Mechanism-guided radiosensitization strategies for nasopharyngeal carcinoma: Current evidence and translational perspectives (Review)

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Abstract. Nasopharyngeal carcinoma (NPC) is a distinct Epstein-Barr virus (EBV)-associated head and neck malignancy with a pronounced endemic distribution in Southern China and Southeast Asia. Intensity-modulated radiotherapy and concurrent chemoradiotherapy (CCRT) have substantially improved locoregional control; however, treatment failure remains common, particularly in locoregionally advanced, recurrent and metastatic disease. The present review summarizes mechanism-guided radiosensitization strategies for NPC according to clinical setting and translational maturity. Platinum-based CCRT remains the standard and most established radiosensitization approach. In selected patients with locoregionally advanced disease and a suboptimal response to induction chemotherapy, the addition of nimotuzumab to CCRT did not improve 2-year progression-free survival (81.0 vs. 80.8%; hazard ratio=0.93). By contrast, tislelizumab combined with chemotherapy markedly improved progression-free survival in recurrent or metastatic disease (hazard ratio=0.52), highlighting that systemic efficacy in this setting should not be conflated with radiosensitization during definitive radiotherapy. Consequently, epidermal growth factor receptor inhibition, DNA damage response targeting, hypoxia modification, immunoradiotherapy and EBV-directed therapies remain dependent on appropriate patient selection and prospective validation. Natural compounds and traditional Chinese medicine-derived agents are mechanistically promising but currently remain hypothesis-generating. Collectively, these approaches converge on key biological processes, including DNA repair, oxidative stress, apoptosis, epithelial-mesenchymal transition, hypoxia, EBV-associated signaling and immune remodeling. Plasma EBV DNA is currently the biomarker with the greatest clinical readiness for risk stratification, whereas most predictive biomarkers remain investigational. Key challenges include heterogeneous evidence quality, uncertain treatment sequencing and overlapping toxicities. Future treatment intensification should be biomarker-informed and tailored to disease stage, patient fitness and therapeutic index.

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Abbreviations: NPC, nasopharyngeal carcinoma; DSBs, double-strand breaks; HR, homologous recombination; NHEJ, non-homologous end joining; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; CSC, cancer stem cell; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; DDR, DNA damage response; ICI, immune checkpoint inhibitor; TCM, traditional Chinese medicine

Key words: nasopharyngeal carcinoma, radioresistance, radiosensitization, radiotherapy, chemotherapy, molecular targeted therapy, immune checkpoint inhibitor, biomarker, Epstein-Barr virus, traditional Chinese medicine

Contents

1. Introduction

Nasopharyngeal carcinoma (NPC) is a distinctive epithelial malignancy characterized by marked geographic and

sex disparities, with endemic concentrations in East and Southeast Asia and a strong association with Epstein-Barr virus (EBV) (1-3). According to the latest GLOBOCAN 2022 estimates, 120,434 new NPC cases and 73,482 mortalities occurred worldwide, corresponding to a global age-standardized incidence rate of 1.3 per 100,000 person-years (1). The disease burden is substantially higher in men than in women, with 86,289 and 34,145 new cases, respectively. Across 185 countries and territories, South-Eastern Asia had the highest NPC age-standardized incidence and mortality rates, at 4.7 and 3.1 per 100,000 person-years, respectively. If these rates remain unchanged, the annual number of NPC cases is projected to increase by 46.40% by 2050 (1). A complementary 2026 analysis based on Global Burden of Disease 2021 data similarly demonstrated a marked increase in annual incident cases, from ~76,256 in 1990 to 118,878 in 2021. East Asia accounted for ~68,039 new cases (57.2% of the global total), and forecasting models predicted that the incidence and prevalence among males may continue to rise through 2036 (2). Advances in intensity-modulated radiotherapy (IMRT) and systemic therapy have substantially improved tumor control, and contemporary guidelines recommend stage-adapted radiotherapy-based treatment for non-metastatic disease (3-5). Patients with recurrent or metastatic NPC may require systemic therapy, immunotherapy and, in selected cases, reirradiation, surgery or focal radiotherapy (5-7).

Radioresistance remains a major obstacle to improving therapeutic outcomes in NPC. Traditional empirical treatment intensification, such as radiation dose escalation or the addition of systemic therapy without biological selection, may improve disease control in some patients but is often accompanied by increased mucositis, xerostomia, bone marrow suppression, nephrotoxicity and late normal-tissue injury. Mechanism-guided radiosensitization offers a more selective strategy by matching therapeutic interventions to dominant resistance pathways, disease stage and biomarker-defined risk (4,8,9).

The present narrative review is organized around clinically relevant mechanisms of radioresistance and experimentally supported radiosensitization strategies, with emphasis on translating radiobiological vulnerabilities into rational combination therapies rather than relying on empirical treatment intensification. To enhance clinical applicability, the evidence is discussed according to disease setting, including primary locoregionally advanced NPC, recurrent/metastatic NPC and special populations such as older adult or frail patients. The review also distinguishes evidence derived from preclinical studies, observational cohorts, phase II trials, phase III trials and guideline-supported treatment recommendations.

2. Radiobiology and the challenge of radioresistance

Mechanisms of radiation-induced cell death. Ionizing radiation exerts cytotoxic effects primarily through DNA damage, including DNA double-strand breaks (DSBs) and the generation of reactive oxygen species through water radiolysis (10,11). Cellular responses to radiation-induced DSBs ultimately determine cell fate, with DNA repair pathways, cell-cycle checkpoints and cell-death mechanisms collectively shaping radiosensitivity (11). Mammalian cells employ two major DSB repair pathways: Homologous recombination (HR), which operates predominantly during S/G_2 and uses a sister chromatid as a repair template, and non-homologous end joining (NHEJ), which functions more broadly throughout the cell cycle (11). Radiation sensitivity also varies across the cell cycle, with cells in G_2/M generally more radiosensitive and those in late S phase more radioresistant (12). This temporal heterogeneity provides a rationale for radiosensitization strategies that modulate cell-cycle progression.

Major mechanisms of radioresistance in NPC. Radioresistance in NPC arises from an intricate network of tumor-intrinsic and microenvironmental factors that collectively attenuate radiation-induced cytotoxicity.

DNA damage repair activation. Enhanced DNA repair capacity represents a cardinal mechanism of radioresistance. NPC cells can exhibit activation of key repair proteins, including DNA-dependent protein kinase catalytic subunit (DNA-PKcs), ataxia telangiectasia mutated (ATM) and poly(ADP-ribose) polymerase-1 (PARP-1) (13,14). These proteins coordinate DSB repair and checkpoint signaling, enabling tumor cells to survive otherwise lethal radiation-induced damage. The long non-coding RNA linc00312 directly binds DNA-PKcs, and its downregulation in radioresistant NPC cells removes this inhibitory interaction and accelerates NHEJ repair (15).

Cell-cycle checkpoint dysregulation. Radiation normally activates cell-cycle checkpoints (G_1/S, intra-S and G_2/M) to halt cell-cycle progression and permit DNA repair (16). However, NPC cells often display checkpoint abnormalities that paradoxically promote survival. Although G_2/M arrest generally provides time for repair, prolonged arrest in radiosensitive phases can be therapeutically exploited. Conversely, aberrant checkpoint activation in radioresistant cells facilitates escape from radiation-induced growth arrest. Proteins such as cell division cycle 25C, CDK1 and cyclin B1 regulate G_2/M transition, and modulation of these molecules by radiosensitizers can override protective checkpoints (17).

Cancer stem cell (CSC) populations. CSCs constitute a critical reservoir of radioresistance in NPC. These cells, characterized by markers including CD133, CD44 and aldehyde dehydrogenase 1, exhibit enhanced DNA repair capacity, preferential activation of survival signaling [such as interleukin-6/signal transducer and activator of transcription 3 (STAT3)], and quiescence in the radioresistant G_0 phase (18,19). Circulating RNA networks, including hsa_circRNA_102115, regulate CSC properties and radioresistance, and curcumin-mediated suppression of these networks enhances radiosensitivity (20,21). The persistence of CSCs after radiotherapy likely underlies disease recurrence, highlighting the need for CSC-targeted radiosensitization strategies.

Hypoxic microenvironment. Tumor hypoxia, present in ~50% of solid tumors, including NPC, profoundly impairs radiation efficacy (22). Hypoxic cells exhibit two- to three-fold greater radioresistance than normoxic cells, because oxygen is required to 'fix' radiation-induced DNA damage through the formation of DNA-peroxy radicals (23). Hypoxia-inducible factor-1α (HIF-1α) coordinates adaptive responses, including upregulation of glycolysis (via glucose transporter 1 and lactate dehydrogenase A), angiogenesis (via vascular endothelial growth factor) and DNA repair genes [DNA repair protein

RAD51 homolog 1 (RAD51) and BRCA2], collectively promoting survival under hypoxic stress (24,25). Moreover, hypoxia fosters immunosuppression through the recruitment of regulatory T cells and M2-polarized macrophages, further attenuating antitumor immunity (26).

EBV-driven oncogenic signaling. EBV infection, etiologically associated with 95% of endemic NPC cases, directly contributes to radioresistance through multiple mechanisms (27). Latent membrane protein 1 (LMP1), a central EBV oncoprotein, activates NF-κB signaling and transcriptionally upregulates ATM, thereby accelerating DNA damage repair (28). LMP1 also drives metabolic reprogramming via the PI3K/Akt-GSK3β-F-box/WD repeat-containing protein 7 axis, stabilizing c-Myc and upregulating hexokinase 2, which enhances glycolysis (the Warburg effect) and reinforces radioresistance (29). In addition, LMP1 induces peroxisome proliferator-activated receptor g coactivator 1-a expression through protein arginine methyltransferase 1-mediated methylation, thereby inhibiting anoikis, facilitating metastasis and further promoting radioresistance (30).

Metabolic reprogramming. Beyond glycolysis, NPC cells exhibit broader metabolic alterations, including enhanced fatty acid synthesis. Fatty acid synthase (FASN), which is frequently upregulated in NPC, is associated with radioresistance, and FASN inhibition sensitizes cells to radiation (31). Crosstalk between metabolism and DNA repair, exemplified by NADPH production that supports antioxidant defenses, creates metabolic vulnerabilities that can be therapeutically exploited (32).

The biological determinants of radioresistance, their clinical contexts and candidate biomarkers are integrated in Fig. 1.

Clinical settings and evidence hierarchy. For clinical interpretation, radiosensitization strategies should be considered according to the treatment context. In primary locoregionally advanced NPC, the benchmark remains definitive IMRT combined with platinum-based chemotherapy, with induction chemotherapy and concurrent chemoradiotherapy supported by guideline-level evidence in selected patients with stage II-IVA NPC (4). In recurrent or metastatic NPC, systemic chemotherapy and immunotherapy have stronger supporting evidence than most local radiosensitization strategies, although selected patients may benefit from reirradiation, surgery or focal radiotherapy when disease distribution and normal-tissue constraints permit (5,7). In older adult or medically frail patients, treatment intensity should be individualized according to renal function, bone marrow reserve, comorbidity, nutritional status and expected late toxicity. Accordingly, each radiosensitizing strategy in the present review is interpreted according to both its underlying mechanism and level of evidence rather than mechanistic plausibility alone.

3. Chemotherapeutic agents: The foundation of radiosensitization

Central role in combined modality treatment. Concurrent chemoradiotherapy (CCRT) represents the standard backbone for numerous patients with locoregionally advanced NPC, whereas induction chemotherapy followed by CCRT is recommended for selected higher-risk patients with stage II-IVA NPC according to contemporary guideline frameworks (4,5,7,33). The radiosensitizing effects of chemotherapy extend beyond simple additive cytotoxicity and involve mechanism-based synergies, including inhibition of radiation-induced DNA repair, redistribution of cells into radiosensitive cell-cycle phases and disruption of protective signaling pathways (34).

Platinum-based agents: DNA damage amplification

Cisplatin. Cisplatin is the prototypical concurrent systemic agent used with definitive radiotherapy in NPC. Preclinical NPC data show that its interaction with radiation is strongly schedule-dependent. A 24-h cisplatin exposure before radiation produced greater cytotoxicity than shorter exposure, while the sequence and interval between treatments also altered the radiation effect (35). Cisplatin efficacy is constrained by DNA repair capacity, with excision repair cross-complementation group 1 (ERCC1) serving as a potential predictive biomarker. High ERCC1 expression was associated with a lower response rate (75.0 vs. 97.7%) in CCRT-treated NPC (36). In another cohort, ERCC1-high tumors had higher recurrence (29.41 vs. 12.5%) and lower 5-year overall survival (OS; 58.82 vs. 84.37%) than ERCC1-low tumors (37).

Other platinum analogs. Lobaplatin, a third-generation platinum compound, has shown feasibility as a concurrent agent in older adult patients with NPC. In a small cohort of 29 patients aged ≥65 years, lobaplatin-based CCRT was associated with no liver or kidney dysfunction and a reported 3-year OS of 100%; however, this result should be interpreted cautiously because of the limited sample size, short-to-intermediate follow-up and non-randomized design (38). The gemcitabine plus cisplatin (GP) regimen has emerged as an established systemic option in recurrent/metastatic NPC, with superior progression-free survival (PFS) compared with fluorouracil plus cisplatin (7.0 vs. 5.6 months) in a phase III trial (39). Thus, platinum selection should be separated by clinical setting: Cisplatin remains a standard radiosensitizer in definitive CCRT, lobaplatin may be considered investigational or individualized in older adult/frail populations and GP is primarily supported in recurrent/metastatic systemic therapy.

Taxanes: Cell cycle-mediated sensitization. Paclitaxel promotes microtubule polymerization and stabilization, inducing G_2/M-phase arrest, a relatively radiosensitive phase of the cell cycle (40). Low-dose paclitaxel pretreatment (0.05 or 1.0 nmol/l for 24 h) enhanced radiosensitivity in CNE-I NPC cells (41). G_2/M accumulation may drive cells toward mitotic catastrophe after irradiation. In locoregionally advanced NPC, GP and docetaxel, cisplatin and fluorouracil (TPF) sequential chemoradiotherapy showed similar long-term efficacy but different toxicity profiles, with more thrombocytopenia in the GP group and more leukopenia and neutropenia in the TPF group (42).

Mechanism-based combination strategies

Autophagy modulation. Radiation-induced autophagy can be cytoprotective or cytotoxic depending on context (43). Chloroquine, which inhibits autophagosome-lysosome fusion, enhanced radiosensitivity in four of five tested NPC cell lines without sensitizing an immortalized nasopharyngeal epithelial cell line (44). The study was limited to cell-line experiments, and *in vivo* confirmation remains necessary. The PARP-1

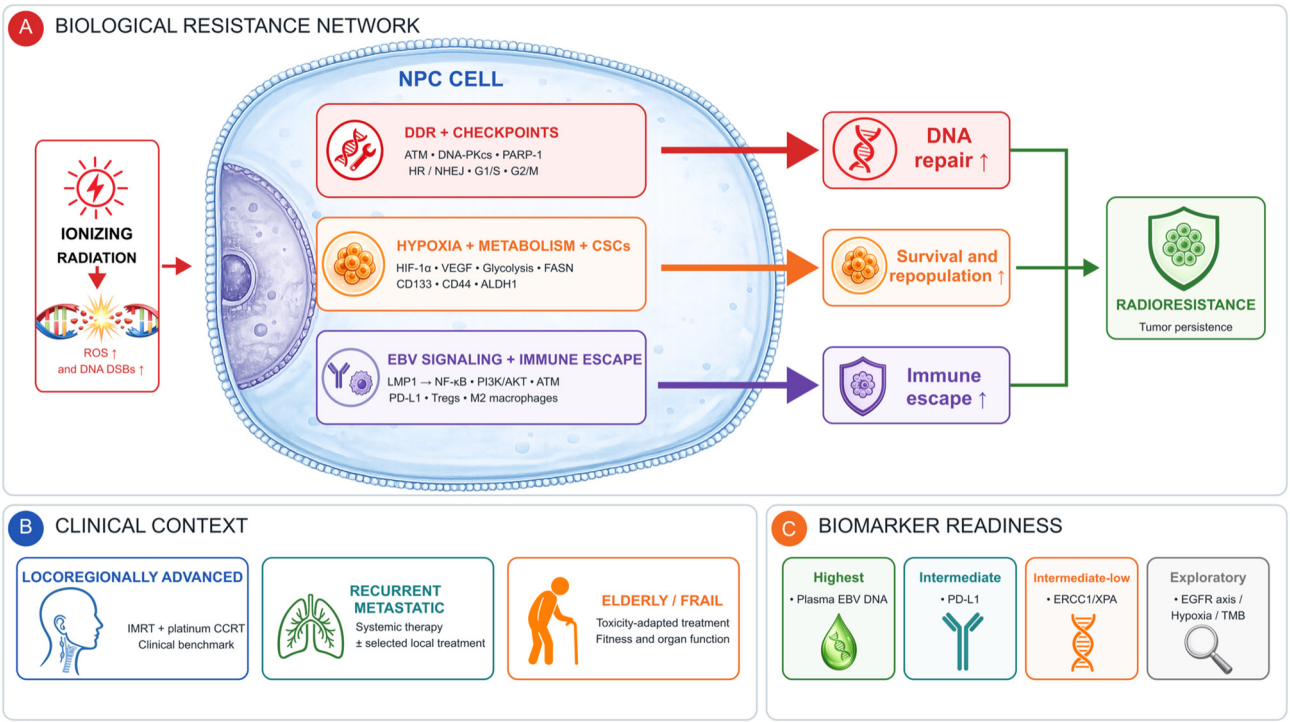

Figure 1. Integrated biological and clinical framework of radioresistance in NPC. (A) Ionizing radiation generates ROS and DNA DSBs. Radioresistance is sustained by three interconnected modules: DDR and checkpoint signaling; hypoxia, metabolic adaptation and CSC persistence; and EBV-associated signaling and immune escape. ATM, DNA-PKcs and PARP-1 coordinate DNA repair through HR or NHEJ. Hypoxia-inducible, metabolic and stemness-associated factors promote survival and repopulation. LMP1 activates NF-κB, PI3K/AKT and ATM-associated signaling, while PD-L1, regulatory T cells and M2 macrophages contribute to immune escape. These processes converge on tumor persistence. (B) The principal clinical contexts are locoregionally advanced, recurrent or metastatic, and elderly or frail disease. Definitive intensity-modulated radiotherapy-based platinum chemoradiotherapy is the benchmark for locoregionally advanced disease; systemic therapy predominates in recurrent or metastatic disease; and treatment intensity should be adapted to fitness and organ function in elderly or frail patients. (C) Plasma EBV DNA has the greatest current clinical readiness. PD-L1 is context-dependent, ERCC1/XPA remains a retrospective platinum-response candidate, and EGFR-axis, hypoxia and TMB markers remain investigational. Arrows indicate biological relationships rather than validated treatment-selection rules. AKT, protein kinase B; ALDH1, aldehyde dehydrogenase 1; ATM, ataxia telangiectasia mutated; CCRT, concurrent chemoradiotherapy; CSC, cancer stem cell; DDR, DNA damage response; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, DNA double-strand break; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; FASN, fatty acid synthase; HIF-1α, hypoxia-inducible factor 1α; HR, homologous recombination; IMRT, intensity-modulated radiotherapy; LMP1, latent membrane protein 1; NF-κB, nuclear factor-κB; NHEJ, non-homologous end joining; NPC, nasopharyngeal carcinoma; PARP-1, poly(ADP-ribose) polymerase 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; TMB, tumor mutational burden; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; XPA, xeroderma pigmentosum group A.

inhibitor 3-aminobenzamide suppresses radiation-induced autophagy by downregulating Beclin1 and enhances apoptosis through caspase-3 activation (13).

Epigenetic reprogramming. DNA methylation is implicated in NPC radioresistance, including interactions with microRNA (miRNA/miR)-mediated regulation (45). 5-Azacytidine enhanced the radiosensitivity of CNE2 and SUNE1 cells *in vitro* and *in vivo*, supporting further investigation of DNA-demethylating strategies in NPC (46).

Predictive biomarkers for chemotherapy-based radiosensitization

ERCC1 and xeroderma pigmentosum complementation group A (XPA). Beyond ERCC1, XPA, another nucleotide excision repair protein, is associated with outcomes after platinum-based chemoradiotherapy. High XPA expression is associated with shorter OS and PFS in patients with NPC receiving platinum-based CCRT (47). Together with retrospective ERCC1 studies (36,37), these findings support prospective evaluation of biomarker-stratified treatment, but they do not justify directing ERCC1/XPA-low tumors to platinum-based CCRT or ERCC1/XPA-high tumors to alternative therapy in routine practice. Assay harmonization, prespecified cut-offs and prospective treatment-by-biomarker interaction testing are required.

Metabolic biomarkers. Nicotinamide N-methyltransferase (NNMT) promotes Akt phosphorylation and enhances proliferation and migration. High NNMT expression is associated with shortened disease-specific survival and metastasis-free survival, suggesting utility as both a prognostic biomarker and a potential therapeutic target (48).

Overall, chemotherapy-based radiosensitization remains the most clinically mature strategy in NPC; however, its value differs by setting. In primary locoregionally advanced disease, platinum-based CCRT and induction chemotherapy are supported by the highest level of clinical evidence. In recurrent/metastatic disease, systemic disease control and immunochemotherapy have clearer roles than radiosensitization alone. Further gains are likely to depend on DNA repair, metabolic and EBV-related biomarkers that can identify patients most likely to benefit from treatment intensification while avoiding unnecessary toxicity.

4. Molecularly targeted therapies: Mechanism-guided radiosensitization

Epidermal growth factor receptor (EGFR) pathway inhibition. The EGFR pathway is clinically relevant in NPC, and EGFR/phosphorylated (p-)EGFR expression has been evaluated as a prognostic biomarker (49). Nuclear EGFR is also linked to radiation response and DNA repair signaling (50). However, EGFR-targeted therapy should not be considered uniformly beneficial. A recent randomized phase 2 trial in patients with a suboptimal response to induction chemotherapy found no PFS improvement from adding nimotuzumab to concurrent chemoradiotherapy (51). These findings support biomarker development rather than unselected anti-EGFR intensification.

Annexin A3 (ANXA3). ANXA3, a calcium-dependent phospholipid-binding protein, is inversely associated with radioresistance in NPC. Low ANXA3 expression facilitates EGFR phosphorylation (Tyr1068) and nuclear translocation, activates DNA-PKcs and accelerates DSB repair. Clinical samples show that ANXA3-low/nuclear EGFR-high tumors are radioresistant, whereas cetuximab (an EGFR monoclonal antibody) reverses this phenotype (52). These findings support combination strategies pairing EGFR inhibitors with radiotherapy.

Anti-EGFR strategies. Mechanistic and early clinical data support continued evaluation of anti-EGFR agents with radiotherapy-based regimens, but efficacy remains uncertain. In a randomized phase 2 trial, 2-year PFS was 81.0% with nimotuzumab plus CCRT and 80.8% with CCRT alone (hazard ratio=0.93; P=0.70), with no improvement in survival outcomes and more frequent low-grade rash (51).

ANXA1-EGFR axis. ANXA1 binds to the intracellular C-terminal tail of EGFR and stabilizes the receptor by competing with the Casitas B-lineage lymphoma (Cbl) E3 ubiquitin ligase, thereby reducing Cbl-mediated EGFR ubiquitination and subsequent degradation. This interaction activates STAT3, promotes programmed death-ligand 1 (PD-L1) expression and contributes to radioresistance. A nine-amino-acid peptide designed to disrupt the ANXA1-EGFR interaction downregulated EGFR and enhanced radiosensitivity in NPC cell and mouse models (53).

DNA damage response (DDR) pathway targeting.
PARP inhibitors. PARP-1 orchestrates single-strand break repair and also regulates autophagy. In addition to their effects on autophagy, PARP inhibitors exploit synthetic lethality in HR-deficient tumors (54). Although NPC typically retains HR proficiency, combination with HR disruptors may sensitize cells to PARP inhibitors plus radiotherapy.

ATM/ATR checkpoint kinase (ATR) inhibitors. ATM and ATR are apical DDR kinases that activate downstream checkpoint and repair pathways. ATR kinase-dead cells exhibit impaired HR, defective G_2 checkpoint function and enhanced radiosensitivity independent of NHEJ status (14). These findings support ATR inhibition as a promising radiosensitization strategy, particularly in rapidly proliferating NPC cells with replication stress.

Ubiquitin-specific protease 5 (USP5)-methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3) axis. Bromodomain-containing protein 7 (BRD7), a tumor suppressor, competes with USP5 for METTL3 binding and promotes proteasomal degradation of METTL3. METTL3 reduction suppresses HR repair proteins (BRCA1 and RAD51), thereby enhancing radiosensitivity. Clinical correlations indicate that BRD7-high/METTL3-low tumors are associated with radiosensitivity and favorable prognosis (55).

Hypoxia-targeted strategies
Hypoxia-activated prodrugs. Tirapazamine (TPZ), a bioreductive alkylating agent, is converted into cytotoxic radicals under hypoxic conditions, selectively damaging hypoxic cells. TPZ downregulates HIF-1α and osteopontin mRNA in HNE-1 cells and enhances radiosensitivity, but shows cell line-dependent efficacy (ineffective in CNE-1), highlighting challenges related to tumor heterogeneity (25).

Vascular normalization. Recombinant human endostatin (Endostar) is an anti-angiogenic strategy evaluated with PF chemotherapy and sequential IMRT in locally advanced NPC. A randomized, open-label multicenter phase II study found the regimen tolerable and reported improved PFS, although confirmatory trials are required (56).

Nanozyme-based oxygen generation. Ferritin-encapsulated platinum nanoparticles target hypoxic NPC cells through transferrin receptor 1, which is upregulated under hypoxia. These nanozymes catalyze H_2O_2 decomposition into O_2, alleviating hypoxia and enhancing radiosensitivity. In a preclinical study, Pt-HFn combined with RT inhibited tumor growth and prolonged survival more effectively than RT combined with sodium glycididazole (57). Sodium glycididazole itself has shown radiosensitizing activity in NPC models by enhancing DNA damage and apoptosis (58).

Signal transduction pathway modulators
STAT3 inhibition. p-STAT3 promotes cyclin D1 expression and suppresses apoptosis. Stattic, a highly selective STAT3 inhibitor, reduces p-STAT3 and cyclin D1 levels, induces apoptosis, and enhances NPC cell sensitivity to cisplatin and radiotherapy (59).

Jun activation domain-binding protein 1 (JAB1)/COP9 signalosome subunit 5 (CSN5) targeting. JAB1, also known as CSN5, participates in signaling that supports NPC cell survival and radioresistance. The curcumin analogue T83 inhibited JAB1 expression, induced G_2/M arrest and apoptosis, and enhanced radiosensitivity in NPC models (60). miR-24 similarly targets JAB1, and its upregulation induces apoptosis and radiosensitization (61).

PI3K/Akt pathway. Leucine zipper tumor suppressor 2 (LZTS2), which is downregulated in NPC, binds the PI3K regulatory subunit p85, prevents p85-p110 interaction and inhibits Akt activation (62). LZTS2 overexpression suppresses proliferation and radioresistance, whereas p85 knockdown reverses these effects (62). Raf kinase inhibitor protein (RKIP), also downregulated in NPC, suppresses ERK and Akt pathways when expressed, and RKIP-low patients exhibit shorter OS and disease-free survival (63).

Collectively, these strategies are most plausible when a measurable molecular vulnerability, such as aberrant EGFR trafficking, defective DNA damage response or hypoxia-driven survival, can be matched to an intervention whose dose, schedule and toxicity permit combination with radiotherapy.

Clinical translation of targeted radiosensitizers remains uneven. Anti-EGFR antibodies have early clinical data in selected locoregionally advanced NPC, whereas a number of DDR inhibitors, peptide inhibitors and nanozyme-based oxygenation strategies remain preclinical or early translational. Eligible patient subgroups should be defined by measurable pathway activation, such as EGFR trafficking, HR deficiency, replication stress, hypoxia markers or dynamic EBV DNA risk, rather than by diagnosis alone. Safety evaluation is essential because DDR inhibition or hypoxia modification may also sensitize normal mucosa, salivary tissue and marrow to radiation.

5. Immune checkpoint inhibitors (ICIs): Redefining the radiosensitization paradigm

Synergy between radiotherapy and immunotherapy. Radiotherapy can produce direct and bystander effects beyond the irradiated cells, although the clinical importance of these effects remains to be elucidated (64). Low-dose radiation can modulate antioxidant responses, DNA repair, apoptosis and antitumor immune responses (65). In NPC, epigenetic mechanisms contribute to immune evasion, providing a rationale for investigating DNA methyltransferase (DNMT) or histone deacetylase (HDAC) inhibitors, together with immune checkpoint blockade (66). These observations support further investigations of immunoradiotherapy, but do not by themselves establish a uniform abscopal effect or radiation-induced PD-L1 response in NPC. NPC-specific *in vitro* evidence indicates that high-dose irradiation can induce an immunogenic cell-death phenotype and enhance dendritic cell (DC) maturation; this supports the proposed pathway from immunogenic cell death to DC maturation, but tumor-antigen release and downstream T-cell priming were not directly demonstrated (67). Separately, radiotherapy-associated PD-L1 upregulation was observed in NPC cell lines and a patient-derived xenograft model, suggesting a context-dependent adaptive checkpoint response that remains to be validated clinically (68).

Programmed cell death protein 1 (PD-1)/PD-L1 axis inhibition
Preclinical mechanisms. The ANXA1-EGFR-STAT3-PD-L1 axis exemplifies radiation-induced immunosuppression. As previously discussed, ANXA1 stabilizes EGFR, activates STAT3 and promotes PD-L1 transcription (53). Disruption of this axis with peptide inhibitors reduces PD-L1 expression and enhances radiosensitivity, demonstrating convergence between targeted and immune-based therapeutic strategies (53).

Clinical evidence in recurrent/metastatic NPC. Camrelizumab, a PD-1 monoclonal antibody, achieved an objective response rate (ORR) of 28.2% in pretreated recurrent/metastatic NPC, with greater efficacy in PD-L1-positive patients (69). Tislelizumab combined with chemotherapy as first-line treatment for recurrent/metastatic NPC markedly prolonged PFS in the phase III RATIONALE-309 trial (hazard ratio=0.52) (70). These data support the use of checkpoint blockade most strongly in recurrent/metastatic disease. In locoregionally advanced NPC, induction chemoimmunotherapy before CCRT remains an evolving strategy; a small non-randomized study reported higher ORR (95.7 vs. 77.8%), complete response rate (39.1 vs. 22.2%) and 24-month event-free survival (88.9 vs. 62.6%) than induction chemotherapy alone (71).

Combination strategies and safety. In a retrospective cohort, TPF induction chemotherapy combined with a PD-1 inhibitor produced a higher ORR (88.5 vs. 71.2%) and complete response rate (29.5 vs. 11.3%) than TPF alone (72). Nevertheless, combined radiotherapy, chemotherapy and immunotherapy may increase mucositis, dermatitis, hematologic toxicity, endocrinopathy, hepatitis, pneumonitis or other immune-related adverse events. Prospective trials should define whether ICIs are best used as induction, concurrent, consolidation or salvage therapy.

Biomarkers for immunotherapy response
PD-L1 expression. Although PD-L1 positivity predicts response to camrelizumab, standardized cutoff values remain undefined (69). Integrating PD-L1 immunohistochemistry with complementary biomarkers may improve patient selection.

EBV DNA. Circulating EBV DNA serves as a dynamic biomarker in NPC and associates with tumor burden and treatment response (73). Early EBV DNA clearance (2 weeks) after induction chemotherapy predicts greater tumor shrinkage (78.9 vs. 56.7% nasopharyngeal volume reduction; 81.6 vs. 59.3% nodal volume reduction) and superior 3-year OS (89.2 vs. 71.4%) and PFS (85.7 vs. 64.3%) (74). Persistent EBV DNA positivity during follow-up, even in the absence of clinical recurrence, supports consideration of metronomic chemotherapy (such as capecitabine) in selected patients, which prolongs modified disease-free survival (12.9 vs. 6.8 months) (75). Longitudinal EBV DNA monitoring (0-2 weeks and 8-12 weeks post-radiotherapy) enables early recurrence detection, with persistent positivity associating with shorter PFS (73).

Tumor mutational burden (TMB) and microsatellite instability (MSI). Although validated in other malignancies, data on TMB and MSI in NPC remain limited. Given NPC's viral etiology and distinct mutational landscape, these biomarkers require prospective validation (76).

Emerging immune-oncology approaches
EBV-targeted vaccines. mRNA vaccines encoding T-cell epitope-rich domains from LMP2 have demonstrated antitumor efficacy in preclinical NPC models, inducing antigen-specific T-cell responses and tumor suppression in murine models (77). This evidence remains preclinical: No clinical benefit as a radiosensitizer has been demonstrated in patients with NPC, no patient subgroup has been prospectively defined beyond the hypothesis of EBV-antigen-positive disease, and safety with concurrent or sequential radiotherapy is unknown. Early clinical studies should assess antigen expression, immune escape, treatment sequencing and overlapping inflammatory or mucosal toxicity before efficacy claims are made.

Epigenetic-immune crosstalk. DNMT and HDAC inhibitors can reverse immune suppression by upregulating antigen-presentation machinery and chemokine expression, potentially synergizing with ICIs (66). This epigenetic reprogramming may convert immunologically cold tumors into hot, immunogenic lesions that are more amenable to checkpoint blockade.

These findings support immunoradiotherapy as a biologically plausible strategy; however, patient selection should be

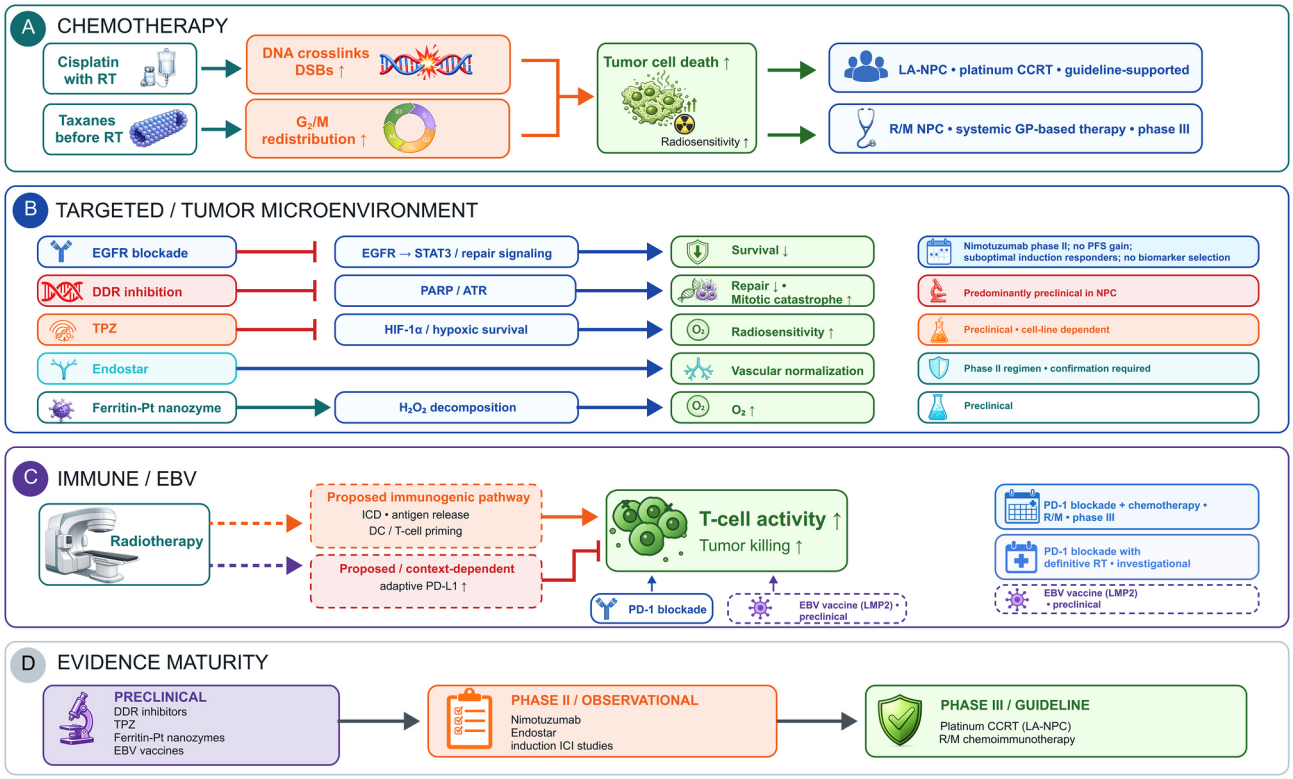

Figure 2. Mechanism-guided treatment strategies across clinical settings and evidence maturity. (A) Cisplatin administered with RT increases DNA crosslinks and DSBs, whereas taxane pretreatment redistributes cells toward the radiosensitive G_2/M phase. These mechanisms increase tumor-cell death and radiosensitivity. Platinum-based CCRT is guideline-supported in locoregionally advanced NPC, whereas gemcitabine-cisplatin-based therapy is a phase III-supported systemic option in recurrent or metastatic disease. (B) EGFR blockade, DDR inhibition and hypoxia-directed strategies have distinct mechanisms and evidence levels. Nimotuzumab did not improve PFS in a phase II trial enrolling patients with a suboptimal response to induction chemotherapy without predictive-biomarker selection. PARP and ATR targeting remains predominantly preclinical in nasopharyngeal carcinoma. TPZ inhibits HIF-1α-associated hypoxic survival in preclinical, cell-line-dependent models. Endostar is shown as a vascular-normalization strategy evaluated in a phase II regimen, whereas ferritin-Pt nanozymes catalyze H_2O_2 decomposition to generate O_2 in preclinical models. (C) The dashed immunogenic pathway represents a proposed sequence in which RT may promote immunogenic cell death, antigen release and dendritic-cell/T-cell priming. The separate dashed pathway to adaptive PD-L1 denotes a proposed, context-dependent immunosuppressive response. PD-1 blockade relieves inhibitory signaling. Phase III evidence applies to PD-1 blockade plus chemotherapy in recurrent or metastatic disease, whereas combination with definitive RT remains investigational. EBV LMP2-directed vaccination remains preclinical. (D) Evidence maturity ranges from preclinical studies to phase II or observational data and phase III or guideline-supported applications. ATR, ataxia telangiectasia and Rad3-related protein; CCRT, concurrent chemoradiotherapy; DC, dendritic cell; DDR, DNA damage response; DSB, DNA double-strand break; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; GP, gemcitabine plus cisplatin; HIF-1α, hypoxia-inducible factor 1α; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; LMP2, latent membrane protein 2; NPC, nasopharyngeal carcinoma; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M, recurrent or metastatic; RT, radiotherapy; STAT3, signal transducer and activator of transcription 3; TPZ, tirapazamine.

guided by PD-L1 expression, dynamic EBV DNA kinetics, and immune microenvironment features rather than treating checkpoint blockade as a uniform radiosensitizing approach. Mechanism-guided treatment strategies across clinical settings and levels of evidence are summarized in Fig. 2.

6. Natural compounds and traditional Chinese medicine (TCM)-derived agents

DDR and checkpoint modulation. Several natural compounds and TCM-derived molecules converge on DDR and checkpoint regulation. Curcumin, the principal curcuminoid derived from *Curcuma longa*, exemplifies this mechanism-based group through multi-pathway modulation, but its clinical translation remains limited by bioavailability, formulation variability and a lack of definitive randomized NPC trials.

miRNA networks. Curcumin downregulates miR-205-5p, thereby derepressing tumor protein p53-inducible nuclear protein 1 (TP53INP1), which promotes apoptosis in radioresistant NPC cells (C666-IR) (78). In addition, curcumin modulates circular RNA (circRNA) networks, particularly the hsa-circRNA-102115-hsa-miR-335-3p-MAPK1 axis, suppressing cancer stem cell properties and enhancing radiosensitivity (20,21). Curcumin also upregulates miR-593, which targets multidrug resistance protein 1 and reverses radioresistance (79).

Cell-cycle modulation. The curcumin analogue T83 targets JAB1/CSN5, induces G_2/M arrest and apoptosis and enhances radiosensitivity in NPC models (60). The parent compound curcumin also alters cell-cycle and radiation-response pathways (80).

Epithelial-mesenchymal transition (EMT), EGFR trafficking and apoptotic regulation. Tetrandrine, ginsenoside Rg3 and berberine illustrate a second mechanism-based group targeting checkpoints, EMT and EGFR-associated signaling. At non-cytotoxic concentrations, tetrandrine enhanced

radiation-induced growth inhibition and apoptosis, increased DNA damage and abrogated G_2/M arrest in NPC cells; combined treatment also reduced xenograft growth (17).

Ginsenoside Rg3 and berberine: EMT and EGFR-related mechanisms. Ginsenoside Rg3 from *Panax ginseng* suppresses radiation-induced EMT, a process that confers radioresistance and metastatic potential (81). Rg3 inhibits EGFR nuclear translocation and reduces DNA-PK expression, thereby impairing DSB repair while promoting apoptosis (81). Berberine similarly sensitizes NPC cells to radiation through Sp1 inhibition and EMT suppression (82). Compared with synthetic EGFR or DDR inhibitors, these agents may affect several pathways simultaneously but have weaker pharmacokinetic standardization and substantially lower clinical evidence.

Oxidative stress and hypoxia modulation. Ras association domain-containing protein 1 (RASSF1A)-associated redox control and gambogic acid illustrate mechanisms that modulate oxidative stress and hypoxia-related survival. RASSF1A overexpression promoted FoxO3a activity and inhibited the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2/thioredoxin reductase 1 axis, increasing oxidative stress and radiosensitivity in NPC models (83). Gambogic acid inhibited HIF-1α expression and sensitized hypoxic NPC cells to radiation (84). These findings remain largely preclinical.

TCM formulas, oral microecology and supportive modulation. Complex TCM formulations differ from single synthetic radiosensitizers because they are usually developed within multi-component and multi-target frameworks. Their effects should therefore be evaluated using quantifiable clinical and biological outcomes rather than by treating TCM syndrome categories as direct molecular entities. A 2024 observational study measured serum inhibin subunit α, inhibin subunit β B, EBV DNA and EBV viral capsid antigen immunoglobulin A in relation to clinical stage; however, its retrospective design precluded causal or treatment-predictive conclusions (85). For radiation injury, a meta-analysis of 30 randomized controlled trials involving 2,562 patients evaluated heterogeneous oral TCM herbal formulations categorized as 'nourishing Yin and clearing Heat' therapy, rather than a single standardized preparation. These formulations were administered as adjuncts to trial-specific control regimens, which varied across studies and included gentamicin, dexamethasone, local anesthetics, vitamin B12, compound borax or chlorhexidine gargles and recombinant human epidermal growth factor. Compared with the control regimens alone, adjunctive TCM therapy delayed the onset of grade I radiotherapy-induced oral mucositis by 10.80 days, increased the cumulative radiation dose delivered before its onset by 5.72 Gy and reduced the risk of grade III-IV oral mucositis (relative risk=0.25). However, the heterogeneity of the herbal formulations and control regimens limits the generalizability of these findings, and further large, rigorously designed randomized trials are required (86). A 2025 double-blind randomized trial included 24 evaluable patients receiving Danggui Buxue Tang (n=11) or placebo (n=13). Grade 2-3 neutropenia occurred in 0/11 and 4/13 patients, respectively (P=0.10), while grade 1 anemia occurred in 1/11 and 4/13 patients, respectively (P=0.33). Conversely, grade 2-3 anorexia was more frequent in the Danggui Buxue Tang group than in the placebo group (10/11 vs. 5/13 patients; P=0.01). RNA sequencing identified differential gene expression associated with B-cell receptor signaling. Due to the small sample size, mixed toxicity findings and absence of statistically significant differences for several outcomes, these results remain exploratory (87).

Modern observations involving oxidative stress, inflammation, epithelial injury, immunity and the oral microbiome should therefore be interpreted as measurable parallel domains rather than literal biomedical translations of TCM syndromes. Within this cautious framework, Shengmai Jianghuang San (SMJHS) inhibits cancer stem cells and hypoxic adaptation through the tenascin C/HIF-1α/YAP1 pathway. SMJHS suppresses proliferation, migration and cancer stem cell biomarker (CD44) expression under hypoxia while downregulating HIF-1α and YAP1, thereby enhancing radiosensitivity (88). Metabolomic profiling indicates multi-target engagement across lipid metabolism and oxidative stress pathways (89).

Shengmai Yin (SMY). SMY reversed radiation-associated EMT in radioresistant NPC cells by inhibiting lipocalin 2 expression (90). DNA methylation analysis also indicates that SMY modulates epigenetic landscapes in radioresistant cells (91).

Dendrobium officinale and modified Sijunzi decoction. Dendrobium officinale was evaluated for radiation-induced oral mucositis and salivary/oral-microbiome changes in patients with NPC (92). Separately, modified Sijunzi decoction was associated with reduced radiation-induced sinusitis in a retrospective study, and network pharmacology implicated JAK-STAT and NF-kB-related pathways (93).

Other bioactive natural compounds and related viral mechanisms. Schisandrin B and emodin provide additional preclinical examples. Schisandrin B targets CDK4/6, induces cell-cycle arrest and enhances NPC radiosensitivity (94). Emodin inhibits EBV reactivation and NPC tumorigenic phenotypes, although the cited study did not test ionizing-radiation sensitization (95).

Light-based cytotoxic approaches outside the ionizing-radiation radiosensitization framework. Photodynamic therapy (PDT) uses non-ionizing visible light and photosensitizers and therefore should not be classified as radiosensitization for ionizing radiation. Studies of Zn-BC-AM, hypericin and hypocrellin are best interpreted as related light-based cytotoxic approaches (96-99). They are retained only to clarify this distinction and are not included in Table I as ionizing-radiation radiosensitizers.

Comparative advantages, limitations and translational requirements. Compared with synthetic agents that usually target a defined molecule such as EGFR, PARP, ATR or PD-1, natural compounds and TCM-derived agents may engage multiple pathways, including DDR, EMT, oxidative stress, hypoxia, inflammation and microecology. This breadth may be advantageous for heterogeneous tumors but also complicates dose standardization, target attribution and regulatory evaluation. A large matched observational cohort reported an association between adjunctive Chinese herbal medicine and clinical outcomes, supported by experimental work, but

Table I. Clinical summary of mechanism-guided radiosensitization strategies in nasopharyngeal carcinoma.

Strategy	Setting	Examples and principal mechanism	Evidence status[a]	Main caveat
Chemotherapy	LA-NPC; R/M	Cisplatin, GP, taxanes: DNA damage; G_2/M redistribution	Cisplatin CCRT, L1; systemic GP, L1; lobaplatin, L2; taxane radiosensitization, L3	Toxicity; sequencing; selection
EGFR signaling	Selected LA-NPC	Nimotuzumab[b], cetuximab, ANXA1/ANXA3-EGFR axes: Survival and repair inhibition	L2-L3	No validated biomarker; skin/mucosal toxicity
DDR targeting	Biomarker-selected research	PARP and ATR/ATM: Repair and checkpoint inhibition	L3	Normal-tissue sensitization; no strategy trial
Hypoxia/TME	Hypoxic or bulky disease	TPZ, Endostar, nanozymes: Hypoxic killing, vascular normalization and O_2 generation	L2-L3	Heterogeneity; delivery; no phase III evidence
ICI + RT	R/M; definitive RT research	PD-1/PD-L1 and EBV targets: immune activation	Systemic R/M chemo-immunotherapy L1; induction studies, L2; definitive-RT radio-sensitization, L3	Timing; immune toxicity; biomarkers
Natural products/ TCM	Preclinical; adjunct/supportive	Curcumin/T83, tetrandrine, Rg3 and SMJHS: DDR, EMT, redox and hypoxia modulation	Radiosensitization, L3; supportive/toxicity studies, L2	Standardization; PK; interactions

[a]Evidence levels indicate study maturity rather than treatment efficacy: L1, guideline-supported or phase III evidence; L2, phase II, observational or small clinical evidence; L3, preclinical or early translational evidence. Ranges indicate that the listed examples have different evidence levels. L1 evidence for ICI-based treatment applies to systemic chemoimmunotherapy in R/M NPC, not definitive-RT radiosensitization. GP is an established systemic regimen for R/M disease and is not classified here as a definitive-RT radiosensitizer. [b]The nimotuzumab finding refers to the randomized phase II trial by Liu *et al* (51), in which nimotuzumab plus CCRT did not improve 2-year PFS compared with CCRT alone in patients with locoregionally advanced NPC who had a suboptimal response to induction chemotherapy (81.0 vs. 80.8%; hazard ratio=0.93; P=0.70). Most DDR inhibitors, nanozymes, EBV vaccines and natural-product radiosensitizers remain preclinical. ANXA, annexin; CCRT, concurrent chemoradiotherapy; DDR, DNA damage response; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; GP, gemcitabine plus cisplatin; ICI, immune checkpoint inhibitor; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; PFS, progression-free survival; PK, pharmacokinetics; R/M, recurrent or metastatic; RT, radiotherapy; SMJHS, Shengmai Jianghuang San; TCM, traditional Chinese medicine; TME, tumor microenvironment; TPZ, tirapazamine; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; CHK1, checkpoint kinase 1; PARP, poly(ADP-ribose) polymerase; WEE1, WEE1 G_2 checkpoint kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

its non-randomized design cannot establish causality (100). Key challenges therefore include limited bioavailability, batch variability, insufficient pharmacokinetic characterization, uncertain herb-drug interactions and a lack of randomized multicenter validation.

Therefore, natural compounds and TCM-derived agents should be regarded primarily as hypothesis-generating or adjunctive candidates until standardized preparations, quality control, optimal dosing, safety with CCRT and interactions with immunotherapy or targeted therapy are prospectively clarified. Natural products and TCM-derived interventions, together with their evidence limitations and translational requirements, are summarized in Fig. 3. Representative mechanism-guided radiosensitization strategies for NPC are summarized in Table I.

7. Conclusions and future perspectives

Synthesis of core findings. The present review indicates that mechanism-guided radiosensitization in NPC has progressed from empirical chemotherapy-based approaches toward mechanism-guided, multimodal therapeutic strategies. The principal conclusions are as follows: i) Mechanistic convergence: Radioresistance emerges from interconnected mechanisms, including enhanced DNA repair, cell-cycle checkpoint adaptation, CSC enrichment, hypoxic microenvironments, EBV-driven oncogenic signaling and metabolic reprogramming; effective radiosensitization therefore requires pathway-informed interventions rather than non-specific treatment intensification; ii) clinical setting matters: Platinum-based chemoradiotherapy remains most established in primary

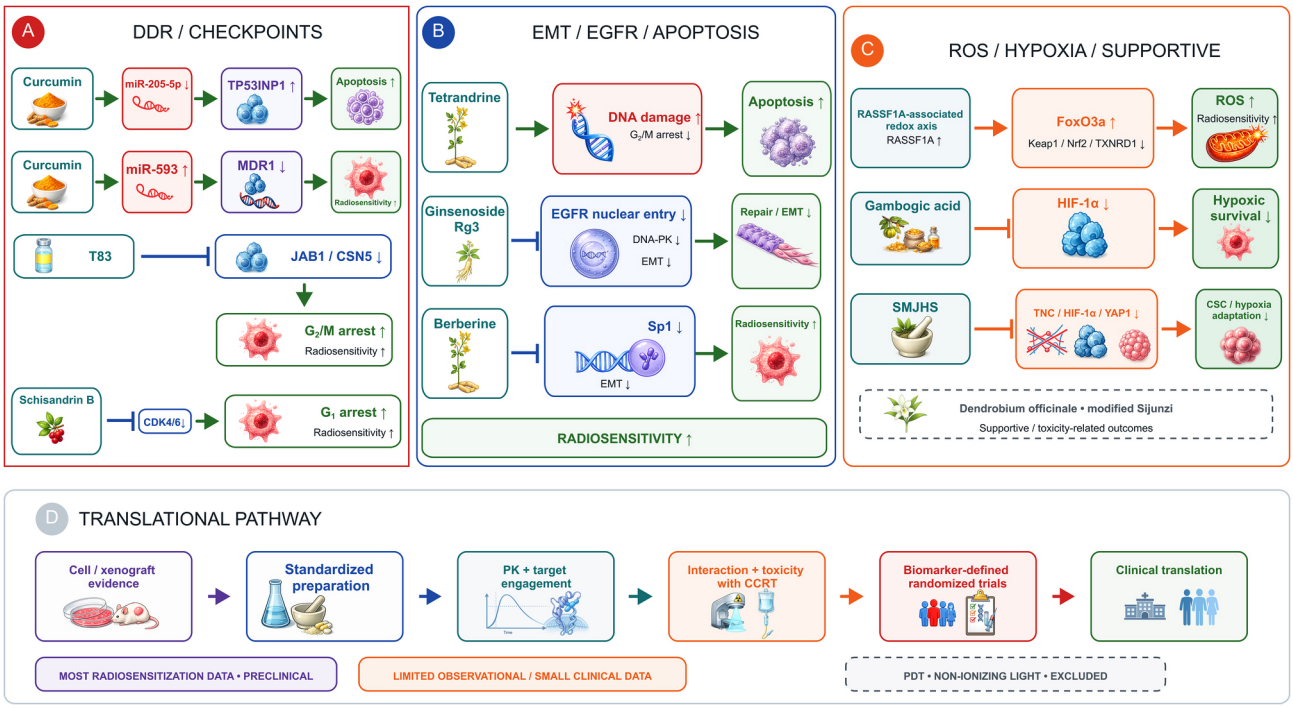

Figure 3. Mechanism-based organization and translational pathway for natural products and traditional Chinese medicine-derived interventions in nasopharyngeal carcinoma. (A) Curcumin regulates two distinct miRNA pathways: Downregulation of miR-205-5p derepresses TP53INP1 and promotes apoptosis, whereas upregulation of miR-593 suppresses MDR1 and increases radiosensitivity. The curcumin analogue T83 inhibits JAB1/CSN5 and promotes G_2/M arrest and radiosensitivity. Schisandrin B downregulates CDK4/6, induces G_1-phase arrest, delays DNA double-strand-break repair and enhances radiosensitivity. (B) Tetrandrine increases DNA damage, abrogates protective G_2/M arrest and promotes apoptosis. Ginsenoside Rg3 suppresses EGFR nuclear entry, DNA-PK expression and EMT, thereby impairing repair and EMT-associated resistance. Berberine inhibits Sp1 and EMT and increases radiosensitivity. (C) RASSF1A is shown as a host-gene redox axis: Increased RASSF1A promotes FoxO3a activity and inhibits the Keap1/Nrf2/TXNRD1 pathway, increasing ROS and radiosensitivity. Gambogic acid inhibits HIF-1α-associated hypoxic survival. Shengmai Jianghuang San suppresses the TNC/HIF-1α/YAP1 axis and cancer stem-cell/hypoxia adaptation. Dendrobium officinale and modified Sijunzi decoction are shown separately because they have mainly been evaluated for supportive or toxicity-related outcomes. (D) Most radiosensitization evidence remains preclinical. Translation requires standardized preparations, pharmacokinetic and target-engagement studies, herb-drug interaction and toxicity assessment with CCRT, biomarker-defined enrollment and randomized validation. Photodynamic therapy is excluded because it uses non-ionizing light. CCRT, concurrent chemoradiotherapy; CDK4/6, cyclin-dependent kinases 4 and 6; CSC, cancer stem cell; CSN5, COP9 signalosome subunit 5; DNA-PK, DNA-dependent protein kinase; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; FoxO3a, forkhead box O3a; HIF-1α, hypoxia-inducible factor 1α; JAB1, Jun activation domain-binding protein 1; Keap1, Kelch-like ECH-associated protein 1; MDR1, multidrug resistance protein 1; miR/miRNA, microRNA; Nrf2, nuclear factor erythroid 2-related factor 2; NPC, nasopharyngeal carcinoma; PDT, photodynamic therapy; PK, pharmacokinetics; RASSF1A, Ras association domain family member 1A; ROS, reactive oxygen species; SMJHS, Shengmai Jianghuang San; Sp1, specificity protein 1; TCM, traditional Chinese medicine; TNC, tenascin C; TP53INP1, tumor protein p53-inducible nuclear protein 1; TXNRD1, thioredoxin reductase 1; YAP1, yes-associated protein 1.

locoregionally advanced NPC, whereas chemoimmunotherapy has stronger evidence in recurrent/metastatic disease and selected induction settings; iii) precision targeting: EGFR inhibition, DDR pathway inhibition and hypoxia-directed strategies provide mechanism-based opportunities to enhance radiotherapy, although numerous approaches still require prospective clinical validation; iv) biomarker hierarchy: Plasma EBV DNA currently has the strongest disease-specific and dynamic clinical readiness; PD-L1 is context- and cut-off-dependent, whereas TMB, ERCC1/XPA, EGFR-axis and hypoxia markers require further prospective validation for treatment selection; and v) natural compounds and TCM-derived agents provide multi-target mechanistic hypotheses and emerging supportive-care signals, but clinical adoption requires standardized preparations, pharmacokinetic characterization and rigorous multicenter trial validation.

Biomarkers, limitations and translational challenges. A central requirement for clinical translation is a practical biomarker hierarchy that distinguishes prognostic association from demonstrated treatment-predictive utility. A 2025 systematic review identified plasma EBV DNA and its kinetics as a robust candidate for risk stratification after chemoradiotherapy, while emphasizing the need to standardize assays and cut-off values (101). In a 2025 meta-analysis of 13 cohorts comprising 1,507 patients receiving ICIs, high pretreatment EBV DNA was associated with worse PFS (hazard ratio=1.72) and OS (hazard ratio=2.03) (102). By comparison, a 2024 meta-analysis of prospective trials reported a higher pooled ORR in later-line immunotherapy when PD-L1 expression was at least 1% (0.37 vs. 0.22), but first-line PFS benefit was not notably different between PD-L1 subgroups and cut-offs of 10 or 25% did not discriminate outcomes (103). A broader 2023 meta-analysis similarly associated lower baseline or decreasing EBV DNA with improved immunotherapy response, whereas positive vs. negative PD-L1 status and high vs. low TMB were not notably associated with ORR (104). Thus, plasma EBV DNA has the highest current clinical readiness; PD-L1 remains context-dependent; ERCC1/XPA is a retrospective platinum-response candidate (36,37,47); EGFR/p-EGFR and

Table II. Comparative clinical readiness of candidate biomarkers in nasopharyngeal carcinoma.

Biomarker	Principal context	Key evidence	Readiness[a]	(Refs.)
Plasma EBV DNA[b]	Risk and response monitoring	Baseline level and kinetics correlate with outcomes	R1	(73,74,101,102,104)
PD-L1[c]	ICI selection in R/M disease	Later-line ORR enrichment at 1%; first-line and cutoff findings inconsistent	R2	(69,76,103,104)
ERCC1/XPA	Platinum CCRT	Retrospective response and survival associations	R3	(36,37,47)
EGFR-axis markers[d]	EGFR-directed RT	Mechanistic/prognostic support; phase II strategy negative	R4	(49-51)
Hypoxia markers[d]	Hypoxia-directed therapy	Preclinical or early translational rationale	R4	(25,57)
TMB[e]	ICI selection	No consistent association with ORR; PFS evidence remains limited.	R4	(104)

[a]Readiness categories are: R1, highest current clinical readiness for risk or response monitoring; R2, intermediate readiness with context-dependent clinical associations; R3, intermediate-low readiness based mainly on retrospective evidence; R4, exploratory or investigational. These categories do not indicate validated treatment-predictive utility. [b]Plasma EBV DNA requires harmonized sampling schedules and cutoffs. [c]PD-L1 results depend on assay, cutoff and treatment line. ERCC1/XPA lacks prospective biomarker-directed trials. [d]EGFR-axis and hypoxia markers lack validated selection thresholds or routine assays. [e]TMB evidence remains limited and no NPC-specific cut-off has been established. CCRT, concurrent chemoradiotherapy; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M, recurrent or metastatic; RT, radiotherapy; TMB, tumor mutational burden; XPA, xeroderma pigmentosum group A.

nuclear EGFR have mechanistic and prognostic support but no validated selection threshold (49-51); and hypoxia markers remain predominantly preclinical or investigational (25,57). Table II provides a direct comparison of these biomarkers and their supporting evidence (25,36,37,47,49-51,57,69,73,74,76, 101-104). Despite notable advances, several obstacles impede optimal radiosensitization.

Biomarker deficiency. The main gap is no longer the absence of candidate markers, but the lack of standardized assays, prospectively validated thresholds, head-to-head incremental-value analyses and trials showing that biomarker-directed treatment improves outcomes. Multiomics panels should therefore be compared against the clinically simpler EBV-DNA benchmark before routine implementation.

Combination strategy optimization. Optimal sequencing, dosing and partner selection remain incompletely defined. NPC cell-line experiments demonstrate that cisplatin exposure duration, sequence and interval relative to radiation can materially alter cytotoxicity, supporting systematic clinical optimization (35).

Therapeutic resistance. Failure of treatment benefit cannot be summarized by a single percentage across chemotherapy, targeted therapy, immunotherapy and natural compounds because the clinical settings and endpoints differ. Resistance reflects interacting DNA-repair, hypoxia, metabolic, stemness and immune mechanisms (9,22,26), while proposed immunotherapy biomarkers remain heterogeneous and variably validated (76).

Normal tissue toxicity and special populations. Combination regimens may produce additive or synergistic toxicities, including mucositis, dermatitis, xerostomia, marrow suppression, nephrotoxicity, ototoxicity and immune-related adverse events. Older adult patients, patients with renal dysfunction, malnutrition, heavy comorbidity burden, prior irradiation or recurrent disease require individualized assessment of therapeutic index rather than automatic treatment intensification.

Clinical guideline and real-world evidence. Current guidelines and evidence summaries support intensity-modulated radiotherapy-based CCRT for locoregionally advanced NPC, induction chemotherapy for selected high-risk disease, and platinum-based chemotherapy plus a PD-1 inhibitor for recurrent or metastatic disease (4,5,7). Existing real-world evidence discussed in the present review includes a 29-patient older adult lobaplatin cohort (38), a retrospective study of a PD-1 inhibitor plus TPF induction chemotherapy (72), a matched observational cohort of adjunctive Chinese herbal medicine (100) and a prognostic model integrating nutritional, inflammatory and post-treatment EBV DNA variables (105). These studies broaden representation of older patients and routine-care populations, but heterogeneous treatment settings and endpoints, non-randomized treatment allocation and residual confounding prevent causal comparisons across strategies.

Accordingly, real-world data should complement rather than replace randomized evidence. Priority analyses should use prespecified treatment definitions, propensity-based or target-trial methods, standardized toxicity and quality-of-life outcomes, and stratification by age, renal function, prior irradiation, endemic region and EBV DNA kinetics. Until such evidence is available, guideline-supported CCRT or chemoimmunotherapy should remain the clinical benchmark, whereas experimental radiosensitizers should be restricted to trials or carefully documented individualized use.

EBV-centered etiopathogenesis-biomarker-target axis. EBV biology should be integrated as a unifying axis that distinguishes NPC from most other head and neck cancers. Etiopathogenetically, EBV latent proteins such as LMP1 promote NF-kB activation, ATM-mediated DNA repair, PI3K/Akt-driven metabolic reprogramming, immune escape and metastatic fitness. As a biomarker, plasma EBV DNA provides a dynamic measure of tumor burden, early response, minimal residual disease and recurrence risk, although assay and cut-off standardization remain necessary (101,102). As a therapeutic target, EBV-associated antigens such as LMP2A and Epstein-Barr virus nuclear antigen 1 support vaccine and T-cell-based approaches, whereas EBV-driven signaling may identify tumors vulnerable to metabolic, immune or DDR-directed radiosensitization. A cohesive EBV-centered framework may therefore integrate etiopathogenesis, risk stratification and therapeutic targeting more effectively than discussing these aspects separately.

Treatment sequencing, overlapping toxicities and special populations. Administration sequence is a central unresolved issue. Cisplatin and taxanes may require defined lead times before radiotherapy to maximize DNA damage or cell-cycle redistribution, whereas ICIs may be used as induction, concurrent, consolidation or salvage therapy depending on stage and trial design. EGFR inhibitors combined with radiotherapy may increase skin and mucosal toxicity; DDR inhibitors may compromise normal-tissue repair; platinum agents may worsen renal, auditory and marrow toxicity; and immunotherapy may add immune-related adverse events. For older adults or medically frail patients, treatment choice should incorporate comprehensive geriatric assessment, renal function, hearing status, nutrition, baseline EBV DNA, comorbidity, patient preference and expected late toxicity.

Future research directions. First, multiomics biomarker integration should combine genomic profiling of DNA repair alterations, transcriptomic signatures including miRNA, long non-coding RNA and circRNA networks and proteomic or phosphoproteomic quantification of DDR proteins, checkpoint kinases and signaling states (106-109). Second, rational combination optimization should include experimental evaluation of fraction timing and dose rate (110), biomarker-selected investigation of dual checkpoint blockade in NPC (111), and disease-specific validation before extrapolating multi-target miRNA radiosensitization findings from other tumor types (112). Third, artificial intelligence models may facilitate individualized induction-chemotherapy selection and risk stratification for distant metastasis in NPC (113,114). Stimuli-responsive nanocarriers may improve tumor selectivity, but the cited pH-activated fullerene nanogel is a photodynamic, light-activated platform rather than an ionizing-radiation radiosensitizer (115). Ultra-high-dose-rate radiotherapy has shown partial reversal of radioresistance in preclinical head and neck squamous cell carcinoma models, but NPC-specific clinical validation is required before extrapolation (116). Long-term comparative studies should also track late toxicity and second-primary cancer risk after NPC radiotherapy (117). Fourth, translational implementation should incorporate validated artificial intelligence-assisted target segmentation (118). Careful mechanistic evaluation of DNA damage checkpoints is also required. In a previous NPC study, CHK1/WEE1 inhibitors were not effective radiosensitizers when administered after irradiation (119), underscoring the importance of treatment sequencing. Standardized post-induction target delineation should also be incorporated (120). Fifth, survivorship research should focus on radioprotective and regenerative strategies to reduce late toxicities, including xerostomia, osteoradionecrosis and cognitive impairment, as well as mechanistic studies of radiation-induced second primary cancers (117,121). Finally, implementation studies should prospectively validate risk models integrating nutritional, inflammatory and post-treatment EBV DNA variables (105) and combined nasopharyngeal-brush plus plasma EBV DNA surveillance (122). Their feasibility, clinical utility and cost-effectiveness require dedicated evaluation rather than being assumed from the current retrospective and diagnostic studies.

Concluding remarks. Mechanism-guided radiosensitization in NPC reflects the integration of molecular oncology, immunology, pharmacology, radiobiology and computational science. Its clinical value will depend less on adding more agents indiscriminately and more on matching strategies to disease setting, EBV-related risk, biomarker-defined vulnerabilities and patient fitness. Chemotherapy, targeted therapy, immunotherapy, and selected natural compounds constitute a broad therapeutic armamentarium, but their optimal use depends on rigorous biomarker validation, rational regimen sequencing, toxicity-aware clinical trial design and equitable access to advanced diagnostics and therapeutics. By aligning therapeutic interventions with the biological determinants of radioresistance, individualized radiosensitization may improve disease control while preserving quality of life.

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Authors' contributions

WD and ZZ conceived and designed the review. WD and ZL developed the literature-search strategy and evidence-synthesis approach and collected and curated the relevant literature. WD drafted the manuscript. ZL and ZZ critically reviewed and revised the manuscript for important intellectual content. ZZ supervised the work and acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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