ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 5, Issue – 3, May - 2022, Page No. : 248 - 253

Proton therapy in oral cancer

[1]Deepak Narang, Reader, Department of Oral Medicine and Radiology, Deshbhagat Dental College, Punjab, India.

[2]Tejveer Singh, Professor, Department of Oral and maxillofacial surgery, Deshbhagat Dental College, Punjab, India.

Corresponding Author: Deepak Narang, Reader, Department of Oral Medicine and Radiology, Deshbhagat Dental College, Punjab, India.

Citation of this Article: Deepak Narang, Tejveer Singh, "Proton therapy in oral cancer", IJDSIR- May - 2022, Vol. – 5, Issue - 3, P. No. 248 – 253.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Radiation therapy is a standard treatment modality for head and neck cancer. However, delivery of radiation therapy to areas of disease in close proximity to critical normal structures, can potentially result in severe toxicity. While advances in conformal radiation techniques, like intensity-modulated radiation therapy (IMRT) have led to improvements in the therapeutic ratio, significant treatment-related morbidity still exists.

Proton therapy has evolved into more sophisticated and costly intensity-modulated proton therapy and has resulted in even greater dose reduction to normal critical structures. Early clinical studies in head and neck cancers, especially for Tumors of the oral cavity and paranasal sinuses, suggest that proton therapy is excellent in terms of local control and is comparable to intensity-modulated radiation therapy photons but with lower rates of morbidity.

Proton therapy is an emerging and promising treatment modality for oral cancers, because of the potential to improve organ sparing and/or safely escalate doses of radiation delivered. Localized radiation therapy to limited areas of the head and neck, such as for a lateralized salivary gland tumor, can be delivered with proton therapy using current techniques.

Proton therapy to the bilateral neck, as required for locally-advanced disease, will require the development of intensity-modulated techniques, intensity-modulated proton therapy (IMPT), using pencil beam scanning. Determining the proper role of proton therapy for oral cancer should be done in the setting of clinical studies, with careful attention to quality assurance, and meaningful measures of disease control, toxicity and quality of life.

The aim of the present review is to examine the value of proton therapy in relation to other treatment modalities in head and neck cancer.

Keywords: Oral cancer, Proton therapy, Radiation therapy.

Introduction

The Food and Drug Administration approved proton therapy utilization as early as 1988. Over the last decade,

there has been a rapid increase in the number of operating proton facilities in the United States, from 2 in 2003 to 22 in 2016.While proton therapy utilization has continued to rise throughout the cancer community, there is an ongoing debate within the cancer community as to whether widespread clinical use is justified given the significant cost[1].

Radiation therapy is recommended in more than two-thirds of oral squamous cell carcinomas (OSCC). Recent publications have demonstrated the importance of the quality of the radiation therapy offered to OSCC patients[2].

Radiation plays a critical role in the treatment of patients with oral cancer in the definitive, adjuvant, as well as recurrent salvage settings. Due to the anatomy of the head and neck and the close proximity of the tumor target to normal critical structures at risk, such as optic nerves, orbits, salivary glands, brain, pituitary grand, carotid arteries, reducing radiation toxicity is paramount[3].

The dose distribution with proton therapy limits dose deposition after a finite distance from the Bragg peak and more normal tissue sparing is expected. Therefore, there has been an increased interest in harnessing the unique physical properties of proton therapy in order to dose escalate radiation delivered to the tumor while decreasing dose to normal tissue with the aim of decreasing treatment toxicity[4].

There are many studies in the development that are assessing the benefit of protons in head and neck cancer. In a study by van der Laan et al, IMPT was superior to intensity-modulated radiation therapy (IMRT) in terms of decreased dose to pharyngeal constrictors, thereby estimating an 8% decrease in grade II to IV dysphagia. Others have proposed that a reduction in dose to the posterior fossa achievable with IMPT may result in decreased treatment-related fatigue. However, these dosimetric-based studies have not yet been analyzed to assess whether they do in fact translate to the proposed clinical benefit[5].

The goal of the present review was to assess the technical and physical requirements that are specific to proton therapy for oral cancer of usual location (oral cavity, larynx, tongue, buccal mucosa, palate). A brief explanation of the physical properties of protons is provided.

Treatment planning for oral cancer – proton therapy

Computed tomography (CT) images are used to arrange proton therapy for the treatment of mouth cancer. The CT scan is often acquired using a single energy spectrum, such as single-energy CT. The proton-stopping power ratio (SPR) from the HU is calculated using a calibration technique based on the stoichiometric composition of the tissues. In single-energy CT, however, each voxel's data is confined to a single dimension. This is problematic since the HU–SPR calibration curves for human tissues do not have a one-to-one correspondence[6,7].

In the presence of materials with variable stoichiometric composition (such as those in metal implants and dental fillings) and complicated heterogeneities, calibration uncertainties can be crucial in HNSCC. Because of image artefacts, materials in the beam entry induce range uncertainties. Dual energy CT, also known as multi-energy CT, has the potential to improve CT to SPR conversion and reduce range uncertainties to less than 1%. It could be especially useful in instances where implanted materials are causing greater calibration uncertainty[7].

In the coming years, dual-energy CT should be particularly important to oral cancer. Aside from dualenergy CT, MRI-based CT has recently been

developed to increase proton range estimation accuracy. Because pseudo-CT approaches are susceptible to metal-induced MRI distortions, they may not be able to overcome the difficulties caused by metallic implants in patients with oral cancer. As a result, proton therapy planning may necessitate greater dental care prior to irradiation. Proton CT is still in its early stages of development; nonetheless, customised proton probes could be a new solution for some uncertain beam pathways[8,9].

In brief, HU or SPR calibration uncertainties and the prevalence of metal materials in patients require caution in the use of CT in oral cancer. Therefore, oral cancer is a relevant area of investigation for improved planning imaging.

Notwithstanding all possible therapeutic gains associated with proton therapy dose distribution, its use in head and neck has been challenged by heterogeneity of volume density, especially sinuses (air gaps, bone) and tumor volume changes and anatomic shifts over the course of treatment. Changes in density and volumes of the course of treatment may adversely impact dose delivery

Advances in photon-based external beam radiation therapy

Technical advancements in photon-based radiotherapy, such as with 3-D CRT and IMRT, allow for a more conformal deposition of the high-dose region and therefore, an improved therapeutic ratio. Three-dimensional conformal planning utilizes multiple radiation beams shaped by a static multi leaf collimator in an effort to better conform radiation dose to the targets of interest.

IMRT further improves this process, through the use of a dynamic multi leaf collimator that can modulate both the shape and intensity of individual beams to create an optimal dose distribution to treat disease and further spare normal tissues. The addition of daily image guidance (IGRT) has led to a decrease in the planning target volume (PTV) for radiation, which has the potential of decreasing normal tissue exposure to high-dose radiation without compromising locoregional control[10].

Although direct comparisons of IMRT to conventional radiation are limited, the literature supports its use given the promising results obtained with respect to disease control, toxicity, and quality of life. The University of California-San Francisco has reported their experience of treating nasopharynx cancer with IMRT[11].

Previous researches on proton therapy in oral cancer

As per Lin A et al, in their in their study, a total of 35 patients were treated, and at a median follow-up of 21.8 months, locoregional control was 100%. An update of their experience, which included 67 patients with a median follow-up of 31 months, continued to show an excellent 4-year locoregional control rate of 98%. Compared to conventional radiation, IMRT is superior in its ability to reduce dose to critical normal organs.[12].

A matched case-control study Jabbari et al comparing IMRT to standard radiotherapy for oral cancer found that xerostomia and quality of life improved over time (starting at 6 months post-treatment) after IMRT, but not after standard RT[13].

Advantages

Unlike photon radiation, proton therapy offers the added advantages of less dose delivered to tissues proximal to the tumor and rapid dose fall off at the distal edge of the tumor. This allows for potential gains with respect to normal organ sparing and provides opportunities for potential dose escalation. Applied in the treatment of head and neck cancer, proton therapy could be utilized in the following ways

- Dose escalation for cancers where locoregional control is currently limited by an inability to adequately deliver therapeutic doses without excessive risk of toxicity.
- Minimizing exposure of normal tissues and decreasing toxicity in patients for whom long-term control is obtained with currently-prescribed doses, but at the cost of potential significant toxicity[14].

Current indications and future applications

There are several indications for delivering proton therapy for Oral cancer. One indication is for treating patients with salivary gland cancers. Previously, these patients were treated with IMRT, but are now currently treated with double scattering or uniform scanning proton therapy.

When compared to IMRT, proton therapy can decrease dose to adjacent normal organs such as the brainstem, cochlea, temporal lobe, and the contralateral salivary glands. Other dosimetric advantages include limiting the area of low dose radiation delivered to normal tissues. These dosimetric gains could potentially translate to improved long-term results such as decreasing rates of chronic xerostomia and radiation-induced secondary malignancies[15].

The potential decrease in radiation-induced malignancy with proton therapy is of particular importance, given the increasing incidence of oropharynx cancer, which is typically diagnosed in younger patients, and for whom long-term disease control is likely.

Pencil beam scanning is being used for the treatment of base of skull malignancies. Treatment of Tumors at this particular site with conventional radiation has traditionally been limited by an inability to deliver adequate doses of radiation without exceeding constraints on critical structures in the brain and optic apparatus[16].

Unlike double scattering or uniform scanning proton therapy, pencil beam scanning allows for enhanced conformal dose around critical structures through modulation of dose in depth, while retaining the rapid dose fall-off from the Bragg-Peak effect.

For both of these indications, it is critical to enroll patients on clinical trials or registries to collect outcome data, thereby assessing the effectiveness and role of proton therapy. Another indication is for reirradiation for recurrent head and neck cancer[17].

Patients who require oral cavity reirradiation generally have poor outcomes, with median survival typically less than 12 months, and reirradiation limited by treatment-related morbidity.

Proton therapy, by potentially allowing for high-dose re irradiation while decreasing normal tissue exposure, may lead to improved outcomes. Lin et al. reported results on 16 patients reirradiated with protons for recurrent nasopharyngeal carcinoma, for which 2-year local control and overall survival were approximately 50%. Priority was given to minimizing toxicity (no patients experienced CNS toxicity) over tumor coverage[18].

Current efforts include the development of pencil beam scanning proton therapy for treatment of the comprehensive, bilateral neck, which is required in the majority of patients with locally advanced mucosal squamous cell carcinoma of the oral cavity.

In order to take full dosimetric advantage of proton therapy, treatment requires a small beam spot size, which can be difficult to achieve when treating a superficial target, such as the neck. Presently at our institution, the minimum deliverable energy for pencil beam scanning is 100 MeV, requiring the use of a range shifter for treatment of targets that extend within 7.5 cm water-equivalent depth of the skin surface.

Further research to quantify and minimize the impact of image artifacts is necessary to ensure robust proton therapy. Adaptive therapy and replanning during the course of therapy may be a clinical necessity in proton therapy given the dosimetric sensitivity to anatomical changes. While from a dosimetric perspective, proton therapy appears superior to IMRT, it is still unclear whether these physical advantages translate to improved clinical outcomes.

Therefore, the importance of enrolling patients who are to receive proton therapy on clinical studies cannot be overstated. These studies should have carefully described clinical endpoints, such as disease control, toxicity, and quality of life, and patients receiving proton therapy should ideally be compared to a control cohort receiving IMRT[19].

Conclusion

For patients with head and neck malignancies, proton therapy is a promising and growing radiation therapy approach. The physical advantages of protons, such as quick dose fall off, may improve the ability to increase radiation dose or better spare organs at danger.

Although preliminary clinical evidence is encouraging, new techniques such as pencil beam scanning and IMPT need to be further developed in order to overcome current constraints and potentially increase the indications for proton treatment. Patients should ideally be treated as part of a clinical trial and compared to a similar cohort of patients who received IMRT.

References

1. Fairchild A, Straube W, Laurie F, Followill D. Does quality of radiation therapy predict outcomes of multicentre cooperative group trials? A literature reviews. Int J Radiat Oncol Biol Phys 2013; 87:246–60. https: //doi .org/ 10. 1016/ j. ijrobp.2013.03.036.

2. Ohri N, Shen X, Dicker AP, Doyle LA, Harrison AS, Showalter TN. Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials. J Natl Cancer Inst 2013; 105: 387–93. https: // doi .org/ 10. 1093/ jnci/ djt001.

3. Wuthrick EJ, Zhang Q, Machtay M, Rosenthal DI, Nguyen-Tan PF, Fortin A, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. J Clin Oncol 2015; 33 :156– 64. https: //doi. Org /10.1200 / JCO. 2014. 56. 5218.

4. McDowell L, Corry J. Radiation therapy quality assurance in head and neck radiotherapy – moving forward. Oral Oncol 2019; 88:180–5. https://doi.org/ 10.1016/j.oraloncology.2018.11.014.

5. Van der Laan HP, van de Water TA, van Herpt HE, Christianen ME, Bijl HP, Korevaar EW, Rasch CR, van t Veld AA, van der Schaaf A, Schilstra C, et al. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: a planning comparative study. Acta Oncol 2013 Apr; 52 (3): 561-569.

6. Bar E, Lalonde A, Royal G, Lu H-M, Bouchard H. The potential of dual-energy CT to reduce proton beam range uncertainties. Med Phys 2017; 44:2332–44. https://doi.org/10.1002/mp.12215.

7. Wohlfahrt P, Möhler C, Stützer K, Greilich S, Richter C. Dual-energy CT based proton range prediction in head and pelvic tumor patients. Radiother Oncol 2017; 125:526–33. https: //doi .org/ 10. 1016 /j. radonc.2017.09.042.

8. Hudobivnik N, Schwarz F, Johnson T, Agolli L, Dedes G, Tessonnier T, et al. Comparison of proton therapy treatment planning for head Tumors with a pencil beam algorithm on dual and single energy CT images. Med Phys 2016; 43:495. https://doi.org/10.1118/1.4939106.

9. Park PC, Schreibman E, Roper J, Elder E, Crocker I, Fox T, et al. MRI-based computed tomography metal artifact correction method for improving proton range calculation accuracy. Int J Radiat Oncol Biol Phys 2015; 91:849–56. https://doi.org/10.1016/j.ijrobp.2014.12.027.

10. Chen AM, Farwell DG, Luu Q, et al. Evaluation of the planning target volume in the treatment of head and neck cancer with intensity-modulated radiotherapy: what is the appropriate expansion margin in the setting of daily image guidance? Int J Radiat Oncol Biol Phys 2011; 81:943-9.

11. Sultanem K, Shu HK, Xia P, et al. Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California San Francisco experience. Int J Radiat Oncol Biol Phys 2000; 48:711-22.

12. Lin A, Kim HM, Terrell JE, et al. Quality of life after parotid sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys 2003; 57:61-70.

13. Jabbari S, Kim HM, Feng M, et al. Matched case-control study of quality of life and xerostomia after intensity modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. Int J Radiat Oncol Biol Phys 2005; 63:725-31.

14. Marur S, D'Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010; 11:781-9.

15. De Crevoisier R, Bourhis J, Domenge C, et al. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. J Clin Oncol 1998; 16:3556-62.

16. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2006; 64:382-91.

17. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with splitcourse concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol 2007; 25:4800-5.

18. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck 2008; 30:281-8.

19. Lin R, Slater JD, Yon moto LT, et al. Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy--dose-volume histogram analysis. Radiology 1999; 213:489-94.