Kiafi *et al. J Cancer Metastasis Treat* 2024;10:31
DOI: 10.20517/2394-4722.2024.79

Journal of Cancer Metastasis and Treatment

Review

Open Access

Check for updates

Photon *vs.* proton radiation therapy in head and neck cancer: a review of dosimetric advantages and patient quality of life

Panagiota Kiafi[1,#], Marina Chalkia[1], Maria Anthi Kouri[1,2,#], Georgios Patatoukas[1], Nikolaos Kollaros[1], Andromachi Kougioumtzopoulou[1], Ourania Nikolatou-Galitis[3], Efthymios Kyrodimos[4], Christos Perisanidis[5], Vassilis Kouloulias[1], Kalliopi Platoni[1]

[1]2nd Department of Radiology, Medical School, Attikon University Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece.
[2]Medical Physics, General Hospital GHA Korgialeneio Mpenakeio-Hellenic Red Cross, Athens 11526, Greece.
[3]Department of Dental School, Stomatology Clinic, National and Kapodistrian University of Athens, Athens 11527, Greece.
[4]1st Department of Otolaryngology, National and Kapodistrian University of Athens, Medical School, Hippocration Hospital, Athens 11528, Greece.
[5]Department of Prosthodontics, National and Kapodistrian University of Athens, Dental School, Evaggelismos General Hospital, Athens 10676, Greece.
[#]Authors contributed equally.

Correspondence to: Dr. Panagiota Kiafi, 2nd Department of Radiology, Medical School, Attikon University Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece. E-mail: pkiafi@yahoo.com; Prof. Kalliopi Platoni, 2nd Department of Radiology, Medical School, Attikon University Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece. E-mail: polaplatoni@gmail.com

How to cite this article: Kiafi P, Chalkia M, Kouri MA, Patatoukas G, Kollaros N, Kougioumtzopoulou A, Nikolatou-Galitis O, Kyrodimos E, Perisanidis C, Kouloulias V, Platoni K. Photon *vs.* proton radiation therapy in head and neck cancer: a review of dosimetric advantages and patient quality of life. *J Cancer Metastasis Treat* 2024;10:31. https://dx.doi.org/10.20517/2394-4722.2024.79

Received: 29 Jul 2024 **First Decision:** 8 Nov 2024 **Revised:** 23 Nov 2024 **Accepted:** 9 Dec 2024 **Published:** 19 Dec 2024

Academic Editor: Ciro Isidoro **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Radiotherapy (RT) is a cornerstone in the management of head and neck cancer (HNC), with the choice of RT type profoundly affecting patient outcomes, symptom severity, and quality of life (QoL). This review examines photon and proton RT types for HNC, focusing on dosimetric advantages, efficacy, and side effect profiles. Understanding these factors is crucial to minimizing adverse effects, enhancing QoL for patients, and effectively improving oncology's clinical praxis. While photon-based therapies, such as intensity-modulated radiation therapy and volumetric modulated arc therapy, are widely used and effective, proton therapy, including intensity-modulated

proton therapy (IMPT) and pencil beam scanning (PBS), offers distinct physical advantages. Photon therapies allow for precise dose distribution but often result in higher integral doses to surrounding healthy tissues. In contrast, protons enable highly conformal dose distributions with minimal exit dose beyond the target, a property that significantly reduces radiation exposure to organs at risk. Background research and comparative analysis demonstrate that proton therapy techniques, particularly IMPT and PBS, outperform photon-based methods in sparing critical structures and thus reducing acute and late treatment-related morbidities, such as xerostomia and dysphagia. As a consequence, patient-reported outcome measures and the overall QoL results suggest that proton therapies lead to better treatment results with fewer severe side effects and improved symptom management. In conclusion, proton therapy, particularly IMPT, shows promise as a treatment of choice for HNC, minimizing toxicities and enhancing QoL. However, continued research and evidence-based approaches are still essential to properly validate and refine proton therapy applications in HNC treatment paradigms and also effectively translate them into future clinical practice.

Keywords: Radiation therapy (RT), IMPT, PBS, IMRT, VMAT, head and neck cancer, patient quality of life, symptoms, toxicity, dosimetry

INTRODUCTION

Epidemiology and significance of HNC

Head and neck cancer (HNC) represents a critical and growing challenge in global oncology. With over 600,000 new cases diagnosed annually and more than 300,000 deaths, HNC stands as the seventh most common cancer worldwide[1-3]. This alarming prevalence is driven by an aging population and the persistent adoption of high-risk behaviors particularly in developing regions[2,3]. As a result, the burden of HNC is expected to rise substantially in the coming decades. Characterized by malignancies arising from squamous cells in the mucosal linings of the head and neck, HNC encompasses cancers of the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, and salivary glands. Laryngeal cancer remains the most frequently diagnosed among these[4]. The etiological landscape of HNC is dominated by prolonged tobacco use, alcohol abuse, and high-risk human papillomavirus infections[5-7].

Current treatment landscape and challenges

To address the growing burden of the disease and its associated challenges, significant advances in treatment approaches have contributed to a decline in cancer-related mortality, leading to an increasing population of HNC survivors[8]. This decline is largely attributed to the advancements in various treatment modalities, including surgery, chemotherapy, and particularly, radiotherapy[5].

Radiotherapy (RT) has been a cornerstone in the treatment of HNC, evolving significantly over the years to improve precision and minimize adverse effects. Traditional photon therapy, which has long been a standard approach, has seen significant advancements with the development of more sophisticated techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). More recently, proton therapy has emerged as a promising alternative, offering potential benefits in reducing the collateral damage to surrounding healthy tissues[9].

The treatment of HNC is inherently complex, often necessitating a multidisciplinary approach tailored to the specific characteristics of the tumor. Radiotherapy, whether through photons or protons, plays a pivotal role in this regimen. Both types of RT aim to maximize tumor control while sparing healthy tissues as much as possible. However, this goal is particularly challenging in the head and neck region due to the concentration of critical structures - such as the salivary glands, oral mucosa, pharyngeal muscles, larynx, spinal cord, and optic pathways - that are highly sensitive to radiation[9]. Even low doses to these organs can

result in debilitating side effects, including xerostomia, dysphagia, and oral mucositis, which profoundly affect speech, swallowing, and overall quality of life (QoL)[10]. After all, the acute and long-term side effects associated with RT can profoundly affect patients' daily lives[3,11,12]. Additionally, excessive radiation exposure to adjacent healthy tissues may increase the risk of long-term complications such as fibrosis, vascular damage, or secondary malignancies, emphasizing the importance of minimizing dose spillover[13]. Precision in radiation delivery is crucial not only for protecting these sensitive structures but also for achieving an optimal therapeutic ratio, where the dose to the tumor is maximized without exceeding the tolerance of normal tissues. As advances in radiotherapy continue, there is a growing focus on the clinical benefits and dosimetric precision provided by both proton and photon radiation therapy.

Clinical benefits and dosimetric precision of proton *vs.* photon radiation therapy

Proton therapy, with its unique ability to deliver targeted doses through the Bragg peak phenomenon, enhances the therapeutic ratio by reducing collateral dose to healthy tissues, thereby lowering the probability of both acute and chronic toxicities[14]. Furthermore, precise dosimetry is essential for overcoming challenges such as tumor hypoxia and anatomical changes during treatment, which can affect the tumor's response to radiation[15]. By reducing the dose to organs at risk (OARs), proton therapy also mitigates the risk of radiosensitization, where sublethal damage to healthy tissues increases their vulnerability to subsequent radiation exposure or other therapies[16].

Photon-based therapies, despite their efficacy, often involve a higher volume of healthy tissue being exposed to low-dose radiation, which can lead to increased acute radiation responses. These include mucositis, radioepidermitis, lymphocytopenia, and other side effects that impair patients' well-being and recovery[3,11]. This exposure is particularly challenging as it can inhibit lymphocyte proliferation and function, leading to a spectrum of toxicities that affect patients' overall health and quality of life during and after treatment[3,11]. Speech, swallowing, and breathing capabilities are commonly harmed in HNC patients undergoing radical treatments[9]. Among these, oral mucositis is a painful disorder characterized by ulcers in the mouth, arising from the rapidly dividing cells in the oral cavity, which are especially vulnerable to irradiation damage[17]. Additionally, radiation-induced mucositis is a significant source of pain and consequently reduces QoL[9]. Another debilitating side effect commonly experienced by HNC patients is radiation-induced xerostomia, or dry mouth, which also severely impacts their quality of life[18].

Proton therapy, in contrast, offers a distinct dosimetric advantage due to its physical properties, particularly the Bragg peak phenomenon, which refers to the sharp increase in energy deposition by protons at a specific depth in tissue, allowing for highly localized dose delivery with minimal exit dose beyond the target. This property reduces radiation exposure to surrounding healthy tissues and minimizes side effects[9,19]. Despite its theoretical superiority, the relative biological effectiveness (RBE) - a measure of the biological damage caused by a given type of radiation - of protons compared to photons is an area of active research. While the RBE for protons is typically considered to be 1.1, indicating that protons are slightly more effective than photons in causing biological damage, this value can vary near the Bragg peak, complicating exact dosimetric comparisons[6,7]. To better understand how these dosimetric advantages influence treatment strategies, it is essential to consider their direct implications on treatment decisions and outcomes.

Implications for treatment decisions in HNC

The selection of the appropriate RT type is a critical decision in the treatment of HNC due to its profound impact on patient outcomes, including the severity of symptoms, the correlation of symptoms with dosimetric values, and related toxicity and overall QoL[20]. While proton therapy has shown promise in reducing severe radiation-induced complications and potentially lowering rehabilitation costs, photon-based therapies remain widely used and effective. This review aims to conduct an extensive examination of

the various RT types available for HNC, with a particular focus on comparing their dosimetric advantages, efficacy, and side effect profiles. Understanding these factors seems crucial, as the ultimate goal of any therapy is not only to treat cancer but also to minimize adverse effects and enhance the QoL for patients. By evaluating the correlation between different RT types and their impact on patient symptoms and QoL, we seek to address a fundamental question in oncology: how can we optimize treatment to ensure that the benefits of cancer control are not overshadowed by the burden of treatment-related side effects? This inquiry is vital in advancing patient-centered care and guiding future therapeutic choices in the management of HNC.

ASSESSING PATIENTS QUALITY OF LIFE

Investigating patients' subjective experiences and symptoms in prospective clinical comparative effectiveness research (CER) for process interventions or oncology treatments is crucial for guiding decision-making procedures[21]. Background research regarding the assessment of QoL in HNC patients indicates that the use of EORTC QLQ-C30 and QLQ-HN35 questionnaires constitutes the gold standard for that assessment. These standardized tools facilitate comprehensive evaluations at various treatment time points, capturing both global QoL (via QLQ-C30) and specific treatment-related side effects such as local pain, xerostomia, swallowing difficulties, sticky saliva, and weight loss (via QLQ-HN35). The majority of studies employ these tools pre-treatment, post-treatment, and in extended follow-up periods, offering a longitudinal perspective on patients' well-being throughout their cancer journey[22-24]. A number of published researches, apart from the QLQ-C30 and QLQ-HN35, provided insights into patient-reported outcomes, and augmented their assessments with additional tools in order to capture further aspects of patient experiences. These supplementary methods included resilience scales, symptom inventories, and functional impairment indices, enhancing the multidimensional understanding of how HNC and its treatments impact patients' QoL[25,26]. However, due to the diversity of assessment tools, variability in data presentation across the studies hinders direct quantitative comparisons, emphasizing the need for standardized reporting practices in future research endeavors to enable more precise comparisons across studies.

According to literature, researchers evaluating radiation therapy for head and neck cancers have also utilized additional methods to assess patient's QoL. These include the MD Anderson symptom inventory for head and neck cancer (MDASI-HN), which evaluates symptom severity such as pain, fatigue, and emotional distress[27-29]. For specifically evaluating swallowing-related QoL, the MD Anderson Dysphagia Inventory (MDADI) assesses functional and emotional aspects associated with dysphagia. This method includes items focused on swallowing difficulty, eating duration, fear of choking, and the broader impact of swallowing issues on daily activities. On the other hand, patient-reported outcome measures have also been used to capture self-reported data on health status, symptoms, and overall well-being[30]. Many studies have used visual analog scales alongside other questionnaires that enable patients to rate specific aspects of their health or symptoms on a continuous scale[31,32]. Additionally, Performance Status Scales like the Karnofsky Performance Status Scale and ECOG Performance Status gauge functional abilities and their influence on QoL[33,34].

Participant demographics varied widely across studies, with sample sizes ranging from 30 to 1,083 individuals. The predominant inclusion of smaller cohorts (21 out of 24 studies with fewer than 200 participants) underscores the logistical challenges in conducting large-scale QoL studies in this patient population. Nevertheless, studies by Liao *et al.*, Van den Bosch *et al.*, and van der Laan *et al.* represented significant outliers with larger participant cohorts, offering valuable insights into QoL variations across diverse patient demographics and treatment modalities[23,24,35].

The findings underscore consistent trends in QoL trajectories: initial decline during the active treatment phase followed by gradual improvement post-treatment[20]. This pattern was evident across various treatment techniques, including radiotherapy (IMRT, VMAT), surgical interventions, and combinations thereof. Notably, studies by Cengiz *et al.* and Lu *et al.* highlighted sustained or improved QoL outcomes even in long-term follow-ups up to 24 years, indicating resilience and adaptation among certain patient groups[36,37].

It is important to mention that throughout background research, the challenges associated with data uniformity and statistical comparability remain the critical existing limitations. Standardizing data collection methodologies and implementing new assessment tools could mitigate these challenges, ultimately fostering a more nuanced understanding of treatment impacts on QoL in HNC patients. Moving forward, efforts to enhance methodological rigor and broaden the scope of QoL assessment tools will be crucial in refining patient-centered care strategies and improving outcomes in this vulnerable population.

THE IMPORTANCE OF RADIATION THERAPY TYPE SELECTION

HNC includes a range of diverse diseases that arise from the mucosal surfaces of the oral cavity, pharynx, and larynx. Recent advances in both molecular and clinical research highlight the variability observed across different subsites within the head and neck region[38]. The high heterogeneity and molecular complexity underscore the need for targeted therapies that offer precise dose distribution and sparing of surrounding healthy tissues, such as the parotid glands, the oral cavity, and the pharyngeal constrictors, which are highly radiosensitive. The type of irradiation, whether photon or proton therapy, significantly influences dose distribution, making the selection of appropriate radiation treatment type crucial[39]. Thus, a comprehensive analysis of the dosimetric profiles of each RT type is essential. Furthermore, in the case of HNC RT, it is important to acknowledge that significant changes in patient anatomy, such as weight loss and tumor shrinkage, can alter the depth of the target and the position of OARs, thus impacting the accuracy of dose distribution. This constitutes another important factor in the adequate selection of treatment. However, the effectiveness of this analysis should focus not only on the radiobiological cancer destruction and patient's treatment but also on the therapeutic effects, including symptoms, dosimetric toxicities to OARs, and eventual impacts on patients' QoL, as previously stated.

In terms of RT, IMRT and VMAT are advanced photon-based radiation techniques widely used in the treatment of HNC. These methods enable the delivery of precise radiation doses with steep dose gradients, significantly enhancing the sparing of surrounding healthy tissues compared to traditional 3D conformal radiotherapy[40,41]. This precision significantly reduces treatment-related toxicity and potentially improves patients' QoL. More precisely, IMRT utilizes multiple static beams with varying intensities, while VMAT delivers radiation through continuous arcs, adjusting the dose rate and gantry speed dynamically. Both techniques allow for more tailored dose distributions, effectively targeting tumors while minimizing exposure to critical structures such as the salivary glands, spinal cord, and brainstem[42]. On the other hand, Proton radiation therapy offers distinct physical advantages over photon therapy due to the Bragg peak phenomenon, which allows protons to deposit their maximum energy directly within the tumor with minimal exit dose, further enhancing the protection of adjacent normal tissues[43]. In HNC, this precise dose distribution is particularly beneficial, potentially reducing long-term side effects and improving functional outcomes for patients[44]. For a more comprehensive understanding of the effects of these advanced techniques on dose distribution, QoL, and symptom severity, a detailed comparison between IMRT, VMAT, and proton therapy would be beneficial. This analysis will illuminate the distinct advantages and potential drawbacks of each treatment approach, especially regarding their influence on patient outcomes.

Comparing intensity-modulated photon radiotherapy and intensity-modulated proton therapy

Both techniques represent two sophisticated approaches that achieve maximizing tumor control while minimizing exposure to surrounding healthy tissues. The primary advantage of IMRT is its ability to deliver high radiation doses to complex tumor geometries while sparing adjacent normal tissues. However, photons, due to their physical properties, deposit energy along their entire path in the biological matter, leading to a higher integral dose to non-target healthy tissues. Contrary to that, IMPT uses protons, which have distinct physical advantages. Protons possess a finite range in tissue, culminating in the Bragg peak - a sharp increase in dose deposition just before they stop. This enables highly conformal dose distributions with simultaneous minimal exit dose, reducing radiation exposure to the surrounding healthy tissues. Therefore, this superior dose distribution of IMPT holds a potential role in reducing treatment-related dosimetric toxicities and, therefore, improving patient outcomes and QoL.

Dosimetric characteristics

Dosimetric studies have highlighted the benefits of IMPT in sparing normal tissues[45]. Research indicates that IMPT can significantly reduce doses to critical structures of normal tissue such as the parotid glands, the contralateral submandibular, the spinal cord, the oral cavity, and the brainstem[46]. Grant *et al.* and Ladra *et al.* focused on the more radiosensitive group of pediatric patients and also demonstrated that IMPT resulted in lower doses to normal tissues compared to IMRT, thereby significantly reducing long-term side effects[47,48]. Additionally, a study focusing on oropharyngeal carcinoma (OPC) worked on the assumption that higher radiation doses to OARs lead to the development of post-treatment symptoms such as mucositis, nausea, dysphagia, and vomiting[49]. Indeed, the results suggested that patients with OPC treated with IMPT may encounter reduced and milder adverse effects during and after therapy[49]. This conclusion was attributed to the decreased beam path toxicities of IMPT due to lower doses to the critical healthy structures. This finding was further supported by Sio *et al.*'s study, which also focused on patients with oropharyngeal cancer[50]. Although IMRT plans can expose non-target organs to very low radiation doses, thereby causing low dosimetric toxicities, the superiority of IMPT in terms of dose distribution is apparent [Figure 1][50].

A comparative dosimetric analysis for OPC patients treated with IMPT showed substantial reductions in mean doses to the hard palate, the mandible, the anterior and posterior oral cavity, the larynx, and the esophagus[49]. Furthermore, the same study proved that lower doses in central nervous system structures led to a decrease in symptoms such as vomiting and nausea[49]. These findings underscored the dosimetric superiority of IMPT over IMRT in sparing healthy tissue from extra radiation exposure[46]. Moreover, recent advancements have underscored the critical role of IMPT in re-irradiation for HNC patients, a group often facing complex cumulative dose challenges. Studies indicate that IMPT's precision can mitigate risks associated with overlapping radiation fields, particularly in OARs[51]. This capability is essential in reducing complications such as carotid blowout syndrome and osteoradionecrosis, which are directly linked to excessive cumulative doses to the carotid arteries and bone structures, respectively, as Embring *et al.* observed[51]. For instance, cumulative dose constraints for carotid arteries have been established at approximately 120 Gy to prevent catastrophic vascular events, emphasizing the importance of sparing strategies achievable with proton therapy[52]. Moreover, IMPT demonstrates enhanced control in composite dose-volume histograms, allowing tailored re-irradiation plans that prioritize tumor control while minimizing severe late toxicities[53]. However, it is important to mention that despite the hopeful dosimetric analysis of IMPT, the efficacy and safety of the method in the clinical context are critical and need to be further studied and analyzed.

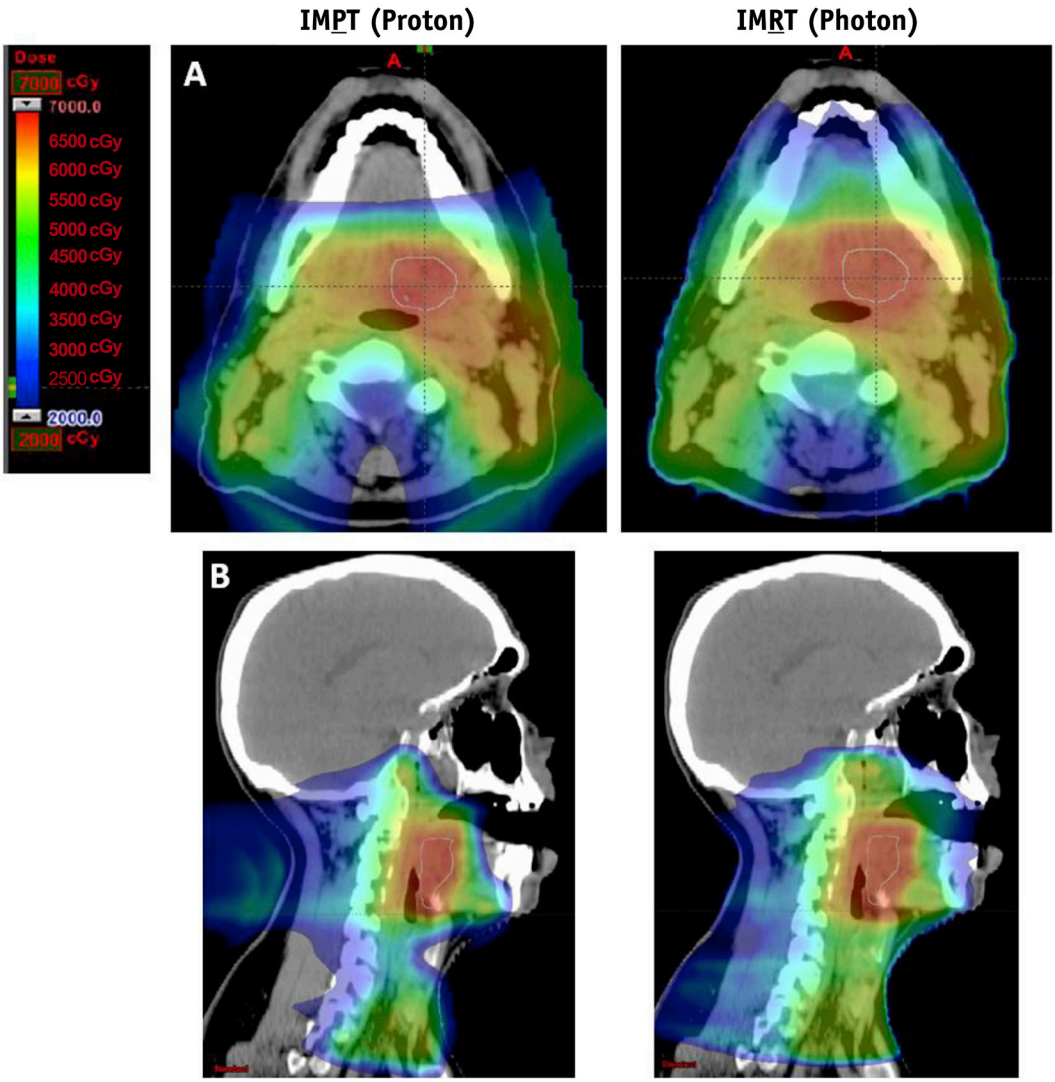


Figure 1. (A) Axial and (B) sagittal images of the dosimetric distribution in IMPT and IMRT, for a patient with oropharyngeal cancer (OPC) after radiation therapy treatment planning. No copyright This work has been identified as being free of known restrictions under copyright law, including all related and neighboring rights. Copyright 2016, Reproduced from Ref.[50].

Patient symptoms and quality of life

While dosimetric advantages of IMPT are evident in literature, the translation of these benefits into improved clinical outcomes and patients' QoL remains crucial. Radiotherapy-induced symptom burden is a significant concern, especially in HNC, where patients experience multiple local and systemic inflammatory responses. Studies using validated PRO tools, such as the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN), have attempted to quantitatively document these effects during the first 3 months post-treatment[21,50]. Their retrospective analysis of OPC patients who were treated with concurrent chemoradiation using IMPT and IMRT revealed potential reductions in symptom burden during the first three months post-treatment with the aid of IMPT[50]. Notably, IMPT was associated with fewer symptoms related to food taste and appetite in the subacute and chronic phases of treatment[50]. However, despite these interesting findings, the overall improvement in QoL using IMPT, as measured by the MDASI-HN PRO, was not able to substantiate an improvement during treatment due to the small cohort used[50].

Other studies corroborate these observations. For example, the study of Hutcheson *et al.* indicated that 20% of patients receiving IMPT required a feeding tube compared to 48% of those receiving IMRT, indicating a potential clinical benefit of IMPT in reducing treatment-related morbidity[54]. However, the discrepancy between physician-reported outcomes and patient-reported outcomes also highlights the need for prospective clinical trials to clarify the findings and validate the clinical significance of IMPT's dosimetric advantages.

Cao *et al.* investigated the prevalence of xerostomia symptoms in OPC patients treated with either IMRT or IMPT, focusing on identifying dosimetric factors associated with the risk of xerostomia[55]. Their findings indicated that the incidence of moderate-severe xerostomia was comparable between the IMPT and the IMRT groups up to 18 months post-treatment. However, IMPT showed significantly lower rates of moderate-severe xerostomia at 18-24 month and 24-36 month periods (6% *vs.* 20%; $P = 0.01$). During the late xerostomia period (24-36 months), high dose/volume exposures (V25-V70) in the oral cavity were correlated with increased rates of moderate-severe xerostomia ($P < 0.05$), whereas salivary gland dosimetric variables did not. Thus, IMPT was associated with reduced late xerostomia in OPC patients, with oral cavity dosimetric parameters being the key predictors[55].

On the other hand, a recent analysis by Grant *et al.* evaluating longitudinal swallowing outcomes in a cohort of OPC patients revealed similar trends in swallowing function between treatments with IMRT and IMPT. The study utilized the MD Anderson Dysphagia Inventory (MDADI) at baseline, 6, 12, and 24 months post-treatment. Specifically, MDADI scores for IMRT were 88.3 at baseline, 73.8 at 6 months, 78.6 at 12 months, and 83.3 at 24 months, compared to 88.2, 77.0, 80.5, and 80.1 for IMPT, respectively. While direct comparisons are still limited due to differences in patient populations and potential confounding factors, the trajectory of swallowing function appears comparable between IMRT and IMPT in this specific research[56].

As previously mentioned, IMRT and IMPT represent advanced radiotherapy techniques with distinct physical properties and dosimetric profiles. However, translating dosimetric advantages into tangible clinical benefits and improved QoL remains an ongoing challenge. Further prospective randomized clinical trials are essential to fully elucidate the potential of IMPT in the management of OPC and to refine radiotherapy strategies for optimal patient care. Currently, there is no prospective Level I evidence for Proton Beam Therapy (PBT) in most adult cancers, including oropharyngeal squamous cell carcinoma (OPSCC). However, TORPEdO, the first UK clinical trial for PBT, shows promise in improving treatment-related toxicities and health-related QoL for patients. This Phase III multicenter, open-label, randomized controlled trial compares IMPT with IMRT to reduce treatment-related toxicities in patients with advanced OPSCC[57]. The trial includes extensive training to minimize variations in radiotherapy planning and a strong translational research component by collecting imaging data, physics data, blood, and tissue samples to refine patient selection for IMPT. TORPEdO enrolled its first patient on February 25, 2020, paused recruitment due to COVID-19, and later resumed activities in 16 centers, aiming to complete recruitment by October 2023[57].

Thus, it is safe to say that overall, both IMRT and IMPT represent advanced radiotherapy modalities designed to optimize tumor control while minimizing damage to healthy tissues. IMRT excels in delivering high doses to tumors with complex geometries and has established efficacy and accessibility, though it often results in higher integral doses to non-target tissues. IMPT, on the other hand, employs the Bragg peak phenomenon to achieve superior dose precision, reducing exit doses and sparing critical structures more effectively. These characteristics make IMPT particularly advantageous for reducing toxicities and

improving outcomes in select patient populations.

Comparing volumetric modulated arc therapy and intensity-modulated proton therapy

Volumetric modulated arc therapy (VMAT) represents a significant advancement in radiation oncology, offering enhanced precision and efficiency in delivering therapeutic doses to malignant tumors while sparing surrounding healthy tissues. VMAT achieves this by enabling dynamic modulation of the radiation beam's intensity and shape during continuous arc rotation of the linear accelerator around the patient. This approach differs from the IMRT technique, which administers radiation from multiple static angles. Collectively, VMAT, IMRT, and IMPT illustrate a technological continuum aimed at optimizing the therapeutic ratio in RT.

The study of Manzar *et al.* aimed to determine if the dosimetric advantages of IMPT over VMAT in treating OPC can be translated into clinical benefits[58]. A total of 46 IMPT and 259 VMAT patients were treated with a median follow-up of 12 months for IMPT and 30 months for VMAT. Their results indicated that IMPT was associated with significantly lower rates of PEG-tube placement as well as with reduced hospitalization within 60 days post-therapy. The benefits of IMPT were even more pronounced in the patient groups treated with concomitant chemoradiotherapy (CRT). Furthermore, IMPT demonstrated a 22.3% relative risk reduction in end-of-treatment narcotic use, with patients also reporting fewer instances of cough and dysgeusia. Additionally, those treated with CRT reported a reduced sense of illness after treatment, decreased reliance on feeding tubes, and improved swallowing function. Provider-assessed toxicities indicated that IMPT resulted in less pain and mucositis, although there was a higher incidence of mucosal infection[58].

Chou *et al.* conducted a comparative study on the outcomes of patients with nasopharyngeal carcinoma who were treated with IMPT and VMAT[59]. The analysis was performed retrospectively using propensity score matching. Survival outcomes were assessed through the Kaplan-Meier method, and the multivariate Cox proportional hazards regression analysis was employed to identify independent survival predictors. Binary toxicity endpoints were analyzed using both the Cox model and logistic regression. A total of 80 patients who received either IMPT or VMAT were included, with a median follow-up time of 24 months. While progression-free survival (PFS) and overall survival were not statistically different between the two groups, outcomes tended to favor the IMPT group. Multivariate analysis revealed that advanced N-stage and body weight loss during radiotherapy were associated with decreased PFS. Notably, the IMPT group experienced significantly fewer instances of nasogastric (NG) tube placement and body weight loss (BWL) during treatment. Stepwise regression analysis identified the mean oral cavity dose as the only predictive factor, with IMPT delivering a significantly lower mean dose. However, IMPT was associated with an increase in grade 3 radiation dermatitis. In conclusion, IMPT was associated with reduced rates of NG tube insertion and BWL by lowering the mean oral cavity dose, potentially leading to better oncologic outcomes[59].

In cases where significant anatomical changes occur in patients undergoing HNC RT, Góra *et al.* highlighted that adaptive radiotherapy (ART) can potentially address the issue by implementing regular replanning during treatment to adjust doses and improve precision[60]. Dosimetric evaluation of recalculated plans using CT1 and CT2 showed increasing doses to OARs for both VMAT and IMPT[60]. According to their results, for VMAT, the target coverage remained acceptable in three cases, whereas it decreased for all IMPT plans. Adaptation of treatment reduced the D2% for the brainstem by 6.7 Gy for VMAT and by 8 Gy for IMPT in specific patients. The D2% reductions for the spinal cord were even more significant, reaching 9 and 14 Gy, respectively. Thus, ART improved target dose homogeneity, particularly for IMPT, with D2%

reductions up to 8 Gy, while D98% increased by 1.2 Gy, enhancing overall dose distribution. Due to the fact that IMPT is more conformal, dosimetric changes were more pronounced compared to VMAT.

To summarize, VMAT and IMPT both aim to optimize radiation delivery while minimizing harm to surrounding healthy tissues. VMAT's efficiency stems from its dynamic arc-based radiation delivery, whereas IMPT demonstrates precision in sparing critical structures. Comparative studies show IMPT's clinical benefits, including reduced rates of feeding tube dependency and body weight loss during treatment. However, VMAT remains effective and widely accessible, offering excellent therapeutic outcomes in many cases. These findings suggest that treatment modalities should be selected based on patient-specific needs and clinical scenarios.

Comparing volumetric modulated arc therapy and intensity-modulated photon therapy with pencil beam scanning proton therapy

Pencil beam scanning (PBS) proton therapy represents a cutting-edge modality in radiation oncology, characterized by its ability to deliver highly conformal proton doses to neoplastic tissues while minimizing radiation exposure to adjacent normal structures[61]. This technique employs a finely collimated proton beam that systematically "paints" the target volume in a raster-like fashion, enabling superior dose distribution and sparing of healthy tissues. In contrast, IMRT and VMAT utilize photon beams and achieve dose modulation through multiple fixed or rotational beam angles, respectively. While IMRT and VMAT have significantly advanced the precision and efficiency of photon-based therapies, PBS proton therapy leverages the distinct dosimetric advantages of protons, such as the Bragg peak, to achieve exceptional tissue sparing and potentially improved clinical outcomes.

In the study by Sharma *et al.*, patient-reported outcomes were collected from individuals treated with either PBS or IMRT/VMAT[62]. QoL was assessed using validated questionnaires administered before RT, and at 3, 6, and 12 months post-RT. The study included 64 patients, with 31 (48%) receiving PBS and 33 (52%) IMRT/VMAT. The results showed that patients treated with PBS experienced significantly lower radiation doses to several normal structures compared to those treated with IMRT/VMAT. These dosimetric advantages of PBS were also reflected in higher scores on both head and neck-specific and general QoL tools. Notably, patients in the PBS group reported significantly less xerostomia at multiple time points, specifically at 6 and 12 months post-treatment. Representative radiation plans demonstrated significant sparing of the anterior oral cavity with PBS compared to IMRT and VMAT [Figure 2]. Generally, the mean radiation dose was considerably lower for PBS patients across most salivary structures, except for the submandibular glands and ipsilateral parotid. Furthermore, structures such as the contralateral buccal mucosa, contralateral parotid and submandibular glands, oral tongue, and upper and lower lips received one-third to ten-fold lower mean doses with PBS[62].

The study by Swisher-McClure *et al.* attempted to evaluate the dosimetric advantages of PBS proton therapy *vs.* IMRT in the treatment of parotid gland cancers[63]. Specifically, the researchers retrospectively analyzed data from eight patients who had received external beam radiation therapy, generating separate IMRT and PBS treatment plans for each patient. Both plans prescribed a dose of 60 Gy for IMRT and 60 Gy (RBE) for PBS. Dose-volume relationships for target volumes and organs at risk were assessed for each treatment technique using the Wilcoxon signed-rank test. Their results indicated that PBS significantly reduced the mean dose to several structures compared to IMRT. These structures included the following: oral cavity (0.58 *vs.* 13.48 Gy, $P = 0.01$), contralateral parotid gland (0.003 *vs.* 4.64 Gy, $P = 0.01$), ipsilateral submandibular gland (16.59 *vs.* 38.94 Gy, $P = 0.03$), the ipsilateral temporal lobe (2.86 *vs.* 9.59 Gy, $P = 0.01$), the mandible (V50: 7.4% *vs.* 12.8%, $P = 0.01$,) and contralateral submandibular gland (0.02 *vs.* 5.34 Gy, $P = 0.01$). Furthermore, PBS significantly reduced the maximum dose delivered to the

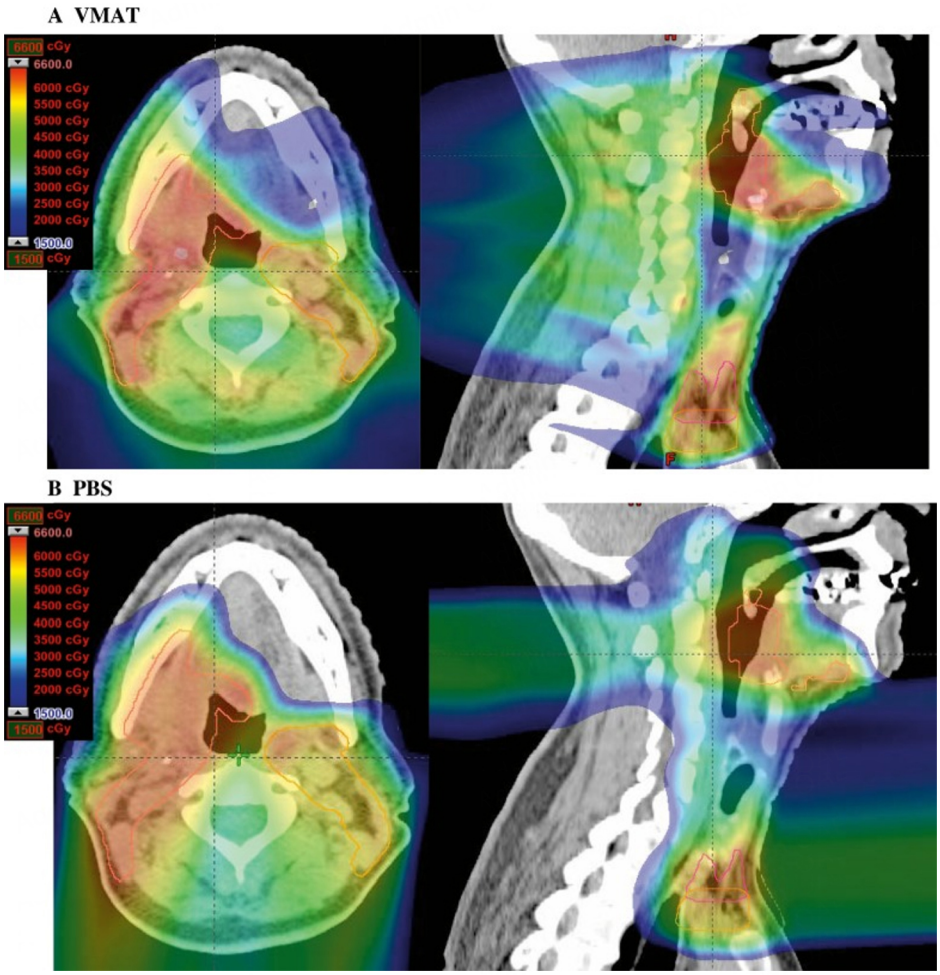
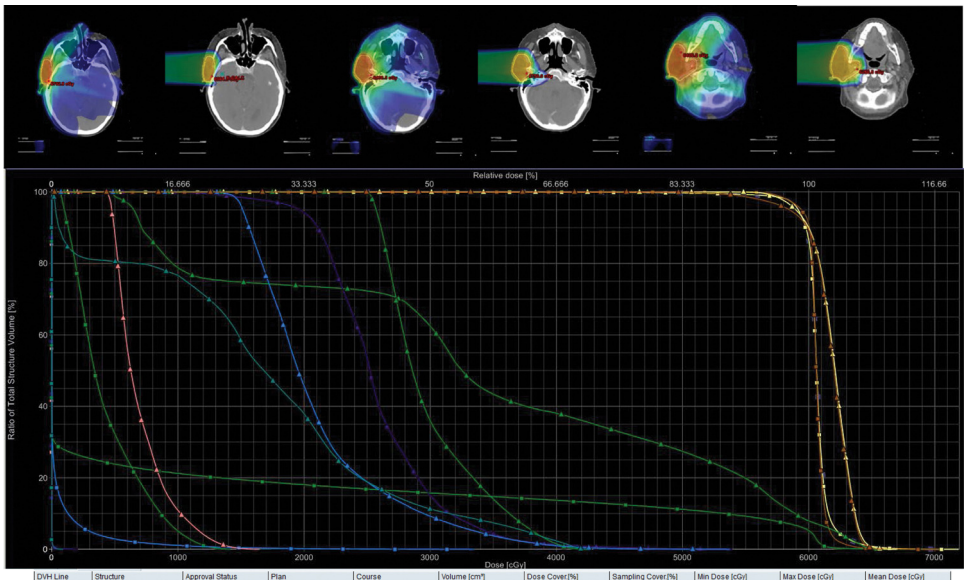


Figure 2. VMAT (A) *vs.* PBS treatment planning comparison (B) for the axial (left) and sagittal (right) planes of patient with tongue carcinoma. Both plans received 60 Gy in 30 fractions while the PBS plan illustarets lower doses to the structures of the oral cavity. Distributed under Creative Commons CC-BY. Copyright 2018, Reproduced from Ref.[62].

brainstem (7.1 *vs.* 30.9 Gy, $P = 0.01$). Thus, the findings suggest that PBS offers superior normal tissue sparing while maintaining target coverage for patients with resected parotid gland cancers [Figure 3]. Consequently, PBS may provide an improved therapeutic index for these patients. However, it is important to mention that prospective evaluations of clinical outcomes with PBS are warranted, with a focus required on disease control, treatment-related toxicities, and patient quality of life[63].

Another study investigated the optimal treatment planning for non-squamous cell carcinoma of the head and neck by comparing the dose distributions of various plans, including PBS with or without a patient-specific aperture system (PSAS), passive-scattering proton therapy (PSPT), and IMRT. Additionally, the study evaluated the clinical results and toxicities of PBS with PSAS, including the changes in QoL of patients. 30 patients were treated using PBS with PSAS. For 20 randomly selected patients, dose distributions of PBS with or without PSAS, PSPT, and IMRT plans were compared [Figure 4]. Additionally, all patients completed EORTC quality of life survey forms (QLQ-C30 and QLQ-HN35) before initiating therapy and 12 months after proton therapy. The results indicated that a 95% conformity number of the PBS with PSAS plan was the optimum, while significant differences were detected among the four plans ($P < 0.05$, Bonferroni tests). Regarding the QoL, no grade 3 or higher acute dermatitis was observed among



DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	PTV60*	Unapproved	PBSbolus	Research	218.1	100.0	100.0	3282.7	7194.0	6064.2
	PTV60*	Approved	original_IMRT	Research	218.1	100.0	100.0	5053.9	6702.9	6193.4
	CTV60	Unapproved	PBSbolus	Research	140.6	100.0	100.0	5347.1	7044.0	6063.1
	CTV60	Approved	original_IMRT	Research	140.6	100.0	100.0	4329.5	6597.0	6176.0
	Oral cooler	Unapproved	PBSbolus	Research	84.5	100.0	100.0	0.0	210.9	0.6
	Oral cooler	Approved	original_IMRT	Research	84.5	100.0	100.0	925.4	5394.2	2580.4
	Mandible	Unapproved	PBSbolus	Research	63.3	100.0	100.0	0.0	6918.0	974.8
	Mandible	Approved	original_IMRT	Research	63.3	100.0	100.0	445.8	6584.2	3401.7
	cord_brainstem	Approved	original_IMRT	Research	50.5	100.0	100.1	5.9	4267.8	1680.6
	cord_brainstem	Unapproved	PBSbolus	Research	50.5	99.2	100.0	0.0	93.0	0.6
	Left parotid	Unapproved	PBSbolus	Research	24.3	100.0	100.0	0.0	0.6	0.3
	Left parotid	Approved	original_IMRT	Research	24.3	100.0	100.0	420.2	1651.1	700.9
	R temporal lobe	Unapproved	PBSbolus	Research	22.8	100.0	100.0	0.0	3352.8	55.6
	R temporal lobe	Approved	original_IMRT	Research	22.8	100.0	100.0	1287.6	5385.0	2113.1
	R middle ear	Unapproved	PBSbolus	Research	0.4	100.0	100.6	61.0	1417.6	428.7
	R middle ear	Approved	original_IMRT	Research	0.4	100.0	99.6	2493.2	4231.8	2994.7

Figure 3. Comparison of dose distribution and dose-volume histograms between IMRT and PBS treatment plans. Copyright 2016, Reproduced from Ref.[63].

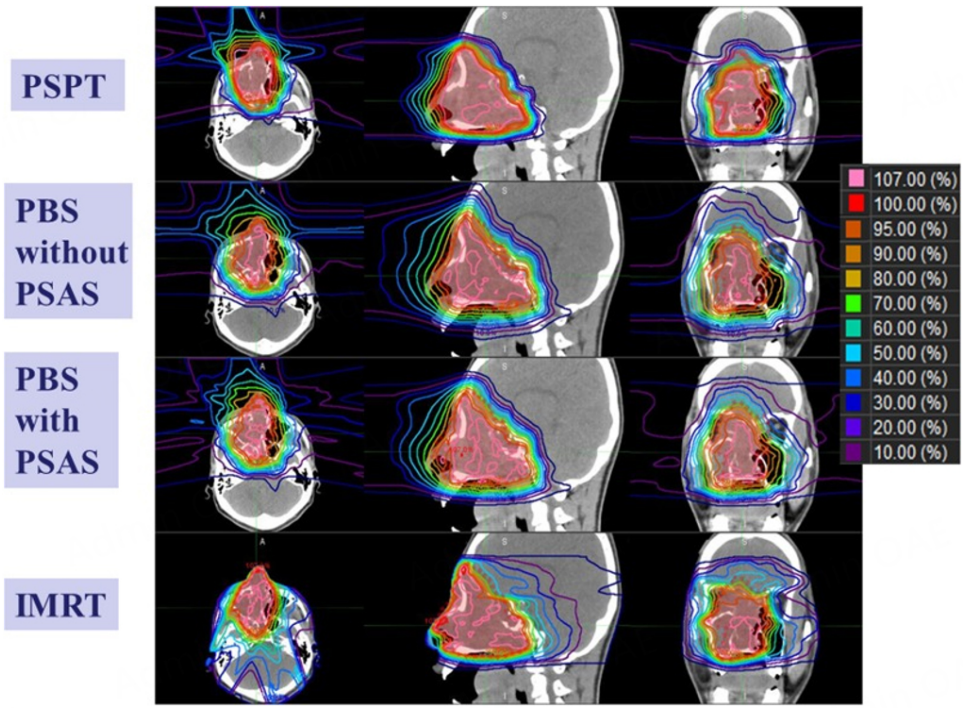


Figure 4. Dosimetric treatment planning comparison for each irradiation method. Copyright 2019, Reproduced from Ref.[64].

the measured toxicities. Most patients experienced increased pain, appetite loss, and weight loss at the end of treatment, but these symptoms improved by the three-month follow-up and returned to pre-treatment levels by the twelve-month follow-up[64].

Eventually, PBS proton therapy offers unparalleled precision in sparing healthy tissues compared to photon-based modalities such as IMRT and VMAT. Studies have demonstrated PBS's superiority in reducing radiation doses to critical structures like salivary glands, the oral cavity, and the brainstem, while maintaining excellent target coverage. Additionally, PBS shows promise in improving patient-reported outcomes, particularly in QoL metrics such as reduced xerostomia and lower toxicities. Despite these advantages, further prospective studies are essential to fully understand PBS's clinical efficacy and long-term benefits in head and neck cancers.

CONCLUSION

In this comprehensive review of radiotherapy types for head and neck cancer (HNC), we focus on the comparison between photon-based therapies, including IMRT and VMAT, *vs.* proton therapy, including IMPT and PBS. This review extends beyond a typical dosimetric analysis, such as dose distribution and protection of OARs, to relevant radiation-induced toxicities and especially patient-oriented QoL. While photon-based therapies such as IMRT and VMAT offer advantages by precisely targeting tumors and sparing healthy tissues, concerns remain regarding their integral dose deposition profiles and potential toxicity risks to surrounding normal tissues. In contrast, proton therapy, particularly IMPT and PBS, leverages the unique physical properties of protons to achieve highly conformal dose distributions with minimal exit dose beyond the target area. This ability not only enhances the protection of OARs but also leads to lower rates of acute and late treatment-related morbidity such as xerostomia, dysphagia, and mucositis. Studies utilizing patient-reported outcome measures consistently indicate improved QoL outcomes among patients treated with proton therapy compared to those treated with photon-based techniques.

In conclusion, this review underscores the pivotal role of proton therapy, particularly IMPT, as a promising treatment option for HNC, offering substantial benefits in minimizing treatment-related toxicities and improving QoL outcomes compared to traditional photon therapies. However, to further solidify its clinical integration, continued research is essential. Specifically, there is a pressing need for long-term longitudinal studies on patient-reported outcomes to assess sustained QoL improvements, particularly with respect to late toxicities such as xerostomia and dysphagia. Additionally, cost-benefit analyses that evaluate the long-term economic impact of proton therapy, considering both direct treatment costs and the potential savings from reduced side effects and rehabilitation, are critical for validating its widespread adoption. Furthermore, comparative toxicity profiles should be addressed through well-designed randomized clinical trials to correlate dosimetric advantages with actual clinical outcomes, particularly focusing on hospitalization rates and functional recovery. Lastly, emerging technologies and hybrid treatment models integrating proton therapy with other modalities, such as immunotherapy or hybrid photon-proton approaches, warrant further exploration to enhance both clinical efficacy and cost-effectiveness. These specific research areas will be crucial in refining proton therapy's application and guiding future clinical practice in HNC treatment.

DECLARATIONS

Acknowledgments

English editing has been performed using Chat GPT Version 3.5 (OpenAI, San Francisco, CA, USA).

Authors' contributions

Conceptualization, investigation, writing - original draft preparation: Kiafi P, Kouri MA
Methodology: Kouri MA, Kiafi P, Patatoukas G, Kouloulias V, Platoni K, Chalkia M, Kollaros N, Perisanidis C, Kougioumtzopoulou A, Nikolatou-Galitis O
formal analysis: Kiafi P, Kouri MA, Patatoukas G, Chalkia M
writing - review and editing: Kiafi P, Kouri MA, Patatoukas G, Kouloulias V, Platoni K, Kougioumtzopoulou A, Perisanidis C, Chalkia M, Nikolatou-Galitis O
supervision: Kouloulias V, Platoni K, Nikolatou-Galitis O
Supervision, writing - review and editing: Kyrodimos E
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424. DOI PubMed
2. Shield KD, Ferlay J, Jemal A, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA Cancer J Clin* 2017;67:51-64. DOI
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-49. DOI
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49:1374-403. DOI
5. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92:709-20. DOI
6. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095-101. DOI PubMed
7. Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. *Clin Oncol* 2003;15:S37-50. DOI PubMed
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30. DOI
9. Strojan P, Hutcheson KA, Eisbruch A, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. *Cancer Treat Rev* 2017;59:79-92. DOI PubMed PMC
10. Yildiz E, Grasl S, Denk-Linnert DM, et al. Long-term swallowing outcome and dysphagia in advanced staged head and neck squamous cell carcinomas after radiotherapy. *J Clin Med* 2022;11:2688. DOI PubMed PMC
11. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. *Int J Radiat Oncol Biol Phys* 1995;31:1141-64. DOI PubMed
12. Kouloulias V, Thalassinou S, Platoni K, et al. The treatment outcome and radiation-induced toxicity for patients with head and neck carcinoma in the IMRT era: a systematic review with dosimetric and clinical parameters. *Biomed Res Int* 2013;2013:401261. DOI PubMed PMC

13. Nepon H, Safran T, Reece EM, Murphy AM, Vorstenbosch J, Davison PG. Radiation-induced tissue damage: clinical consequences and current treatment options. *Semin Plast Surg* 2021;35:181-8. DOI PubMed PMC
14. Lane SA, Slater JM, Yang GY. Image-guided proton therapy: a comprehensive review. *Cancers* 2023;15:2555. DOI PubMed PMC
15. Beckers C, Pruschy M, Vetrugno I. Tumor hypoxia and radiotherapy: a major driver of resistance even for novel radiotherapy modalities. *Semin Cancer Biol* 2024;98:19-30. DOI
16. Sminia P, Guipaud O, Viktorsson K, et al. Clinical radiobiology for radiation oncology. In: Baatout S, editor. Radiobiology textbook. Cham: Springer International Publishing; 2023. pp. 237-309. DOI
17. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;14:199-212. DOI
18. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770-6. DOI PubMed
19. Blanchard P, Gunn GB, Lin A, Foote RL, Lee NY, Frank SJ. Proton therapy for head and neck cancers. *Semin Radiat Oncol* 2018;28:53-63. DOI
20. Kiafi P, Kouri MA, Patatoukas G, et al. Unravelling quality of life for head and neck cancer patients after VMAT radiation therapy: insights from toxicity, dosimetry and symptoms correlation. *Clin Pract* 2024;14:1085-99. DOI PubMed PMC
21. Basch E, Abernethy AP, Mullins CD, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. *J Clin Oncol* 2012;30:4249-55. DOI
22. Sari S, Beduk Esen CS, Yazici G, Yuce D, Cengiz M, Ozyigit G. Do grape and black mulberry molasses have an effect on oral mucositis and quality of life in patients with head and neck cancer? *Support Care Cancer* 2022;30:327-36. DOI PubMed
23. Liao KC, Chuang HC, Chien CY, et al. Quality of life as a mediator between cancer stage and long-term mortality in nasopharyngeal cancer patients treated with intensity-modulated radiotherapy. *Cancers* 2021;13:5063. DOI PubMed PMC
24. Van den Bosch L, van der Laan HP, van der Schaaf A, et al. Patient-reported toxicity and quality-of-life profiles in patients with head and neck cancer treated with definitive radiation therapy or chemoradiation. *Int J Radiat Oncol Biol Phys* 2021;111:456-67. DOI
25. Viganò A, De Felice F, Iacovelli NA, et al. M. D. Anderson symptom inventory head neck (MDASI-HN) questionnaire: Italian language psychometric validation in head and neck cancer patients treated with radiotherapy ± systemic therapy - A study of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). *Oral Oncol* 2021;115:105189. DOI
26. Xu MJ, Plonowska KA, Gurman ZR, et al. Treatment modality impact on quality of life for human papillomavirus-associated oropharynx cancer. *Laryngoscope* 2020;130:E48-56. DOI
27. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. *Head Neck* 2007;29:923-31. DOI
28. Pocobelli G, Ziebell R, Fujii M, et al. Symptom burden in long-term survivors of head and neck cancer: patient-reported versus clinical data. *EGEMS* 2019;7:25. DOI PubMed PMC
29. Tuomi L, Fransson P, Wennerberg J, Finizia C. A longitudinal study of the Swedish MD anderson dysphagia inventory in patients with oral cancer. *Laryngoscope Investig Otolaryngol* 2020;5:1125-32. DOI PubMed PMC
30. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights* 2013;6:61-8. DOI PubMed PMC
31. Klimek L, Bergmann KC, Biedermann T, et al. Visual analogue scales (VAS): measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). *Allergo J Int* 2017;26:16-24. DOI PubMed PMC
32. Åström M, Thet Lwin ZM, Teni FS, Burström K, Berg J. Use of the visual analogue scale for health state valuation: a scoping review. *Qual Life Res* 2023;32:2719-29. DOI PubMed PMC
33. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG performance status assessments with new technologies. *J Oncol* 2016;2016:6186543. DOI PubMed PMC
34. Atkinson TM, Andreotti CF, Roberts KE, Saracino RM, Hernandez M, Basch E. The level of association between functional performance status measures and patient-reported outcomes in cancer patients: a systematic review. *Support Care Cancer* 2015;23:3645-52. DOI PubMed PMC
35. der Laan HP, Van den Bosch L, Schuit E, Steenbakkers RJHM, van der Schaaf A, Langendijk JA. Impact of radiation-induced toxicities on quality of life of patients treated for head and neck cancer. *Radiother Oncol* 2021;160:47-53. DOI PubMed
36. Cengiz M, Ozyar E, Esassolak M, et al. Assessment of quality of life of nasopharyngeal carcinoma patients with EORTC QLQ-C30 and H&N-35 modules. *Int J Radiat Oncol Biol Phys* 2005;63:1347-53. DOI
37. Lu N, Qin T, Hu W. Impact of changes in psychological resilience during treatment with intensity-modulated radiotherapy on nasopharyngeal carcinoma patients: a prospective study. *Ann Palliat Med* 2022;11:123-34. DOI PubMed
38. Stadler ME, Patel MR, Couch ME, Hayes DN. Molecular biology of head and neck cancer: risks and pathways. *Hematol Oncol Clin North Am* 2008;22:1099-124, vii. DOI PubMed PMC
39. Vanderwaeren L, Dok R, Verstrepen K, Nuyts S. Clinical progress in proton radiotherapy: biological unknowns. *Cancers* 2021;13:604. DOI PubMed PMC

40. Bhide SA, Newbold KL, Harrington KJ, Nutting CM. Clinical evaluation of intensity-modulated radiotherapy for head and neck cancers. *Br J Radiol* 2012;85:487-94. DOI PubMed PMC
41. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol* 2011;84:967-96. DOI PubMed PMC
42. Cheng QR, Fan MX, Hao J. et al. Chest CT features of children infected by B.1.617.2 (Delta) variant of COVID-19. *World J Pediatr* 2022;18:37-42. DOI
43. Liu H, Chang JY. Proton therapy in clinical practice. *Chin J Cancer* 2011;30:315-26. DOI PubMed PMC
44. Kutuk T, Atak E, Villa A, Kalman NS, Kaiser A. Interdisciplinary collaboration in head and neck cancer care: optimizing oral health management for patients undergoing radiation therapy. *Curr Oncol* 2024;31:2092-108. DOI PubMed PMC
45. Moreno AC, Frank SJ, Garden AS, et al. Intensity modulated proton therapy (IMPT) - the future of IMRT for head and neck cancer. *Oral Oncol* 2019;88:66-74. DOI PubMed PMC
46. Blanchard P, Garden AS, Gunn GB, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. *Radiother Oncol* 2016;120:48-55. DOI PubMed PMC
47. Grant SR, Grosshans DR, Bilton SD, et al. Proton versus conventional radiotherapy for pediatric salivary gland tumors: acute toxicity and dosimetric characteristics. *Radiother Oncol* 2015;116:309-15. DOI
48. Ladra MM, Edgington SK, Mahajan A, et al. A dosimetric comparison of proton and intensity modulated radiation therapy in pediatric rhabdomyosarcoma patients enrolled on a prospective phase II proton study. *Radiother Oncol* 2014;113:77-83. DOI PubMed PMC
49. Holliday EB, Kocak-Uzel E, Feng L, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: a case-matched control analysis. *Med Dosim* 2016;41:189-94. DOI
50. Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. *Int J Radiat Oncol Biol Phys* 2016;95:1107-14. DOI PubMed PMC
51. Embring A, Onjukka E, Mercke C, et al. Re-irradiation for head and neck cancer: cumulative dose to organs at risk and late side effects. *Cancers* 2021;13:3173. DOI PubMed PMC
52. Scartoni D, Giacomelli I, Pertile R, et al. Proton therapy re-irradiation provides promising clinical results in recurrent brain meningioma. *Acta Oncol* 2023;62:1096-101. DOI
53. Ko M, Yang K, Ahn YC, et al. Dosimetric comparison and selection criteria of intensity-modulated proton therapy and intensity-modulated radiation therapy for adaptive Re-plan in T3-4 nasopharynx cancer patients. *Cancers* 2024;16:3402. DOI PubMed PMC
54. Hutcheson K, Lewin J, Garden A, et al. Early experience with IMPT for the treatment of oropharyngeal tumors: acute toxicities and swallowing-related outcomes. *Int J Radiat Oncol Biol Phys* 2013;87:S604. DOI
55. Cao J, Zhang X, Jiang B, et al. Intensity-modulated proton therapy for oropharyngeal cancer reduces rates of late xerostomia. *Radiother Oncol* 2021;160:32-9. DOI PubMed PMC
56. Grant SR, Hutcheson KA, Ye R, et al. Prospective longitudinal patient-reported outcomes of swallowing following intensity modulated proton therapy for oropharyngeal cancer. *Radiother Oncol* 2020;148:133-9. DOI PubMed PMC
57. Thomson DJ, Cruickshank C, Baines H, et al. TORPEdO: a phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer. *Clin Transl Radiat Oncol* 2023;38:147-54. DOI
58. Manzar GS, Lester SC, Routman DM, et al. Comparative analysis of acute toxicities and patient reported outcomes between intensity-modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) for the treatment of oropharyngeal cancer. *Radiother Oncol* 2020;147:64-74. DOI
59. Chou YC, Fan KH, Lin CY, et al. Intensity modulated proton beam therapy versus volumetric modulated arc therapy for patients with nasopharyngeal cancer: a propensity score-matched study. *Cancers* 2021;13:3555. DOI PubMed PMC
60. Góra J, Kuess P, Stock M, et al. ART for head and neck patients: on the difference between VMAT and IMPT. *Acta Oncol* 2015;54:1166-74. DOI
61. Lattery G, Kaulfers T, Cheng C, et al. Pencil beam scanning bragg peak FLASH technique for ultra-high dose rate intensity-modulated proton therapy in early-stage breast cancer treatment. *Cancers* 2023;15:4560. DOI PubMed PMC
62. Sharma S, Zhou O, Thompson R, et al. Quality of life of postoperative photon versus proton radiation therapy for oropharynx cancer. *Int J Part Ther* 2018;5:11-7. DOI PubMed PMC
63. Swisher-McClure S, Teo BK, Kirk M, Chang C, Lin A. Comparison of pencil beam scanning proton- and photon-based techniques for carcinoma of the parotid. *Int J Part Ther* 2016;2:525-32. DOI PubMed PMC
64. Iwata H, Toshito T, Hayashi K, et al. Proton therapy for non-squamous cell carcinoma of the head and neck: planning comparison and toxicity. *J Radiat Res* 2019;60:612-21. DOI PubMed PMC