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First in Human Pilot Study of Nimotuzumab with Proton Chemoradiation for Locally Advanced Head and Neck Squamous Cell Carcinoma: Acute Tolerability and Initial Clinical Response

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Abstract

To provide the first clinical assessment of the acute safety, feasibility, and initial efficacy of definitive intensity-modulated proton beam therapy (IMPT) combined with concurrent cisplatin and nimotuzumab for locally advanced head and neck squamous cell carcinoma (HNSCC).

The combination of nimotuzumab and photon radiotherapy is established, but its safety profile with proton beam therapy (PBT) is unknown. The distinct physical (higher entrance dose) and biological (variable RBE) properties of protons could alter the toxicity and efficacy of molecular targeted agents. No prior clinical series has reported on this trimodal regimen.

We retrospectively analyzed eight patients with stage III–IVA or IVC HNSCC. All received definitive IMPT (median dose 70 Gy (RBE)), with six receiving concurrent cisplatin and two (cisplatin-ineligible) receiving PBT plus nimotuzumab only. Acute toxicities (CTCAE v5.0) and 6-month tumor response (RECIST 1.1) were evaluated.

The cohort (median age 49.5 years) predominantly had nasopharyngeal primaries (5/8). Acute grade ≥3 toxicities included hematologic events (5/8, 62.5%), mucositis (4/8, 50%), and dermatitis (3/8, 37.5%). No unexpected synergistic toxicity was observed. At 6 months, all eight patients (100%) achieved in-field disease control (six partial responses, one stable disease). One patient with stable local disease experienced distant progression. In this first reported cohort, the combination of IMPT, nimotuzumab, and cisplatin (where eligible) was feasible and demonstrated a manageable acute toxicity profile comparable to photon-based benchmarks. These initial safety and efficacy data support the rationale for prospective multicenter trials to validate long-term outcomes.

Introduction

Head and neck tumors are a collective term for neoplasms arising in anatomical regions such as the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, and salivary glands. These areas are densely packed with structures responsible for essential functions such as swallowing, phonation, and respiration, making the balance between tumor control and functional preservation a paramount challenge in treatment [1, 2]. Head and neck squamous cell carcinoma (HNSCC) is the most common histological type, accounting for approximately 90% of head and neck malignancies [3]. For patients with locally advanced (stage III-IV) disease, concurrent cisplatin-based chemoradiotherapy (CCRT) delivered with photon-based intensity-modulated radiotherapy (IMRT) has been established as the standard of care, significantly improving survival compared to radiotherapy alone [4, 5]. However, this benefit comes at the cost of substantial acute toxicity including severe mucositis, dermatitis, and dysphagia and significant long-term functional impairments [6].

Intensity-modulated Proton beam therapy (IMPT) offers a potential advance in treatment precision. By exploiting the physical properties of the Bragg peak, PBT can deliver a maximal radiation dose to the tumor while significantly reducing the exit dose to deep-seated organs at risk (OARs). Dosimetric studies consistently demonstrate that PBT can spare OARs such as the contralateral parotid gland, swallowing muscles, and cochlea compared to even the most advanced photon-based IMRT. However, this physical precision introduces a specific clinical consideration: the higher entrance dose characteristic of PBT is associated with an increased incidence of clinically significant radiation dermatitis.

Concurrently, molecular targeted agents have been integrated into treatment paradigms to improve efficacy. Nimotuzumab is a humanized monoclonal antibody that targets the epidermal growth factor receptor (EGFR), a pathway ubiquitously overexpressed and linked to poor prognosis in HNSCC. Crucially, nimotuzumab has a distinct pharmacologic profile. Due to its intermediate binding affinity and bivalent binding requirement, it preferentially targets tumor cells with high EGFR density, leading to a markedly lower incidence of severe skin rash a dose-limiting toxicity of other EGFR inhibitors like cetuximab. Its efficacy as a radiosensitizer combined with photon-based CCRT is established in several countries, including China, Japan where it is approved for HNSCC.

Despite these parallel advances, a critical knowledge gap exists. While the combination of nimotuzumab with photon radiotherapy is well-documented, there are no prior clinical reports on its combination with proton beam therapy. This gap is scientifically significant. The distinct biological properties of protons, including variable relative biological effectiveness (RBE) and the potential for more complex, less repairable DNA damage, mean that the safety and efficacy profile of a drug-radiation combination validated with photons cannot be directly extrapolated to protons. Therefore, the combination of "proton therapy + HNSCC + molecular targeted drug" remains virtually unexplored in clinical radiation oncology.

The present study was designed to address this gap directly. This first-in-human evaluation aimed to assess the acute safety, feasibility, and initial treatment response of definitive PBT combined with nimotuzumab, with or without cisplatin, in patients with locally advanced HNSCC. By evaluating these short-term endpoints, this pilot study provides the necessary foundational data on acute-phase safety and tolerability required to justify and inform the design of future prospective, multicenter trials to evaluate long-term efficacy and functional outcomes.

Methods and Materials

Study Design and Patient Characteristics

This was a retrospective, single-institution pilot study analyzing consecutive patients with HNSCC treated with PBT combined with nimotuzumab ± cisplatin. The institutional review board approved the study; written informed consent was obtained from all participants for the use of their clinical data.

Inclusion criteria were: histologically confirmed HNSCC; American Joint Committee on Cancer (AJCC) 8th edition stage III–IVA or stage IVC, or recurrent disease referred for definitive PBT; Eastern Cooperative Oncology Group (ECOG) performance status 0–2 at baseline. Exclusion criteria were: prior radiotherapy to the head and neck region, prior anti-EGFR monoclonal antibody therapy, insufficient documentation to permit dosimetric or toxicity analysis, or follow-up < 180 days from the start of radiotherapy.

Table 1: Patient demographics and baseline characteristics[13]

ID	Age	Primary site	T stage	N stage	M stage	Stage (UICC 8th)	HPV/p16 Status	ECOG PS	Baseline eGFR	Comorbidities	Prior Surgery	Staging Modality
P 01	50-59	Oropharynx	T4a	N2c	M0	IVA	Negative	1	Normal (WNL Cr)	Hypothyroidism, Asthma, s/p Cholecystectomy	No	PET CT, CT, MRI, Biopsy
P 02	80-89	Hypopharynx	T4a	N2c	M0	IVA	Not Tested	2	Normal (WNL Cr)	History of Brain Trauma	No	CT, MRI, Biopsy
P 03	50-59	Nasopharynx	T4	N0	M0	IVA	EBV DNA Negative	2	90 mL/min/1.73m²	Hypertension	Yes (Endoscopic Skull Base)	(MRI, Post op Pathology
P 04	40-49	Nasopharynx	T4	N2	M1	IVC	EBER+ (EBV+)	2	90 mL/min/1.73m²	None Documented	No	PET CT, MRI
P 05	30-39	Nasopharynx	T3	N2	M0	III	EBV DNA+	0	Normal (WNL Cr)	Hypertension	No	CT, MRI, Biopsy, PET/CT
P 06	50-59	Nasopharynx (Recurrent)	rT3	N0	M0	III	EBER+ (EBV+)	0	Normal (WNL Cr)	Hypertension	No	MRI, Biopsy, PET/CT
P 07	10-19	Nasopharynx	T3	N2	M0	III	EBV DNA+	0	Normal (WNL Cr)	None	No	CT, MRI, Biopsy, PET/CT
P 08	20-29	Left Orbit / Skull Base	N/A	N/A	N/A	IVA	EBV Negative	1	Normal (WNL Cr)	Hypertension (chemo induced)	Yes (Left Orbital Resection)	PET/CT, MRI, Biopsy

[13] Abbreviations: HNSCC, head and neck squamous cell carcinoma; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; WNL, within normal limits; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Principles of Proton Beam Therapy

Patients were immobilized with custom thermoplastic head and shoulder masks. Planning CT scans (3 mm slice thickness) were fused with MRI and/or PET/CT for target delineation. Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were contoured per institutional protocols consistent with international consensus guidelines [15]. Plans were generated using pencil beam scanning with robust optimization (±3 mm setup, ±3.5% range uncertainty). The standard curative prescription was median 70 Gy (RBE) delivered in 33--36 fractions (RBE = 1.1). Organ-at-risk (OAR) constraints followed institutional standards and QUANTEC guidance where applicable.

Principles of Systemic Therapy (Nimotuzumab and Cisplatin)

The anticipated systemic therapy plan was weekly nimotuzumab (100 mg or 200 mg per institutional practice) concurrent with radiotherapy. For cisplatin-eligible patients, the intended regimen was weekly cisplatin (30–40 mg/m²) or three-weekly high-dose cisplatin (100 mg/m² on days 1, 22, and 43), based on patient performance status, renal function, and comorbidities.

Treatment Response and Toxicity Assessment

Acute toxicities (during radiotherapy and up to 90 days post-treatment) were graded using CTCAE v5.0 [16]. Tumor response at 6 months (± 4 weeks) after treatment completion was assessed using RECIST 1.1 criteria [17].

Statistical Analysis

Given the small, descriptive nature of this pilot cohort, no formal hypothesis testing was performed. Continuous variables are presented as medians with ranges, and categorical variables are summarized as counts and percentages.

Results

Eight consecutive patients were included. Median age was 49.5 years (range 13 80); 5 male / 3 female. Primary sites: nasopharynx (4), recurrent nasopharynx (1), oropharynx (1), hypopharynx (1), orbit/skull base (1). Stage distribution (AJCC8, as recorded): IVA (n = 3); IVC (n = 1); III (n = 2); III (recurrent) (n = 1). Baseline ECOG ranged from 0 to 2(Table 1).

All patients initiated definitive PBT. The delivered treatment details are summarized in Table 2. Six patients received concurrent cisplatin (range 1–5 documented cycles); two received no cisplatin. Nimotuzumab was administered to all patients (documented cycles 3 to ≥6). No nimotuzumab discontinuations due to acute toxicity were recorded.

Table 2: Treatment delivery details[14]

Patient ID	RT Fractions (Delivered/Planned)	Nimotuzumab Doses	Cisplatin (cycles, regimen, notes)	Feeding Tube (Y/N)
P 01	30/30	5 (200 mg weekly)	0 (Poor general condition)	N
P 02	33/33	3 (200 mg weekly)	1 (Weekly x1)	N (Refused)
P 03	36/36	6 (100 mg weekly)	3 (40mg d1 3; then weekly)	N
P 04	Multi-site	5 (100 mg weekly)	0 (Received Nab Paclitaxel instead)	N (Refused)
P 05	33/33	≥3 doses	2 cycles (50mg d1 3)	N
P 06	30/30	≥5 doses (200 mg weekly)	~5 cycles (40mg weekly)	N
P 07	35/35	≥4 doses (100 mg)	2 cycles (concurrent with Paclitaxel)	N (IV nutrition)
P 08	33/33	Multiple (100 mg weekly)	~5 cycles (40 50mg weekly)	N

[14 Abbreviations: RT, radiotherapy; Gy, Gray; RBE, relative biological effectiveness.

Cohort-wide dosimetric analysis confirmed PBT's ability to meet strict OAR constraints. The median maximum dose (Dmax) to the brainstem was 50.9 Gy (RBE) (range, 31.9–60.4), and the median spinal cord Dmax was 37.7 Gy (RBE) (range, 6.2–44.6). Representative axial and sagittal dose distributions for two nasopharynx cases are shown in Figure 1.

(A-B) P03 (nasopharynx): axial (A) and sagittal (B) views demonstrate conformal high-dose coverage of the primary target with steep posterior dose fall-off limiting exposure to the brainstem and spinal cord, and relative sparing of the bilateral parotids. (C-D) P05 (nasopharynx): axial (C) and sagittal (D) views show similar target coverage with posterior fall-off and lateral sparing across the parotids. Isodose levels are shown as exported from the clinical plan (e.g., high-dose ≈ 70 Gy [RBE], intermediate ≈ 50 Gy [RBE], low ≈ 30 Gy [RBE]).

Grade ≥3 hematologic events occurred in 5/8 patients (62.5%): neutropenia (n=4), anemia (n=3), and lymphopenia (n=2). Grade 3 mucositis was observed in 4/8 patients (50%), and Grade 3 dermatitis in 3/8 patients (37.5%). No treatment-related deaths occurred within the acute 90-day window. Acute toxicities are detailed in Table 3.

Table 3: Acute toxicities (highest grade per patient, CTCAE v5.0).[15]

Patient ID	Dermatitis	Mucositis	Dysphagia / Odynophagia	Pain	Hematologic (Highest Grade)	Other Significant Toxicities
P 01	Grade 1	Grade 2	Grade 3	Grade 2 (Oropharyngeal)	Gr2 Neutropenia, Gr2 Anemia	Gr2 Aspiration Pneumonia, Gr2 Hypoalbuminemia
P 02	Grade 3	Grade 3	Grade 3 (Baseline)	Grade 2 (Throat)	Gr1 Anemia	Gr1 Hypokalemia, Gr2 Dyspnea
P 03	Grade 3	Grade 2	Grade 2	Grade 3 (Headache)	Gr3 Neutropenia, Gr2 Anemia	Gr1 Hyponatremia, Gr1 Transaminitis
P 04	Grade 2	Grade 3	Grade 3 (Baseline)	Grade 3	Gr3 Neutropenia, Gr3 Anemia	Gr3 Anorexia, Gr1 Hyponatremia
P 05	Grade 2	Grade 2	Grade 2 (Implied)	Grade 2 (Nausea/Vomiting)	Gr3 Neutropenia, Gr3 Hyponatremia (Na 120.7)	
P 06	Grade 1	Grade 3	Not Explicitly Graded		Gr2 Cystitis (Asymptomatic)	Gr1 CSF Leak (suspected, resolved)
P 07	Grade 3	Grade 3	Grade 3 (Secondary)	Grade 2 (Neck), Gr2 (Rash)	Gr3 Lymphopenia, Gr1 Anemia	Gr2 Allergic Rash (Urticaria)
P 08	Grade 1	Grade 1	≤ Grade 1	Grade 2 (Nausea)	Gr3 Lymphopenia, Gr1 Thrombocytopenia	Gr2 Transaminitis (ALT 99 U/L, drug related)

[15] Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; Gr, Grade.

At the 6-month RECIST 1.1 assessment, six patients (75%) achieved a partial response, one patient (12.5%) had stable disease, and one patient (12.5%) had progressive disease due to distant metastasis. No in-field local failures were observed during this follow-up interval.

Discussion

The technological evolution of radiotherapy for HNSCC from 3D conformal radiotherapy (3DCRT) to intensity-modulated radiotherapy (IMRT) and now to proton beam therapy (PBT) has been fundamentally driven by the goal of enhancing dose conformity to the tumor while sparing adjacent organs at risk (OARs). IMRT represented a major advance over 3DCRT, using dynamic multileaf collimators to sculpt dose distributions and better protect critical structures. PBT represents the next logical step in this progression, exploiting the unique physical property of the Bragg peak. This allows protons to deposit their maximum energy at a precisely defined tissue depth, with virtually no exit dose, thereby offering the potential for superior sparing of OARs involved in acute toxicity, such as the swallowing musculature and contralateral salivary glands, compared to even advanced photon-based IMRT [6, 21].

However, the transition from photons to protons is not merely a physical one; it introduces a critical biological difference. While clinical practice typically applies a constant relative biological effectiveness (RBE) of 1.1, the actual RBE of protons is variable and increases with linear energy transfer (LET), particularly near the distal edge of the Bragg peak [12]. This higher LET results in a greater proportion of complex, clustered DNA double-strand breaks that are less efficiently repaired by cellular mechanisms than the damage patterns induced by conventional photon radiation [16]. This key biological difference the capacity of protons to induce more severe and less repairable DNA damage creates a pivotal uncertainty. It fundamentally underscores why safety and efficacy data from photon-based treatment regimens cannot be directly extrapolated to proton therapy. This is especially relevant when proton therapy is combined with molecular targeted agents like nimotuzumab, which are designed to inhibit DNA damage repair pathways such as those mediated by EGFR [16]. Our study was therefore designed to directly address this unanswered translational question, providing the first clinical safety assessment specifically for the proton-nimotuzumab combination.This is, to our knowledge, the first case series to evaluate the acute-phase safety and initial efficacy of proton beam therapy (PBT) combined with cisplatin and nimotuzumab for locally advanced HNSCC. While the safety of cisplatin plus nimotuzumab with photon-based radiotherapy has been reported, its safety profile with PBT remains unconfirmed. Given the distinct physical and biological differences between proton and photon radiation particularly the higher linear energy transfer (LET) and more complex DNA damage induced by protons such evaluation was warranted. Our results showed that acute adverse events were comparable between the PBT and photon therapy groups, with a trend toward favorable initial response in the PBT cohort, demonstrating the regimen's feasibility and preliminary safety.

Comparison to Photon IMRT Outcomes

For context, Patil et al. (2019) reported toxicity rates in a cohort of locally advanced HNSCC treated with IMRT (70 Gy/35 fx) plus weekly cisplatin and nimotuzumab [27]. They observed Grade ≥3 oral mucositis in 55.8% and Grade ≥3 dermatitis in 29.2% of patients. In contrast, our series had 50% Grade 3 mucositis and 37.5% Grade 3 dermatitis. This indicates that, despite the theoretical concern that PBT's higher entrance dose [18, 23] and variable RBE [12, 16] could exacerbate skin and mucosal toxicity when combined with an EGFR inhibitor, the use of nimotuzumab with its intrinsically milder dermatologic profile appears to mitigate this risk within a PBT context. This provides initial clinical evidence for the biological feasibility of this combination, aligning with the hypothesis that PBT's deep tissue sparing and nimotuzumab favorable toxicity can synergize to maintain efficacy while managing side effects. Although cross-study comparisons are imperfect, this suggests that using PBT with nimotuzumab did not increase, and may have reduced, acute mucocutaneous toxicity compared to photon-based regimens.

Role of CCRT and EGFR-Targeted Agents

Even with optimal CCRT, outcomes for many patients are suboptimal, motivating integration of molecularly targeted therapies. In HNSCC, overexpression of EGFR is ubiquitous and linked to aggressive disease. The pivotal Phase III trial by Bonner et al. (2006) showed that adding the anti-EGFR monoclonal antibody cetuximab to RT significantly improved loco regional control and overall survival versus RT alone [8]. Long-term follow-up confirmed that cetuximab+RT reduced mortality [8]. However, cetuximab's clinical use has been limited by dermatologic toxicity: treatment-related acneiform rash is common, with Grade ≥3 rash reported in up to ~17% of patients [37]. These skin toxicities can impair quality of life and even force treatment interruptions.

Nimotuzumab is a humanized anti-EGFR antibody with intermediate binding affinity, developed to preserve anti-tumor efficacy while reducing cutaneous side effects. It is approved for HNSCC in many countries[6]. In contrast to cetuximab, nimotuzumab bivalent binding requirement means it preferentially targets tumor cells with high EGFR expression, sparing normal skin [7]. Retrospective and randomized studies have shown that adding nimotuzumab to chemo radiation can improve outcomes. For example, a recent large propensity-matched cohort in China reported that weekly nimotuzumab added to IMRT-based CCRT significantly improved 3-year OS and PFS, with only 0.2% of patients experiencing severe nimotuzumab-related adverse events [37]. Importantly, these studies consistently note very low rates of severe rash [37]. Taken together, nimotuzumab appears to retain the radio sensitizing benefit of EGFR inhibition while markedly mitigating dermatologic toxicity relative to cetuximab.

Proton-Specific Biological Considerations and Nimotuzumab

The primary rationale for this study rested on the unproven assumption that the safety of a drug-radiotherapy combination is immutable to the type of radiation used. Protons, with their increased LET and potential for elevated RBE in certain regions, can induce more complex clustered DNA damage than photons [12, 16]. EGFR is intimately involved in DNA damage repair signaling pathways; upon activation by radiation-induced damage, EGFR translocates to the nucleus and facilitates repair processes such as non-homologous end joining (NHEJ) and homologous recombination (HR) by recruiting key DNA repair proteins like DNA-PKcs [16]. Inhibition of EGFR can therefore impair these repair mechanisms, potentially sensitizing cells to radiation.

It is plausible that the enhanced, less repairable DNA damage from protons could be synergistically potentiated by EGFR inhibition, potentially leading not only to improved tumor control but also to an increased risk of in-field or cutaneous toxicity. Our observation that the regimen was deliverable without unexpected severe toxicities is thus reassuring. The absence of a dramatic increase in mucositis or dermatitis suggests that the theoretically anticipated synergistic toxicity may not be clinically significant when nimotuzumab is combined with proton therapy. This finding is distinct from what might be expected with cetuximab, which has a higher rate of severe skin reactions [8, 37]. Our study therefore provides foundational safety data specifically for the proton-nimotuzumab combination, which cannot be directly inferred from photon trials.

Current Study: PBT with Nimotuzumab (± Cisplatin)

Against this background, we conducted a first-in-human series of PBT combined with nimotuzumab, with or without concurrent cisplatin, in locally advanced HNSCC. This retrospective case series included eight patients treated with a median dose of 70 Gy (RBE) over 33–35 fractions. All patients received weekly nimotuzumab, and six of eight also received concurrent cisplatin. All patients completed radiotherapy and the intended number of nimotuzumab cycles, demonstrating feasibility.

We hypothesized that PBT's deep-tissue sparing could reduce mucosal and salivary toxicity, while nimotuzumab mild dermatologic profile might offset the higher skin dose from protons, which is associated with an increased likelihood of Grade ≥3 radiation dermatitis (reported in 25-35% of patients in PBT series) compared to IMRT [10, 24, 25]. Preliminary response assessment at 6 months showed in-field disease control in 8 of 8 patients (100%; six partial responses, one stable disease), consistent with expected CCRT outcomes. Notably, 5 of 8 patients (62.5%) experienced Grade ≥3 hematologic toxicity, reflecting the intensity of platinum chemotherapy; despite this, no treatment interruptions occurred, and all patients recovered hematologically and completed therapy. Acute mucositis and dermatitis were each limited to Grade 3.

Toxicity and Safety Profile

We provide detailed OAR dosimetry to contextualize safety. The median maximum dose to the brainstem was 50.9 Gy (RBE) and to the spinal cord 37.7 Gy (RBE). Only one patient (with a base of skull tumor) exceeded the conventional brainstem constraint (Dmax 60.4 Gy (RBE)), yet no acute neurotoxicity occurred. While many PBT series do not report such granular dose data, transparent dose reporting is important for quality assurance. Our plans achieved excellent sparing of deep OARs, consistent with prior PBT planning studies.

Overall, the combination of PBT with nimotuzumab ± cisplatin was well tolerated. All patients completed planned therapy without delay or discontinuation. Apart from expected hematologic effects of cisplatin (62.5% Grade ≥3), we observed no unexpected safety signals. Importantly, there were no cases of Grade 4 mucositis or dermatitis, and any grade 5 events or treatment-related deaths. This favorable acute toxicity profile aligns with preclinical and clinical data: nimotuzumab is generally well tolerated, and our series did not reveal any synergistic toxicity beyond that expected from chemo radiation.

That said, the unique biology of protons demands vigilance. As noted by Durante and Loeffler, protons can exhibit higher LET near the distal end of the beam, which could theoretically amplify the effects of DNA-targeting agents like nimotuzumab [12]. While our small cohort showed no alarming safety signals, longer follow-up is needed to monitor for late effects. Notably, we did not see a clear excess of mucosal or skin toxicity from the EGFR inhibitor.

Implications and Future Directions

This study has several important limitations. The sample size is very small (n=8) and the design is retrospective, which limits statistical power and introduces selection bias. Furthermore, follow-up was short, precluding any conclusions about disease control durability or late toxicity. Comparisons to the Patil et al. photon cohort are indirect and hypothesis-generating at best, given differences in stage, systemic therapy, and supportive care [27]. Finally, our findings may not be generalizable until validated in larger populations.

Despite these limitations, this pilot study establishes the feasibility of combining PBT with nimotuzumab (and concurrent cisplatin when possible) in locally advanced HNSCC. The regimen was deliverable and yielded encouraging short-term responses with a manageable acute toxicity profile. Prospective studies are now needed to confirm these observations. Future trials should ideally be multi-institutional and randomized, with standardized chemotherapy schedules and stratification for HPV/p16 status. Longer follow-up is essential to assess late side effects, loco regional control, and survival. Incorporation of patient-reported outcomes and quality of life measures will be critical to determine whether PBT's dosimetric advantages translate into meaningful clinical benefit.

Our preliminary data suggest that proton therapy can be safely combined with an EGFR antibody without exacerbating acute mucosal or skin toxicity. The results align with theoretical dosimetric advantages of protons and the known safety of nimotuzumab. This first clinical experience supports further exploration of proton-based chemo radiation with molecular targeted agents in HNSCC. If validated, this approach could refine treatment paradigms by improving the therapeutic ratio in locally advanced head and neck cancer.

Conclusion

This first in human retrospective case series demonstrates that proton beam therapy (PBT) combined with nimotuzumab, with or without concurrent cisplatin, is both feasible and associated with a manageable acute toxicity profile in patients with locally advanced or recurrent HNSCC. All patients completed planned PBT and nimotuzumab, and early disease control at six months was encouraging (100% in field control). Importantly, the rates of grade 3 mucositis (50%) and dermatitis (37.5%) were comparable to or lower than those reported in photon IMRT cohorts with nimotuzumab and cisplatin [27], providing the first clinical evidence that the distinct biological properties of protons do not exacerbate the toxicity of this EGFR inhibitor. This suggests that the dosimetric advantages of PBT and the favorable toxicity profile of nimotuzumab may act synergistically.

In summary, this study provides the first clinical evidence that the combination of proton beam therapy and nimotuzumab is feasible and does not result in exacerbated acute toxicity, despite the distinct biological properties of proton radiation. This justifies further prospective investigation to determine if this unique combination can improve the therapeutic ratio in locally advanced HNSCC.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants. The study protocol was reviewed and approved by the Institutional Review Board of Hebei Yizhou Cancer Hospital, Hebei, PR China. Approval number/date were not assigned under institutional policy; documentation is available from the corresponding author upon request.

Consent for publication

Written informed consent was obtained from all participants (legal guardian in the case of the adolescent patient) for the publication of their de-identified clinical details. This study does not contain any individual person's identifiable data, images, or personal information.

Availability of data and materials

De-identified data underlying the findings are available from the corresponding author upon reasonable request and subject to institutional approvals.

Competing interests

The authors declare that they have no competing interests.

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Figures

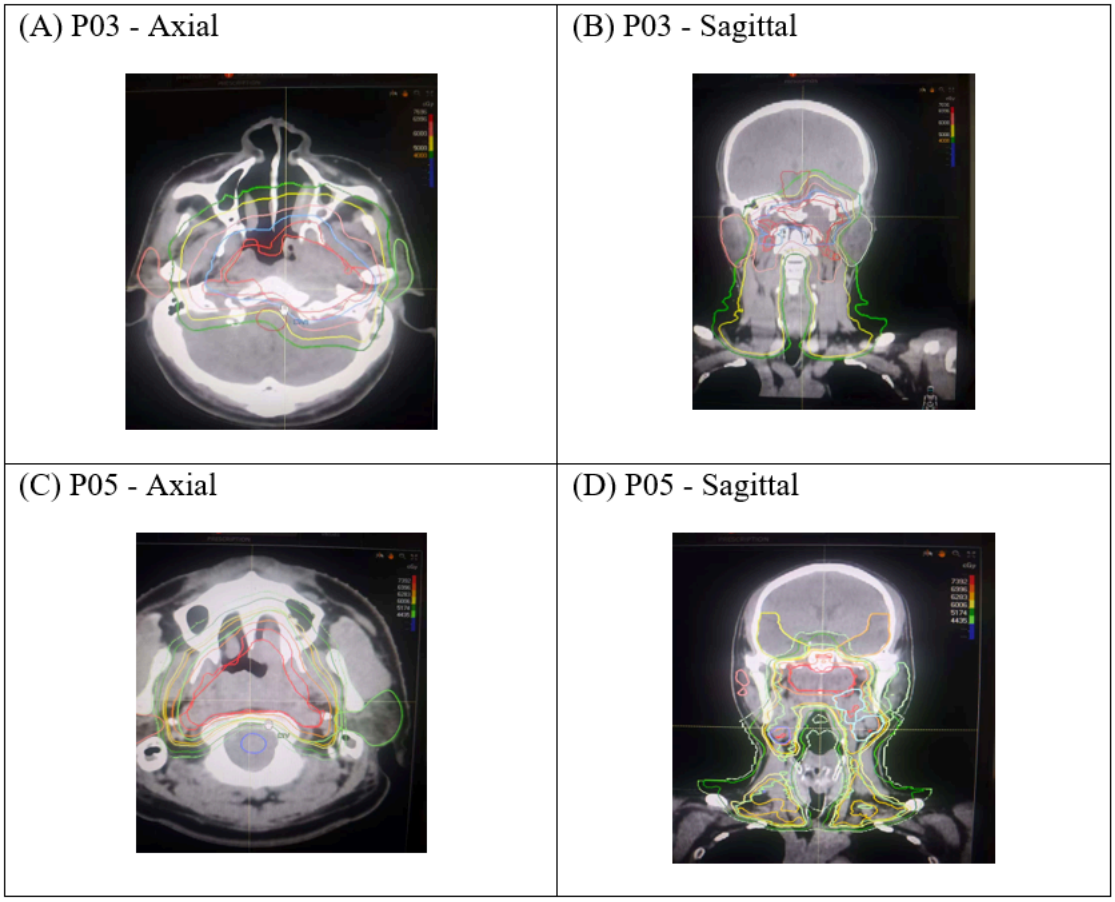


Figure 1

Dose distributions of two HNSCC cases.

(A-B) P03 (nasopharynx): axial (A) and sagittal (B) views demonstrate conformal high-dose coverage of the primary target with steep posterior dose fall-off limiting exposure to the brainstem and spinal cord, and relative sparing of the bilateral parotids. (C-D) P05 (nasopharynx): axial (C) and sagittal (D) views show similar target coverage with posterior fall-off and lateral sparing across the parotids. Isodose levels are shown as exported from the clinical plan (e.g., high-dose ≈ 70 Gy [RBE], intermediate ≈ 50 Gy [RBE], low ≈ 30 Gy [RBE]).