



# Novel Technological Aspects of Radiation Therapy in Head and Neck Cancer

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## SUMMARY

Radiation therapy (RT) is an important treatment modality in head and neck cancer (HNC) irrespective of stage, histology, and location of the primary tumor in both curative and palliative setting, with or without other treatment modalities such as surgery or chemotherapy. Based on advances with better imaging and introduction of sophisticated software for treatment and planning systems, radiation oncology of HNC witnessed major advantages resulting in both improved local control and better sparing of organs at risk. From computed tomography to magnetic resonance imaging and introduction of positron emission tomography with various radiotracers it became possible not only to diagnose and stage HNC with more confidence but also to introduce these technologies in RT treatment planning, and to use it during the RT course for the evaluation of response and additionally sculpture RT fields. Furthermore, it became possible to predict outcome based on anatomic and metabolic changes in HNC. Community of radiation oncologists successfully adopted transition from two-dimensional to three-dimensional RT and then to intensity modulated RT, as well as stereotactic radiotherapy (either single- or multi-fraction) regimens. There is renewed interest in heavy particles with both neutrons, carbon-ions and protons, the latter two being used more frequently in the recent years. This review article summarizes the most important aspects of novel RT technologies in HNC.

**Keywords:** Head and neck cancer; radiotherapy, treatment.

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## Introduction

Radiation therapy (RT) plays an important role in the overall armamentarium of treatment possibilities in head and neck cancer (HNC). Irrespective of stage and histology or primary tumor subsite, it can be used for both cure and palliation and used as sole treatment modality or in combination with surgery and/or

chemotherapy (CHT) in both human papilloma virus (HPV)- and HPV+ patients.[1,2] In the past several decades, many novel technologies enriched our capabilities in RT of HNC. While some of these are related to various diagnostic aspects, also used in RT planning process, other is inherent to RT. This review article summarizes some of the most widely used ones, but also discusses some of those with significant potential for influencing RT of the HNC in the future.

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### **Positron Emission Tomography (PET) with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)**

Besides its use in the diagnosis and staging, PET-CT has increasingly been used in both treatment planning and monitoring the treatment response of HNC, mostly with <sup>18</sup>F-Fluorodeoxyglucose (FDG). A number of non-<sup>18</sup>F-FDG radiotracers also attracted significant attention in the past decade. Among hypoxia radiotracers, uptake changes of <sup>18</sup>F-Fluoromisonidazole (MISO) early during the RT + CHT course was shown as useful tool in predicting treatment response.[3] It was also proposed it could guide clinical hypoxia-based RT planning,[4] including RT boosting based on PET definition of hypoxic volumes.[5] In one study,[6] with patients with HPV+ oropharyngeal carcinomas (OPCs) it enabled lymph node RT dose reduction which led to impressive 2-year locoregional control (LRC), DM free rate, and 2-year OS of 100%, 97%, and 100%, respectively, with less toxicity. <sup>18</sup>F-Fluoroazomycinarnobifuranoside (FAZA) is another radiotracer exploring hypoxia and was shown to be capable of estimating the reduction of the hypoxic volume of patients scanned during the RT course.[7] However, the main challenge with hypoxic tracers was that hypoxic regions within the tumor regions are not static. Since hypoxic regions move continuously during radiotherapy course, the practical use of those tracers is questioned.

Copper-labeled radiotracers were used to predict response in patients undergoing a baseline PET scan before treatment[8] as well as in predicting response to neoadjuvant RT-CHT.[9] Amino acid methionine (MET) had also been investigated as L-[methyl-<sup>11</sup>C] MET in its possible role in offering better delineation of tumors in the process of RT planning.[10] Some studies showed that it can be useful predictive or prognostic tool in heavy ion RT.[11] Some studies indicated its usefulness in side effects monitoring, since a correlation between parotid gland salivary flow and the metabolic clearance of the parotid was noted with the regional salivary clearance decreasing with increasing of the regional radiation dose.[12] Furthermore, individual radiation dose response of parotid glands could be measured by <sup>11</sup>C-MET PET in patients with salivary gland cancers.[13] Finally, [<sup>18</sup>F] fluorothymidine (FLT), radiopharmaceutical that trace cell proliferation, was used to monitor early response to RT since FLT uptake can significantly decrease between consecutive scans performed during RT.[14] Not only a change in FLT uptake during RT or RT-CHT was shown to be strong predictor of long-term outcome[14] but also metabolic tumor volume and the total lesion proliferation could also differentiate responders from non-responders.[15]

Serial FLT (performed before RT-CHT and during it) was also useful in documenting changes in tumor proliferation volume, shown to be of predictive of PFS.[16]

In addition to PET-CT, we recently also witnessed the use of hybrid whole-body PET-MRI in an attempt to successfully merge molecular imaging of PET and the high spatial resolution and high tissue contrast information from MRI. It has been used only sporadically in HNC with somewhat conflicting results when staging and restaging with PET-MRI were compared to PET-CT in primary or recurrent HNC of various HN subsites.[17] It was also shown that PET-MRI guided tumor delineation during the RT planning process can provide more information than other imaging.[18] German researchers developed an accurate and robust multimodal deformable image registration strategy and integrated combined PET/MR data into RT treatment planning.[19] They had showed that biologically individualized RT based on combined PET/MRI in terms of dose painting was possible. The same researchers also focused on image quality of RT-customized PET/MRI in HNC patients using a dedicated hardware setup.[20] Simultaneous PET/MRI using RT positioning aids was clinically feasible while image quality obtained with a RT setup met planning requirements indicating its use for personalized RT planning.

### **Intensity Modulated Radiation Therapy (IMRT) and Stereotactic Body Radiation Therapy (SBRT)**

In the past 30 years, three-dimensional (3D) RT enabled higher RT doses and better sparing of organs at risks (OARs), leading to improved LRC, and less side effects of RT in HNC. Superior form of this treatment is IMRT which employs multiple radiation beams, each being subdivided into a smaller radiation beamlets with varying individual beamlet intensities. HNC was one of the first and most successful stories of the use of IMRT due to large volumes needing RT, and close proximity of OARs such as parotid, eyes or brain stem successfully being spared with the IMRT.[21,22] Dose-metric/planning studies have mostly documented superiority of various IMRT techniques over 2D or 3D RT in both the conformity and dose distribution,[23] irrespective of the primary tumor site as well as sparing OARs. On the other side, LRC and OS as well as quality of life, patient-related symptoms, or saliva flow rate[24] have only infrequently been used as endpoints. When investigated, frequently there was no improvement in LC control[25,26] likely due to a similar PTV coverage. Rare studies noted improved cancer specific survival (CSS)[27] or LRC and relapse-free survival (RFS). This was observed for exclusive RT while in the post-oper-

ative setting IMRT offered better LC.[28] Almost all of these studies showed significant sparing of OARs, in particular xerostomia.[26,27] However, when survival analysis was focused on in nasopharyngeal carcinoma (NPC), Zhang et al.[29] used meta-analytic (MA) approach (eight studies, 3570 patients) to document significantly superior OS and LC in IMRT group versus 2D/3D. Using MA, Marta et al.[25] analyzed five prospective randomized clinical trials (PRCTs) with 871 patients of which 82% were those with NPC, showing no difference in OS and LRC. However, there was a significant reduction of Grade 2-4 xerostomia in IMRT-treated patients ( $p < 0.0001$ ). Gupta et al.[30] analyzed seven PRCTs with 1155 patients. Five studies used xerostomia as an endpoint while one study each used OS or LRC as an endpoint. IMRT led to reduction of 36% in risk reduction (RR) in Grade  $>2$  acute xerostomia and reduction of 56% in Grade  $>2$  late xerostomia. Due to a 24% RR reduction of LRC and 30% RR reduction in OS, authors called for a cautious interpretation of their results since the latter results were observed only in NPC patients and having analyzed only two studies.

Initially, the IMRT was used either as serial tomotherapy, step-and-shoot (SS) or dynamic/sliding window (SW) approach and was done sequential way, with its two phases built on experience obtained from the era of 2D/3D RT.[31] Past two decades witnessed major emphasis being placed on the use of arc approaches, most notably helical tomotherapy and intensity modulated arc therapy (IMAT) and the latter's subsequent and advanced form, known as volumetric modulated arc therapy (VMAT). VMAT was expected to bring advantage over IMRT or IMAT due to its enhanced flexibility in the delivery by facilitating alternating dose rate and gantry speed during dynamic movements of accelerator jaws and multileaf collimators, allowing the whole target to be treated using 1 or 2 arcs, although complex cases may require more.

A special advantage of IMRT is that it enables inhomogeneous dose distributions to be delivered to various volumes (primary and elective) with different dose per fraction without increasing the overall treatment time, the technique called simultaneous integrated boost (SIB). SIB allows all volumes to be treated within the single treatment plan without matching RT fields. With SIB technique clinicians started irradiating three clearly different (risk-wise) areas at the same time. It also enabled increase in the dose per fraction to the boost volume (e.g., 2.2 Gy/fraction), while, at the same time, kept the dose to the low risk/elective volume at a lower level (e.g., 1.6 Gy/fraction). SIB IMRT approach

was shown to be dosimetrically better than sequential IMRT[31] and was more practical due to using a single plan from the start. Recent MA[32] compared sequential boost IMRT with SIB IMRT in HNC (seven studies and 1049 patients). Interestingly, there was no difference in any of the endpoints used; OS ( $p=0.71$ ), PFS ( $p=0.79$ ), LRFs ( $p=0.91$ ), and DMFS ( $p=0.63$ ) including no difference in side effects. However, they contrasted previous findings that SIB was better than sequential IMRT,[33] leading to less side effects,[34] others showed superiority of sequential IMRT[35] due to a better coverage of the high dose regions, conformity and homogeneity, including less monitor units (MUs) being used.

Most recent planning studies compared several IMRT techniques showing similar PTV coverage, but improved homogeneity with 2 arcs with VMAT versus fixed field/SS IMRT.[36] While mean doses to the OARs were lower for VMAT with 2 arcs versus SW, VMAT also offered improved sparing of the contralateral parotid with a comparable PTV coverage compared to SW IMRT.[36] Double arc VMAT was superior to a single arc VMAT regarding PTV coverage and OAR sparing.[37] Contrasting these, the study of Bertelsen et al.[38] showed that a single arc VMAT may be either similar (PTV coverage) or only slightly better (elective nodal coverage) in patients with OPC or hypopharyngeal cancers. Other observed lower integral doses to the body with VMAT plans,[36] while other showed that with tomotherapy one can achieve better coverage of the low risk (elective) areas and can also achieve better dose conformity than VMAT or IMRT.[39] When doses to OARs have been evaluated, lowest dose for mandible was achieved with VMAT, all other organs with tomotherapy. One should not forget that with VMAT there is up to 50% reduction in MU,[35,36] an important aspect in the daily work of the busy departments of radiation oncology worldwide. Not to be forgotten, too, is that in spite of shorter delivery time with VMAT,[35,39] it remains vitally dependent on the number of fields used in IMRT plans. In one study[40] in patients with OPC, rotational/arc IMRTs were preferable to SS/SW due to a faster fraction delivery and better sparing of OARs without a higher integral dose.

Stereotactic RT was also used in the primary treatment of HNC, mostly as a boost given after previous either IMRT or conventional RT. Single or fractionated stereotactic radiosurgery (SRS) or fractionated SBRT proved to be feasible and effective in the boost phase of the comprehensive RT treatment.[41,42] The Korean

study[42] reported on 24 patients with extracranial HNC, mostly consisting of NPC (n=19), treated with fractionated stereotactic RT as a boost. The median boost dose to NPC was 16 Gy (range, 8-40 Gy) after the median conventionally fractionated RT dose of 55.8 Gy (range, 36-61.2 Gy). Complete response was seen in 95% patients with LC rates and OS at 4 years being 89% and 75%, respectively, achieved without occurrence of unexpectedly severe complications (one mucosal necrosis which eventually and completely healed). Subsequent reports in a small patient cohorts reconfirmed feasibility and efficacy of both single and multifraction SBRT. Siddiqui et al.[43] reported on ten primary HNC treated with single fraction of 13-18 Gy or 36-48 Gy in 5-8 fractions to obtain tumor control rate of 66.7% at 2 years with the median survival time (MST) of 28.7 months and 2-year OS of 50%. Grade 3 side effects were seen only in two patients after 36 and 48 Gy given in 6 and 8 fractions, respectively. Several single institutional studies with limited number of patients used SBRT as a boost with 28 fractions delivering total doses ranging 10-38 Gy and reporting on MSTs of >31.5 months with a 3-5-years OS of 46.2-60%.[44] Most recently, Baker et al.[45] provided detailed analysis and the long-term data on 195 patients with OPC treated with fractionated SBRT boost (3x5.5 Gy) after IMRT was initially been given with 46 Gy in 23 daily fractions. Five-year OS, DSS, LC, and RC as well as late grade >3 toxicity were 67%, 85%, 90%, 93%, and 28%, respectively.

In a SRS domain, single fractions were used to boost NPC after initial RT was given with conventionally fractionated RT. Chang et al.[41] treated 23 patients with Linac-based technique delivering the median of 12 Gy (range 7-15 Gy) following the median of 66 Gy (range 64.8-70 Gy) of conventional RT. In all 23 patients (100%) receiving SRS, following conventional RT-LC was achieved at a mean follow-up of 21 months (range 2-64 months) with no SRS-related complications. SRS delivered through Gamma Knife (GK) was also used as planned boost after RT-CHT in cases of selected sinonasal cancers and NPCs.[46] The mean initial RT dose delivered by IMRT was 64.3 Gy (range, 54-70 Gy) at 2 Gy per fraction. After the median interval of 2.2 months from the end of IMRT, SRS boost with the median margin dose of 13 Gy (range, 12-20 Gy) was delivered. All patients achieved local control with no Grades 3-5 toxicity. Robotic SRS using the RT linear accelerator known as Cyber Knife was also used in either primary as SRS only (n=6), or as a SRS boost (n=7) or in post-operative setting (n=8) or for re-irradiation (n=6) in the study of Ozyigit et al.[47] in 27 cases of

nose and paranasal cancers. The median dose to the tumor was 31 Gy (range, 15-37.5 Gy) in median of 5 fractions (range, 3-5 fractions). LC was seen in >75% cases with the 2-year survival for the whole group of 77.1% which was accompanied with 7% cases of brain necrosis and visual disorder each, bone necrosis in further 7% while 4% of patients experienced trismus.

Both IMRT and SBRT had also been used to treat recurrent disease. Majority of studies were single-institutional, retrospective reports on a small number of patients and unfortunately, with different patient, tumor and treatment (RT, surgery, and CHT) characteristics making any firm conclusion rather impossible. Nevertheless, recent report[48] recently summarized the results in the setting of recurrent HNC. For the IMRT and SBRT, respectively, the median (and the range) of 2-year OS was 49% (32-59%) and 29% (28-58%), respectively. Corresponding figures for the LRC were 62% (52-67%) and 52% (28-64%), respectively. These results have been achieved with a variety of RT dose and fractionation characteristics. Ozyigit et al.[49] reported on a retrospective study comparing 3D RT (57 Gy in 2 Gy per fraction) versus SBRT (30 Gy over 5 consecutive days). No difference was found in LC rates or CSS rates, but serious late toxicities were more frequent in 3D RT group (48% vs. 21%, p=0.04). Interestingly no difference was found in the fatal complications in the two groups of patients. Summarizing the existing literature, Alterio et al.[50] indicated that with standard fractionation, the dose of >60 Gy may be preferable, while in the case of SBRT, the dose equivalent to 40 Gy in 5 fractions seemed necessary, in both cases focusing on visible tumor. When reirradiation was used in the post-operative setting; however, it did not lead to significant improvement in OS. It offered better LRC and DFS, but at the expense of severe acute toxicity.[51] These side effects have also been significant burden in exclusive reirradiation series, including documented cases of carotid blowout syndrome (CBOS). As documented by Ho and Phan,[48] although not very frequent (1-8%) CBOS is still fatal in most patients. While some experienced higher incidence of CBOS,[52] going as high as 17% with 15% dying of it, simple measures have been proposed (administering SBRT every other day, limiting median carotid artery dose to <34 Gy, excluding patients with a tumor surrounding >180° of the carotid artery) to minimize the risks.[53] Other late high grade (>3) toxicity remains a much more frequent event, although one may notice somewhat lower rate with SBRT (7%) when compared to IMRT (39%). In addition to fractionated SBRT, Oda



et al.[54] reported on GK SRS after previous fractionated RT in 14 patients of which 11 had NPC. Tumor margin doses ranged 10-27 Gy (median, 15 Gy), and the maximal tumor doses ranged 22-40 Gy (median, 28 Gy). Response rate (RR) was 43%, while stable disease was in 14 of the patients. A second SRS was performed in four out of six re-growing tumors, of which response was seen in three, making the total control rate of 79%.

Finally, important, although still sporadic, reports highlighted the advantage of IMRT over 3D regarding their respective cost-effectiveness.[55] They have included different health-care systems of different countries but unequivocally showed that IMRT was considered more cost effective than 3D. What these studies did not include were other benefits IMRT likely carries. These include shorter treatment times when VMAT is used, as well as lower short- and long-term costs related to toxicities (xerostomia, dysphagia, and dental problems), such as intensive supportive care which is frequently needed in HNC patients treated with intensive radical RT/CHT.[56]

## Heavy Particles

### Carbon Ions

Carbon ions have also been used to treat both primary and recurrent non-squamous cell HNC. In the Japanese experience, 289 patients with adenoid cystic carcinoma (ACC) of the head and neck,[57] estimated 5-year OS, PFS, and LC rates were 74%, 44%, and 68%, respectively. Of all patients, 15% experienced grade  $\geq 3$  late toxicity, osteoradionecrosis (ORN) of the jaw bone being the most common. Two patients (0.7%) treated for NPC died from a bleeding ulcer at the tumor site. In 26 patients with mucoepidermoid carcinoma,[58] the 3-year rates of LC, PFs and OS were 95%, 73%, and 89%, respectively. Acute and late toxicity were judged to be moderate with no Grade 5 toxicities.

The German researchers[59] treated 229 patients with recurrent HNC of which 54.1% were ACC, 26.2% were squamous cell carcinomas, 8.3% were adenocarcinomas, and 11.4% were other tumor entities. The median local PFS was 24.2 months, and the median OS was 26.1 months. Acute grade  $\geq 3$  toxicity was rare, while late toxicities were of grades  $> 3$  (n=18; 14.5%) only. When carbon ion RT was coupled with IMRT in high-risk NPC,[60] the estimated 5-year LC, DPFS, and OS rates were 90%, 86%, and 86%, respectively. There were 20% acute and 16% chronic Grade 3 side effects, respectively, and no toxicity  $> 3$  was observed. Adding carbon ion boost to IMRT was also used in 52 patients with ACC of the minor salivary gland tumors of the

nasopharynx.[61] The estimated 5-year LC, DPFS, and OS were 49%, 54%, and 69%, respectively. Overall, Grade 3 toxicity was moderate with 12% acute and 8% late side effects. In a Phases I-II (ACCEPT) study,[62] Cetuximab was added to RT composed of IMRT and carbon ion boost to treat 23 patients with ACC of the HN. Nine patients underwent surgery, none of which was R0. There was no Grades 4-5 toxicity. The 3-year DFS was 67%, and median OS was 54 months. In a setting of a Phase II study,[63] patients with various malignant salivary gland tumors were treated with carbon ions followed by IMRT. Grade 3 mucositis was observed in 26% of patients and 38% patients reported adverse events of the ear. The most common observed late effects were Grade 1 xerostomia (49%), hearing impairment (25%), and adverse events of the eye (20%), with no visual impairment or loss of vision. Grade 1 central nervous system necrosis occurred in 6%, and 1 Grade 4 internal carotid artery hemorrhage without neurologic sequelae. Three-year the LC, PFS, and OS were 81.9%, 57.9%, and 78.4%, respectively.

### Neutrons

Neutrons have been used primarily for salivary gland tumors and only rarely reports included non-squamous cell carcinomas. The LC rates for advanced salivary gland tumors were mostly around 60-75%.[64,65] Recently, Stannard et al.[66] reported on an experience where the median dose 20.4 Gy was given in 12 fractions in 4 weeks or in 15 fractions in 5 weeks to 335 patients which included 176 unresectable, 104 macroscopically residual, and 55 unresected tumors. LRC was 39.1% at 10 years and DSS was 53.7% at 10 years. In majority of published studies, Grades 3-4 late toxicity was around 10-15% at 5-10 years. Some studies, however, reported on higher incidence of toxicity, such as that of Maor et al.[67] who reported on  $>$ Grade 3 late toxicity being observed in 39.7%. In their study, Grade 4 ORN occurred in four patients (5.9%). This treatment approach has largely been abandoned today and is only sporadically practiced in few centers worldwide.

### Protons

With clinical data slowly emerging, dosimetric studies brought better understanding of both advantages and challenges with this treatment modality in HNC. Spot-scanned beams and intensity modulated proton beams (IMPT) were shown to provide better sparing of OARs when compared to scattered proton beams. [68] IMPT allowed extraordinary conformity of treatment plans and dose escalation in clinical scenarios

when OARs such as optic chiasm and/or optic nerves in the immediate vicinity of paranasal sinus tumors. [69] Normal tissue control probability (NTCP) models confirmed the benefit of using IMPT in cases of NPC to decrease the dose to parotid glands, [70] to swallowing muscles [71] or to oral cavity and spinal cord. [72] Data pointed to ipsilateral and well lateralized targets in the neck as preferable for protons. On the other side, when more central and or/bulky or bilateral target volumes need to be treated, delivery of IMPT may be faced with significant uncertainty of delivered dose deposition due to both anatomic and physical properties of both the patient and the tumor. [73] Among efforts to address these issues and increase robustness of IMPT planning, multi-field optimization (MFO) [74] and weekly verification scans and adaptive re-planning [75] have been proposed. More recent studies reconfirmed the feasibility of improving tumor coverage and reducing integral dose to OARs with MFO-IMPT relative to IMRT and helical tomotherapy in cases of NPC. [76] In the post-operative setting of OPC, too, dosimetric superiority of IMPT over IMRT or VMAT was also suggested. [76]

Still the vast majority of reports and patients therein were of non-SQC histology. Several single-institutional series [77,78] reported on chordomas and chondrosarcomas as well as nasal cavity and paranasal sinus cancers, some of which, however reported on high rates of late toxicity (42%) which may have compromised good LC (4-year, 54%), [77] but with higher doses LC was achieved in 70-100% and for prolonged periods of time. [78] In the first long-term report of 64 patients with the base of skull tumors treated with protons, [79] 44 were treated with spot scanning and 20 with IMPT. High median total doses for chordomas and chondrosarcomas were given to achieve 5-year LC of 81% and 94% for the two histologies, respectively. The corresponding figures for OS were 100% and 91%, respectively, accompanied with limited toxicity and no brain stem injury.

In NPC, with or without photons, [80] excellent LC (up to 100%) and OS (28 months) were observed. Even in T4 tumors, local failure was around 6% after 3.5 years. However, late toxicities (radiographic temporal lobe changes) were frequently observed (29%). Recent reports on the use of IMPT, however, point toward the decrease in toxicity when compared to IMRT. [81] Gastrostomy tube dependency (20% vs. 65%) significantly favored IMPT as a consequence of improved oral cavity sparing as was confirmed in other studies, too. [82]

In the nose and sinonasal region, protons also proved to offer better dosimetry, and safe dose escalation which was coupled with reduced side effects and

improved results (LC in 90% cases) in various histological forms. [83] When protons have been compared to IMRT in patients with nasopharyngeal, nasal cavity and paranasal sinus cancer, protons offered improved sparing of oral cavity, esophagus, larynx, and parotid glands. [84] When prolonged follow-up was provided, [85] LC was 50% at 5 years, with 16% Grade 3, and 11% Grade 4 toxicity, but most commonly being of wound complications. For non-surgical candidates, too, passively scattered proton therapy provided good 2- and 3-years OS rates of >60% and LC rates of 70-95% observed with mixed histologies and disease stages. [86]

Rare reports provided the data about feasibility of using protons in periorbital tumors. In one such retrospective study, [87] 13 out of 14 operated patients with primary lacrimal sac or nasolacrimal duct carcinomas, received post-operative RT with protons or IMRT with a median dose of 60 Gy, while eight patients received CHT. With the globe spared in all (n=10) non-exenterated tumors, 90% of patients either maintained or improved visual acuity. Another report [88] on 20 patients with orbital and ocular adnexa tumors provided results after orbit-sparing surgery, followed by protons. After 60 Gy (RBE), there were no local recurrences after a median follow-up of 27 months, but there were one regional and one distant recurrence (total, 10%). Treatment was well tolerated with only 20% of patients having a decrease in visual acuity.

OPC is another cancer where improvement of results with IMPT is expected largely due to significant change toward more HPV+ patients in recent years. [2] When accelerated photon RT and concurrent proton boost were used in 29 patients with advanced OPC, [89] only 3 (11%) late Grade 3 toxicity was observed with LC of 84% at 5 years. In the setting of OPC, MFO IMPT seems as mandatory for covering complex bilateral target volumes with successful delivery. In one such attempt, researchers used IMPT in 26 p16+ OPC to achieve low rates of Grade 3 mucositis (15%) and 19% of patients required feeding tube, which compared favorably with the historical (IMRT) rates of 48%. [90] In a case-matched analysis [91] with 50 IMPT and 100 IMRT, there was no difference in OS (p=0.44) or in PFS (p=0.96). When considering the pre-planned composite endpoint of Grade 3 weight loss or G-tube presence, the ORs were OR=0.44; p=0.05 at 3 months after treatment and OR=0.23; p=0.01 at 1 year after treatment. One study [92] reported on 50 patients treated with IMPT (92%, MFO), of which 98% had Stage III/IV disease, 64% received concurrent therapy, and 35% received induction CHT. Importantly, 98% were p16 pos-

itive. No grade >4 toxicities were observed. The 2-year OS and PFS rates were 94.5% and 88.6%, respectively.

Protons were also used in reirradiation of HNC patients with recurrent or progressive disease. Recent multi-institutional report highlighted excellent results obtained with 1-year LRF of 25%, DMFS of 84% and OS of 65.2%, respectively. These results were accompanied by low risk of acute Grade 3 toxicity (dysphagia, 9.1%, mucositis, 9.9%, esophagitis, 9.1%, and dermatitis, 3.3%), late Grades 3–4 dermatitis (8.7%) and dysphagia (7.1%) and Grade 5 bleeding in 2.9% patients.[93]

## Conclusion

RT remains one of the cornerstones of treatment of HNC. This is so irrespective if it was given alone,[94] together with CHT[1,95] or in specific HNC patient populations.[2] Importantly, novel technological aspects of RT, such as IMRT, SRS, SBRT, or heavy particles significantly improved RT effectiveness on both T and N level. This was accompanied with decreased toxicity, making improved therapeutic benefit easily documented in contemporary clinical studies. Additional efforts should be made to further optimize these approaches in clinical studies within a framework of a more formal research setting.

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