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# A REVIEW ON PROTON THERAPY FOR VARIOUS CANCERS

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## ABSTRACT
Proton therapy or proton beam therapy is a type of radiation therapy. It uses protons rather than x-rays to treat cancer. A proton is a positively charged particle. At high energy, protons can destroy cancer cells. This therapy can be used alone or it may be combined with x-ray radiation therapy, surgery, chemotherapy and / or immunotherapy. It is a type of external-beam radiation therapy, which painlessly delivers radiation through the skin from a machine outside the body. It is useful for treating tumors which have not spread and are near important parts of the body, i.e., cancers near the brain and spinal cord. It is also used for treating children because it lessens the chance of harming healthy, growing tissue. This review is briefly focussed on the applications of proton therapy on various cancers.

**KEYWORDS:** proton therapy, proton beam therapy, cancer.

## INTRODUCTION
Proton therapy is a type of a treatment uses high-energy beams to treat tumors. Radiation therapy using X-rays has long been used to treat cancers and benign tumors. Proton therapy is a newer type of radiation therapy that uses energy from positively charged particles called protons. Research on the role of radiotherapy in the management of cancer has been intensified in the last 2 decades.[1,2,3] During the whole course of disease treatment, 60% –70% of all cancer patients need to undergo radiotherapy[1], mostly with photon therapy, which is delivered with linear accelerators. The protons can penetrate a certain depth in tissues which depends on the energy of proton. The proton has physical advantages over photon by depositing the majority of its energy at the site of 'Bragg Peak', beyond which there is no energy delivered.[4] With the development of pencil beam scanning technique, the newest generation of proton equipment can also perform Intensity Modulated Proton Therapy (IMPT) which yields highly conformal dose distribution around the target volumes.[5] According to various studies and reviews, the current indications of proton therapy include pediatric, head and neck, lung, liver, pancreatic and prostate cancers.[6,7,8] This review paper is focussed on the proton therapy involving various cancers.

### Head and neck cancers
Several recent studies have confirmed the dose reduction to normal tissues using proton therapy for oropharyngeal carcinoma, compared with Intensity Modulated Radiation Therapy (IMRT).[9,10,11] In a study, Holliday et al. reported that there were significantly lower doses to the brain stem, cerebellum, posterior oral cavity, pharyngeal constrictors and the esophagus in proton therapy plans compared with IMRT plans using a case-matched control analysis.[9] However, not every head and neck cancer patient could benefit from proton therapy due to tumor size and the relationship between tumor and the surrounding organs at risk. So, comparative dosimetric planning needs to be done for each patient to choose the best technique to be applied.

Proton Beam Therapy (PBT) is an option when normal tissue constraints cannot be met by photon-based therapy for tumors of the ethmoid sinus, maxillary sinus, salivary gland, periorbital, nasopharynx and mucosal melanoma from the updated 2017 National Comprehensive Cancer Network guidelines. PBT is uniquely suited for Head and Neck Cancers with the complex anatomy of tumors and important sensitive organs at risk, such as brain stem, optic chiasm, and optic nerve. A proton treatment protocol by Maquilan et al first reported the acute toxicities in patients with low-grade gliomas or meningioma who received 54 Gy.[12]

### Breast Cancer
Compared to IMRT, proton therapy beam scanning was found to potentially reduce the mean heart dose close to 0–0.5 Gy for left-sided breast cancer, which makes it possible to cover the internal mammary node in the target for breast cancer radiotherapy without a significant dose to the heart.[13] Other studies also confirmed that proton therapy possessed a better dose distribution

profile and reduced mean heart dose compared with IMRT.[14,15] Another advantage of proton therapy is that it can dramatically decrease the volume of normal tissue receiving low radiation dose, which could also lead to a lower incidence of secondary malignancy. Several studies on proton therapy for breast cancer have demonstrated a reduction of irradiated volumes in normal tissue.[13,16,17]

**Lung Cancer**

Criticism of proton therapy for lung cancer comes from the uncertainties related to the respiratory movement and tissue density which could dramatically affect the range of proton. In a study, Chang et al. confirmed the feasibility of proton therapy for lung cancer using a 4-dimensional computed tomography to delineate an internal gross tumor volume and expanding a margin of 5 mm to form planning target volume. No grade 4 or 5 toxicities were observed in this study after a median follow-up of 6.5 months.[18]

**Hepatocarcinoma**

In operable hepatocarcinoma patients, due to their underlying poor performance status and associated comorbidities, they can benefit from local treatments such as stereotactic radiotherapy which can yield up to 90% of local control.[19] However, for large tumors > 5 cm or specific anatomic situations (i.e. hepatic hilum, central tumor) are not eligible for these local photon therapies. In these settings, proton therapy has proved its ability to deliver higher doses to target volumes without increasing the risk of hepatic toxicities.[20,21]

**Liver cancer**

The tolerated dose of normal liver is relatively low and 80% of patients with liver cancer have chronic liver disease, which further reduces the tolerated dose of normal liver. Although liver cancer cells are highly sensitive to radiation, the usage of photon radiotherapy is limited for liver cancer. However, PBT can significantly decrease the normal liver dose and most of the normal liver can be completely unirradiated, which makes it possible to use dose escalation. A phase I study suggested that 72 GyE in 24 fractions using PBT for patients with inoperable hepatocellular carcinoma was safe and effective.[22]

**Pediatric cancer**

Due to the improved survival of pediatric cancer patients over the past 10 years, more attention has been paid on decreasing long-term side effects to improve patients' quality of life. It was reported that > 60 % of these cancer survivors will experience one or more radiation-related late toxicities and many of these adverse events would be life-threatening. It is well demonstrated that proton therapy can spare many normal tissues and reduce the integral dose to organs at risk. A meta-analysis with 650 patients in 23 primary studies showed that proton therapy could reduce the radiation dose to normal tissues.[23]

\With more data from children treated with PBT, the proton beam model policy adopted by the American Society of Radiation Oncology in 2017 supports PBT in children with solid neoplasms and it is now an option for many Children's Oncology Group protocols.[24] Many studies have confirmed the feasibility of PBT in pediatric cancer and achieved excellent outcomes compared to photon therapy. The advantage of PBT is recognized for craniospinal irradiation. A phase II clinical study reported the long-term results of PBT in 59 patients (aged 3–21 years) with medulloblastoma.[25]

**Prostate cancer**

The role of proton therapy for prostate cancer has been controversial. Several dosimetric studies have demonstrated that proton therapy for prostate cancer could lower the mean dose to the rectum and bladder compared to volumetric modulated arc therapy.[26, 27, 28] However, in terms of high dose volume, proton did not have obvious advantages over photon therapy due to the anatomic location of the rectum and bladder. It was noted that proton therapy only treated primary prostate without irradiating regional lymph nodes.

**Eye tumors**

Although the incidence of eye tumors is very low, there is a relatively longstanding experience for plenty of patients with eye tumors treated with PBT, yielding excellent survival outcomes with ocular conservation and visual preservation. Lane et al. showed the findings of PBT in 3088 patients with uveal melanoma.[29]

## CONCLUSION

Even though it is costly, there is less radiation dose outside the tumor in proton therapy and also it causes fewer side effects. Proton therapy is the most technologically advanced method to deliver radiation treatments to cancerous tumors available in few hospitals today.

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