Review Article

Proton beam therapy for Oral cancer and treatment challenges in India

Abstract

Oral cancer poses a significant threat in India, often leading to fatal outcomes or functional impairment for affected individuals. Effectively managing oral cancer proves to be a complex task due to the influence of prognosis and recurrence factors on treatment strategies. While surgery and chemotherapy are conventional options, radiotherapy also plays a crucial role. However, radiotherapy comes with several drawbacks. To address these challenges, proton beam therapy, a form of particle therapy, has emerged as a promising alternative. This review provides an overview of proton beam therapy for oral cancer and examines the current status of its availability and affordability in India, reflecting contemporary trends worldwide.

Keywords: Proton beam therapy, oral cancer, treatment, India, radiotherapy, complications.

Introduction

According to the 2020 National Cancer Registry Programme Report, which analysed cancer incidence data from 28 Population-Based Cancer Registries spanning 2012-2016, oral cancer ranks as the second most prevalent cancer in males and seventh in females [1].

Over two decades ago, the introduction of intensity-modulated radiation therapy (IMRT) significantly improved precision in targeting while minimizing radiation exposure to adjacent structures, thereby reducing toxicities [2]. Despite these advancements, the use of photons in radiation therapy still poses challenges, leading to chronic toxicities that impact Quality of life (QoL). A need arose for a novel radiation therapy approach that allows dose escalation while minimizing radiation to non-targeted tissues.[3] To overcome this challenge, in 1946, Harvard physicist Robert R. Wilson proposed the use of protons to precisely target small volumes within the body. Almost a decade later, the first patients received treatment through proton beam therapy (PBT) [4]. While proton beam therapy has been extensively discussed in the literature concerning head and neck cancer, there is a notable gap in knowledge among dentists and oral physicians regarding its application, availability, and significance in the context of oral cancer.

This review seeks to provide a comprehensive summary of recent literature regarding the application of PBT in the context of oral cancer. It covers the treatment and planning processes, clinical treatment toxicities and outcomes, comparative evaluation with conventional radiotherapy, future perspectives and as well as limitations for the use of proton therapy in India.

Proton beam therapy – particle therapy – physics and History

Proton therapy, a form of charged-particle therapy, differs from photon therapy regarding energy transfer within tissues as proton velocity is inversely proportional to the energy transferred within tissues.[5]

In 1946, Robert Wilson was the first to identify the potential medical benefits of proton therapy. He recognized that the unique physical properties of protons—specifically the Bragg peak and their decreasing velocity as they move through tissue—could be harnessed to effectively target diseases located deep within healthy tissue.[6] The advantages of proton therapy were recognized early in its history by Wilson as well as the early treatment centers at Lawrence Berkeley Laboratory, the Gustav Werner Institute and the Harvard Cyclotron Laboratory.[7]

Unlike photons, protons exhibit greater sensitivity to the tissues they traverse. PBT is an external beam radiation therapy characterized by minimal to no exit dose.

BRAGG PEAK

The concept of a "peak" was initially discovered by William Bragg in the early 1900's and is known as the "Bragg peak." The Bragg peak, or energy deposition as a function of tissue depth, has potential to deliver higher doses to a target volume while maintaining dose-constraints of nearby critical structures.[8] As protons are propelled toward the tumour, these heavy, charged particles release their radiation dose within a narrow range of tissue depth, known as the "Bragg peak." (Figure 1) This Bragg peak can be precisely localized at any depth within the tissue, allowing for targeted radiation of the tumour while minimizing radiation-related toxicities in the surrounding healthy tissue. The modification of the proton beam results in the creation of a plateau known as the Spread Out Bragg Peak (SOBP). This adaptation enables the treatment to conform not only to larger tumors but also to more intricate 3D shapes. Achieving this involves the utilization of variable thickness attenuators, such as spinning wedges[9]

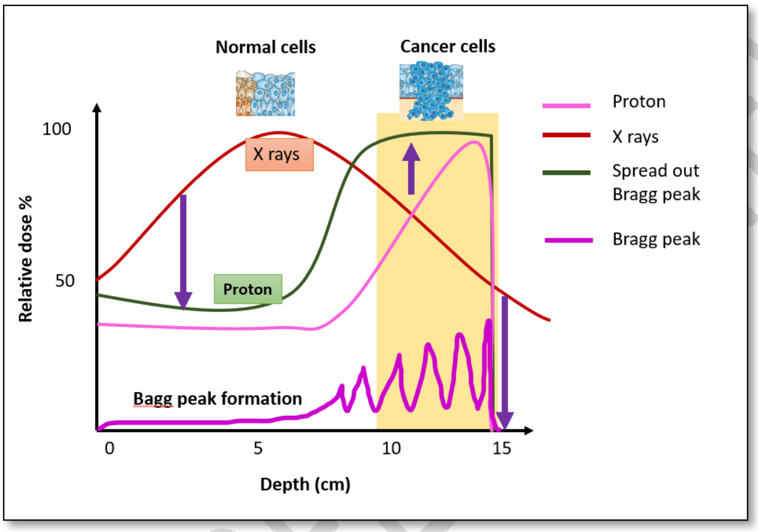


Figure 1 Bragg peak effect in proton therapy comparing to the conventional radiotherapy (X Ray) in normal and cancer cells

Factors that may impact Bragg peak [9]

- Localization are artifacts (e.g., dental or surgical hardware)
- Air space in cavities (e.g., air-filled sinuses or oral cavity)
- Patient's anatomical fluctuations (e.g., weight change, tumour shrinkage, or daily variations in patient positioning)

To address this challenge, Optimal treatment plans should incorporate brief and dependable beam paths that steer clear of tissue irregularities, including the oral cavity, spinal cord, salivary glands, and other vital structures.

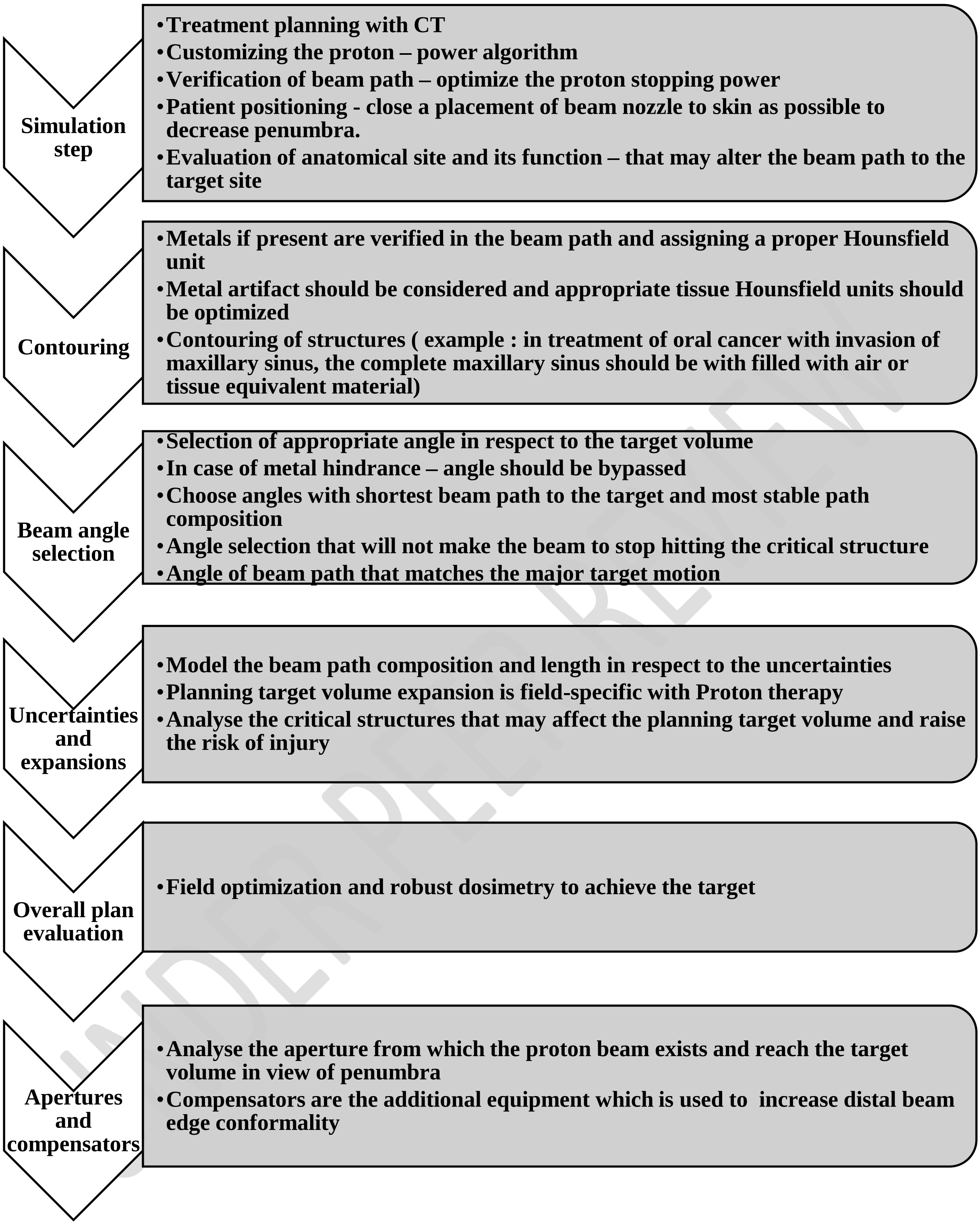
The radiation planning for PBT differs from IMRT due to the distinctive physical properties of protons. At the atomic level, the heavier mass of protons reduces the scattering angle and refines the dose distribution, resulting in a more precise and defined radiation range. The Bragg peak is localized to the specified tumor volume, and the minimal exit dose contributes to a highly accurate dose delivery. However, the complexity of tumors, characterized by varying thickness and depths, necessitates a spread-out Bragg peak to cover the entire selected volume. This approach may eliminate the skin-sparing effects associated with the entrance dose, potentially leading to skin toxicities, particularly in superficial tumours [10]. PBT is delivered through two primary modes: passive-scatter proton therapy and intensity-modulated proton therapy (IMPT). In passive-scatter proton therapy, akin to three-dimensional photon therapy, scattering foils are employed to disperse the proton beam. However, this method is less flexible compared to active scanning which is also called as pencil beam scanning. It is the most recent advancement of delivering proton therapy. In the treatment of head and neck cancer, IMPT holds advantages over passive-scatter proton therapy (PSPT) because of its enhanced flexibility in addressing complex and irregularly shaped tumours. IMPT allows for personalized treatment plans, to precisely target the tumour [11].

Two approaches in IMPT: INTENSITY MODULATED PROTON THERAPY

Single-field optimization: Each proton beam individually covers the target volume, and multiple-field optimization, where the proton beams collectively cover the target volume [12]. Multiple-field optimization: enhanced conformality and intensity modulation compared to single-field optimization, making it more responsive to treatment uncertainties [12]. In summary, IMPT offers an increased relative biological effectiveness and reduces radiation exposure to healthy surrounding tissue.

Treatment planning for oral cancer with proton beam therapy

The treatment planning for oral cancer presents challenges, primarily in the need to eliminate undesired radiation to surrounding supportive structures. This is crucial to prevent potential radiation-induced side effects in the head and neck region. The process of simulation of proton therapy is simplified and explained in the flowchart which is based and adapted from the Guidelines and considerations are in use at the University of Florida Proton Therapy Institute and pertinent for double scattered proton therapy in head and neck cancer as well as in other sites.[13,14]



Comparative evaluation with IMRT

While IMRT plans may inadvertently expose nontarget organ structures like the anterior oral cavity and brainstem to low-radiation dose beam path-related toxicity, IMPT presents clear dosimetric advantages. IMPT demonstrates superior capability in further safeguarding these surrounding normal tissues in patients undergoing treatment for oropharyngeal cancer [15,16].

Blanchard and collaborators conducted a case-matched analysis, comparing 100 patients treated with IMRT to 50 oropharyngeal cancer patients treated with IMPT in a 2:1 ratio. Both treatment groups exhibited favourable disease control and progression-free survival, with no statistically significant difference. Notably, IMPT was linked to a significant reduction in severe (Grade 3) weight loss observed at the 3-month follow-up [17].

The observed decrease in toxicities among oropharyngeal cancer (OPC) patients undergoing IMPT is likely attributed to the diminished irradiation to healthy structures situated in the oral cavity, salivary glands, larynx, and oesophagus [18].

In a recent study conducted by Terence T. Sio et al., the initial comparative outcomes of patient-reported experiences between IMPT and intensity-modulated radiation therapy (IMRT) were examined. The study revealed a reduction in symptom burden among patients treated with IMPT during the subacute recovery phase following treatment. This analysis was based on the assessment of symptom burdens in 35 patients undergoing chemo-IMPT and 46 patients undergoing chemo-IMRT [19].

According to the existing literature, IMPT presents superior outcomes in terms of overall survival rate, locaregional control, improved quality of life, and reduced toxicity when compared to IMRT.

In a retrospective study conducted by Saif Aljabab et al. in the USA, patients with oropharyngeal squamous cell carcinoma (OPSCC) treated with IMPT demonstrated promising results. The findings indicated an absence of local, regional, or marginal recurrences and a favourable toxicity profile, highlighting the potential efficacy and safety of IMPT in the management of OPSCC [20].

Limitations

PBT has been associated with fewer reported acute toxicities, primarily attributed to the reduced exposure of surrounding tissues to elevated radiation doses. However, it's essential to note that certain studies indicate potential adverse events with PBT, including skin toxicities, temporal lobe necrosis, and neurological toxicities [21]. In a study analysing toxicity and quality of life in head and neck cancer patients treated with PBT, the most frequently observed side effects were radiation dermatitis (93%; n = 13), oral mucositis (93%; n = 13), and dry mouth (79%; n = 11). Among these, radiation dermatitis emerged as the most prevalent Grade 3 toxicity, affecting 36% of patients.[22]

PBT has been employed in clinical settings for over two decades, yet the high costs associated with constructing and operating proton therapy facilities have constrained its widespread adoption. However, recent technological advancements have contributed to making proton therapy more affordable and accessible, thereby facilitating an increase in studies exploring its clinical advantages. When evaluating dosimetry and treatment-related toxicities in patients receiving treatment for malignant diseases of the nasal cavity and paranasal sinuses, a comparison was made between proton beam radiation therapy (PBRT) and intensity-modulated radiation therapy (IMRT) administered to the ipsilateral head and neck. The findings suggest that charged particle therapy, such as PBRT, may offer superior outcomes compared to photon therapy, potentially leading to improved results in patients with these specific malignancies [23,24,25].

Availability and Affordability of proton beam therapy in India

An analysis of the National Cancer Database focusing on patients treated with PBT in the USA revealed that individuals treated in an academic setting and those in the highest median household income quartile were more inclined to receive PBT. These results indicate a correlation between higher socioeconomic status and the likelihood of receiving PBT among patients [26].

In a cross-sectional study conducted by Zhongying Xia et al., the investigation focused on assessing the inequality in the accessibility of proton therapy for cancer and its economic determinants in 196 countries including India. The study results revealed a pronounced level of inequality, with the total Gross Domestic Product (GDP) significantly influencing whether a country possessed a practical Proton Therapy (PT) centre. Additionally, both total GDP and GDP per capita significantly impacted the number of centres. The findings underscored the existence of substantial inequality in the accessibility of PT centres worldwide. Economic development emerged as the predominant factor influencing the adoption of PT, suggesting that as global economies continue to grow, an anticipated increase in the number of PT centres can be expected in the near future [27].

The accessibility and affordability of proton therapy in India hinge on factors like location, healthcare facility, and individual patient needs. Proton therapy is offered in major cities across the country, with dedicated cancer treatment centres equipped with proton therapy technology, including renowned facilities like the Apollo Proton Cancer Centre in Chennai, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) in Mumbai, and Tata Memorial Centre in Mumbai. The cost of proton therapy varies significantly based on factors such as cancer type and stage, the number of required sessions, the chosen healthcare center, and additional medical expenses. As a comparative estimate, proton beam therapy is considered approximately three times more expensive than conventional radiotherapy in India.

Future perspectives

Proton therapy for oral cancer needs the following improvements and insights [9]

- On board imaging, which is an advanced imaging technique that uses images to confirm the radiation therapy given to the patient precisely reflects the patient's treatment plan
- Automated proton plan adaptation: which will create a system that ensures the precise delivery of proton therapy, facilitating a broader integration of this advanced form of radiotherapy.
- Treatment outcomes with chemo + PBT have been discussed in literature. Studies focusing on immunotherapy + PBT have to be evaluated through further clinical trials
- Cancer treatment responsiveness at the biological level expressed by angiogenic, inflammatory, proliferative, and anti-tumour immune response. These factors should be evaluated in respective to proton beam therapy for better clinical outcome.

Cost effectiveness models in proton beam therapy

A Markov decision-analytic model is the most commonly used approach in cost-effectiveness analysis. This model starts with a hypothetical population characterized by predefined disease attributes, prognosis, and treatment variables. After receiving a specified intervention, such as proton beam therapy (PBT) or intensity-modulated radiation therapy (IMRT), patients undergo probabilistic transitions through different health states during the posttreatment follow-up period.[28]A thorough cost-of-care analysis compared total medical charges between case-matched patients receiving proton beam therapy (PBT) and those receiving intensity-modulated radiation therapy (IMRT), revealing no significant differences in average medical costs.[29]

Conclusion

Due to the inherent physical characteristics of protons that allow for maximal radiation dose to the target volume while minimizing exposure to normal tissue, PBT holds theoretical advantages over IMRT. The collective clinical evidence highlighted in this review indicates that PBT stands out as a favourable radiotherapy option for the treatment of head and neck cancer. However, making proton therapy readily available in developing countries poses significant challenges. In the current landscape, the imperative is to concentrate efforts on ensuring trouble-free accessibility and availability of this advanced treatment for a broader population.

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