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TARGETING EGFR DURING CHEMORADIOTHERAPY FOR HEAD AND NECK CANCER: THE EVOLVING ROLE OF NIMOTUZUMAB

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ABSTRACT:
Background: Concurrent cisplatin-based radiotherapy is the standard curative treatment for locally advanced head and neck squamous cell carcinoma (LA-HNSCC); however, treatment failure remains common. Epidermal growth factor receptor (EGFR) contributes to tumor proliferation, DNA damage repair, and radioresistance. Nimotuzumab is a humanized anti-EGFR IgG1 antibody whose intermediate affinity and requirement for bivalent binding may favor tumor-selective activity with limited severe dermatologic toxicity.
Objective: To critically review the biological rationale, clinical efficacy, safety, and unresolved questions surrounding the use of nimotuzumab in HNSCC.
Methods: PubMed/MEDLINE, ClinicalTrials.gov, oncology journal websites, and reference lists were searched for English-language reports available until July 2026. Randomized trials and systematic reviews were prioritized, while non-randomized studies were used to contextualize the activity, safety, and feasibility. This was a narrative rather than a systematic review compliant with the PRISMA guidelines.
Results: A randomized phase IIb study reported improved response and five-year survival when nimotuzumab was added to chemoradiotherapy, although its small sample size and factorial design limited precision. In a randomized phase III trial involving 536 patients, weekly nimotuzumab 200 mg added to radiotherapy and weekly 30 mg/m ² cisplatin improved progression-free survival (hazard ratio [HR] 0.69), locoregional control (HR 0.67), and disease-free survival (HR 0.71). A prespecified 2024 long-term conference report, at a median follow-up of 8.86 years, showed higher 10-year overall survival with nimotuzumab-chemoradiotherapy than with chemoradiotherapy alone (33.5% versus 22.5%; HR 0.811, 95% confidence interval 0.664–0.995; P=0.044), without a significant increase in late adverse events. A favorable survival signal was observed in HPV-negative oropharyngeal cancer, although the small HPV-positive population precluded a reliable comparison by HPV status. A meta-analysis of seven randomized trials involving 1,012 patients also favored nimotuzumab for survival and tumor response outcomes; however, clinical and geographic heterogeneity limited generalizability. Evidence in postoperative and recurrent/metastatic settings remains inconclusive or nonrandomized.
Conclusion: The addition of nimotuzumab to weekly cisplatin-based definitive chemoradiotherapy improved disease control and may provide a long-term survival benefit, particularly in predominantly HPV-negative populations. Nevertheless, cisplatin-based radiotherapy remains the standard curative treatment. Broader adoption requires full peer-reviewed reporting of mature survival results, multicenter validation using contemporary treatment schedules, and prospective biomarker-based patient selection.

KEYWORDS: nimotuzumab, epidermal growth factor receptor, EGFR, head and neck squamous cell carcinoma, chemoradiotherapy, cisplatin, radiotherapy, targeted therapy, radiosensitization.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is biologically heterogeneous and arises from anatomically and functionally complex sites, including the oral cavity, oropharynx, hypopharynx, and larynx. A large proportion of patients in low- and middle-income countries present with stage III–IV disease. Concurrent chemoradiotherapy (CRT) is a major organ-preserving curative approach for unresectable locally advanced tumors. After surgery, concurrent cisplatin is used for patients with selected high-risk pathological features. Treatment failure remains clinically important, and intensification must be balanced against mucositis, dysphagia, aspiration, nephrotoxicity, ototoxicity, marrow suppression, nutritional deterioration, and treatment interruption.

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) established the central role of chemotherapy administered concomitantly with radiotherapy. Its 2009 update included 93 trials and 17,346 patients, and the later individual patient data update included 107 randomized trials and 19,805 patients. The survival advantage was driven primarily by concomitant chemotherapy, confirming cisplatin-based CRT as the

comparator against which targeted radiosensitizers should be judged [1,2]. Importantly, a targeted agent that is less toxic than cisplatin is not necessarily equivalent to cisplatin, as illustrated by randomized HPV-positive oropharyngeal trials in which radiotherapy plus cetuximab produced inferior tumor control and survival compared with cisplatin [3,4].

EGFR is an attractive therapeutic target because it is commonly expressed or overexpressed in HNSCC and is implicated in aggressive behavior and resistance to ionizing radiation. Nimotuzumab has generated particular interest in India, Cuba, China, and other regions because it combines EGFR blockade with a comparatively favorable dermatologic profile. The central clinical question is no longer whether nimotuzumab has activity but whether the magnitude and certainty of benefit justify its addition to modern CRT, in which patients, and with which chemotherapy backbone.

Methods of the Narrative Review

A literature search was performed for publications available until July 2026 using PubMed/MEDLINE, ClinicalTrials.gov, and the websites of relevant peer-reviewed journals and major oncology meetings. Search terms were combined around "nimotuzumab," "h-R3," "EGFR," "head and neck," "HNSCC," "radiotherapy," "chemoradiotherapy," "cisplatin," "phase II," "phase III," "randomized" and "meta-analysis." Priority was given to randomized trials, trial follow-up reports, systematic reviews, meta-analyses, and major evidence-defining studies of concurrent CRT. References of included articles were reviewed to identify additional studies. Evidence from nasopharyngeal carcinoma was not used to establish conclusions for non-NPC HNSCC because of its distinct epidemiology, biology, and systemic treatment paradigms.

This article is a narrative review rather than a systematic review. No protocol was registered, duplicate screening was undertaken, and formal risk-of-bias scoring was performed. Consequently, effect estimates were reported from the original publications and should be interpreted alongside the limitations of each source.

EGFR Biology and the Rationale for Radiosensitization

EGFR is a transmembrane receptor tyrosine kinase that belongs to the ERBB family and is frequently expressed or overexpressed in HNSCC. Ligand binding promotes receptor dimerization and activates downstream RAS–RAF–MAPK, PI3K–AKT–mTOR, and JAK–STAT signalling pathways, thereby supporting tumor cell proliferation, survival, angiogenesis, invasion, and metastatic progression [5,6]. Ionizing radiation can activate EGFR signalling, promote accelerated tumor cell repopulation, and enhance the repair of radiation-induced DNA damage. Nuclear translocation of EGFR is also associated with the activation of DNA-dependent protein kinase and repair of DNA double-strand breaks. EGFR blockade during fractionated radiotherapy may therefore impair DNA damage repair, reduce tumor cell repopulation, promote apoptosis, and enhance locoregional tumor control [5,6].

Nimotuzumab is a humanized IgG1 monoclonal antibody that targets the extracellular domain of EGFR [7,8]. By inhibiting ligand binding and receptor activation, it suppresses downstream proliferative and survival signalling. In addition, nimotuzumab may engage immune effector mechanisms, including natural killer cell activation, antibody-dependent cellular cytotoxicity, dendritic cell maturation, and expansion of EGFR-specific T-cell responses [23]. In contrast to higher-affinity anti-EGFR antibodies, nimotuzumab has an intermediate monovalent affinity and generally requires bivalent attachment for stable binding. Sustained binding is therefore more likely to occur in tumor cells with moderate-to-high EGFR density, whereas normal tissues with lower receptor density are less likely to retain the antibody. This affinity–avidity model provides a plausible explanation for the relatively low incidence of severe acneiform rash, hypomagnesemia, and infusion reactions reported with nimotuzumab; however, it should not be interpreted as evidence that the antibody is devoid of clinically relevant toxicity [7,8,23].

Clinical Development of Nimotuzumab with Radiotherapy

Early and phase II evidence

Early trials established the feasibility of combining nimotuzumab with radiotherapy alone or with cisplatin. The most influential early randomized evidence was an Indian open-label phase IIb study of patients with inoperable advanced squamous cell carcinoma. Patients were allocated to radiotherapy or chemoradiotherapy cohorts for treatment with or without nimotuzumab. Nimotuzumab was administered weekly during radiation. At six months, the overall response was reported as 100% with nimotuzumab plus CRT versus 70% with CRT alone, and the corresponding figures for nimotuzumab plus radiotherapy and radiotherapy alone were 76% and 37%, respectively. Five-year overall survival was 57% versus 26% for nimotuzumab plus CRT versus CRT (P=0.03), while the radiotherapy-only comparison was not statistically significant [9].

These results provide a durable efficacy signal and support phase III evaluation. Nevertheless, the small sample size, open-label design, multiple treatment cohorts, older radiation techniques, and limited power make the effect size uncertain. This study is best considered hypothesis-generating rather than definitive. Subsequent prospective and real-world series, including early studies of nimotuzumab combined with radiotherapy in

patients with unresectable or inoperable HNSCC, have generally reported encouraging response and survival outcomes with acceptable tolerability [10,11,21,22]. However, their predominantly single-arm designs, small sample sizes, and variable chemotherapy or radiotherapy schedules limit causal inference.

Definitive phase III evidence

Patil et al. conducted a randomized, open-label phase III trial at the Tata Memorial Centre in India involving 536 previously untreated patients with non-metastatic stage III or IV HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx. Patients received curative radiotherapy (66–70 Gy) and weekly cisplatin 30 mg/m², either alone or with weekly nimotuzumab 200 mg. The primary endpoint was progression-free survival (PFS) [12].

The addition of nimotuzumab significantly improved PFS (HR 0.69; 95% confidence interval [CI] 0.53–0.89; P=0.004), locoregional control (HR 0.67; 95% CI 0.50–0.89; P=0.006), and disease-free survival (HR 0.71; 95% CI 0.55–0.92; P=0.008). The initial overall survival analysis showed a non-significant trend (HR 0.84; 95% CI 0.65–1.08; P=0.163). Grade 3–5 adverse events were broadly comparable, although grade ≥3 mucositis was more frequent with nimotuzumab in reports of the trial. These findings demonstrate clinically relevant disease-control benefits but require context: the trial was conducted at one center, used weekly cisplatin 30 mg/m² rather than the globally evidence-rich 100 mg/m² every three weeks schedule, and enrolled a largely HPV-negative population [12].

Patil et al. subsequently reported a prespecified long-term analysis at the 2024 American Society of Clinical Oncology annual meeting [13]. At a median follow-up of 8.86 years (95% CI 8.59-9.16), the 10-year overall survival was 33.5% (95% CI 27.6-39.4) with nimotuzumab-CRT versus 22.5% (95% CI 16.7-28.8) with CRT alone. The difference was statistically significant (HR 0.811; 95% CI 0.664-0.995; P=0.044), corresponding to an absolute 10-year survival gain of 11.0 percentage points. The median overall survival was 3.69 years (95% CI 2.90-4.49) with nimotuzumab-CRT and 2.78 years (95% CI 2.31-3.69) with CRT (log-rank P=0.04). Among patients with HPV-negative oropharyngeal cancer, the median overall survival was 2.48 versus 1.80 years (HR 0.724; 95% CI 0.546-0.959; P=0.02). Late adverse events were recorded in 380 patients and did not differ significantly between the treatment groups. These mature findings convert the non-significant overall survival trend in the original report into a statistically significant long-term benefit and support the hypothesis that improved locoregional control can translate into delayed survival gains. Interpretation nevertheless requires care: only 24 patients were HPV-positive, the subgroup finding is most applicable to HPV-negative disease, late toxicity ascertainment was incomplete, and the long-term results remain available as an abstract rather than a full peer-reviewed article.

Quality of life and treatment burden

In a prespecified quality-of-life analysis, 423 of the 536 phase III participants were evaluable using the EORTC QLQ-C30 and HN35 instruments. Symptoms and functioning worsened during CRT and generally improved afterward. Longitudinal analysis found no significant between-arm differences in global health status or most functional and symptom scales. Thus, the improvement in PFS, locoregional control, and disease-free survival did not appear to be purchased at the cost of sustained quality-of-life deterioration [14]. Missing questionnaires and survivorship effects remain possible sources of bias; however, these data strengthen the tolerability argument.

Postoperative chemoradiotherapy

Definitive and postoperative CRT are distinct clinical settings. The positive Tata Memorial phase III study evaluated definitive treatment, not adjuvant treatment, after resection. A randomized placebo-controlled postoperative phase III program evaluated the addition of nimotuzumab to cisplatin-based CRT in high-risk resected HNSCC. Conference reporting in 2025 indicated no statistically significant improvement in disease-free or overall survival after a median follow-up of approximately five years [15]. Until a full peer-reviewed report clarifies the subgroups, treatment delivery, and biomarker effects, nimotuzumab should not be automatically extrapolated from definitive CRT to routine postoperative intensification.

Recurrent/metastatic disease: Yadav et al- Evidence Outside the curative setting

Yadav et al. reported a prospective, interventional, non-randomized study from the Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, involving 124 patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Patients were divided 1:1 between platinum/taxane-based chemotherapy plus nimotuzumab and chemotherapy alone (62 patients per arm). The addition of nimotuzumab was associated with a higher objective response rate (38.2% versus 19.0%; P=0.023), a higher disease control rate (74.5% versus 43.1%; P=0.0007), and longer median progression-free survival (5.2 versus 3.2 months; P=0.009) [16]. This combination is reported to be active and well tolerated. However, the non-randomized single-center design, potential selection and treatment-allocation bias, chemotherapy-backbone heterogeneity, absence of a mature overall-survival comparison, and pre-immunotherapy treatment context mean that the findings are supportive but not practice-defining.

Meta-analyses and Evidence Synthesis

Two 2024 quantitative reviews consolidated geographically dispersed literature. Guan et al. included seven randomized controlled trials with 1,012 patients with locally advanced squamous head and neck cancers treated with radiotherapy or CRT, with or without nimotuzumab. The pooled analysis favored nimotuzumab for overall survival (HR 0.75; 95% CI 0.62–0.90), PFS (HR 0.69; 95% CI 0.54–0.87), complete response (RR 1.52; 95% CI 1.24–1.86), and objective response (RR 1.32; 95% CI 1.17–1.48) [17]. Zheng and colleagues likewise concluded that nimotuzumab added to radiotherapy or CRT improved response and survival with controllable toxicity [18].

The numerical consistency between the pooled PFS estimate and the large phase III trial is encouraging. Nevertheless, a pooled estimate cannot remove the limitations shared by its components. The trials differed in terms of tumor site, stage, endemic context, radiotherapy technique, concurrent chemotherapy, nimotuzumab exposure, follow-up, and endpoint definitions. Some included nasopharyngeal or mixed head-and-neck populations, and several trials were small-sized. Publication and language biases are plausible. The large Tata Memorial study may have heavily influenced the pooled precision. Accordingly, the meta-analyses raise confidence that the drug is active but do not establish that every CRT-eligible patient benefits or that nimotuzumab should be routinely added to standard thrice-weekly high-dose cisplatin.

Table 1. Principal clinical evidence for nimotuzumab during radiotherapy or chemoradiotherapy in head-and-neck cancer. AE, adverse event; CR, complete response; CRT, chemoradiotherapy; DFS, disease-free survival; HR, hazard ratio; LRC, locoregional control; N-CRT, nimotuzumab plus chemoradiotherapy; NS, not statistically significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, risk ratio; RT, radiotherapy.

Study	Design / population	Treatment comparison	Key efficacy result	Safety / QoL	Main limitation
Reddy et al., 2014 [9]	Randomized open-label phase IIb; inoperable advanced SCCHN; small factorial cohorts	RT or CRT ± weekly nimotuzumab	6-mo ORR: 100% vs 70% for N-CRT vs CRT; 5-y OS: 57% vs 26%	Generally tolerable	Small, older-era, open-label study
Patil et al., 2019 [12]	Randomized open-label phase III; n=536; stage III/IV nonmetastatic HNSCC	RT 66–70 Gy + weekly cisplatin 30 mg/m² ± nimotuzumab 200 mg weekly	PFS HR 0.69; LRC HR 0.67; DFS HR 0.71; initial OS HR 0.84 (NS)	Grade 3–5 AEs broadly similar; more mucositis reported	Single centre; weekly low-dose cisplatin; largely HPV-negative
Menon et al., 2021 [14]	QoL analysis of phase III trial; n=423 evaluable	N-CRT vs CRT	Efficacy as parent trial	No significant longitudinal between-arm QoL difference	Missing QoL data; secondary analysis
Patil et al., 2024 [13]	Long-term ITT analysis of randomized phase III trial; n=536; median follow-up 8.86 y	N-CRT vs CRT	10-y OS 33.5% vs 22.5%; HR 0.811 (95% CI 0.664-0.995), P=0.044; median OS 3.69 vs 2.78 y	Late AEs assessed in 380 patients; no significant between-arm difference	Abstract-level report; single centre; weekly cisplatin 30 mg/m²; only 24 HPV-positive patients
Yadav et al., 2020 [16]	Prospective, interventional, non-randomized, single-centre; R/M SCCHN; n=124	Platinum/taxane chemotherapy + nimotuzumab vs chemotherapy alone (62 per arm)	ORR 38.2% vs 19.0% (P=0.023); DCR 74.5% vs 43.1% (P=0.0007); median PFS 5.2 vs 3.2 mo (P=0.009)	Combination reported active and well tolerated	Non-randomized allocation; single centre; heterogeneous chemotherapy; pre-immunotherapy context

Guan et al., 2024 [17]	Meta-analysis; 7 RCTs; n=1,012	Nimotuzumab + RT/CRT vs RT/CRT	OS HR 0.75; PFS HR 0.69; CR RR 1.52; ORR RR 1.32	Overall manageable	Clinical and geographic heterogeneity
Zheng et al., 2024 [18]	Systematic review/meta-analysis of LA-HNC	Nimotuzumab + RT/CRT vs RT/CRT	Improved survival and response	No clear overall increase in all-grade AEs	Variable study quality and regimens

Safety and Practical Administration

The commonly studied definitive schedule is nimotuzumab 200 mg intravenously once weekly during radiotherapy, generally for six to seven doses, administered alongside weekly cisplatin in the pivotal phase III trial. Premedication and monitoring should follow the approved local product information and institutional protocols. This schedule is evidence-descriptive, not a prescription for an individual patient; renal function, hearing, performance status, nutritional state, aspiration risk, and cisplatin fitness must be assessed separately.

Nimotuzumab itself may cause fever, chills, nausea, asthenia, blood-pressure changes, rash and infusion reactions. Severe acneiform rash is uncommon relative to cetuximab, which is consistent with its binding biology. However, combination therapy retains the toxicities of both radiation and cisplatin. In the pivotal trial, severe mucositis was increased in some analyses, and supportive care remained essential: dental assessment, dietetic input, pain control, hydration, antiemesis, electrolyte monitoring, swallowing rehabilitation, skin/oral care, and early management of infection or aspiration. A favorable antibody toxicity profile must not obscure the substantial acute burden of intensified CRT.

Patient Selection and Biomarkers

An ideal predictive biomarker has not yet been established. EGFR overexpression provides a biological rationale for treatment; however, immunohistochemical EGFR levels have not been prospectively validated as a treatment-selection test for nimotuzumab in HNSCC. Stable binding may require sufficient receptor density; however, a clinically reproducible threshold is lacking. EGFR amplification, ligand expression, downstream pathway activation, and immune microenvironment features warrant further study.

HPV status is critical. The definitive phase III population was predominantly HPV-negative, with only 24 participants being HPV-positive in the long-term analysis. In the HPV-negative oropharyngeal subgroup, the median overall survival improved from 1.80 years with CRT to 2.48 years with nimotuzumab-CRT (HR 0.724; 95% CI 0.546-0.959; P=0.02) [13]. HPV-positive oropharyngeal cancer has distinct biology and a better prognosis, and the very small HPV-positive sample precludes a reliable estimate of the benefit in that population. Evidence from cetuximab de-intensification trials warns against assuming that an EGFR antibody can replace cisplatin [3,4]. Current evidence on nimotuzumab addresses its addition to, not substitution for, cisplatin in fit patients. For cisplatin-ineligible patients, nimotuzumab plus radiotherapy may be considered only in jurisdictions where it is approved and after acknowledging the weaker comparative evidence.

Potential candidates for discussion in a multidisciplinary setting are patients with unresected, high-risk, predominantly HPV-negative LA-HNSCC who are fit for weekly cisplatin and are being treated in jurisdictions where nimotuzumab is approved and accessible to patients. The routine use of these agents after completing CRT as maintenance therapy is unsupported. Routine postoperative addition is also not supported by current randomized reports.

Nimotuzumab in the Contemporary Treatment Landscape

The treatment landscape now includes immune checkpoint inhibitors for recurrent/metastatic HNSCC and perioperative immunotherapy strategies for selected resectable diseases. Trials adding immunotherapy concurrently or sequentially to definitive CRT have produced mixed results, emphasizing that biological rationale alone does not guarantee improved cure rates. Nimotuzumab differs from immune checkpoint blockade by directly targeting EGFR and enhancing local radiosensitivity, which may explain its strongest signal in the locoregional endpoints.

Cetuximab remains the best-known anti-EGFR antibody in HNSCC, but adding cetuximab to cisplatin-RT did not improve outcomes in RTOG 0522 and increased acute toxicity [19]. Panitumumab intensification has also been unsuccessful in randomized studies [20]. Nimotuzumab's favorable phase III signal is therefore notable, but cross-trial comparison is hazardous. Differences in antibody affinity, patient biology, chemotherapy dose, HPV prevalence, and trial conduct may all contribute to this discrepancy.

Limitations of the Current Evidence

 External validity: The most influential definitive trial was conducted at a single high-volume Indian center, used weekly cisplatin 30 mg/m², and enrolled a predominantly HPV-negative population; these features limit generalizability to other populations and cisplatin schedules.

 Comparator uncertainty: weekly cisplatin 30 mg/m² was used; the incremental value over radiotherapy with three-weekly cisplatin 100 mg/m² was unknown.

 Biomarker uncertainty: no validated EGFR expression, genomic, or immune biomarker identifies patients most likely to benefit.

 Heterogeneity: Meta-analyses combine tumor sites, radiotherapy techniques, chemotherapy backbones, and sometimes biologically distinct nasopharyngeal populations.

 Publication maturity: The statistically significant 10-year survival benefit is currently supported by a prespecified long-term meeting abstract rather than a full peer-reviewed article; late toxicity data were available for 380 of 536 randomized patients.

 Setting specificity: The definitive benefit cannot be assumed to apply to postoperative CRT or maintenance after CRT.

 Health economics: cost-effectiveness will vary by country, drug price, competing regimens, and the downstream value of preventing recurrence.

Future Research Priorities

The next generation of trials should be multicenter and stratified by p16/HPV status, primary site, smoking exposure, T/N stage, and planned cisplatin schedule. A contemporary trial should use intensity-modulated radiotherapy with rigorous quality assurance and report cumulative cisplatin dose, radiotherapy interruptions, feeding tube dependence, aspiration, hearing and renal outcomes, patient-reported quality of life, and late swallowing function. Overall survival and locoregional failure should be complemented by competing risk analyses and patterns of distant relapse.

Translational studies should evaluate quantitative EGFR expression, amplification, radiomic phenotypes, circulating tumor DNA clearance, and immune-effector markers. Prospective pharmacoeconomic studies are particularly relevant in resource-constrained settings such as India. Finally, combinations of nimotuzumab with checkpoint inhibition should be studied only in well-designed trials with careful attention to overlapping mucosal toxicity and sequence, rather than being adopted empirically.

Clinical Interpretation

Current evidence supports three practical conclusions. First, cisplatin-based concurrent radiotherapy remains the evidence-based curative benchmark. Second, adding nimotuzumab to weekly cisplatin-RT improves disease control endpoints and produces a statistically significant long-term overall survival benefit in the predominantly HPV-negative definitive treatment population studied: an 11.0-percentage-point absolute improvement in 10-year survival, with no statistically significant increase in reported late adverse events [13]. Third, the evidence is insufficient to use nimotuzumab as routine maintenance after CRT, to replace cisplatin in otherwise fit patients, or to intensify postoperative therapy outside a trial. Treatment decisions should account for local regulatory approval, cost, access, cisplatin fitness, HPV status, and the abstract-level maturity and limited external validity of long-term evidence.

CONCLUSION

Nimotuzumab may therefore be considered as an additional treatment option for carefully selected patients with predominantly HPV-negative, unresected LA-HNSCC who are suitable for cisplatin-based chemoradiotherapy, particularly in jurisdictions where the drug is approved and accessible. Treatment decisions should be made following multidisciplinary discussions. Broader adoption requires full peer-reviewed publication of long-term findings, multicenter validation using contemporary radiotherapy and standard cisplatin schedules, and prospective biomarker-based patient selection.

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