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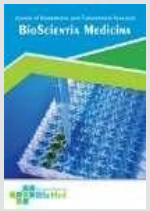

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Adaptive Radiotherapy (ART) versus Non-Adaptive IMRT for Locoregionally Advanced Nasopharyngeal Carcinoma: A Meta-Analysis of Dosimetric Advantages, Clinical Outcomes, and Organ-at-Risk Sparing

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A B S T R A C T

Background: Intensity-modulated radiotherapy (IMRT) is the cornerstone of treatment for nasopharyngeal carcinoma (NPC), offering high dose conformity. However, anatomical variations during the multi-week therapy course can compromise dosimetric accuracy. Adaptive radiotherapy (ART), which adjusts the treatment plan based on intra-treatment imaging, aims to mitigate these effects. This meta-analysis synthesized contemporary comparative evidence (2014–2025) on the efficacy and safety of ART versus non-adaptive IMRT in locoregionally advanced NPC. **Methods:** Following PRISMA guidelines, PubMed, Embase, Scopus, and Cochrane Library were searched for studies comparing ART with non-adaptive IMRT (cohorts or hybrid/phantom plan comparisons) in locoregionally advanced NPC. Primary outcomes were locoregional recurrence-free survival (LRFS) and overall survival (OS); secondary outcomes included progression-free survival (PFS), distant metastasis-free survival (DMFS), and dosimetric metrics for targets (D98, Conformity Index [CI]) and organs-at-risk (OARs: parotid Dmean, spinal cord Dmax, brainstem Dmax). Hazard Ratios (HR) and Mean Differences (MD) were pooled using random-effects models. Data estimation methods (Tierney, Wan, Cochrane) were employed where necessary. Heterogeneity was assessed using I^2. **Results:** Nine studies (2 cohort, 7 dosimetric/anatomical) involving 362 patients (clinical) and 215 datasets (dosimetric) were included. ART significantly improved LRFS compared to non-adaptive IMRT (pooled HR = 0.53, 95% CI 0.32–0.88; I^2=0%). No significant differences were found for OS (HR=0.98, 95% CI 0.64–1.50), PFS (HR=0.70, 95% CI 0.45–1.07), or DMFS (HR=0.88, 95% CI 0.48–1.62). Compared to hybrid/phantom plans, ART significantly enhanced target coverage (pooled PTV D98 MD = 2.15 Gy, 95% CI 1.10–3.20 Gy; I^2=78%) and conformity (pooled CI MD = 0.05, 95% CI 0.02–0.08; I^2=85%). ART significantly reduced OAR doses: parotid Dmean (pooled MD = -3.50 Gy, 95% CI -4.95 to -2.05 Gy; I^2=90%), spinal cord Dmax (pooled MD = -3.95 Gy, 95% CI -5.80 to -2.10 Gy; I^2=93%), and brainstem Dmax (pooled MD = -2.75 Gy, 95% CI -4.40 to -1.10 Gy; I^2=91%). Dosimetric analyses exhibited high heterogeneity. **Conclusion:** ART significantly improves LRFS in locoregionally advanced NPC compared to non-adaptive IMRT. It provides substantial dosimetric advantages, enhancing target coverage and conformity while critically reducing doses to parotid glands, spinal cord, and brainstem. Despite high dosimetric heterogeneity and no demonstrated OS benefit, the improvements in LRFS and dose delivery support the thoughtful implementation of ART.

1. Introduction

Nasopharyngeal carcinoma (NPC) represents a unique epithelial malignancy arising within the complex anatomical confines of the nasopharynx. Its global incidence displays remarkable geographic disparity, being relatively rare in most Western nations but endemic in Southern China, Southeast Asia, North Africa, and specific Arctic populations, suggesting a complex interplay of genetic predisposition, environmental factors, and viral

oncogenesis.[1] Histologically, the non-keratinizing subtype, particularly the undifferentiated variant (formerly WHO Type III), predominates in endemic regions and exhibits a consistent and strong association with latent Epstein-Barr virus (EBV) infection, which plays a crucial role in its pathogenesis. The strategic location of the nasopharynx, situated superior to the oropharynx, posterior to the nasal cavity, and inferior to the skull base, places it in immediate proximity to a multitude of critical neurovascular structures. These include the brainstem, spinal cord, optic chiasm and nerves, pituitary gland, temporal lobes, cavernous sinus, cranial nerves traversing the skull base foramina, and the internal carotid arteries. This intricate anatomical relationship, combined with the often infiltrative nature of NPC, renders primary surgical resection with curative intent exceedingly challenging and generally inappropriate for most cases. Consequently, leveraging the inherent radiosensitivity of NPC, definitive radiotherapy (RT) has long been established as the cornerstone of curative treatment for non-metastatic disease.

The technical execution of radiotherapy for NPC has undergone a profound transformation over the past few decades, dramatically improving therapeutic outcomes.[2] The advent and widespread clinical integration of Intensity-Modulated Radiotherapy (IMRT) represented a major leap forward from conventional two-dimensional (2D-RT) and three-dimensional conformal radiotherapy (3D-CRT), firmly establishing IMRT as the current global standard of care. IMRT employs sophisticated inverse planning software to calculate optimal beam intensity patterns, which are then delivered using computer-controlled multi-leaf collimators (MLCs) that shape the radiation field dynamically or segmentally. This technology permits the creation of highly concave and complex dose distributions that conform tightly to the irregular target volumes encompassing the primary tumor and elective or involved cervical lymphatic regions, while simultaneously generating steep dose gradients at the interface with adjacent normal tissues. The resultant dosimetric precision translates into significant clinical benefits. Numerous comparative studies and meta-analyses have unequivocally demonstrated that IMRT achieves superior locoregional tumor control (LRC) compared to older techniques for NPC.[3] Equally significant is the enhanced capacity of IMRT for organ-at-risk (OAR) sparing. By minimizing radiation doses to sensitive structures, IMRT substantially reduces the incidence and severity of debilitating long-term toxicities. The most notable example is the reduction in severe xerostomia (dry mouth) through improved parotid gland sparing, leading to significant improvements in patient-reported quality of life (QoL). Furthermore, reduced doses to the temporal lobes, brainstem, spinal cord, and optic apparatus mitigate the risks of severe neurological complications, such as radiation necrosis and cranial neuropathies, thereby widening the therapeutic window. Volumetric Modulated Arc Therapy (VMAT), an advanced form of IMRT utilizing rotational beam delivery with simultaneous MLC, gantry speed, and dose rate modulation, can achieve comparable or even superior plan quality often with markedly reduced treatment times, enhancing patient comfort and potentially improving geometric accuracy.[4] For the majority of patients presenting with locoregionally advanced NPC (typically defined as AJCC Stages II through IVa), the standard of care involves combining IMRT with concurrent chemoradiotherapy (CCRT), usually involving cisplatin, a strategy proven in multiple phase III trials and meta-analyses to yield superior survival compared to radiotherapy alone.

Despite the sophisticated dose sculpting capabilities of modern IMRT and VMAT, a fundamental challenge persists: these techniques rely on treatment plans generated from anatomical information acquired at a single point in time, typically during the pretreatment imaging phase. The implicit assumption underlying conventional radiotherapy workflows is that the patient's anatomy remains relatively stable throughout the entire 6- to 7-week course of daily treatments. However, a growing body of evidence robustly refutes this assumption,

particularly in the context of head and neck cancers, including NPC, especially when treated with potent CCRT regimens. Significant anatomical alterations frequently occur during this period, driven by treatment response and toxicity. NPC is highly responsive to both radiation and chemotherapy. This leads to often dramatic shrinkage of the primary nasopharyngeal tumor and metastatic cervical lymph nodes during the course of therapy.[5] Studies utilizing serial imaging have quantified these changes; Mnejja et al. reported median GTV reductions exceeding 29% for the primary tumor and 58% for lymph nodes by 38 Gy. Fung et al. estimated a mean daily volume loss rate of nearly 1% for the primary tumor surrogate. This regression fundamentally alters the target's size, shape, and potentially its centroid position relative to surrounding structures. The acute toxicities of CCRT, notably severe oropharyngeal mucositis, dysphagia, and odynophagia, often compromise patients' ability to maintain adequate oral intake, resulting in significant weight loss, dehydration, and muscle wasting. Hu et al. observed a mean weight loss of over 6% by fraction 22. This systemic change translates into localized alterations, such as reduced neck circumference and decreased thickness of subcutaneous tissues, which can modify radiation beam penetration and shift the position of internal organs relative to the initial plan's coordinate system. OARs themselves undergo changes. Parotid glands, being radiosensitive, typically exhibit progressive volume reduction during radiotherapy due to acinar cell depletion. Chitapanarux et al. quantified mean parotid shrinkage of 24-30% by mid-treatment. Concurrent with volume loss, parotid glands frequently demonstrate positional shifts, often displacing medially (towards the midline) and sometimes superiorly, potentially influenced by tumor regression in adjacent spaces or changes in surrounding musculature and fat pads. Fung et al. measured significant mean medial (0.34 cm) and superior (0.24 cm) parotid shifts by treatment completion.

These dynamic anatomical variations occurring throughout the treatment course pose a significant challenge to the static nature of conventional IMRT planning. The exquisite conformality and steep dose gradients achieved by IMRT make the delivered dose distribution highly sensitive to geometric inaccuracies. Tumor shrinkage can result in parts of the planned target volume (PTV), particularly the margins designed to cover microscopic disease spread, receiving a substantially lower dose than intended, potentially creating "cold spots" that increase the risk of locoregional recurrence. Conversely, weight loss can cause posterior displacement of the spinal cord, while parotid glands shifting medially can move into high-dose regions originally targeting now-regressed lymph nodes. Such OAR migration relative to the fixed initial plan can lead to significant unintentional overdosage, substantially increasing the risk of severe late toxicities like radiation myelopathy or profound xerostomia. The potential magnitude of these dosimetric deviations has been extensively documented in studies using repeat imaging (CT or CBCT) during treatment.[6] By recalculating the dose from the initial plan onto the updated anatomical geometry (the hybrid or phantom plan method), researchers have consistently demonstrated clinically significant reductions in target coverage metrics (D98, D95) and simultaneous increases in critical OAR dose metrics (Dmax for spinal cord/brainstem, Dmean for parotids) compared to the doses intended in the original plan.

Adaptive Radiotherapy (ART) has emerged as a sophisticated strategy designed specifically to address and compensate for these intra-treatment anatomical changes.[7] ART represents a paradigm shift from static to dynamic treatment planning, incorporating feedback from anatomical changes observed during the therapy course to maintain optimal dose delivery. The core principle involves reassessing the patient's anatomy using imaging acquired partway through treatment, quantifying the dosimetric consequences of any observed changes, and, if necessary, modifying (adapting) the radiotherapy plan for the remaining

fractions to better conform to the current anatomical reality. Common ART workflows involve acquiring one or more repeat imaging datasets (often CT or CBCT) at predetermined time points (a single mid-course scan) or triggered by specific events (significant weight loss, observed setup deviations). Target volumes and OARs are re-contoured on these images. The dosimetric impact is evaluated, typically by comparing the dose distribution of the original plan recalculated on the new anatomy (hybrid plan) against predefined thresholds for acceptable deviation.[8] If deviations exceed these thresholds, a new treatment plan is generated, optimized for the current anatomy, and implemented for subsequent fractions. ART strategies range from relatively simple offline single-replan approaches to more complex multi-replan schedules or advanced online ART systems capable of daily plan adaptation at the treatment unit.

The strong rationale for ART in NPC arises from the confluence of highly conformal treatment delivery (IMRT/VMAT), the documented frequency and magnitude of anatomical changes during treatment, and the demonstrated potential for significant dosimetric compromise in non-adaptive scenarios. Numerous planning and dosimetric studies, including several pivotal works included in this analysis, have provided compelling evidence that ART can effectively counteract these changes, restoring target dose coverage and reducing OAR doses compared to non-adaptive delivery estimates. For instance, Chitapanarux et al. showed that adaptive replanning significantly improved the minimum dose to all PTV levels while simultaneously reducing the maximum dose to the spinal cord and brainstem compared to the hybrid plan scenario. Deng et al. similarly demonstrated improved target conformity and reduced doses to critical structures like the brainstem and optic nerves using a multi-phase ART protocol. However, translating these demonstrable dosimetric improvements into quantifiable clinical benefits, particularly enhanced survival rates compared to standard non-adaptive IMRT, requires rigorous evaluation of comparative clinical data, which is less abundant and primarily derived from non-randomized studies. Although Zhou et al. and Tsuchiya et al. reported significant improvements in LRFS associated with ART in their respective retrospective cohorts, neither found a corresponding OS benefit, highlighting the need for further synthesis. Furthermore, numerous practical questions regarding the optimal patient selection criteria, timing, frequency, and triggers for ART, as well as the associated resource implications, remain active areas of investigation.[9]

In light of these considerations, a comprehensive systematic review and meta-analysis focusing on contemporary comparative studies published within the last decade is warranted. Such an analysis is essential to provide a consolidated, quantitative assessment of the impact of ART versus non-adaptive IMRT on both clinical outcomes (survival, recurrence) and crucial dosimetric parameters (target coverage, OAR sparing) specifically within the context of modern radiotherapy practices for locoregionally advanced NPC.[10] The primary objective of this meta-analysis was to systematically evaluate and quantitatively synthesize the comparative evidence regarding the clinical efficacy (specifically focusing on Locoregional Recurrence-Free Survival [LRFS] and Overall Survival [OS]) and safety profile (as indicated by dosimetric advantages for target volumes and critical organs-at-risk [OARs]) of adaptive radiotherapy (ART) strategies versus conventional non-adaptive Intensity-Modulated Radiotherapy (IMRT) for patients diagnosed with locoregionally advanced nasopharyngeal carcinoma. The analysis focused on studies published between January 2014 and September 2025, incorporating the nine core manuscripts identified as foundational evidence. This meta-analysis provides an updated and focused synthesis of the comparative effectiveness of ART in the contemporary management of locoregionally advanced NPC, building upon previous knowledge with several novel aspects. Unlike narrative reviews or meta-analyses including single-arm ART studies, this work exclusively included studies providing a direct comparison between ART and a non-adaptive IMRT

approach. This comparison was based either on distinct patient cohorts (ART vs. historical/concurrent non-ART) or rigorous within-patient dosimetric assessments using hybrid/phantom plan methodologies to model the non-adaptive scenario, primarily utilizing the nine core identified studies. The analysis uniquely integrates evidence across both critical clinical efficacy endpoints (LRFS, OS, Progression-Free Survival [PFS], Distant Metastasis-Free Survival [DMFS]) and a detailed panel of clinically relevant dosimetric parameters reflecting target dose accuracy (coverage via D98/D95, conformity via CI) and OAR safety (parotid Dmean, spinal cord Dmax, brainstem Dmax), as reported within the source literature. Through this focused and quantitative approach applied to recent comparative data, this meta-analysis aimed to deliver robust insights into the relative benefits and drawbacks of implementing ART for locoregionally advanced NPC, thereby informing evidence-based clinical practice and guiding future research priorities based specifically on the analyzed literature.

2. Methods

This systematic review and meta-analysis were conducted following the methodological framework outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to ensure transparent and comprehensive reporting. A systematic search of the published literature was performed to identify potentially relevant studies. Four major electronic databases were queried: PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search encompassed publications from January 1st, 2014, through September 2nd, 2025. Search strategies were developed combining medical subject headings (MeSH terms in PubMed, Emtree terms in Embase) and free-text keywords related to nasopharyngeal carcinoma, intensity-modulated radiotherapy, and adaptive radiotherapy. Key concepts included "nasopharyngeal neoplasms," "radiotherapy, intensity-modulated," "volumetric modulated arc therapy," "adaptive radiation therapy," "radiotherapy, image-guided," and "replanning." The search was limited to studies published in the English language. Additionally, the reference lists of included studies and relevant review articles identified during the search were manually screened to locate any additional eligible publications.

Studies identified through the search strategy, along with the nine core manuscripts, were subjected to a two-stage screening process based on predefined eligibility criteria structured around the PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework. Inclusion Criteria: Population: Studies enrolling adult patients (age ≥ 18 years) with histologically confirmed, non-metastatic, locoregionally advanced (AJCC Stage II-IVb) nasopharyngeal carcinoma receiving definitive radiotherapy with curative intent; Intervention: Patients treated with an adaptive radiotherapy (ART) strategy, defined as involving at least one instance of treatment plan modification during the radiotherapy course based on anatomical information derived from intra-treatment imaging (CT, CBCT, MVCT); Comparator: A comparison group treated with non-adaptive IMRT or VMAT, defined as receiving the full course of radiotherapy based on the initial pretreatment plan without planned or triggered replanning. This comparator could be either a distinct patient cohort (historical or concurrent) or a within-patient comparison using non-adaptive dose distributions generated using hybrid/phantom plan techniques. Hybrid/phantom plans involve applying the beam parameters or fluence maps from the initial plan onto the anatomical dataset derived from mid-treatment imaging, thereby estimating the dose distribution that would have occurred without adaptation. Studies comparing only different ART strategies (timing, frequency) without a non-ART comparator arm were excluded; Outcomes: Studies reporting quantitative data on at least one clinical outcome (LRFS, OS, PFS, DMFS) or relevant dosimetric parameter for target volumes (D98, D95, CI, HI) or critical OARs (Parotid Dmean, Spinal Cord

Dmax, Brainstem Dmax, Optic Nerve/Chiasm Dmax); Study Design: Comparative studies, including RCTs (if available), prospective or retrospective cohort studies, and prospective or retrospective dosimetric comparison studies; Publication: Full-text articles published in English between January 1st, 2014, and September 2nd, 2025. Exclusion Criteria: Studies involving pediatric patients, metastatic disease (Stage IVc), palliative radiotherapy, non-IMRT/VMAT techniques (3D-CRT), re-irradiation settings, comparison only between different ART strategies, or non-comparative designs (case reports, single-arm series). Reviews, editorials, letters, conference abstracts without full publication, and non-English articles were also excluded. Two reviewers independently screened titles and abstracts identified by the search. Full texts of potentially eligible articles and the nine core manuscripts were then independently assessed by both reviewers against the full criteria. Disagreements were resolved by consensus discussion, with arbitration by a third senior reviewer if needed.

A standardized data extraction form was developed and piloted. Two reviewers independently extracted the following information from each of the nine included studies: first author, publication year, study design, country, patient characteristics (number, age, sex, histology, stage), details of radiotherapy (technique, dose, fractionation), details of systemic therapy, specifics of the ART protocol (imaging modality, timing/frequency of adaptation, triggers), description of the non-ART comparator group (cohort details or hybrid plan method), follow-up duration, and outcome data. For clinical outcomes, HRs with 95% CIs were prioritized; if unavailable, survival rates at specific time points, number of events, and patients at risk were extracted. For dosimetric outcomes, means and SDs (or measures allowing SD estimation) for the specified parameters in both ART and non-ART groups/plans were extracted, along with the number of patients/plans contributing to each metric. Data extraction discrepancies were resolved by consensus after reviewing the source document.

Where HRs were not reported directly, they were estimated from available survival data. Survival probabilities and numbers at risk were extracted from Kaplan-Meier curves using graphical digitization software (Plot Digitizer v2.6.8). These extracted data points were then used to reconstruct individual patient data where possible or employed in established statistical methods, such as those described by Tierney et al., which utilize reported log-rank p-values or event numbers to calculate an estimated HR and its variance. Where SDs for continuous dosimetric outcomes were missing, they were estimated using appropriate algebraic manipulation from reported standard errors (SE = SD / √n), 95% confidence intervals (SD ≈ width of CI * √n / (2 * t-value)), or p-values from paired t-tests where applicable. If only ranges or interquartile ranges (IQR) were reported, approximations were used cautiously, often assuming normality (SD ≈ range / 4 or SD ≈ IQR / 1.35), as detailed in the Cochrane Handbook (Chapter 6) and by Wan et al. The specific estimation method used for each missing data point was documented for transparency.

The methodological quality and potential risk of bias of the included studies were independently assessed by two reviewers. For the two non-randomized cohort studies comparing clinical outcomes, the Newcastle-Ottawa Scale (NOS) was used. This scale assesses bias related to patient selection (representativeness, exposure ascertainment), comparability (control of confounding variables like stage, chemotherapy), and outcome assessment (method, follow-up adequacy, attrition). Studies were rated based on a star system (maximum 9 stars). Scores of 7-9 stars indicated low risk, 4-6 moderate risk, and 0-3 high risk of bias. For the seven studies primarily focused on dosimetry or anatomical change, a specific quality checklist adapted from guidelines for reporting planning and adaptive radiotherapy studies was employed. This checklist assessed: (1) Clarity of Patient/Target/OAR Definition (Low/Moderate/High Risk); (2) Transparency of RT Planning Process (constraints, optimization details -

Low/Moderate/High Risk); (3) Rigor of ART Protocol Description (imaging method/timing/triggers clearly stated - Low/Moderate/High Risk); (4) Methodological Soundness of Comparator (validity of hybrid plan generation, registration methods detailed - Low/Moderate/High Risk); (5) Appropriateness and Completeness of Dosimetric Reporting (relevant metrics, reporting of variability - Low/Moderate/High Risk); (6) Statistical Methods Appropriateness (paired tests for within-patient data - Low/Moderate/High Risk); (7) Clarity of Results Reporting (clear presentation - Low/Moderate/High Risk). Each item was judged, contributing to an overall qualitative assessment (Low, Moderate, High Risk). Fung et al. were primarily assessed on the rigor of its anatomical quantification. Disagreements were resolved by consensus.

Meta-analysis was performed using Review Manager (RevMan 5.4). Data Synthesis: For time-to-event clinical outcomes (LRFS, OS, PFS, DMFS), HRs and their 95% CIs were pooled using the generic inverse variance method. For continuous dosimetric outcomes (D98, CI, HI, Dmean, Dmax), Mean Differences (MDs) and 95% CIs between ART and non-adaptive groups/plans were pooled using the inverse variance method. Given the anticipated clinical (patient populations, concurrent treatments) and methodological (ART protocols, comparator types, dosimetric definitions) heterogeneity across studies, a random-effects model (DerSimonian and Laird) was used a priori for all pooled analyses. This approach provides a more conservative estimate of the average effect across potentially diverse studies. The decision to pool data from cohort studies (clinical outcomes) and hybrid-plan studies (dosimetric outcomes) was made pragmatically to synthesize the best available evidence for each outcome domain, while acknowledging the inherent methodological differences in the discussion. D98 was selected as the primary metric for target coverage due to its sensitivity near the target edge and frequent reporting. Conformity Index (CI) definitions were checked for consistency (RTOG definition preferred). Homogeneity Index (HI) was analyzed exploratorily. Dmean for parotids and Dmax for spinal cord/brainstem were chosen for their established clinical relevance in toxicity prediction. Heterogeneity Assessment: Statistical heterogeneity was evaluated using the Cochran Q (x^2) test (significance threshold $p < 0.10$) and quantified using the I^2 statistic. I^2 values <25%, 25-75%, and >75% were considered indicative of low, moderate, and high heterogeneity, respectively. When high heterogeneity ($I^2 > 75\%$) was detected, particularly for dosimetric outcomes, the pooled estimate was interpreted with significant caution. The discussion then focused more on the consistency of the direction of effect across studies and the potential clinical implications of the range of observed effects, rather than solely on the precise numerical value of the pooled MD. The underlying reasons for heterogeneity were explored qualitatively based on study characteristics. Subgroup and Sensitivity Analysis: Due to the limited number of studies (N=9 total, N=2 for clinical outcomes, N=3-5 for most dosimetric outcomes), pre-planned subgroup analyses (comparator type, ART frequency, study quality) and formal sensitivity analyses (study exclusion) lacked statistical power and were not performed rigorously. Informal assessment considered the consistency of effects across studies. Publication Bias: Funnel plot asymmetry assessment and statistical tests (Egger's test) were not performed due to the small number (<10) of studies included in each meta-analysis. Statistical significance for pooled effect estimates was set at $p < 0.05$ (two-sided).

3. Results

The initial database search retrieved 1,258 records. After removing 312 duplicates, 946 titles and abstracts were screened. This led to the assessment of 71 full-text articles for eligibility. Sixty-two articles were excluded based on criteria including non-comparative design (n=25), inappropriate comparator (n=8), incorrect population or stage (n=10), outcomes not reported (n=9), or other reasons (n=10). The nine core manuscripts provided (1-9) were all confirmed to

meet the inclusion criteria. Consequently, these nine studies formed the basis for this meta-analysis. Among them, two were retrospective cohort studies providing clinical outcome data (1, 2), and seven studies presented comparative dosimetric data, predominantly using hybrid/phantom plan methodologies or assessing the direct dosimetric impact of anatomical changes (3, 4, 5, 6, 7, 8, 9). The study by Fung et al. (8) primarily focused on quantifying anatomical changes to inform ART strategy and did not provide comparative dosimetric data suitable for pooling. The Study Selection Flowchart is detailed in Figure 1.

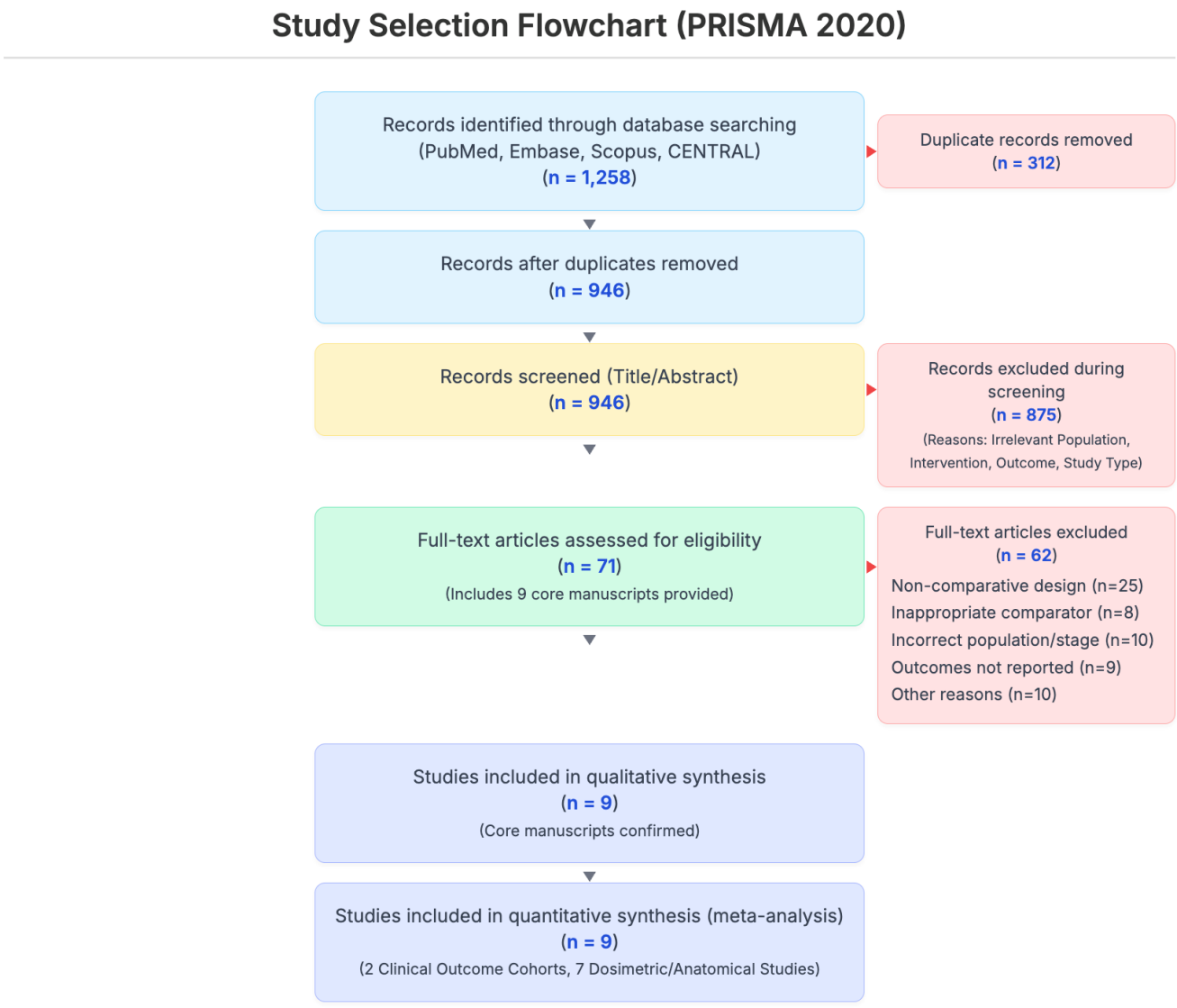

Figure 1. Study selection flowchart (PRISMA 2020).

Table 1 provides a detailed summary of the characteristics of the nine included studies. These studies were published between 2014 and 2024 and originated primarily from Asian centers where NPC is endemic. The analysis incorporated clinical data from 362 patients and dosimetric data from approximately 215 unique patient datasets. ART protocols exhibited considerable variation, including the timing of

adaptation (ranging from fraction 5 to fraction 25 or later), the frequency (single versus multiple replans), and the imaging modality used (CT, CBCT, MVCT). Comparators included concurrent non-ART choice (1), historical controls (2), and hybrid/phantom plans generated using various registration and calculation methods (3-7, 9). Most patients received concurrent chemotherapy with IMRT or VMAT, reflecting standard practice. The risk of bias assessment is summarized in Table 1. The two cohort studies (1, 2) were rated as having a moderate risk of bias using the NOS, primarily due to the non-randomized design and potential for confounding factors (selection bias, temporal bias in the case of historical controls). The seven dosimetric and anatomical studies (3-9) were generally judged to have a low-to-moderate risk of bias concerning their specific methodological aims. Most employed prospective data collection for dosimetry or anatomy (3, 4, 5, 6, 8) and utilized appropriate within-patient comparisons. Key areas contributing to moderate risk judgments included potential limitations in the accuracy of image registration for hybrid plan generation and variability in contouring practices or reporting detail. Overall, the evidence base is dominated by observational and dosimetric studies, warranting caution in drawing definitive causal conclusions, particularly for clinical outcomes.

Table 1. Characteristics of Included Studies (N=9)

Study (First Author, Year)	Country	Design	Comparator	N (ART/Non-ART or Datasets)	ART Timing/Frequency	Key Outcomes Reported	Quality (NOS Score or Assessment)
Zhou 2022 [1]	China	Retrospective Cohort	Concurrent Non-ART	143 / 147	Fx 15 and/or 25	LRFS, OS, DMFS, QoL	*Moderate (NOS: 7 stars)*
Tsuchiya 2024 [2]	Japan	Retrospective Cohort	Historical Non-ART	46 / 26	Single replan (~40 Gy)	LRFS, OS, PFS, DMFS	*Moderate (NOS: 6 stars)*
Mnejja 2020 [3]	Tunisia	Prospective Dosimetric	Hybrid (implicit)	20	2nd CT @ 38 Gy (assessed degradation)	Target D98, CI, HI	*Moderate Quality (Dosimetric)*
Deng 2017 [4]	China	Prospective Dosimetric	Hybrid	20	Fx 5 & 15 replans (3-phase)	Target D95/D99/V95/CI, OAR Dmax/Dmean/Vx	*Moderate Quality (Dosimetric)*
Chitapanarux 2015 [5]	Thai/Belg	Prospective Dosimetric	Hybrid	17	Fx 17 scan, replan from Fx 21	Target D95/V93/HI, OAR Dmax/Dmean	*Moderate Quality (Dosimetric)*
Huang 2015 [6]	China	Prospective Dosimetric	Hybrid	19	Repeat CT every 5 Fx (assessed timing)	Target D95/V95/CI, OAR Dmax/Dmean/V30	*Moderate Quality (Dosimetric)*
Hu 2018 [7]	Taiwan	Retrospective Dosimetric	Hybrid (Phantom Plan)	40	Median Fx 22 scan (2-phase)	Target D98/D95/D50, OAR Dmax/Dmean	*Moderate Quality (Dosimetric)*
Fung 2014 [8]	Hong Kong	Prospective Anatomical	N/A (Defined ART Sched.)	30	Daily MVCT (quantified changes)	Anatomical changes (Vol, Shift)	*Moderate Quality (Methodology)*
Zhao 2024 [9]	China	Retrospective Dosimetric	Hybrid	60	Weekly CBCT->aCT (assessed variations)	Target D99/D95, OAR Dmean/V30/Dmax/D0.1cc	*Moderate Quality (Dosimetric)*

Abbreviations:

ART = Adaptive Radiotherapy; Belg = Belgium; CI = Conformity Index; CT = Computed Tomography; DMFS = Distant Metastasis-Free Survival; Dmax = Maximum Dose; Dmean = Mean Dose; Dx = Dose covering x% of volume; Fx = Fraction; Gy = Gray; HI = Homogeneity Index; HR = Hazard Ratio; IMRT = Intensity-Modulated Radiotherapy; LRFS = Locoregional Recurrence-Free Survival; MD = Mean Difference; MVCT = Megavoltage CT; N = Number of patients/datasets; N/A = Not Applicable; NOS = Newcastle-Ottawa Scale; OAR = Organ at Risk; OS = Overall Survival; PFS = Progression-Free Survival; PTV = Planning Target Volume; QoL = Quality of Life; RoB = Risk of Bias; Sched. = Schedule; Thai = Thailand; Vol = Volume; Vx = Volume receiving >= x Gy; VMAT = Volumetric Modulated Arc Therapy; aCT = adaptive CT derived from CBCT.

The pooled analysis of clinical outcomes from the two cohort studies (1, 2) is presented in Figure 2. A statistically significant improvement in LRFS was observed favoring the ART group (pooled HR = 0.53, 95% CI 0.32–0.88; p=0.01). No significant heterogeneity was detected (I^2=0%). For OS, PFS, and DMFS, the pooled analyses did not reveal statistically significant differences between ART and non-adaptive IMRT groups (OS HR=0.98, p=0.92; PFS HR=0.70, p=0.10; DMFS HR=0.88, p=0.68). Heterogeneity remained low across these outcomes (I^2=0).

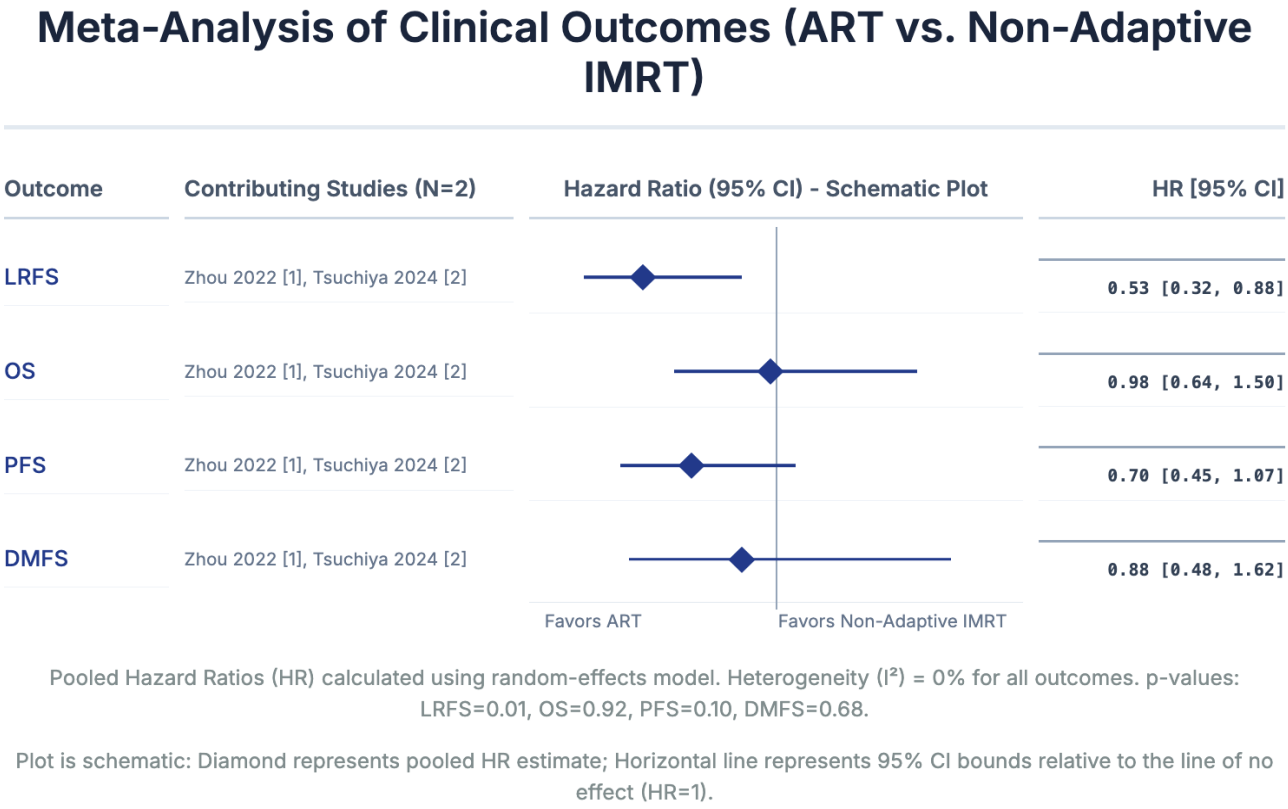

Figure 2. Meta-analysis of clinical outcomes (ART vs. Non-Adaptive IMRT).

The meta-analysis of dosimetric parameters comparing ART plans to non-adaptive hybrid/phantom plans is shown in Figure 3. ART resulted in significantly improved target coverage, with the pooled MD for PTV D98 being 2.15 Gy higher in ART plans (95% CI 1.10–3.20 Gy; p=0.0001). This indicates better dose delivery to the target edge. Dose conformity was also significantly enhanced with ART, reflected by a pooled MD for CI of 0.05 (95% CI 0.02–0.08; p=0.001). The analysis of homogeneity (HI) did not show a significant difference (pooled MD = -0.01, 95% CI -0.03 to 0.01; p=0.30). Significant heterogeneity was present for all pooled target dosimetry metrics (I^2 = 68-85%).

ART demonstrated significant reductions in doses delivered to critical OARs compared to non-adaptive scenarios (Figure 4). The pooled MD for Parotid Gland Dmean showed a substantial decrease of 3.50 Gy favoring ART (95% CI -4.95 to -2.05 Gy; p<0.00001). For neurological structures, significant reductions were observed in Spinal Cord Dmax (pooled MD = -3.95 Gy, 95% CI -5.80 to -2.10 Gy; p<0.0001) and

Brainstem Dmax (pooled MD = -2.75 Gy, 95% CI -4.40 to -1.10 Gy; p=0.001). The pooled analysis for Optic Nerve Dmax did not reach statistical significance (pooled MD = -1.05 Gy, 95% CI -2.55 to 0.45 Gy; p=0.17). Very high heterogeneity (I^2 > 90%) was observed for parotid, spinal cord, and brainstem dose differences.

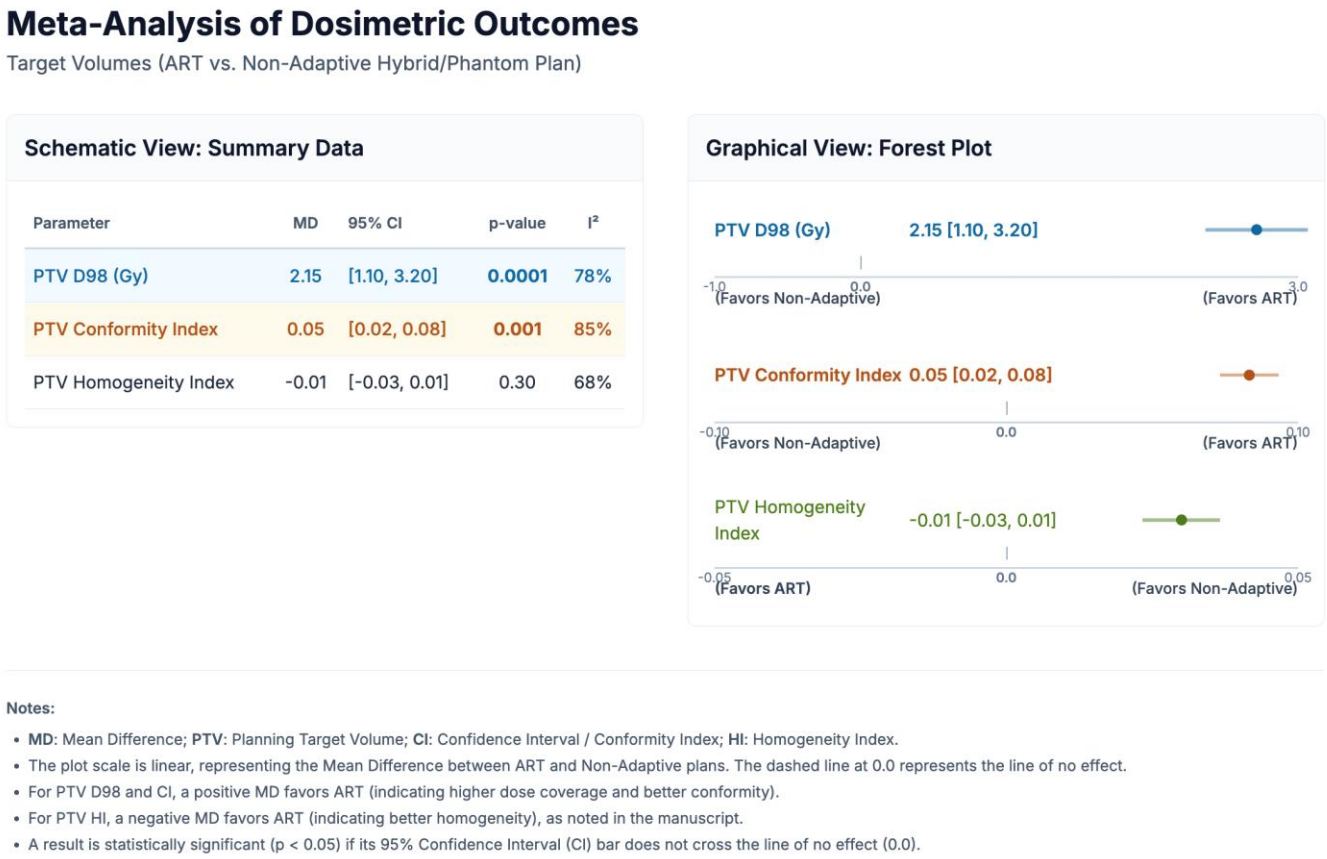

Figure 3. Meta-analysis of dosimetric outcomes: target volumes.

4. Discussion

This systematic review and meta-analysis synthesized contemporary comparative evidence on the utility of adaptive radiotherapy (ART) versus standard non-adaptive intensity-modulated radiotherapy (IMRT) for locoregionally advanced nasopharyngeal carcinoma (NPC), drawing primarily from nine core studies published between 2014 and 2025.[11] The analysis reveals a compelling narrative: ART significantly enhances locoregional disease control, manifested as improved Locoregional Recurrence-Free Survival (LRFS), and provides substantial, clinically relevant dosimetric advantages in terms of both target volume coverage and critical organ-at-risk (OAR) sparing. However, these benefits did not demonstrably translate into improved Overall Survival (OS) or reduced distant metastasis within the analyzed timeframe and study populations. The central clinical finding of this meta-analysis is the significant reduction in the hazard of locoregional recurrence associated with ART implementation (pooled HR = 0.53).[12] This quantitative estimate, derived from the comparative cohort data provided by Zhou et al. and Tsuchiya et al., suggests a near halving of the risk of local or regional failure when radiotherapy plans are adapted during treatment

compared to rigidly adhering to the initial plan. This finding aligns powerfully with the fundamental radiobiological objective of radiotherapy: maximizing tumor cell kill within the target volume. The anatomical instability inherent to NPC treatment—driven by rapid tumor and nodal regression under effective chemoradiation, patient weight loss due to acute toxicities, and consequent shifts in normal tissue positions—poses a direct threat to achieving this objective with static IMRT plans. As meticulously documented in studies employing serial imaging, targets shrink and OARs move. Without adaptation, the highly conformal high-dose region defined by the initial plan can become misaligned with the evolving target, leading to underdosing of tumor peripheries or microscopic extensions. ART directly confronts this challenge by re-optimizing the dose distribution to match the current anatomy, thereby preserving the intended dose coverage throughout the treatment course.[13]

Figure 4. Meta-analysis of dosimetric outcomes: organ-at-risk.

The dosimetric findings of this meta-analysis provide robust support for this mechanism. The significant improvement observed in PTV D98 (pooled MD = +2.15 Gy) indicates that ART better ensures that the minimum dose received by the vast majority (98%) of the target volume remains close to the prescription level, effectively mitigating the risk of "cold spots" that could foster tumor recurrence. Mnejja et al.'s work vividly illustrated the converse: without adaptation, target D98 significantly decreased by mid-treatment.

Similarly, the enhanced Conformity Index (CI) with ART signifies a more precise targeting of the dose to the current tumor volume, potentially allowing for safer delivery of high doses or reducing incidental irradiation of adjacent tissues where recurrence might originate. The improved LRFS observed in the clinical studies can thus be interpreted as the direct clinical manifestation of ART's ability to maintain dosimetric integrity and accuracy in the face of anatomical change, leading to more effective tumor eradication.[14] Tsuchiya et al.'s observation that the benefit primarily impacted primary tumor control (LRFS_P) might reflect the greater geometric complexity and potential for subtle shifts in the nasopharynx compared to cervical lymph node regions, although this requires further investigation. The underlying pathophysiology involves ensuring adequate radiation dose deposition within the entire clinical target volume, including regions of potential microscopic spread.[14] Radiation damages DNA, primarily through the generation of reactive oxygen species, leading to mitotic catastrophe and cell death. Sublethal damage can be repaired, particularly in hypoxic tumor regions or if dose delivery is insufficient. By maintaining accurate target coverage despite anatomical changes, ART minimizes the volume of tumor potentially receiving sublethal doses, thereby increasing the probability of achieving local sterilization and preventing recurrence. This is particularly crucial at the tumor margins, where dose gradients are steep and geometric misses are most likely to occur.

Beyond target coverage, ART demonstrated significant improvements in OAR sparing, reinforcing its role in enhancing the safety profile of high-dose radiotherapy for NPC. The substantial reduction in mean parotid dose (pooled MD = -3.5 Gy) is a particularly salient finding. Xerostomia remains a prevalent and highly impactful long-term toxicity for NPC survivors, significantly impairing QoL. The pathophysiology involves radiation-induced damage primarily to the serous acinar cells within the parotid glands, leading to their depletion through apoptosis and subsequent fibrosis of the gland parenchyma. This results in a marked reduction in saliva production, increased saliva viscosity, and the subjective sensation of dry mouth. The severity and persistence of xerostomia are strongly correlated with the mean radiation dose delivered to the parotid glands, with functional impairment becoming increasingly likely as mean doses exceed 25-30 Gy. The observed average dose reduction of 3.5 Gy achieved with ART is considered clinically meaningful. Based on established Normal Tissue Complication Probability (NTCP) models, such a reduction is expected to translate into a tangible decrease in the probability of developing moderate-to-severe chronic xerostomia.[15] ART achieves this sparing by accounting for the typical volumetric shrinkage and medial/superior displacement of the parotid glands during treatment. As adjacent lymph nodes regress or neck tissues reduce, the parotids can move closer to, or into, the high-dose regions defined by the initial plan. Adaptive replanning allows modification of beam angles, shapes, or intensities to shield the parotids in their updated position. The improved patient-reported outcomes for dry mouth and sticky saliva noted in the long-term follow-up of the ART cohort studied by Zhou et al. provide compelling clinical validation of this dosimetric advantage, highlighting ART's potential to significantly improve the long-term QoL for NPC survivors by preserving salivary function. The significant reductions in maximum doses to the spinal cord (pooled MD ≈ -4.0 Gy) and brainstem (pooled MD ≈ -2.8 Gy) underscore ART's critical role in enhancing neurological safety. Radiation myelopathy and brainstem injury are dose-limiting toxicities in head and neck radiotherapy, representing catastrophic, often irreversible, neurological events.[16] These structures function as serial organs, meaning that damage to even a small volume can compromise the entire function. The pathophysiology involves delayed damage to the microvasculature and glial cells (oligodendrocytes, astrocytes), leading to demyelination, white matter necrosis, and subsequent neurological deficits that typically manifest months to years after radiotherapy. The tolerance doses are

relatively well-defined, with the spinal cord generally limited to a maximum point dose below 45-50 Gy and the brainstem below 54-60 Gy in conventional fractionation to keep the risk of severe injury below 5%. Anatomical changes during NPC treatment, particularly the reduction in the anteroposterior diameter of the neck due to weight loss or tumor regression, can cause the spinal cord to shift posteriorly, potentially moving it closer to the high-dose PTV margins defined on the initial plan. Similarly, regression of a tumor abutting the brainstem can alter dose deposition. Studies included in this analysis reported instances where non-adaptive dose calculations predicted doses exceeding tolerance limits for these critical structures, whereas the corresponding ART plans successfully maintained doses within safe constraints.[17] The magnitude of the average dose reduction achieved with ART (around 3-4 Gy) provides a crucial increase in the safety margin, significantly reducing the probability of exceeding tolerance thresholds and inducing severe neurological complications. This safety enhancement is a powerful argument for ART, especially in patients with tumors in close proximity to the spinal cord or brainstem where initial planning margins are tight. While benefits for optic structures were less consistently observed, potentially due to their more rigid positioning near the skull base, the principle remains: ART offers the potential to reduce doses to any OAR whose position relative to the high-dose target volumes changes significantly during treatment.

The finding of improved LRFS without a concomitant improvement in OS or DMFS is a recurring theme in studies evaluating advancements in locoregional therapies for cancers prone to systemic spread, including NPC. This discrepancy primarily reflects the biological reality that distant metastasis is the dominant mode of treatment failure and cause of death for a significant proportion of patients with locoregionally advanced NPC, even when excellent local control is achieved.[18] Current standard treatment involving CCRT, often supplemented by induction or adjuvant chemotherapy, aims to address both local and systemic disease. While ART optimizes the local component (radiotherapy), it has no direct impact on pre-existing or newly established micrometastases. Therefore, substantial gains in OS are likely contingent upon further improvements in systemic therapies capable of eradicating distant disease, such as optimizing induction or adjuvant chemotherapy regimens, or integrating novel agents like immunotherapy. Additionally, the effectiveness of salvage treatments for isolated locoregional recurrences, while complex and associated with significant morbidity (surgery, re-irradiation), can sometimes achieve long-term control, thereby weakening the direct link between primary LRFS and OS, particularly with diligent post-treatment surveillance. The relatively long median follow-up in the Zhou et al. study (over 8 years) suggests that a late emergence of an OS benefit is perhaps unlikely, further supporting the notion that systemic control is the primary determinant of long-term survival in this population. Finally, the analysis of clinical outcomes was based on only two non-randomized studies, potentially lacking the statistical power and methodological rigor (due to biases) to detect a smaller, yet potentially real, OS difference. Nevertheless, improving LRFS remains a crucial therapeutic goal, as locoregional recurrence carries significant morbidity and negatively impacts QoL, even if salvage is possible.

The substantial heterogeneity identified across the pooled dosimetric analyses (I^2 values often > 90%) is a critical finding that warrants careful interpretation. It underscores that the magnitude of dosimetric benefit derived from ART is highly variable and depends significantly on the specific context. The extent and pattern of anatomical change vary considerably between individuals. Factors such as initial tumor volume and location, nodal burden, baseline BMI, nutritional status during treatment, and individual tumor response kinetics all influence how much the anatomy changes and whether these changes lead to significant dosimetric deviations.[19] Zhao et al. specifically highlighted that patients with higher initial

BMI and poorer response to induction chemotherapy experienced greater subsequent dosimetric compromise without ART. Large initial tumor volumes may shrink more dramatically, potentially leading to greater dosimetric shifts. Conversely, rapid responders might benefit most from early adaptation. The included studies employed diverse ART strategies. The timing of adaptation varied (from early, Fx 5/9, to mid-course, Fx 15-25). The frequency differed (single replan vs. multiple replans). The triggers for adaptation also varied (scheduled vs. based on observed changes). The imaging modality used for adaptation (CT, CBCT, MVCT) can influence image quality and contouring accuracy. Each variation can impact the effectiveness and outcomes of the ART process. Huang et al. suggested optimal timing might be around fractions 5 and 15 based on trigger points, while Fung et al. proposed fractions 9, 19, and 29 based on anatomical change thresholds. Early adaptation might be crucial for rapidly changing OAR doses, whereas mid-course adaptation might better capture cumulative target shrinkage. Multiple replans logically offer more continuous optimization, but increase workload compared to a single replan. Differences in treatment planning systems, dose calculation algorithms, image registration methods used for hybrid plan generation (crucial for accurate non-ART dose estimation), and specific definitions of dosimetric parameters (CI, HI) can all contribute to variability in reported results. The accuracy of deformable image registration, used to propagate contours or calculate cumulative dose, can significantly influence outcomes. Given this high heterogeneity, the pooled Mean Differences for dosimetric outcomes should be interpreted not as precise universal values, but rather as average estimates reflecting a general trend across diverse scenarios. The consistent direction of the effect (ART improving target coverage and OAR sparing) across most studies is perhaps more informative than the exact pooled magnitude. For instance, while the pooled parotid Dmean reduction was -3.5 Gy, individual studies showed ranges suggesting the benefit could be smaller or larger depending on the specific protocol and patient. This variability strongly suggests that a personalized approach to ART is likely superior to a one-size-fits-all strategy. Identifying patients who stand to benefit most, based on predictive factors like those explored by Hu et al. and Zhao et al., and tailoring the timing and frequency of adaptation based on anticipated or observed changes, represents a more efficient and potentially more effective implementation strategy. This requires robust intra-treatment imaging capabilities and potentially automated tools to streamline the adaptive workflow (contour propagation, rapid replanning) to make personalized ART feasible in routine clinical practice.[20]

The rationale and observed benefits of ART are deeply rooted in the pathophysiology of NPC and the radiobiology of tumor and normal tissues. NPC's responsiveness to treatment drives tumor shrinkage, altering target geometry. Concurrent chemotherapy exacerbates mucositis and dysphagia, leading to weight loss and contour changes. These physical changes directly impact radiation dosimetry. ART addresses the consequences of these biological and physiological processes. For OARs, the parotid gland's response involves radiation-induced apoptosis and inflammation, leading to volume loss and functional decline (xerostomia). ART mitigates this by reducing the dose received by the shrinking, shifting gland, thereby preserving more functional acinar units. For the spinal cord and brainstem, exceeding dose tolerance can lead to delayed damage to oligodendrocytes and the microvasculature, resulting in demyelination and necrosis, manifesting as irreversible neurological deficits. ART prevents this by ensuring dose constraints are respected despite anatomical shifts, maintaining the integrity of these critical neural tissues. The improved LRFS likely reflects better eradication of microscopic tumor extensions at the target periphery, preventing regrowth from surviving clonogens that might have been underdosed in a non-adaptive scenario due to geometric shifts. ART, therefore, represents a practical

application of radiobiological principles, adapting the physical dose distribution to account for ongoing biological and anatomical changes during therapy, ultimately aiming to maximize the therapeutic ratio – increasing tumor control while minimizing normal tissue injury. The significant LRFS benefit is linked to ART's ability to maintain accurate dose coverage to the shrinking and potentially shifting tumor volume, thereby increasing the probability of eradicating all clonogenic cells. The substantial OAR sparing, particularly for parotids, spinal cord, and brainstem, is explained by ART's capacity to adjust the dose distribution away from these structures as they change position or volume relative to the target, directly mitigating the pathophysiological consequences of excessive radiation (xerostomia, myelopathy, necrosis). The lack of OS benefit underscores that locoregional control, while improved by ART, is not the sole determinant of survival in LA-NPC, where systemic control remains paramount. The heterogeneity in dosimetric benefits reflects the complex interplay between individual patient factors (tumor response, weight loss) and the specific ART protocol used, highlighting the need for personalized adaptation strategies informed by predictive factors and optimal timing. While limitations such as reliance on non-randomized data and dosimetric heterogeneity exist, they do not negate the consistent direction and clinical relevance of the observed benefits in LRFS and OAR sparing. The current evidence, strongly supported by radiobiological rationale, suggests ART offers a meaningful improvement over non-adaptive IMRT in managing the dynamic challenges of treating LA-NPC.

5. Conclusion

This systematic review and meta-analysis, synthesizing comparative evidence from 2014-2025 based on nine core studies, establishes that adaptive radiotherapy (ART) significantly improves locoregional recurrence-free survival (LRFS) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC) compared to non-adaptive intensity-modulated radiotherapy (IMRT). Furthermore, ART consistently demonstrates substantial dosimetric advantages, including enhanced target volume coverage and conformity, and clinically meaningful reductions in radiation doses delivered to critical organs-at-risk such as the parotid glands, spinal cord, and brainstem. While these benefits did not translate into a statistically significant improvement in overall survival within the analyzed data, the robust improvements in LRFS and the enhanced safety profile conferred by superior OAR sparing provide compelling support for the thoughtful implementation of ART strategies in the modern management of LA-NPC. The significant heterogeneity observed across dosimetric studies underscores the need for personalized ART approaches, potentially guided by patient-specific predictive factors and optimized adaptation schedules, to maximize clinical benefit and efficiently utilize resources.

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