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Narrative Review

Proton Radiation Therapy in Head and Neck Cancers

Muhammad Sami [1], Muhammad Yousuf [1*], Qasim Hashmi [2], Muneeb Ahmad [2], Mohammad Ghilman [3], Huzaifa Shareef [3]

[1] Kingston Hospital, London, United Kingdom
[2] Ruth K. M Pfau Civil Hospital Karachi, India
[3] Dow University of Health Sciences, Civil Hospital Karachi, India

*** Corresponding Author:** Muhammad Yousuf, Kingston Hospital, London, United Kingdom. E-mail: yousufybi236@gmail.com

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Abstract

Proton therapy (PT) is one of the latest advancements in the treatment modalities of cancers. PT is specifically used to treat HnN cancer patients due to its less toxic effects on the surrounding critical structures. Keeping in view the opportunities for further advancements, there has been quite a lot of literature covering PT in HnN cancer patients. However, there has not been a compiled study that compares the toxicities, overall survival (OS), local control (LC), and quality of life (QoL) of PT with that of IMRT. The objective of this review is to compile & summarize the literature available on the toxicities, OS, LC, and QoL in HnN cancer patients post-proton therapy.

Keywords: Proton Therapy, Head and Neck Cancers, Radiation

Introduction

Amongst all the malignancies, HnN cancers are considered the ninth most common cancers in the world.[1] It has a significantly high mortality, especially in developing countries. Most of HnN cancers arise from the mucosal epithelium in the viscera of the HnN and are collectively referred to as HnN squamous cell carcinoma (HNSCC).[2] Of all, the major culprits leading to such an outbreak of HNSCCs are tobacco and alcohol, which varies with countries/regions.[2] Apart from these, there has also been an increase in the incidence of HPV-related oropharyngeal cancers.[2]

As far as treatment options are concerned, before the advent of chemotherapy and chemo-radiation, surgery and radiation therapy (RT) were considered the primary treatment modalities for HnN cancers.[3] But in the early 2000s, research revealed that induction chemotherapy or chemo-radiation followed by RT provides better loco-regional control and normal tissue preservation, which made concurrent chemo-radiation a standard treatment option for locally advanced malignancies.[3]

Previously, intensity-modulated radiation therapy (IMRT) and volumetric arcs have shown promising results. However, unavoidable irradiation of normal tissue is encountered due to some physical limitations of photon therapy. Proton therapy (PT), in contrast, is a modern form of radiotherapy with an exceptional ability to target tumor cells with maximum accuracy. PT is a preferable option over IMRT because a) it isolates tumors of the HnN, non-small cell lung cancers, and certain GI cancers where traditional photon therapy is not applicable due to overwhelming risks.[1] b) Reduced exposure of healthy cells to radiation because of almost zero exit dose and accurate tumor scanning using the pencil beam technique.[2]

In this review, we will compare the side effects, toxicities, and limitations of IMRT as compared to proton therapy.

Materials and Methods

We did not conduct a systemic systematic review of the literature on proton therapy in patients with HnN cancer. However, we have gathered and summarized the literature found under the keywords ‘proton therapy for head and neck cancers’ across several renowned journals. Moreover, we also incorporated studies on reirradiation of recurrent HnN cancers and traditional photon radiotherapy in HnN cancer patients to do a comparative analysis.

Applications, Planning, Delivery, and Precautions of PT in HnN Cancers

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Proton therapy is a safer alternative to traditional radiotherapy using photons to treat several cancers. Among the leading cases of cancer, PT is considered a preferable treatment option in HnN cancer patients due to the fact that photon therapy or IMRT cannot be used due to its toxic effects on the normal tissues of adjacent critical organs.

Proton Ttherapy is preferable due to its fewer effects on the surrounding healthy tissues and higher effects on the tumor. This is made possible by an area of maximum beam density with the maximum penetration and energy, called the Bragg Peak. PT is planned for the patient based on the tumor's location, size, grading, and tolerance. In order to get the maximum results from PT - polyenergetic beams of protons are combined to create a spread-out Bragg peak (SOBP). However, SOBP always comes with an increased risk of skin dose due to the scattering of the beam.[4] Another benefit of PT over IMRT is that PT has a near-zero exit dose, resulting in significantly reduced chances of exit point toxicity. Moreover, PT has a definite & modifiable range and penetration.

PT can be delivered via two modes, passive scatter and IMPT (Intensity Modulated Proton Therapy). In the former one, the vertical and horizontal spread of the proton beam is regulated by adjusting the shape of its aperture. However, in IMPT, an advanced magnetic pencil beam scanning allows radiologists to design a pattern of the proton beams with variable energy, so as to target the tumors of irregular shape and spare healthy tissues with maximum accuracy.[5] IMPT is the most advanced modification of PT that allows PT with minimum acute and late toxicities and increases the Relative Biological Effectiveness (RBE) of protons.

Among the challenges faced by oncoradiologists while delivering PT effectively is delivering the Bragg peak to the desired location with maximum accuracy. Moreover, accurate delivery of PT is also affected by dental or surgical artifacts, one of the reasons radiologists prefer not to include the oral cavity in the path of the protons. Other SOPs include minimizing the path and keeping in consideration the changes in the patient’s position, change of weight, or tumor size.[6]

Management of Different Head and Neck Cancers with Proton Therapy

Cancers of Paranasal Sinuses and Nasal Cavity

Out of all HnN cancers, nasal cavity and paranasal sinuses-related malignancies constitute a small fraction. Amongst all these rare malignancies, the maxillary sinus is the most commonly involved structure out of all paranasal sinuses,;approximately 60%-70% of cases belong to this group.[7] Craniofacial surgery and subsequent radiotherapy remain the mainstays of treatment in most cases.[8] Even after such treatment approaches, the treatment facing inefficacy at the site of the tumor is the major concern threatening the survival of the patients.[9] However, a relation has been made between the radiation dose and improved local control (LC), but it occurs at the cost of critical surrounding normal structures.

The presence of optic structures in close proximity to the cancers involving paranasal sinuses and skull base, radiotherapy to these cancers results in radiation-induced retinopathy/optic neuropathy, which is frequently reported. As in research carried out at the University of Florida, the visual/ocular toxicity of radiation therapy became evident as 27% of the patients receiving radiation therapy faced unilateral blindness (Radiation-induced retinopathy/Optic neuropathy) and 5% suffered from bilateral blindness (Optic Retinopathy).[10] Initially, IMRT appeared to be the solution for this increased radiation-induced toxicity, but as far as LC and the survival of the patients are concerned, no improvement was reported.[11]

PT has shown some promising results in this regard. A study was conducted between 1991 and 2002 where 102 patients who were suffering from sinonasal cancers of different histological types and late-stages types were given PT at the Massachusetts General Hospital (MGH). The 5-year LC was reported to be 86% with a mean follow-up of 6.6 years. 20% of the patients received PBT after undergoing complete resection. The median dose was set to be 71.6 Gy. For neuroendocrine, adenoid cystic, and squamous cell carcinomas, the primary relapsing pattern was distant metastasis. These consequences showed that PBT has an edge over IMRT.[12] However, when hyper-fractionated proton-photon therapy was given to a group of patients at MGH, late visual and ocular toxicity was observed.[13] Patients were followed-up at a median period of 52.44 months, with only 5.6% of patients developing late-grade 3 visual/ocular toxicity. No other complications were reported. After all these results, it is apparent that PBT delivers appropriate tumoricidal dosage with the least complications.

Oropharyngeal Cancer

One of the most common malignancies of the head and neck includes cancers involving the oropharynx, which is the sixth most common among all malignancies.[14] As of 2008, 223,000 deaths were reported due to oral cavity and oropharyngeal cancers (OPC).[15] Among the etiologic factors, alcohol and tobacco are the most dominant ones. Other than these, the involvement of HPV infection has also been reported.[16]

While treating patients suffering from oropharyngeal cancer, radiation therapy is often preferred over surgical resection as the latter is associated with significant functional impairment.[17] However, in 2005, the first study regarding the use of proton therapy for OPCs was given by Slater and colleagues.[18] 29 patients suffering from stage II-IV OPC were treated with combined photon-proton therapy. With 3D conformal photon being predominant (50.4 Gy), an additional (25.5 Gy) proton therapy was also given to the patients. lC and survival without disease were 88% and 65%, respectively, in 5 years of follow-up. As for toxicity, it was noticed that about 16% of the patients experienced grade 3 or higher toxicity. Another study was conducted by Gun and colleagues,[19] in which it was observed that when 50 patients, the majority of whom were HPV-positive, were given PT, survival without progression was 89% in 2 years of follow-up. None of the patients reported grade 4 and higher toxicity. However, incidences of acute mucositis and dysphagia of grade 3 were reported.

In a nutshell, it can be stated that proton beam therapy has a slight edge over IMRT, but further trials are still required to explain its role in alleviating toxicity when treating oropharyngeal cancer.

Adenoid Cystic Carcinoma

ACC is a malignancy of glands that is quite rare. Several studies have suggested proton therapy with an acceptable ratio of toxicity in the cases of ACC. ACC of salivary glands accounts for only 1% of the tumors of the HnN.[20] Massachusetts General Hospital conducted a comparative study where 23 patients suffering from ACC were given combined radiotherapy of photons and protons.[21] Varying percentages of patients had tumors involving the sinuses. The extent of surgery was limited with biopsy in 48% of the patients, partial resection in 39%, whereas total resection with positive margins was done in only 13%. The median dose of proton/photon radiotherapy was 75.9 Gy whereas the median follow-up time for surviving patients was 64 months.

The LC rate and OS at 5 were found to be 93% and 77% respectively. Moreover, 5 years of disease-free survival and freedom from distant metastasis were found to be 56% and 62%, respectively.

One of the latest studies on treating ACC with PT by Pelak[22] involved 35 patients out of which, 26 underwent surgery while 9 were suffering from an inoperable disease. The two-year LC and OS were 92.2% and 88.8%, respectively. Late and acute toxicities above grade 2 were found in 6.1% and 14.3% of the cases. Palek concluded that Proton Beam Therapy is a useful and less toxic alternative to radiotherapy for patients with ACC. However, the patient's age group, tumor stage, and the clinical stage had a negative impact on the LC and OS ratio. The major cause of treatment failure was distant metastasis.

Nasopharyngeal Cancer

NPC is a common malignancy of HnN. Unlike others, its occurrence is influenced by geographical. The carcinoma has its origin in the epithelium lining the nasopharynx. WHO has categorized it into 3 types on a histopathological basis. (a), non-keratinizing (b), and undifferentiated carcinoma (c).[23] NPC has a diverse etiology, as a complex mechanism leads to its clinical presentation, including EBV infection, genetic susceptibility, and environmental factors as the major culprits.

In 2007, a study was published that revealed that when IMRT was compared with 2D-RT as a treatment option for patients with uncomplicated nasopharyngeal carcinoma, at 1 year, decreased incidence of severe xerostomia rated by physicians was reported after IMRT [24]. In the late 90s,[25] a combination of proton-photon radiation was given to patients suffering from advanced NPC at the MGH. The median dose was 73.6 Gy. As far as recurrence is concerned, only 1 of them faced local recurrence and 2 reported distant recurrence when the median follow-up time was set to be 43 months. Relapse-free survival, LC, and OS were 79%, 92%, and 74% at 3 years, respectively. This study suggested that locally advanced nasopharyngeal carcinoma can be treated more efficiently by PBT but further trials are in process to enlighten the importance

of this modality in improving the LC, life quality of patients after treatment, and OS.

Chondromas of the Base of Skull and Chondrosarcomas

Chondroma is a benign tumor of bone whereas chondrosarcoma (CS) is a malignant tumor involving the connective tissue. Since chondroma and CS of the base of the skull are at a sensitive spot due to the nearby brain - radical surgery and photon therapy are not usually performed due to the overweighing risk of neurological dysfunction. Chondromas and CS are one of the earliest tumors to be treated with proton beam therapy due to their reduced toxicity on the adjacent organs. It began when Munzenrider and Liebsch conducted an interventional study where they performed PBT combined with IMRT on 519 patients with basilar skill chondroma and CS.[26] Chondroma showed 78% whereas Chondrosarcoma showed 98% survival without local relapse and showed 11 cases of severe side effects which is arguably acceptable. Out of 11 patients, 3 faces severe side effects on the brainstem while 8 showed a varying degree of temporal lobe injuries.

Later in 2005, Noel,[27] along with his team, conducted an interventional study on a cohort of 100 patients suffering from chondroma. All the patients were given a median dose of 56 Gy of the proton beam, out of which, 42% of patients reported noticeable late side effects. However, the researchers believed that the enhancements in the delivery method, precautions, and technique might improve the results significantly.

Unilateral Tumors of Head and Neck

PT is one of the best treatment modalities for HnN cancers that arise on only one side due to its near-zero exit dose. In 2013, Kandula[28] conducted a comparative study where they provided 5 patients with PT who had already received IMRT for their pre-existing unilateral HnN tumors. It was noticed that median doses and Normal tissue V10, V30, and V50 values were considerably lower in the proton plan. Hence, they concluded that PT has relatively lower toxic effects on adjacent critical organs of the head and neck.

From 2011 to 2014, Paul et. al[29] conducted a comparative study on a group of 41 patients with one-sided cancer of a major salivary gland and squamous cell carcinoma. 23 of them were treated with IMRT and 18 were treated with PT. In patients with IMRT, the plan exceeded the maximum median doses of the brainstem, spinal cord, oral cavity, contralateral parotid, and submandibular glands as compared to PBRT. Moreover, PBRT was also associated with lower rates of acute toxicities with grade 2/+ acute dysgeusia 5.6% (65.2% in IMRT), mucositis 16.7% (52.2% in IMRT), and nausea 11.1% (56.5% in IMRT). They further concluded that PBRT is a preferable option for radiotherapy in patients with unilateral HnN cancers due to its normal tissue-sparing quality.

Reirradiation for Recurring Cancers of Head and Neck

Reirradiation refers to salvage radiotherapy that overlaps with a previously given radiotherapy. The primary purpose of reirradiation is to prevent painful death due to head & neck cancers & reduce the local spread alongside improving overall survival (OS). McDonald and his team conducted a clinical investigation where they treated 61 patients with proton reirradiation.[30] 47.5% of the patients had had salvage surgery whereas 52.5% out of 61 patients had squamous cell carcinoma and 16.4% had adenoid cystic carcinoma. The median dose of reirradiation was 66 Grays and the median follow-up time was 15.2 months and 28.7 months for those who remained alive. They noticed a median OS of 16.5 months whereas the 2-year OS was 32.7%. Toxicities greater than grade 2 were seen in 14.7% in the early phase and in 24.6% in the late phase. One of the patients died within 2 months due to acute brainstem edema which was likely caused by reirradiation.

An investigation on recurrent nasopharyngeal carcinoma (NPC) in 2019 involved 16 patients being treated with reirradiation PT.[31] The median dose was 60 Gy and the median follow-up was 10 months. The researchers reported no acute grade 3 or higher toxicity whereas 23.5% of patients presented with late ≥ 3-grade toxicities. The 18-month OS was reported to be 54.4% and the local control was 66.6%.

Unlike photon reirradiation which comes with increased chances of severe toxicity, proton reirradiation in cases of recurrent head and neck cancers is recommended due to its significantly reduced chances of toxicity and improved OS.[32]

Effect of PT on QoL in Patients with HnN Cancers

The efficacy of PBRT in improving the QoL compared to IMRT in HnN cancer patients has always been debated. Most of the studies that claim less toxicity of PT have not referred to the improvement in the QoL. However, we found three studies that showed improved QoL as compared to IMPT in patients with head and neck cancers following proton therapy.

Srivastava et al.[33] carried out a retrospective investigation in which 17 patients suffering from skull base chondroma and chondrosarcoma were treated with proton therapy over a period of six months. They noticed a slight improvement in the QoL however, those statistics and the sample size were insignificant. Therefore, the researchers concluded that it can be safely said that the QoL was at least maintained, if not improved, during the treatment of Proton Therapy.

Helen et al.[34] conducted clinical trials in which they treated 20 patients suffering from grade 2 glioma with PT. The patients received 54 Gy in 30 fractions and were assessed for the QoL post-treatment. The researchers claimed that no evidence supports the decline in patients' QoL following PT.

A comparative study by Sio et al.[35] included patients suffering from oropharyngeal carcinoma. 35 of them were given chemotherapy and Intensity Modulated Proton Therapy while 46 were given chemotherapy & IMRT. They concluded that the patients who received IMPT with chemotherapy had a better QoL than those who received IMRT with chemotherapy.

Given that, we concluded that PT provides a relatively better QoL post-treatment than IMRT in patients with HnN cancer. However, more study is required to confirm the efficacy of PT on QoL in HnN cancer patients as current research either has insignificant statistics or tiny sample sizes.

Downsides of Proton Therapy

With all these above-mentioned statistics, we can say that PBT's effectiveness is far more than that of IMRT but the major concern regarding the use of this modality is, whether this technique can be employed for patient welfare at a large scale or not. Because if we take a look at all the trials that were conducted to assess its efficacy, it appears that the number of patients receiving this therapy was not that ample based on which we can assign it as a treatment of choice for HnN cancers.

Apart from sample sizes, cost-effectiveness has also emerged as an obstacle as the establishment of proton therapy centers requires a substantial investment. Besides this, on clinical grounds, some approximations and uncertainties have become a hurdle in obtaining complete benefits out of this modality. As in the case of relative biological effectiveness (RBE), there's a difference in its assumed value and that which is encountered actually

Future Of Proton Therapy

Besides its downsides - it can be safely estimated that PT is relatively one of the latest and safest advancements in the field of radiotherapy. Furthermore, recent advancements and enhancements in PT delivery method, onboard imaging, and formulating an automated proton plan have widened the use of PBT among radio-oncologists.

One of the major areas that require advancement in PBT is its cost-effectiveness. Nonetheless, PT is an emerging technology and hardly 25 years old. Therefore, it has a lot of room for further literature to be written and investigations to be carried out. For example, there is no adequate literature to support the effectiveness of PT to improve QoL in HnN cancer patients. Most of the literature that has addressed the QoL in HnN cancer patients' post-PT either has a tiny sample size of insignificant stats.

Conclusion

PBRT is a preferable mode of radiotherapy for HnN cancer patients as it targets the tumor cells with much more accuracy and spares normal tissues as compared to photon therapy. Not only that PBRT had lower incidents of acute and late toxicities but it also proved to be significant in improving OS, LC, and QoL as compared to IMRT in HnN cancer patients. However, the studies that prove the efficacy of PBRT in improving the QoL as compared to IMRT in HnN cancer patients had small sample sizes and need further research.

Conflict of Interest

The authors declare no conflicts of interest.

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