Adaptive radiotherapy for head and neck cancer: practical clinical benefits and future perspectives

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Abstract

Background: Head and neck cancer (HNC) HNC is typically diagnosed in a locally advanced yet potentially curable stage, for which radiotherapy (RT), either alone or in combination with concurrent chemotherapy, is usually the main treatment of choice. The technological advancement in RT technology, including intensity-modulated radiation therapy (IMRT), Volumetric modulated arc therapy (VMAT), and image-guided radiation therapy (IGRT), yield precise delivery of radiation beams to the target and better sparing of normal tissues. Patients with HNC often experience anatomical changes during RT, which may result in unintended dosimetric shifting affecting the side effect profile and potentially the efficacy of the treatment. The small deviations from geometric data might greatly change the dose distribution in target volume and organ at risk from what is planned. During the RT of HNC, the parotid, minor salivary glands, submandibular, pharynx, larynx, spinal cord, and brain stem often exposed with substantial doses of radiation. Radiation-induced xerostomia is usually triggered by quantitative and qualitative changes in the salivary glands.

Aim: The aim of the study is to assess the real benefit of adaptive radiotherapy (ART) during the treatment in HNC, and also reveal the precise criterias to patient selection, optimal number and timing of re-planning, and convenient approaches to image registration and dose calculation.

Methods: Several case reports which were published over the period of last 18 years were studied analyzed. We performed an electronic review of articles published in PubMed/MEDLINE and authorized medical journal from January 2006 to December 2024. Our study was including to numerous articles Based on high reliability sources worldwide clinical and literary experience dealing with locally advanced HNC and anatomical/dosimetric variation in the context of ART.

Results:Numerous randomized prospective and retrospective trials have shown that adaptive radiotherapy (ART) in HNC demonstrates improved target coverage and reduction in doses to critical structures and suggests improved local control and reduced toxicity. Artificial Intelligence (AI) software program to facilitate radiotherapy replanning is a promising solution to improve treatment accuracy and efficiency and potentially improve the therapeutic ratio. Despite the large evidence-based information data, the diverse strategies of ART in HNC remain controversial, as well as the documented dosimetric and clinical advantages associated with these modalities.

Conclusions: The accumulated information from many reliable studies and ongoing retrospective studies give hopes, that in the future, it will be possible to determine the exact criteria for conducting adaptive radiotherapy, such as correct patient selection. The ideal frequency and timing of re-planning and convenient approaches of dose-volume calculation and advanced technological modalities of image registration modes. **(TCM-GMJ May 2026; 11 (1): P56-P61)**

Keywords: Head and neck cancer (HNC), Radiotherapy (RT), Intensity-modulated radiation therapy (IMRT), Volumetric modulated arc therapy (VMAT), Image-guided radiation therapy (IGRT), Adaptive radiotherapy (ART), Artificial Intelligence (AI)

Introduction

HNC is the seventh most common cancer globally, accounting for an estimated 890,000 new cases and 450,000 deaths each year. Expectations for tobacco and alcohol consumption are increasing, along with a growing burden of HPV [1].

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HNC is typically diagnosed in a locally advanced yet potentially curable stage, for which radiotherapy (RT), either alone or in combination with concurrent chemotherapy, is usually the treatment of choice. Radiotherapy improves clinical, form, and functional outcomes for cancer patients [2]. Currently, almost 75% of patients with HNC will benefit from radiotherapy, whether primary or adjuvant therapy after surgical resection. Radiotherapy is also used in procedures aimed at organ preservation, including avoiding laryngectomy through the use of Radical RT with concurrent chemotherapy [3]. Over the last decade, the technological advancement in radiation therapy technology, including intensity-modulated radiation therapy (IMRT), Volumetric modulated arc therapy (VMAT), and image-guided radiation therapy (IGRT), yield precise delivery of radiation beams to the target and better sparing of normal tissues [4].

Patients with HNC often experience anatomical changes during the course of RT, which may result in unintended dosimetric shifting affecting the side effect profile and potentially the efficacy of the treatment. These modifications can be related to multiple factors, such as shrinkage of large tumor and/or nodal masses, weight loss, and resolution of postoperative changes [5].

Adaptive radiotherapy may be divided into main two categories: anatomy-adapted (A-ART) and response-adapted (R-ART) RT. Anatomy-adapted radiotherapy is the process of re-planning patients based on structural and spatial changes occurring during the course of the treatment, with the intent of minimizing overdosage of sensitive structures (e.g. parotid, submandibular glands), improving dose homogeneity, and preserving coverage of the target volume (TV) [6, 7]. In contrast, Response-adapted RT is an attractive approach for dose escalation, since persistent or refractory disease, over the treatment period, may be directly targeted, effectively reducing the volume of disease being boosted with additional dose [8, 9]. The process of A-ART involves obtaining a new set of images during treatment and adjusting the parameters of the radiotherapy plan in response to the updated findings, which means re-planning patients during treatment either in response to a stimulus, such as weight loss or tumor shrinkage, or at pre-defined intervals throughout radiation [10].

Patients undergoing radiation therapy, particularly with concurrent chemotherapy. The likelihood and severity of complications are up to various factors, including the total radiation dose, delivery time, and specific areas of the head and neck receiving radiation early radiation side effects are usually found in tissues with a high proliferative activity that counteracts permanent physiological cell loss (turnover tissues), such as epidermis or mucosae [11]. This term includes inflammation of the oropharyngeal mucosa (mucositis), painful swallowing (odynophagia), difficulty swallowing (dysphagia), hoarseness, lack of saliva (xerostomia), orofacial pain, laryngeal radionecrosis, dermatitis, hair loss, nausea, vomiting, inadequate nutrition, hydration, and weight loss [12]. Early and late radiation effects are independent of each other with regard to their pathogenesis and, in general conclusions from the severity of early reactions on the risk of late effects cannot be drawn [13]. Late radiation sequelae, in contrast to early effects, with some exceptions, are irreversible and progressive, with increasing severity occurring with longer follow-up times. The risk for the manifestation of a chronic reaction, in most instances, remains throughout the patient's lifespan. RT can damage blood vessels which supply muscles, nerves, and bones this process can result a progressive „radiation fibrosis Syndrome", that serves as a cause of variety of complications, such as loss of saliva, radiation recall myositis, osteoradionecrosis, pharyngoesophageal stenosis, oral cavity necrosis, dental caries, fibrosis, damaged wound healing, dermatological events, lymphedema, hypothyroidism, hyperparathyroidism, lightheadedness, dizziness and headaches, secondary cancer, also neurological/functional problems, caused by damage of the critical structures (e.g. eye, ear, cranial nerves) [12]. Weight loss during RT (estimated to occur in almost 80% of HNC patients) is relevant to the acute toxicities of radiation and concomitant chemotherapy.

According to the randomized trial the most significant risk of severe weight loss in patients undergoing chemoradiation with previous surgical resection with a rate of 83.3% ($p<0.001$). The incidence of severe weight loss in patients with normal weight in comparison to overweight patients was significant. Advanced tumor stage and approach of the treatment modality in HNC patients which result in synergizing of treatment toxicities, may these factors can be used as reliable indicators of severe weight loss during radiation therapy [14]. The small deviations from geometric data might greatly change the dose distribution in target volume and organs at risk from what is planned, and intensify the side effects of radiation therapy in a defective cycle [15]. In addition to volume changes, the spatial orientation of the head and neck risk organs appears to change during treatment, with a typical pattern of superior and medial displacement thought from shrinkage of the target tumor and weight loss associated with it. The implication of this change means that critical structures may migrate closer to high-dose regions, resulting in an unplanned overdosage of these organs (e.g. parotid gland, submandibular gland, pharynx, larynx, esophagus) [10].

Oral mucositis is the most severe and frequently dose-limiting early side effect of chemo-radiotherapy for HNC. Erythema, focal and confluent mucositis/ulceration are the lead symptoms. Almost all patients with curative radiotherapy in this region develop some form of mucositis, with usually more than 50% confluent reactions [16]. Sunaga T. et al. conducted retrospectively analyzed 94 patients with HNC who developed oral mucositis (OM) during RT. Patients with a smoking history had a significantly later development of oral mucositis than those without smoking history. In contrast to this, patients undergoing chemoradiation had an earlier development of oral mucositis than those undergoing solely RT.

Chronic effects of radiotherapy include mucosal atrophy non-healing ulceration, and telangiectasia, which render the epithelium vulnerable. The early radiation response of the esophagus (mainly manifest as esophagitis) mirrors that of the oral mucosa. In the chronic phase of the pathological processes, strictures may develop.

During the RT of HNC, the submandibular, parotid, and minor salivary glands are often exposed to substantial doses of radiation [17]. Despite the fact that parotid and submandibular salivary glands can be adequately delineated on contrast-enhanced CT scans, during irradiation, these critical structures typically shrink during RT, potentially resulting in decreased gland sparing [18].

Radiation caries, with a very fast manifestation, is a frequent complication of RT, in HNC patients. The response is based on both direct radiation effects at the dentinenamel border zone and indirectly on radiation effects in the salivary glands and the associated changes in the oral cavity [16]. Rigorous pre-treatment dental restoration or extractions are of major importance, because of the risk of osteoradionecrosis, if extractions are required after RT. Treatment strategies include maintaining optimal oral hygiene and managing xerostomia. Resistance to cavities can be improved by using topical fluorides and/or remineralizing agents (high in calcium phosphate and fluoride) with dental trays.

Exposure of the pharynx and larynx, particularly with concurrent chemotherapy, can produce numerous adverse events, such as severe dysphagia, compromising nutrition, damage to the protection barrier of the airway, and reduced quality of life. Hypothyroidism is a common toxicity experienced after radiotherapy for HNC. Intensive weight loss during the treatment course has a certain effect on overdosing of the thyroid gland. Thyroid volume and thyroid V60 are independent predictors of radiation-induced hypothyroidism (RIHT) in patients with HNC [22].

The spinal cord and brainstem are also of interest as hot spots may occur in them throughout RT, which may overtake conventional dosimetric constraints, that were chosen to keep myelopathy and brainstem necrosis rates nominal. Skin erythema is closely related to vascular radiation effects, with intermittent phases of vasodilation. The clinical manifestation is dry desquamation (radiodermatitis sicca), followed by moist desquamation. According to the turnover time of human epidermis of 20–45 days, this phase is usually seen at 2–3 weeks after the onset of radiotherapy. Any variation in overall treatment time can have a large influence on epidermal tolerance, which primarily implies accelerated hypofractional schemes. The re-planning algorithm allows the radiation plan to adapt to changes in the tumor and normal tissue anatomy. This helps reduce the dose to sensitive structures such as the parotid glands, while also minimizing dose inhomogeneity and inadequate target coverage. However, numerous questions remain about the precise patient Selection, optimal number and timing of re-planning, and convenient approaches to image registration and dose calculation [5].

Methods

Several case reports which were published over the period of last 18 years were studied analyzed. We performed an electronic search of articles published in PubMed/MEDLINE and autorised medical journal from January 2006 to December 2024. The search was performed using the following keywords: adaptive radiotherapy (ART), anatomical adaptive radiotherapy (A-ART), response adaptive radiotherapy (R-ART), HNC, parotid glands, submandibular glands, radiation induced xerostomia, treatment related adverse events (TRAE), Artificial Intelligence (AI), AI-based ART and target volume. Our search included numerous articles based on high reliability sources worldwide clinical and literary experience dealing with locally advanced HNC and anatomical/dosimetric variation in the context of ART.

Results and discussion

Numerous randomized prospective and retrospective trials have shown that adaptive radiotherapy (ART) in HNC demonstrates improved target coverage and reduction in doses to critical structures and suggests improved local control and reduced toxicity. Yu-Chang Hu and colleagues demonstrated that Adaptive radiotherapy (ART) has potential dosimetric benefits In terms of improvement quality coverage, in patients with stages of nasopharyngeal cancer. ART could significantly improve the PTV-1 target volume coverage of D98 (15.4 vs. 12.3 Gy, $p < 0.000$). Based on the D98 of PTV-1, the factors of a large initial weight (> 60 kg, $p < 0.000$), large body mass index (BMI) (> 21.5, $p < 0.000$), obvious weight loss (> 2.8 kg, $p < 0.000$), concurrent chemoradiotherapy ($p < 0.000$), and stages III-IV ($p < 0.000$) favored the use of ART [25]. During the randomized trial, Maheshwari et.al, Sixty patients with locally advanced (III-IV stage) HNC were randomized into two arms to receive definitive radiotherapy up to a curative dose of 70 Gy with concurrent weekly chemotherapy (cisplatin - 40 mg/m2). Repeat CT scan was acquired after the 3rd week of chemoradiation. Patients in the study arm underwent re-planning, whereas those in the control group continued with the first IMRT plan. At the end of the study, it was a statistically significant escalation in the mean dose of right and left parotids in the control arm of 5.56 ± 4.99 Gy (p-value = 0.04) for the right parotid and 3.28 ± 3.32 Gy (p-value = 0.03) for the left parotid. The maximal dose of the spinal cord also increased statistically significantly in the control arm, 1.25 ± 2.14 Gy (p-value = 0.04), compared to the adaptive arm [26]. According to the prospective study, Srivastava R. et. al, re-scanning and re-planning at the 20th fraction of the treatment shows a 27% (13 - 42%) diminish in parotid volumes, and therefore 21% (7 - 35%) increase in parotid mean doses. The initial plan calculated on repeat-CT and CBCT found a 15% (9 - 26%) increase in planning risk volume (PRV) spine maximum doses, which were decreased by re-planning on repeat-CT. The body maximum doses escalated by 6,5% (4–8%) in four patients and 22% in one patient. These results demonstrated a statistically significant difference in the parotids, (PRV) spine and skin doses with a p-value (statistical significance at alpha <0.05) of 0.01, 0.007, and 0.02, respectively [27]. A variety of dose-volume parameters have been correlated with salivary endpoints, including subjective xerostomia and objective stimulated/unstimulated salivary flow [28]. Joel Castelli and colleagues showed that weekly replanning reduced the mean dose by 5.1 Gy (12.2 Gy maximum) and the absolute risk of xerostomia by 11% (p-value < 0.01) (30% maximum). The PG overdose and the dosimetric advantage of re-planning increased with the tumor shrinkage and the neck thickness reduction (p-value < 0.001) [29].

In patients undergoing radiotherapy who experience hot spots in the spinal cord or brainstem, it has been consistently reported that re-planning can reduce these maximum doses to within the predetermined limits. Most authors recommend re-planning when these limits (spinal cord maximum dose <45–48 Gy and brainstem maximum dose <54 Gy) are exceeded during radiotherapy. During the study, Duma et al. revealed a significant improvement in the dose to the oral cavity, larynx, and spinal cord with ART [30].

The 3-phase radiotherapy protocol, Ki Fung W.W. et. al, in patients with nasopharyngeal carcinoma cases demonstrated improved dosimetric results to the OARs. Also, after re-planing the doses to 95% of all the target volumes (PTV D95%) were increased with better dose uniformity, whereas the organs at risk (OARs) received higher doses compared with the corresponding ART plans. Without replanning, the total dose to 1% of the brainstem and spinal cord (D1) significantly increased by 7.87 ± 7.26% and 10.69 ± 6.72%, respectively (p-value = 0.011 and 0.001, respectively) [31]. In addition, Deng s. et. al, adaptive radiation therapy showed potential dosimetric benefits of remarkable dose–volume reductions, including mean doses to the glottis, V50 for the supraglottis, and V55 for the skin [32]. Accordingly, numerous retrospective studies have shown that ART in HNC demonstrates improved target coverage and reduction in doses to critical structures and suggests improved local control and reduced toxicity [33].

The process of radiotherapy treatment planning involves obtaining the patient's anatomy through radiographic imaging during treatment simulation and then designing the customized beam arrangement, beam number, geometry, intensity, and modulation during plan optimization. This leaves space for a personalized approach to treatment [34]. Despite the significant clinical benefit of ART, One of the biggest challenges with adaptive replanning, the time required to manually resimulate, recontour, and replan patients can be draining on a department's resources [35]. Recently, the utilization of an intelligence software program to facilitate radiotherapy re-planning is a promising solution to improve treatment accuracy and efficiency and potentially improve the therapeutic ratio. A novel online adaptive platform with intelligence-assisted workflows on daily CBCT has become available and has demonstrated feasibility. For HNC, ART can be beneficial in evaluating PTV margin reductions down to as tight as 1 mm [35].

Using the re-planning program system of the Ethos, Dohopolski et al. simulated ART on oropharynx cancer patients with a 1 mm PTV margin which showed dosimetric superiority compared with conventional radiotherapy with a 5 mm margin, reducing on average 11 Gy for ipsilateral and 12 Gy for contralateral submandibular gland, 8 Gy for parotids, and similar levels of sparing for other relevant OARs [36].

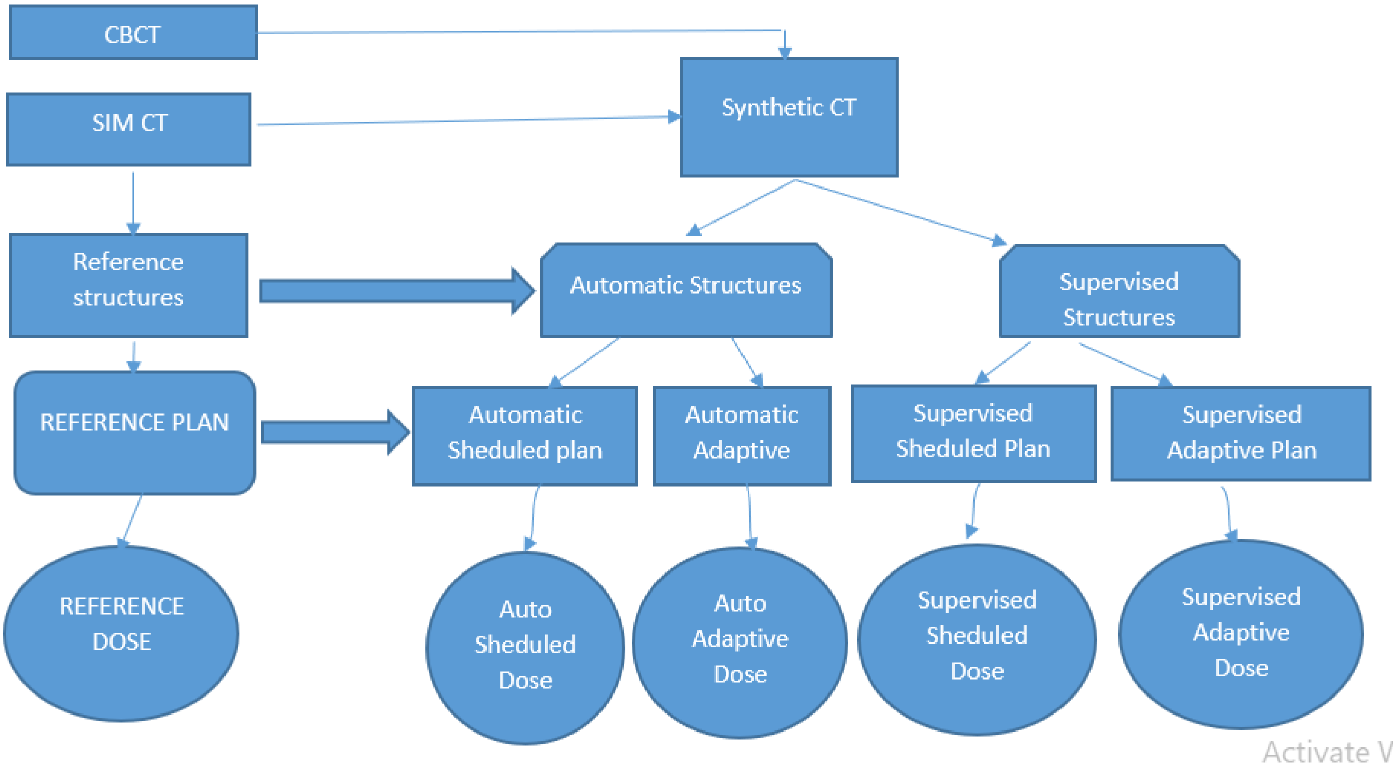
The AI-based solution program is based on a modified convolution-neural network. For automatic segmentation, the AI model is used for auto-contouring in situations in which organ deformation and volume changes are considered minor and under circumstances, where surrounding normal tissues do not strongly affect the spatial positioning and shape of the target volume (Figure 1) [37]. However, contouring of targets is a very difficult problem and can be confounded by issues about large deformation, volume changes, and motion of the surrounding anatomical structures. In such cases, the previously detected normal tissues are used in combination with a deformable registration algorithm to interpret the target from the planning CT to the new image.

Figure 1. AI-based daily adaptive workflow. Abbreviations: CBCT - cone beam computed tomography; CT - computed tomography; Sim CT - simulation computed tomography.

Conclusion

Numerous patients undergoing chemoradiation treatment for HNC experience spatial and volumetric changes in target volumes (TVs) and organs at risk (OARs) due to tumor response, weight loss, inflammation, and radiation-induced damage. Comparative analyses between initial and adaptive planning consistently show significant reductions in critical normal tissue volumes. Randomized and retrospective studies underscore the clinical significance of adaptive radiotherapy (ART) to mitigate the increased OAR dose exposure inherent in prolonged courses without re-planning, especially when using advanced modalities like IGRT, IMRT, or VMAT, which may otherwise elevate toxicity risk. The integration of artificial intelligence (AI) has shown promise in alleviating the considerable workload barrier to ART's broader clinical implementation. Nevertheless, despite substantial evidence of ART's dosimetric and clinical benefits, there remains a lack of consensus on optimal strategies, highlighting the complexity of integrating ART into standard practice. Current challenges include the identification of consistent predictive factors and the development of precise criteria for patient selection, frequency, and timing of re-planning. Continued research and the accumulation of robust data are crucial for refining ART protocols and achieving efficient, evidence-based adaptive radiotherapy in clinical settings.

Figure 1. AI-based daily adaptive workflow. Abbreviations: CBCT - cone beam computed tomography; CT - computed tomography; Sim CT - simulation computed tomography.



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