation, percutaneous ethanol injection therapy, transcatheter arterial chemoembolization, internal radiotherapy, and external beam radiotherapy (EBRT) are also the major treatments for HCC for non surgical patients. In the past, EBRT for HCC was less common due to the low tolerance of surrounding normal tissues and concern about radiation-induced liver disease.

Due to the physical properties of proton beams, proton therapy is potentially very beneficial for sparing OARs, especially if the tumour is proximal to OARs. Many studies in Japan demonstrated that proton therapy is better than conventional photon therapy for local tumour control of primary liver tumours.

A clinical study conducted by Nakayama et al. (27) at the University of Tsukuba to evaluate the safety and efficacy of proton therapy for the treatment of HCC involved 333 patients, the authors strongly recommended proton beams to be applied to those patients are risky or contraindicated for other treatment options. They reported proton beam therapy can be used to treat the patients with HCC safely and effectively: ‘The overall survival rates at 1, 3, and 5 years were 89.5%, 64.7%, and 44.6%, respectively (p.5499). This is very encouraging clinical experience to show us the abilities of the proton beams for the HCC treatment.

Another clinical study involving 162 patients with HCC in Japan by Chiba et al. (28) also showed very promising results. The authors reported: ‘For the patients with or without transarterial embolization and percutaneous ethanol injection treated with proton therapy. The overall survival rate was 23.5% and the local control rate was 86.9% at 5 years, respectively (p.3799). The conclusion of the study showed proton beam therapy is effective, well-tolerated, safe and repeatable for patients

with HCC.
Another interest dosimetric study to investigate the impact of tumour size on the risk of radiation-induced liver disease (RILD). Toramatsu et al. (29) compared RILD for SSPT and IMRT for HCCs patients using probability models showing that when the nominal diameter of GTV was more than 6.3 cm, the average RILD risk was 94.5 % for IMRT and only 6.2 % for SSPT.

This was much lower than that for IMRT. They summarized HCC can be more safely treated with SSPT, especially if its nominal diameter is more than 6.3 cm. (p.1). For the Unresectable HCC and Intrahepatic Cholangiocarcinoma, a phase II clinical studies (30) conducted by multi-institutional concluded that hypofractionated proton beams therapy provided high local control rates for HCC. The local control rate was 94.8% and the overall survival rate was 63.2% at 2 years, respectively (p.460).

In summary, many clinical studies conducted at different centres showed that proton therapy has better local control rates for HCC patients as well as reduced hepatic toxicity. Proton therapy has significant dosimetry advantages compared with conventional X-rays therapy; hence it provides a better clinical outcome for the management of liver tumours (31-32).

Lung cancer
Lung cancer is the third most common cancer in Malaysia and the second most common cancer in males, with 11256 newly diagnosed cases between 2012 and 2016. Eighty-nine per cent of lung cancer cases were detected at stages III and IV, and the 5-year survival rate is only 11% (Azizah et al. 2019; MySCan 2018). Radiotherapy and chemotherapy are the primary treatments for lung cancer, and proton therapy is the most common particle therapy used to treat lung cancer because it reduces the residual dose to adjacent normal tissues.

In a clinical study conducted by Kanemoto et al. (33) to determine disease control rates for lung cancer. A total number of 74 patients with stage I non-small-cell lung cancer (NSCLC) were treated with high dose proton therapy. They concluded that: 'Radiation dose plays the a significant factor for the local control rate of stage I lung cancer using high dose proton therapy' (p.7).

A similar study performed by Bush et al. (34) in phase 2 clinical trial to determine the efficacy and toxicity of high-dose proton beam therapy. 86 patients with stage I lung cancer were treated with proton beams and the 3-year local control and disease-specific survival rates were 74%, and 72%, respectively. The authors concluded high dose proton beams can be administered safely with minimal toxicity to the patient and offers better local tumour control compared to conventional photon therapy (p.1198).

Studies also showed proton beams also can significantly reduce residual dose to the normal tissues compared to conventional X-ray beams. In a dosimetric study performed by Change et al. (35), the team compared the patients with NSCLC treated by photon IMRT technique and proton therapy. In all cases, the doses to lung, spinal cord, heart, oesophagus, and integral dose were lower with proton therapy (p.1087).

Most of the lung cancer cases in Malaysia are detected at stages III and IV and those groups of patients are also suitable to treat with proton therapy, usually, the group of patients were inoperable or ineligible for chemotherapy because of co-existing disease or refusal. Proton therapy also showed good local control and low toxicity. Nakayama et al. (36) reported: 'For the patients with stage III NSCLC, proton beams play a definite role to treat the patients those who are unsuitable for surgery or chemotherapy (p.979). Several studies also showed that proton therapy with concurrent chemotherapy is safe to use in the treatment of unresectable stage III NSCLC (37-39).

Breast cancer
In Malaysia, the most common cancer is breast cancer with more than 21634 newly diagnosed cases between 2012 and 2016, almost half of these cases (47.9%) were detected at a late stage (III & IV) (8). The main approach to treat breast cancer is surgery and followed by external beam radiotherapy for women with early-stage breast cancer (40), this is the golden standard and the benefits for breast cancer patients is undeniable, but the complications of acute effects and long term effects are also always of concern.

Several studies reported radiotherapy to cause the risk of ischemic heart disease (41-43) due to the irradiation to breast tumours always involves some residual radiation to the heart, major complications to the coronary are proportional to the mean dose to the heart for up to 20 years (41). In a dosimetric study conducted to compare photon, photon/electron, and proton beams to investigates the use of proton radiation for the treatment for post-mastectomy patients, the researchers showed that proton therapy provided better spare surrounding normal tissues including cardiopulmonary structures without compromising coverage to the treated target (44). MacDonald & Patel et al. (45) conducted a clinical trial that involved 12 breast cancer patients who were evaluated for complications during treatment, the early clinical outcome showed that proton therapy for post-mastectomy radiotherapy is feasible and well-tolerated. Proton therapy was also suitable for partial breast irradiation, Bust et al. (46) reported minimal toxicity and excellent ipsilateral breast recurrence-free survival for patients treated with proton therapy in a 5 years follow-up clinical trial, proton therapy proved to be adaptable to all breast sizes and lumpectomy cavity configurations. However, the clinical benefits of breast cancer need further justification.

Paediatric cancer

The abilities of proton therapy spare normal tissues can be significantly beneficial for children because their bodies are still developing, and they have a longer life expectancy. Many countries recognised proton therapy as a standard treatment for paediatric cancer. According to the Malaysian National Cancer Registry Report, a total number of 3006 children aged below 14 years old were diagnosed with cancer. Brain and central nervous system (CNS) being the second most paediatric cancer, treatment of paediatric CNS requires multimodal treatment combined of surgery, chemotherapy and radiation therapy.

Radiotherapy always plays pivotal roles in the treatment of paediatric CNS tumours for children. A systematic review in Japan conducted by Masashi et al. concluded proton therapy has an equivalent therapeutic effect compared with photon therapy and reduces residual dose to OAR [47].

Another systematic review conducted by the Washington State Health Care Authority, the report showed that proton therapy had a superior net health benefit for ocular tumours and an incremental net health benefit for adult brain/spinal tumours and paediatric cancers. Additionally, proton therapy resulted in lower lifetime costs compared with conventional photon therapy for paediatric cancer [48].

MAJOR CHALLENGES TO HAVE PROTON THERAPY IN MALAYSIA

In Asian countries other than Japan, proton therapy is an advanced technique and the next generation of radiotherapy. In the last decade, many Asian countries began to look into the benefits of proton therapy over conventional radiotherapy using X-rays. Over the last twenty years, many centres in the United States, European countries and Japan have been generating a lot of research and clinical data.

The main problem to implementation of proton centre is the high cost of setting up a proton centre and the cost-effectiveness of the treatment, as a proton centre has higher capital and operating costs compared to a conventional radiotherapy unit (49). If the therapeutic effects and local control of IMRT techniques can provide an outcome similar to that of proton beams, it is not clear whether Malaysia should invest in proton facilities with higher cost. Answering this question requires analysis of the kinds and numbers of patients in Malaysia who can benefit from proton beams therapy.

The capital cost to establish a proton centre with multiple treatment rooms can cost > US$100 million, and even a compact single room proton centre costs about US$ 30 million. The capital costs are far more than those required for a traditional radiotherapy unit (50). In comprehensive studies in Australia, the capital cost of a proton centre ranges from between AU$ 34 million (single room) to AU$ 260 million (multi-room facility), whereas a conventional single room radiotherapy only costs about AU$5 million (51).

The cost-effectiveness of proton beams also differs for different types of cancer. To investigate the cost and cost-effectiveness of proton therapy, a review conducted by Verma et al. (52), stating that: 'Paediatric brain tumours are found was the most cost-effective for proton beams, followed by left-breast cancers because of exposes to high cardiac dose, advanced stages of NSCLC, and head and neck cancers at high risk of acute mucosal toxicities. However, the cost-effectiveness of proton was not superior to photon beams for the early stage of NSCLC and prostate cancer. Hence, careful patient selection plays a pivotal role in assessing cost-effectiveness (p.1483).

Apart from the high capital cost, the operating cost to maintain a proton centre is also higher than that advanced conventional radiotherapy. Collaboration between public and private sectors may be a good way to address the high capital and operation cost required to set up a proton centre. Malaysia is a leading medical tourism destination in Asia because it is known to provide excellent medical services with affordable cost (53), thus it attracts millions of foreigners seeking healthcare services each year. Higher treatment fees for those international and private patients will be able to cover part of the high operation costs.

Currently, only Taiwan provides proton therapy cancer treatment in Asia other than China and no proton centre in Southeast Asia, but within 2 years from now, Singapore, Thailand and India will treat their first patient with proton beams. This suggests that Malaysia will lose potential patients who need proton therapy cancer treatment.

Collaboration between the private and public sectors would allow part of the capital cost of setting up a proton centre to be covered by the income generated from private patients who pay for the proton therapy treatment, in the meantime, some local cancer patients also could benefit from proton therapy treatment.

CONCLUSION

Instead of using photons or electrons, proton therapy uses beams of high energy charged particles to kill cancerous tumours. The nature characteristic of charged particles - Bragg peak, enable proton beams to deposit most their energy inside the tumour, thereby minimising residual dose to nearby healthy tissues.

Nowadays, proton therapy has become more accessible and popular, nearly 200,000 patients are already treated with proton beams. However, the number is still much lower than that of patients treated with conventional photons. The clinical evidence for successful proton treatment still needs to be enhanced.

Some of the studies were case-series and dosimetric based, although these studies have shown very promising results but not necessarily reflect on the outcome in terms of OAR toxicities, overall survival, and high level of clinical evidence. More clinical studies are still needed to support the benefits of proton beam therapy. The cancer patterns in other countries differ from those in Malaysia. For example, prostate cancer is dominant cancer in the United States but not in Malaysia. Based on the prevalence of cancer types in Malaysia, such as NPC, liver, and breast cancers, the proportion of local patients suitable for proton beam treatment is higher than in the United States. The combination of proton therapy with other treatments, such as chemotherapy, targeted therapy, immune therapy or surgery, should also be considered as ways to decrease toxicities and improve the quality of life in patients after treatment.

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