

Review

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Review

Does Adaptive Radiotherapy for Head and Neck Cancer have a favorable impact on dosimetric, clinical, and toxicity outcomes? A Review

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Simple Summary: This review article aimed to explore the importance of Adaptive Radiotherapy (ART) in the treatment of Head and Neck Cancer (HNC) and specifically to uncover the impact of ART on improving target volume coverage and normal tissue sparing, resulting in optimal dosimetric, clinical, and toxicity outcomes.

Abstract: We performed electronic research for articles published in PubMed, MEDLINE, and ScienceDirect databases from January 2004 to January 2023. The systematic review of twenty (20) peer-reviewed articles about dosimetric parameters and eight (8) articles about clinical outcomes confirmed the dosimetric advantages of ART through better target coverage and Organs at Risk (OARs) sparing, with subsequent benefits on decreased toxicity and improved clinical outcome, precisely local control of the disease. ART replanning is a sustainable strategy for minimizing toxicity by improving normal tissue sparing. Furthermore, it enhances target volume coverage by correctly determining the specific amount of dose to be delivered to the tumor. In conclusion, this review confirms that ART benefits dosimetric, clinical/therapeutic, and toxicity outcomes.

Keywords: Head and Neck cancer; Adaptive Radiotherapy (ART); Intensity-modulated Radiation Therapy (IMRT); anatomic changes; dosimetric changes; time of adaptation; clinical outcomes

Introduction

Head and Neck Cancers (HNC) still represent some of the most common malignancies in developing countries, accounting for 5% of all cancers, both in males and females, with over 800,000 new cases reported worldwide each year, being responsible for more than 400,000 deaths annually [1,2]. The incidence of HNC exhibits significant regional variations, with higher prevalence in South and Southeast Asia and certain parts of Europe [3,4].

HNC encompasses various cancer types, including those affecting the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands [5]. The primary risk factors include tobacco and alcohol use, but in recent years, human papillomavirus (HPV) infection has also emerged as a significant risk factor, especially for oropharyngeal cancer [6–9]. Men face a higher risk of developing HNC than women, and the likelihood of diagnosis increases with age, with most cases occurring in individuals over the age of 40. Treatments for HNC usually involve surgery, radiation therapy (RT), chemotherapy, or a combination of these approaches, with the specific treatment plan tailored to the cancer's stage and location [10].

Survival rates vary based on several factors, mainly the stage at diagnosis and the tumor's location, but in general, the 5-year survival rate is around 60% [11].

Most studies and statistics show that more than 65% of HNC patients have locoregionally advanced disease at diagnosis [12]. Chemoradiotherapy with systemic administration of a platinum-based regimen in combination with fractionated radiotherapy to a dose of 63–70 Gy is the standard of care for locoregional organ-sparing therapy of head-and-neck squamous cell carcinoma. Modern radiotherapy practice evolves imaging techniques, such as computer tomography during treatment, to accurately deliver high curative radiation doses to the tumors [13]. In this direction, the transition from two-dimensional conventional radiotherapy (2D-RT) to three-dimensional conformal radiotherapy (3D-CRT) and, nowadays, to intensity-modulated radiation therapy (IMRT) contributed the most to achieving the maximum therapeutic effect [14].

Apart from the significant therapeutic results, the issue of adverse acute effects of chemoradiotherapy treatment schedule for head and neck cancer is still substantial. Chemotherapy, radiotherapy, and the combination of these two can cause several acute but also delayed adverse effects, such as weight loss and anxiety. Significant acute radiation-induced toxicities include severe mucositis, dermatitis, xerostomia, and dysphagia, which may require a feeding tube. Significant late or chronic toxicities include xerostomia, dysphagia, and fatigue, which have been shown to impact quality of life years after treatment [15,16].

HNC poses a significant challenge in the field of RT due to the complex and dynamic anatomical structures, proximity to critical organs, and inter-fractional variations in the tumor and surrounding healthy tissues [17]. However, in the contemporary practice for HNC RT, it is often usual that radiation oncologists carry out the treatment plan without accounting for the actual anatomical changes that may result from swelling of the irradiated areas, the daily normal-tissue volume alterations, the tumor shrinkage, and the loss of body mass and weight [18,19]. All these changes can displace the target and the organs at risk (OARs) from their original position, affecting the accuracy of the radiation dose delivered without avoiding and protecting surrounding healthy tissues. Progress in image-guided RT has shown that volumetric changes to target volumes and OARs are often seen during intensity-modulated radiation therapy for HNC patients [19]. Moreover, the changes may result in an ill-fitting immobilization mask [13].

Although weight loss or reduction of nodular volume may be apparent on physical examination, these changes have resulted in unintended (or, at the very least, unmonitored) deviation from the initial planning geometry. Clinical target volume (CTV) undercoverage and/or organ at risk (OAR) overdosing may occur despite the application of isocentric image-guided alignment [20–22].

Therefore, adaptive radiotherapy (ART), with its ability to dynamically adjust the treatment plan in response to the patient's anatomical changes and deviations, has emerged as a promising solution to enhance target volume coverage in tumor size, shape, and position, guaranteeing that the tumor receives the intended radiation dose and minimize radiation-induced toxicity, improving the patient's quality of life during and after treatment. Additionally, ART offers the opportunity for optimal dose escalation when clinically indicated, potentially increasing the likelihood of tumor control without increasing the risk of damage to healthy tissues. Furthermore, ART can minimize treatment interruptions, as it quickly adjusts the treatment plan to accommodate sudden changes in anatomy, such as those caused by weight loss during treatment. ART considers each patient's unique anatomical changes as a highly personalized approach, leading to better treatment outcomes [23]. This individualized treatment can improve therapeutic outcomes and provide a more customized treatment experience [18,24].

ART for HNC can typically be employed to assess and correct tumor response and weight loss. Radiation oncologists are expected to utilize image-guided scans as the basis for treatment to help enhance adaptation planning for treatment response [25,26].

Therefore, ART is implemented to correct all morphological variations by actively adapting the treatment plans into three different timeframes: between therapy sessions (Offline Adaptive), immediately before a therapy session (Online Adaptive), and during a therapy session (Real-time Adaptive) [27].

With all the principles mentioned above, this review article focuses on exploring the impact of Adaptive Radiotherapy on dosimetry, clinical, and toxicity outcomes. Additionally, it will help

evaluate whether Adaptive Radiotherapy improves the target volume coverage and/or normal tissue sparing.

Methods and Materials

We performed an electronic search of articles published in PubMed/MEDLINE and Science Direct from January 2004 (2007) to January 2020 (2023). The search was accomplished according to PRISMA GUIDELINES, using the following keywords: ART, HNC, parotid gland, and target volume. Additionally, reference lists were screened for studies with topics relevant to the current review. Retrospective and prospective studies were both included.

Articles were selected based on the relevance of the project studied. The eligibility criteria for the current review include:

- Report on dosimetric/anatomic changes.
- studies with ≥ 10 patients

All included studies were reviewed to collect the following data: number of patients, therapy practice, number of replans, anatomic and dosimetric variations, and dosimetric and clinical benefits of ART. Studies with a limited number of < 10 patients were excluded. The flow chart diagram of the literature review is shown in Figure 1.

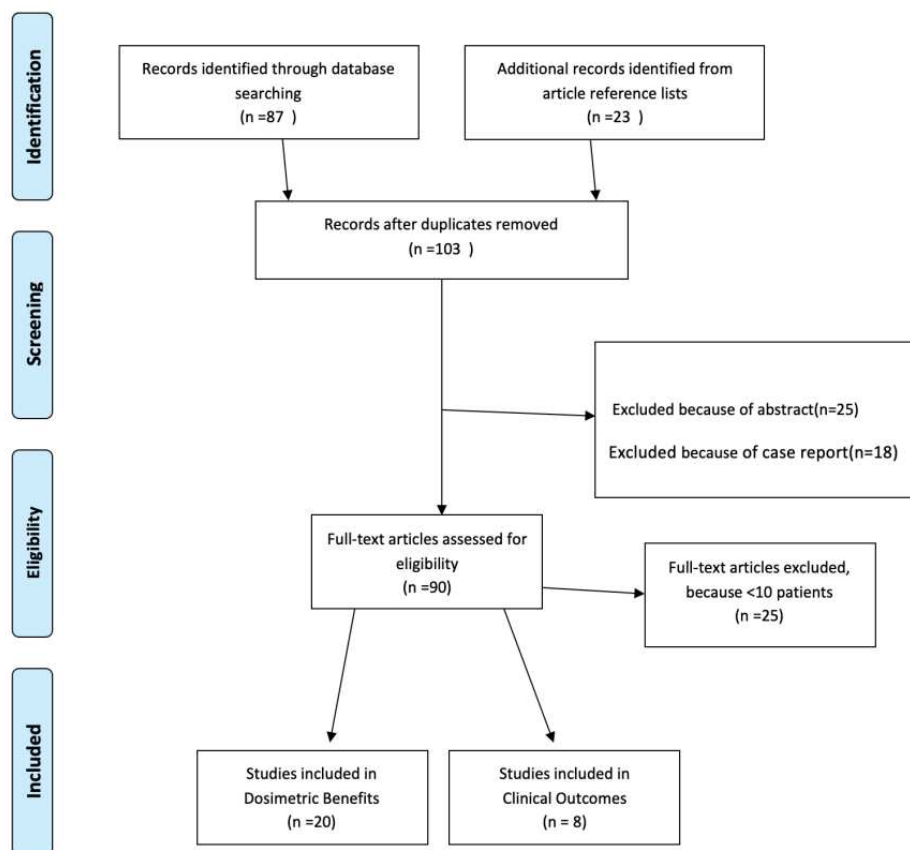


Figure 1. Flow chart diagram.

Results

Radiotherapy Planning

Over the past 20 years, the standard of care for radiotherapy of HNC has transitioned from 2D RT to 3D-conformal radiotherapy (3D-CRT) and eventually to intensity-modulated radiation therapy (IMRT) [28]. Initially, conventional radiotherapy approaches were rigid, delivering a fixed dose to the tumor and surrounding tissues. IMRT has demonstrated its superiority with its ability to decrease adverse effects on normal tissues, such as reducing xerostomia without compromising the therapeutic dose of radiation to target volumes of both primary and lymph nodes [29]; however, because of the unique features of IMRT, such as inverse planning procedures, any anatomical changes in patients resulting from weight loss or tumor shrinkage can substantially impact the radiation dose delivered. For this reason, the ART concept was introduced, offering improved precision, reduced toxicities, and improved patient outcomes [30,31].

Further innovations in modern radiotherapy practice include apart from intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiotherapy (SBRT), image-guided radiotherapy (IGRT), and protons or heavy ions [30,32].

The standard 3D-CRT approach, until the late 90s, involved the employment of 6 MV photon beams and a technique known as the three-field method. This method utilizes two lateral fields opposite each other to irradiate the primary tumor and cervical lymph nodes in the upper and lower neck regions. Additionally, a third anterior field irradiates the supraclavicular lymph nodes. The two lateral and anterior fields share the same isocenter to ensure precise radiation delivery. They are carefully aligned at this isocenter level, preventing any overlap of radiation fields at the junction line. It is also important to periodically adjust the junction line during treatment to ensure a gradual transition in the dose distribution to minimize adverse effects. This three-field technique involved several sequential dose boosts associated with specific prescription doses [31,33].

In contrast to the “older” three-field treatment approach, IMRT employs varying beam intensities and segments to deliver radiation that conforms to the tumor's shape and results in a steep dose drop-off at the tumor-normal tissue boundary. IMRT is well-suited for head and neck cancer (HNC) due to its complex tumor geometry and proximity to critical structures, as well as minimal organ movement. Two standard IMRT planning techniques for HNC are split-field and extended-field IMRT. The split-field approach treats the primary tumor and upper neck with IMRT, using a conventional anterior field for the lower neck and supraclavicular regions. Extended-field IMRT treats all tumor volumes simultaneously but requires attention to avoid overdosing to the larynx. For treating bilateral tumors, a standard setup involves nine coplanar 6 MV photon beams evenly positioned around the patient at angles of 0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320°. In unilateral tumors, seven coplanar beams are utilized, angled from the side of the cancer. Care is taken to avoid directing the radiation laterally and, when necessary, to adjust the gantry angle slightly to prevent the beam from passing through the shoulder. The treatment's isocenter is typically chosen at the central point within the area to be irradiated, given that head and neck treatments often involve relatively large treatment fields.

The delineation of target volumes is further improved with functional imaging and the fusion of 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) scans with CT scans, although variability in delineation remains a challenge. IMRT planning has transitioned from manual planning to computer-based inverse planning, which offers better dose distribution to tumor volumes and improved sparing of critical structures [34–37].

VMAT, an advanced version of IMRT, further improves treatment by optimizing treatment delivery. In traditional IMRT, the treatment plan involves numerous small radiation fields created using the multileaf collimator (MLC). This can be done by sequentially positioning the MLC leaves to form these fields and then delivering radiation (the step-and-shoot method) or by continuously adjusting the MLC leaves while the radiation beam is on (the sliding window method). In contrast, VMAT allows for simultaneous motion of the MLC and gantry, adjusting factors like MLC leaf speed, gantry speed, and dose rate, all during real-time treatment. VMAT has become a popular choice for

treating head and neck cancers due to the region's complex anatomy. A typical VMAT plan includes 2-3 full or partial arcs, depending on whether the treatment addresses bilateral or unilateral targets. VMAT plans utilize a more significant number of beam angles, resulting in a more precise dose distribution within the target area when compared to traditional IMRT. VMAT plans maintain similar target coverage as fixed gantry IMRT but offer improved uniformity. Notably, the delivery time for VMAT plans is significantly shorter, taking about 5 minutes, whereas fixed gantry IMRT plans typically require 10-15 minutes. Figure 4 provides a comparison of dose distributions between a two-arc VMAT plan and a nine-beam IMRT plan for a patient with laryngeal cancer and bilateral cervical lymph node involvement. VMAT and IMRT effectively cover the target volumes with comparable organ-at-risk (OAR) sparing. Occasionally, VMAT may enhance the sparing of contralateral OARs [38–40].

Fractionation

Radiation treatment schedules for head and neck cancers are not universally standardized. Typically, standard radiation therapy refers to daily doses of 1.8 to 2 Gy, given five days a week in 33 to 35 fractions, delivering a therapeutic dose of 70 Gy. However, to enhance the outcomes of head and neck cancer treatments, different radiation schedules have been developed. Over the past twenty years, two primary altered fractionation schedules, hyperfractionation and accelerated fractionation, have been extensively studied.

Hyperfractionation usually involves delivering two smaller doses of radiation daily in more fractions while maintaining or slightly shortening the overall treatment duration. This approach provides a higher biologically effective dose to the tumors and increases the tolerance of late-responding normal tissues. Several randomized trials have demonstrated that hyperfractionation significantly improves the control of tumors in both local and regional areas and enhances survival rates compared to standard fractionation. It's worth noting that hyperfractionation can lead to more severe acute mucositis, but the incidence of late complications remains within the range observed with conventional fractionation schedules.

Accelerated fractionation, on the other hand, reduces the overall treatment duration while keeping the number of dose fractions, total dose, and individual fraction sizes mostly unchanged or slightly reduced. The fundamental concept behind accelerated fractionation is that by shortening the treatment duration, there's less time for tumor cells to regenerate or repopulate during the treatment course. Clinical research on accelerated fractionation has demonstrated a significant improvement in local and regional control and survival rates. These accelerated schedules can also result in severe acute mucositis, but they do not appear to increase the risk of late complications.

Both hyperfractionation and accelerated fractionation schedules necessitate a minimum interval of 4.5 hours between fractions to allow normal tissues to repair after sublethal radiation injuries. Fractionation in radiotherapy is a critical factor significantly affecting treatment effectiveness [30,41–44].

A meta-analysis by Bourhis and colleagues [45], which reviewed 15 trials comparing conventional radiotherapy with hyperfractionation and accelerated radiotherapy for squamous cell carcinoma (SCC) patients, concluded that altered fractionation radiotherapy led to better tumor control and improved survival compared to conventional therapy. Additionally, research by Fu and colleagues indicated that both hyperfractionation and accelerated fractionation were more effective than conventional fractionation for locally advanced cancer [46,47].

Daily Imaging

Modern radiation therapy practice requires frequent imaging, which is necessary to improve treatment precision and outcomes. Daily imaging is essential, specifically during ART for head and neck cancer, for several key reasons:

1. **Anatomical Variability:** The head and neck region experiences significant anatomical changes, including weight loss, tumor regression, and patient positioning shifts. Daily imaging, often

via cone-beam computed tomography (CBCT), detects these changes and ensures precise tumor targeting while sparing critical structures.

2. **Patient Positioning:** Accurate patient setup is essential for effective radiation therapy. Daily imaging verifies patient positioning, minimizing the risk of radiation toxicity to normal tissues.
3. **Dose Escalation:** Daily imaging enables safe dose escalation by adapting treatment plans to current anatomy. This can improve local control and overall treatment outcomes.
4. **Reduced Margins:** Smaller treatment margins, made possible by daily imaging, minimize radiation exposure to nearby healthy tissues, which is crucial in the head and neck region where critical structures are close to the tumor.

Online and Offline Adaptive Planning in Radiation Therapy

The two primary approaches to ART are offline and online adaptive radiotherapy. Online adaptive planning, often called "real-time" adaptive planning, is a technique where treatment plans are adjusted daily during therapy. This approach is particularly relevant in situations where anatomical changes, such as tumor shrinkage or variations in patient positioning, occur frequently and necessitate immediate action.

Offline adaption, or "inter-fractional" adaptive planning, is suitable for systematic or slow progressive changes (e.g., tumor regression, weight loss). The treatment team can decide to apply an adaption based on an observed deviation in anatomy (on imaging or visible physical alterations) or follow a protocol with predefined action levels and/or surveillance scans [18,25,26,46,48].

Table 1 Provides an overview of the main differences between online and offline adaptive radiotherapy, highlighting their strengths and weaknesses in various clinical contexts. The choice between these approaches depends on the specific needs of the patient and the clinical circumstances.

Table 1. Main differences between Online ART and Offline ART.

Aspects	Online ART	Offline ART
Timing of Plan Adaptation	Real-time, daily or even intra-fractional	Periodic, often weekly or bi-weekly
Imaging Frequency	Daily, often using CBCT	Periodic, less frequent imaging (e.g., weekly)
Adaptation Response Time	Immediate	Delayed, typically days to weeks
Treatment Efficiency	Time-consuming, may extend treatment duration	Less time-consuming, may minimize treatment interruptions
Anatomical Changes	Continuously monitored	Assessed periodically
Resource Requirements	Requires significant resources, including advanced imaging equipment	Requires fewer resources, often relies on conventional imaging
Precision in Tumor Targeting	High, allowing rapid response to changes	Good, with adaptations at intervals
Patient Comfort and Experience	Potential for longer treatment times	Potential for more consistent treatment times

Handling of Clinical Uncertainties	Offers real-time adaptation to uncertainties	May not address uncertainties as quickly
Clinical Applications	Applicable in dynamic or rapidly changing clinical scenarios	Suited for more stable anatomical conditions

The frequency of CT scans for replanning therapy, is a critical consideration to maximize the benefits of this adaptive approach. The timing and frequency of CT scans for replanning in head and neck cancer treatment vary, with some advocating for daily scans while others perform scans depending on patient responses and clinical protocols. Typically, these scans occur at critical points during treatment, such as the start and specific intervals, to assess anatomical changes and adjust treatment plans. The goal is to precise tumor targeting while minimizing side effects and radiation exposure to healthy structures [19].

Dosimetric Considerations

Several studies have collectively investigated the dosimetric benefits of ART in head and neck cancer treatment. Various imaging methods, timing of evaluation, and frequencies of replanning were utilized in these studies. Expected dosimetric outcomes included volume shrinkage in target structures and changes in radiation doses to organs at risk (OARs) [20,21,49–61].

Volume Shrinkage

All studies reported varying degrees of volume shrinkage in target structures, such as the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). The extent of volume reduction ranged from approximately 11% to over 80%, with differences likely related to individual patient responses and tumor characteristics.

Dose Improvement to OARs

Multiple studies demonstrated improvements in radiation doses to OARs, particularly the parotid glands. Dose reductions in parotid glands ranged from approximately 3% to over 25%, reducing xerostomia and other side effects. Spinal cord and brainstem doses were also lowered, enhancing treatment safety.

Replanning Strategies

The studies utilized various strategies for ART, including daily cone-beam computed tomography (CBCT), weekly CT scans, and different timing for evaluation. Some studies performed multiple replans, showing adaptability in the ART process. One study applied an online ART approach, offering real-time adaptability.

Quality Assurance (QA)

Ensuring the accuracy and reliability of ART is paramount. Comprehensive quality assurance procedures, encompassing imaging, contouring, plan adaptation, and dose calculation, are essential to maintain the integrity of ART. Rigorous QA programs help guarantee safe and effective treatment delivery [19].

Table 2 summarizes the dosimetric benefits of online ART in terms of target coverage and the sparing of critical OARs in various replanning strategies for HNC patients.

These studies have explored the advantages of online ART, considering factors such as total dose, imaging method, timing of evaluation, the number of replanning events, volume shrinkage, and benefits to OARs. Duma et al. [62] conducted a study with 11 patients, demonstrating parotid gland sparing with minimal spinal cord dose variation. Two studies underscore the significant dosimetric advantages of online ART in enhancing target coverage for HNC patients. Jensen et al.

[63] conducted a comprehensive investigation involving 72 patients who underwent 15 replanning events. Their findings revealed a substantial improvement in target coverage, suggesting that online ART can dynamically adapt to changes in patient anatomy and ensure more precise irradiation of the tumor volume. Similarly, Schwartz et al. [64] reported increased target coverage and improved dose homogeneity in a cohort of 22 patients. These results further emphasize that online ART can adapt to anatomical variations and optimize target coverage and dose distribution.

Table 2. Dosimetric Benefits of ART in Target Covering and OAR's Sparing.

Author (year)	Pts No	REPLANNING STRATEGIES				DOSIMETRIC BENEFITS			
		TOTAL DOSE (Gy)	Imaging method	Time of evaluation	No of Replanning	Volume Shrinkage	Parotid (Dmean/V26)	Spinal Cord/Brains Stem (Dmax)	Benefit from ART
Zhao (2011) [65]	33	37.5 Gy (20 – 50 Gy)	CT	1 st at 15 th (+/- 5) fr 2 nd at 12 th (+/- 4) fr 3 rd after 15 th fr	1	GTVp: - 13.9%; GTVn: - 71.9%; CTV: - 3.5%;	Decreased mean dose (p <0.05)	NR	Decreased PG dose
Capelle (2012) [49]	20	66 Gy (54-60 nodes; 66 Gy primary)	CT	15 TH fr	1	Median Volume Loss: PTV60/66 = - 16% (0-45%); PTV54 = - 6.8 (-1.2 – 19%); GTV = - 28.8% (-1.6 – 60%); CTV60 = - 4.1% (-0.1 – 10%); PG =	CohA Adjuvant CRT: PG: Dmean = - 1.2 Gy/V26 = -6.3% CohB Definitive CRT: PG: Dmean = - 1.2 Gy/V26 = -6.3%	SC: Dmax = 1.2 Gy	15/23 Pts improved TV dose coverage

						17.5% (-1 - 46%)			
Duma (2012) [62]	11	64 postop 70 radical	MVC T	16 th fr (9 th - 21 st)	1	NR	PG: no variation of dose	SC: -0.14 Gy	---
Jensen (2012) [63]	72 15 replanned	70.4	Weekly CT	Weekly	2-4	NR	CPG: -11.5%	NR	8% Improvement of coverage
Schwarz (2013) [64]	22	70		16 th and 22 nd Fr	1-2	NR	-0.7 Gy	NR	Increase coverage and dose homogeneity
Bhandari (2014) [21]	15	NR	CT	3 rd week of treatment Between 18 th and 20 th fr	1 (HP vs AP)	Mean Volume Loss: GTV = -44.32 cc; CTV = 82.2 cc; PTV = -149.83 cc	RPG Dmean= +5.56+/- 4.99 Gy (p<0.04); LPG Dmean =+3.28+/- 3.32 Gy (p<0.003);	SC Dmax = +1.25+/-2.14 (p=0.04) BS Dmax = +3.88+/-3.22 (p<0.02)	TV and OARs
Lu J (2014) [50]	12	66 to Primary GTV (D95)	CT	25 th fr	1 (HP vs AP)	Mean Volume Change: PGTV = -16.4 +/- 27.3; PTV1 = +3.8+/- 6.3; PTV2 = -8.8+/- 12.0 cc; rPG = -24.6+/-	RPG = -24.6+/-11.9; LPG = -35.1+/-20.1	SC and BS: 8/12 No-ART Pts exceeded the constraint without replanning	TV and OARs

						11.9; IPG = - 35.1+/- 20.1			
		REPLANNING STRATEGIES				DOSIMETRIC BENEFITS			
Author (year)	Pts No	TOTAL DOSE (Gy)	Imaging method	Time of evaluation	No of Replanning	Volume Shrinkage	Parotid benefit (Dmean/V26)	Spinal Cord/Brainstem (Dmax)	Benefit from ART
Oltenu (2014) [51]	10	70.2 Gy	PET-CT	10 th , 20 th and last day of treatment for dose sum	2 (11 th -20 th fr and 21 st - 30 th)	Reduced GTV volumes (18.6-93.3%) after 18 th fr	PG: reduced median dose 4.6-7.1% (p>0.05)	OARs: dose-differences from -7.1to 7.1%	TV and OARs
Real (2014) [52]	10	68.4 - 70.2 Gy	CT	Weeks 3, 5, and 7 of treatment	1	PTVs mean relative shift = 0.1 cm (not taken in consideration for replan); PG volume decreased mainly for Ipsilateral PG	NR	SC mean relative shift = 0 cm	PGs
Castelli (2015) [53]	15	70 Gy	Weekly CT	Weekly	Weekly replanning	CTV70 decreased by a mean value of 31% (ranging 3% to -13%) PG volumes decreased by a mean value of 28.3% (ranging	PG Dmean: -4.8 Gy (67% Pts) and -3.9 Gy (33% Pts) Median contralateral PG dose-decrease: -2.0 Gy. (from 27.9 to 25.9 Gy)	NR	PG reduced dose

						from 0.0 to 63.4%			
Zhang (2016) [54]	13	70	Weekly CT	Weekly	6 weekly replans	Mean Volume Reduction CTV70=24.4 3%	With standard IMRT: Mean PG overdose of 4.1 Gy vs planned dose. In Replan: PG mean dose -3.1 Gy compared planned dose	NR	PG Benefit >4 Gy (34% one PG - 15% both PGs)
Van Kraanen (2016) [55]	19	70	Daily CBCT	10 th fr	1 (10 th fr or max in 2 nd week of treat)	In 5 th week: decreased CTVn & CTVnboost <-10%	Margin reduction and improvement in OAR dose ≈ 1 Gy/mm	NR	PGs: improved D99% with - at least - 3 Gy
Dewan (2016) [56]	30	GTV= 70 Gy; CTV = 66 Gy; PTV = 60 Gy	Weekly CT	20 th fr	1 (+ 1 hybrid)	Shrinkage: GTV: 47.62%; CTV: 43.76%; PTV: 39.69%. IPG: 33.65%; CPG: 31.06%	Mean dose to ipsilateral parotid was significantly reduced with replanning by 26.04+29.14 % (p= 0.001).	SC: Replanning reduced mean Dmax, D2% and D1% by 28.26 + 10.27%, 30.87+ 12.83% and 31.20 + 13.09% respectively as compared to delivered dose (p<0.01)	TV and OARs
Deng (2017) [57]	20	66 – 71.6 Gy	CT	5 th and 15 th frs	2 replans + 2 hybrid replans (5 th and 15 th fr)	Increase in V95; PTVnx: Decreased	Left PGs: Dmean = 3.67 Gy; V30 = 3.66 Gy	In ART plans: SC: Dmax decrease	TV and OARs

						Vmax and V110		d by 2.42 Gy; BS: Dmax decrease d by 2.42 Gy	
Suru cu (2017) [19]	51	70.2 Gy	CT and CBCT	After median dose of 37.8 Gy (27 - 48.6)	1 (in 34/51 pts)	Median TVRR: 35.2% (-18.8 - 79.6%)	IPG Dmean = -6.2%; CPG Dmean = -2.5%;	SC Dmax = -4.5% BS Dmax = -3.0%	TV and OARs
		REPLANNING STRATEGIES				DOSIMETRIC BENEFITS			
Author (year)	Pts No	TOTAL DOSE (Gy)	Imaging method	Time of evaluation	No of Replanning	Volume Shrinkage	Parotid benefit (Dmean/V26)	Spinal Cord/Brainstem (Dmax)	Benefit from ART
Castelli (2018) [58]	37	70 Gy	Weekly CT	weekly	Weekly replanning	NR	Median contralateral PG dose-decrease: -2.0 Gy. (from 27.9 to 25.9 Gy)	NR	PGs: reduced dose in 89% of Pts; CTV: increased dose in 67% of Pts; Both benefits: in 56% of Pts
Aly (2018) [20]	10	70 Gy	CT	Mainly in 10 th fr and 15 th fr	Mean 2 (range 0-5)	Volume Reductions: GTV _p = 25%; CTV _p = 18%; GTV _n = 44%; CTV _n = 28%; PTV70 = 11%; PTV60 no	PG volume decrease 28% during treatment	NR	Improved coverage of PTV70 and PTV60

						signific change			
Hay (2020) [60]	20	65 Gy	CT and CBCT	At fraction 16 th	1 (19 th fr)	NR	NR	SC: 3 Pts exceed max dose without replan	Benefit in OARs
Mne jja (2020) [59]	20	69.96 Gy	CT	At dose 38 Gy	1 (19 th fr)	Reduction in TV: 58.56% (GTVnodes); 29.52% (GTVtumor)	NR	NR	Deteriora tion of Tumor Coverage in no- ART Pts
Avk sho 1 (2023) [61]	21	NR	CT and CBCT	Frequenc y of adapts at the discretio n of treat physicia n	1-5 Median 13.5 th and 19 th fr	NR	IPG: -13.2 (node+ pts) - 11.24% (T3/4 disease pts) CPG: - 3.78 (node+ pts) - 1.68 (T3/4 disease pts)	SC Dmax: - 9.65 (node+ pts) -9.32 (T3/4 disease pts) BS Dmax: -6.41 (node+ pts) -5.38 (T3/4 disease pts)	PTV coverage PTV dose homogen eity OARs

Clinical Considerations

Table 3 summarizes the clinical outcomes of ART for head and neck cancer across different tumor sites, demonstrating the potential benefits of ART in improving locoregional control, survival rates, and toxicity profiles. The studies collectively support the utility of ART in enhancing the therapeutic landscape for head and neck cancer patients.

Table 3. ART Studies - CLINICAL OUTCOMES.

	No PTS	REPLANNING STRATEGIES					CLINICAL ENDPOINT		
Author (year)	ART (NO ART)	TUMOR SITE	TOTAL DOSE (Gy)	No of Replanning	Timing (fraction)	Follow-up (months)	LOCOREGIONAL CONTROL and SURVIVAL	ACUTE TOXICITY (%)	LATE TOXICITY
Zhao (2011)	33 (66)	NPC	70	1	15 th (+/- 5)	38	3-year LRFS 72.7% (ART); 68.1% (No-ART) p = 0.3	NR	Less xerostomia and mucosal with ART for N2 and N3 pts
Schwartz (2012)	22 (0)	OPC	66-70	1 or 2	16 th and 22 nd	31	2-year LRC=95%	G III mucositis: 100%, G II xerostomia: 55% G III xerostomia: 5%	Full preservation or functional recovery of speech and eating at 20 months
Yang (2013)	86 (43)	NPC	70-76	1 or 2	15 th and/or 25 th Fr	29	2-year LRC = 97.2% (ART); 82.2% (No-ART) p = 0.04 2-year OS = 89.8% (ART); 82.2% (No-ART) p = 0.47	NR	Improvement in OoL with ART
Chen (2014)	51 (266)	LAHNC	60 ^b 70 ^a	1	40 Gy (10-58 Gy)	30	2-year LRC = 88% (ART); 79% (No-ART) p = 0.01 2-year OS = 73% (ART); 79% (No- ART) p = 0.55	G III : 39% (ART) 30% (No-ART) P = .45	G III = 14% (ART) 19% (No-ART) P = .71
Kataria (2016)	36 (0)	LAHNC	70	1	54 Gy	-----	2-year DFS = 72%. 2- year OS = 75%	G II-III mucositis=100%	- G II xerostomia = 8% - G II mucosal = 11%. - No G III toxicity

Surucu (2017)	51 (17)	LAHNC	70.2	1	37.8 Gy (47 – 48.6)	17.6 mos	Median DFS: 14.8 (0.9 – 57.5) mos Median OS: 21.1 (4.5 – 61.4) mos Residual Disease: 11.8 % Locoregional Control: 64.7% Metastatic disease: 23.5%	Mucositis 35.3% Xerostomia NA Dysphagia 41.2%	Mucositis NA Xerostomia 3.3% Dysphagia 20%
Mostafa (2021)	49 (0)	LAHNC	70	1	42 Gy (37-44.1)	median 18 months (6.5 – 31)	1-year PFS 89.7%; 2-year PFS 70.2% 1-year OS 89%; 2-year OS 83 %	G II-III mucositis: 32.6 – 36.7 % G II-III Xerostomia: 44.9 - 16.3%	-----
Zhou (2022)	290 (147)	NPC	NA	1-2	15 th -25 th Fr	median (months) 104 ART; 96 no- ART	8-year LRFS ART 87.4%; No-ART 75.6% 8-year DMFS ART 82.3%; No-ART 76.8% OS: 60.9 % (ART) / 59.4 % (no- ART)	NR	G I-II Xerostomia: ART 96.5% - no-ART 90.5% G III-IV Xerostomia: ART 3.5% - no-ART 9.5%

Nb pts: number of patients; LAHNC: locally advanced head and neck cancer; OPC: oropharynx cancer; NPC: nasopharyngeal carcinoma; Nb: number; ART: adaptive radiotherapy; Fr: fraction; LRC: loco-regional control; LRFS: loco-regional free survival; DFS: disease-free survival; OS: overall survival.

Regarding Nasopharyngeal Cancer (NPC), two fundamental studies explain the potential benefits of ART in improving clinical outcomes. Zhao et al. [65] evaluated clinical results in a cohort of 33 patients who received ART compared to 66 patients who underwent a non-ART treatment. Their results indicated a 3-year locoregional failure-free survival (LRFS) of 72.7% for the ART group compared to 68.1% for the non-ART group. Notably, the ART approach showed even non-significant reduced xerostomia and mucosal issues, particularly in N2 and N3 patients, underlining the potential benefits of ART in improving patient comfort and quality of life. Yang et al. [66] conducted a study involving 86 patients with NPC, of which 43 received non-ART treatment. Their findings demonstrated significant improvements in clinical outcomes for the ART group, with a 2-year locoregional control (LRC) rate of 97.2% compared to 82.2% in the non-ART group. Additionally, the ART group's 2-year overall survival (OS) rate was 89.8%, while the non-ART group had an OS rate of 82.2%.

Similar studies for Oropharyngeal Cancer (OPC), like the study from Schwartz [64], examined ART in 22 OPC patients, and their results revealed an impressive 2-year local-regional control rate of 95%. Notably, this study highlighted a favorable toxicity profile, indicating that most patients either maintained or achieved complete preservation or functional recovery of speech and eating within a relatively short period of 20 months.

In locally advanced head and neck cancer (LAHNC), two critical studies, Chen's study [67] and Mostafa's study [68], collectively underscore the potential benefits of ART in LAHNC, showing improved disease control without a significant increase in acute toxicity, which can ultimately translate into enhanced survival rates for patients. The variation in clinical endpoints between the two studies highlights the multifaceted nature of ART's impact on LAHNC, demonstrating that this approach can be tailored to individual patient needs while striving for improved therapeutic efficacy and quality of life.

The last category of studies encompasses a mixed head and neck cancer population. In the survey from Zhou et al. 2022 [69], in a substantial cohort of 290 patients who received ART, investigators compared their clinical outcome to 147 patients who underwent non-ART treatment. The findings were particularly promising, with ART demonstrating an impressive 8-year locoregional failure-free survival (LRFS) of 87.4%, compared to 75.6% in the non-ART group. Notably, ART was associated with a reduction in xerostomia, with a notably favorable rate of Grade I-II and a lower rate of Grade III-IV xerostomia compared to the non-ART approach [19,64–70].

Conclusions

In conclusion, our review paper reveals a comprehensive and evolving landscape in adaptive radiotherapy in HNC. The primary goal of radiotherapy in HNC is to enhance local control while maintaining patients' quality of life.

Adaptive radiotherapy, with its ability to modify treatment plans in response to anatomical changes during therapy, has shown great promise in improving the therapeutic outcomes for HNC patients. Studies consistently demonstrate that adaptive radiotherapy provides better target volume coverage and conformality, resulting in enhanced dose delivery to the tumor while minimizing radiation exposure to adjacent healthy tissues. This is particularly critical in HNC treatment, where precision is vital to balance therapeutic efficacy with patient well-being.

The clinical implications of adaptive radiotherapy are promising. Enhanced target coverage and reduced toxicity improve local control and overall survival rates. Additionally, adapting treatment plans in real-time or periodically allows for individualized patient care, addressing the unique challenges of head and neck cancers, such as anatomical changes due to weight loss, tumor shrinkage, or edema. Reduced radiation exposure to surrounding normal tissues translates into a lower incidence of acute and chronic side effects. Patients undergoing adaptive radiotherapy experience fewer instances of xerostomia, dysphagia, and other debilitating complications. This improves the quality of life during and after treatment and enables patients to tolerate fully prescribed courses of radiotherapy better.

However, the successful implementation of adaptive radiotherapy is contingent on several factors, including robust imaging techniques, skilled staff, and resource availability. Furthermore, large-scale prospective clinical trials are needed to solidify the existing evidence and establish guidelines for the broader application of adaptive radiotherapy in head and neck cancer treatment.

In summary, adaptive radiotherapy has the potential to revolutionize head and neck cancer treatment by optimizing target volume coverage and sparing normal tissues. With its dosimetric and clinical benefits, adaptive radiotherapy is promising for enhancing the therapeutic outcomes and overall well-being of head and neck cancer patients. Further research, technological advancements, and clinical standardization will continue to refine the role of adaptive radiotherapy in managing this challenging disease.

Abbreviations

HNC: Head and Neck Cancer, **RT:** Radiation Therapy, **CT:** Computed Tomography, **3DCRT:** Three-Dimensional Conformal Radiation Therapy, **OARs:** Organs at Risk, **IMRT:** Intensity-Modulated Radiation Therapy, **IMPT:** Intensity-modulated Proton Therapy, **IGRT:** Image-Guided Radiation Therapy, **ART:** Adaptive Radiation Therapy, **R-ART:** Response-Adapted Radiation Therapy, **A-ART:** Anatomy-adapted Radiation Therapy, **CBCT:** Cone Beam Computed Tomography, **PET:** Positron-Emission Tomography, **GTV:** Gross Tumor Volume, **CTV:** Clinical Tumor Volume, **PTV:** Planning Tumor Volume.

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