Med. Psychol. Health Res. J. **(2027),** Volume 3, Issue 1, 142-152

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: https://doi.org/10.5281/zenodo.23863332

Pregabalin for Radiation-Induced Neuropathic Pain in Head and Neck Cancer: A Randomized Controlled Trial

Seyed Taher Mousavi [1], Ali Reza Nasseri[2*]

[1]Assistant Professor of Neurosurgery, Department of Neurosurgery, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Assistant Professor of Radiotherapy, Department of Radiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info
Received: 23.06.2026
Accepted: 31.10.2026
Available Online: 31.10.2026
Checked for Plagiarism: Yes

Keywords:
Pregabalin; Radiation-Induced Neuropathic Pain; Head and Neck Cancer; Opioid-Sparing Effect

A B S T R A C T

Introduction: Radiotherapy for head and neck cancer frequently induces severe neuropathic pain, significantly impairing patient quality of life and adherence to treatment. Despite this high clinical burden, effective prophylactic interventions remain largely unestablished. Therefore, this randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy of prophylactic pregabalin in preventing radiation-induced neuropathic pain.

Material and methods: This randomized, double-blind clinical trial evaluated 60 patients with head and neck cancer divided into two equal groups of 30 using convenience sampling and the Cochran formula. Conducted at Shahid Madani Hospital, the procedure involved administering prophylactic pregabalin or a comparator during radiotherapy. Serial assessments monitored neuropathic pain trajectories, rescue analgesic consumption, and safety profiles throughout the intervention and follow-up periods.

Results: Prophylactic pregabalin significantly attenuated radiation-induced neuropathic pain progression (week 6 DN4: 4.1 plus minus 1.0 vs 7.1 plus minus 1.2, P<0.001) and reduced cumulative opioid consumption (285.4 plus minus 48.2 mg vs 542.8 plus minus 76.5 mg, P<0.001) across both sexes without significant between-sex divergence.

Conclusion: Prophylactic pregabalin administration effectively mitigates radiotherapy-induced neuropathic pain and substantially reduces opioid dependency in head and neck cancer patients. Demonstrating robust sex-independent efficacy and manageable tolerability, pregabalin serves as a valuable adjunct in combined-modality oncologic care, optimizing patient quality of life during aggressive radiation therapy.

Introduction

Head and neck malignancies represent a substantial global oncological burden, consistently ranking among the leading causes of cancer-related morbidity and mortality worldwide. The anatomical complexity of the upper aerodigestive tract, coupled with its dense concentration of vital vascular, glandular, and sensorimotor neural structures, renders this region uniquely vulnerable to both primary neoplastic invasion and the debilitating toxicities of definitive therapeutic interventions.

For the majority of patients presenting with locally advanced disease, high-dose radiotherapy, delivered either as an organ-preserving primary definitive modality or as adjuvant therapy following extensive surgical resection, forms the bedrock of curative-intent management protocols [1]. Despite transformative technological advancements in radiation delivery, including intensity-modulated radiotherapy and volumetric modulated arc therapy designed to conform closely to target volumes and spare adjacent healthy organs at risk, normal tissue collateral damage remains an almost inevitable

Corresponding Author: **Ali Reza Nasseri (AR_naseri@gmail.com - ORCID: 0000-0001-9714-2379)*
1 Email: taher_musavi@gmail.com - ORCID: 0000-0003-2609-6066)

clinical consequence. Ionizing radiation does not distinguish completely between malignant clonogens and adjacent healthy cellular architecture within the high-dose treatment field. Consequently, ionizing radiation triggers an immediate cascade of cellular injury, microvascular disruption, and acute inflammatory signaling across the mucosa, connective tissues, and peripheral nerve plexuses. Among the acute toxicities experienced by patients undergoing head and neck irradiation, radiation-induced pain represents one of the most pervasive, severe, and clinically intractable challenges encountered by treating oncologists [2].

The pathophysiological continuum of pain within this patient population is predominantly dual in nature, presenting as a complex, mixed nociceptive-neuropathic syndrome. In the initial phases of radiation treatment, extensive mucosal epithelial denudation and ulceration precipitate severe radiation-induced oral and pharyngeal mucositis, generating intense somatic nociceptive pain. However, as cumulative radiation dosage steadily mounts, ionizing radiation induces direct mechanical compression and sustained metabolic insult to peripheral nerve fibers. This injury manifests as persistent perineural edema, microvascular ischemia secondary to endothelial obliteration of the vasa nervorum, and progressive intraneural and perineural soft tissue fibrosis. These pathological events collectively generate a distinct neuropathic pain state that frequently escapes clinical detection and defies conventional analgesic strategies [3].

Radiation-induced neuropathic pain is clinically characterized by distressing sensory aberrations, including persistent burning sensations, electric shock-like shooting paroxysms, lancinating sensations, hyperalgesia, and severe mechanical or thermal allodynia. These symptoms affect anatomical distributions corresponding to the trigeminal, glossopharyngeal, and cervical sensory dermatomes. Unlike self-limiting nociceptive mucosal insults that resolve following re-epithelialization after treatment completion, neuropathic injury reflects sustained structural and functional damage to primary afferent neurons. As radiation progresses, the continuous barrage of peripheral nociceptive and neuropathic inputs induces central neuroplastic adaptations, including hyperexcitability of wide dynamic range neurons within the dorsal horn and brainstem sensory nuclei, firmly entrenching the pain in a self-sustaining central sensitization state [4].

The clinical ramifications of inadequately controlled neuropathic pain during head and neck radiotherapy are exceptionally severe and far-reaching. Intractable orofacial and pharyngeal pain directly impedes normal mastication, deglutition, and articulate phonation. The resulting dysphagia precipitates profound protein-calorie malnutrition, rapid weight loss, and chronic dehydration, often necessitating urgent enteral access through nasogastric or percutaneous endoscopic gastrostomy tube placement. Crucially, severe pain crises represent one of the primary drivers of unanticipated radiotherapy interruptions, dose reductions, and treatment prolongation. In definitive cancer therapy, unintended radiation treatment breaks are known to compromise locoregional tumor control, accelerate accelerated tumor repopulation, and directly diminish overall survival rates [5].

From an epidemiological and humanistic standpoint, this refractory pain syndrome exerts a devastating toll on emotional well-being and health-related quality of life. Patients frequently develop secondary psychological sequelae, including severe clinical depression, generalized anxiety, sleep architecture disruption, and debilitating demoralization. Even after successful cancer eradication, persistent post-radiation neuropathic pain may endure for months or years as a permanent chronic disability. This survivorship dilemma highlights the need for oncology teams to recognize that pain management during radiotherapy is not merely supportive comfort care, but an integral determinant of curative therapeutic delivery and post-treatment survivorship [6].

Historically, pharmacotherapeutic approaches to radiation-induced pain have relied predominantly on the classical World Health Organization analgesic stepladder, leaning heavily on escalating doses of nonsteroidal anti-inflammatory drugs, acetaminophen, and systemic opioids. While systemic opioids remain indispensable for attenuating acute inflammatory and somatic nociceptive pain associated with mucosal disruption, their therapeutic efficacy in suppressing neuropathic pain components is notoriously modest and often clinically disappointing. Neuropathic pain pathways involve aberrant electrical firing and neuroplastic maladaptation's that do not readily respond to standard mu-opioid receptor agonism alone [7].

Furthermore, reliance on high-dose opioid regimens exposes fragile head and neck cancer patients to a spectrum of dose-limiting toxicities. Constipation, extreme somnolence, cognitive blunting, respiratory depression, and severe opioid-induced nausea exacerbate pre-existing nutritional and physical decline. Moreover, prolonged opioid administration introduces significant risks of pharmacological tolerance, physical dependence, and paradoxical opioid-induced hyperalgesia, wherein the analgesic itself lowers sensory thresholds and exacerbates overall pain sensitivity. These clinical realities emphasize that conventional reactive opioid monotherapy fails to address the underlying neurobiological drivers of radiation-induced nerve dysfunction [8].

Given these therapeutic limitations, contemporary international neuropathic pain guidelines advocate for the use of adjuvant neuromodulator agents, among which the gabapentin class holds a prominent position. Gabapentin act as selective, high-affinity ligands for the alpha-2-delta auxiliary subunit of voltage-gated calcium channels localized on presynaptic neuronal terminals within the central and peripheral nervous systems. By binding to these specific sub-units, agents such as pregabalin suppress voltage-dependent calcium influx into hyperactive nerve terminals. This downregulates the exocytotic release of key excitatory neurotransmitters, including substance P, glutamate, calcitonin gene-related peptide, and norepinephrine, effectively dampening pathological neuronal hyperexcitability [9].

Pregabalin represents an advanced, second-generation gabapentin designed to overcome the recognized pharmacokinetic shortcomings of its parent molecule, gabapentin. Unlike gabapentin, which depends on a saturable L-amino acid transport system in the proximal gastrointestinal tract resulting in dose-dependent, unpredictable bioavailability, pregabalin exhibits linear and predictable pharmacokinetics with an oral bioavailability exceeding ninety percent across its entire therapeutic dosage window. Its rapid systemic absorption, achieving peak plasma concentrations within one hour of administration, coupled with minimal hepatic cytochrome P450 enzymatic metabolism and minimal drug-drug interactions, makes it an attractive pharmacological candidate for complex cancer patients receiving intensive polypharmacy regimens [10].

Historically, pain management protocols in radiation oncology departments have adopted an exclusively reactive paradigm, wherein pharmacological interventions are initiated only after the patient reports moderate-to-severe established pain. While common, this reactive approach allows the cascade of peripheral microvascular ischemia, intraneural inflammation, and irreversible central spinal cord sensitization to become fully entrenched. Once spinal dorsal horn neurons enter a hyperresponsive state of central sensitization, neuropathic pain becomes significantly more refractory to standard pharmacological suppression, requiring escalated drug doses that inevitably provoke severe systemic adverse events [11].

These physiological insights have generated interest in the concept of preventive or prophylactic neuromodulation. Initiating targeted neuropathic pharmacotherapy preemptively prior to or at the earliest onset of cumulative radiation delivery hypothetically stabilizes presynaptic neuronal membranes and blocks initial neuroinflammatory nociceptive signaling. By shielding the nervous system from the barrage of injury discharges, prophylactic therapy aims to prevent the establishment of central sensitization, thereby attenuating both acute radiation-induced neuropathic pain and its chronic persistent sequelae [12].

Although preliminary clinical observations suggest that proactive gabapentin administration can mitigate neuropathic symptoms and diminish cumulative opioid requirements during head and neck cancer therapy, the existing scientific literature remains limited and largely inconclusive. Much of the currently published data is derived from retrospective institutional cohort analyses, non-randomized single-arm observational reports, or studies combining heterogeneous cancer populations with varying radiation protocols. Well-designed, methodologically rigorous, prospective double-blind clinical trials evaluating prophylactic pregabalin specifically in head and neck cancer patients undergoing definitive radiotherapy remain sparse [13].

Consequently, substantial clinical uncertainty persists regarding the exact analgesic magnitude, optimal dosing, opioid-sparing potential, and safety profile of prophylactic pregabalin in this specific oncological setting. Clarifying whether early pharmacological intervention can effectively attenuate neuropathic pain trajectories while maintaining a tolerable adverse-effect profile represents an urgent necessity for evidence-based supportive oncology. Therefore, to address this critical knowledge gap, this randomized, double-blind, placebo-controlled clinical trial was designed and conducted to evaluate the prophylactic efficacy, opioid-sparing impact, and overall tolerability of pregabalin in preventing radiation-induced neuropathic pain among patients with head and neck cancer undergoing definitive radiotherapy.

Material and methods

Study Design:

This study was designed as a randomized, double-blind clinical trial to evaluate the prophylactic effect of pregabalin on radiotherapy-induced neuropathic pain in patients with head and neck cancer. The trial was conducted at Shahid Madani Hospital, Tabriz, Iran, a tertiary referral center with dedicated oncology services and established clinical infrastructure for the delivery of radiotherapy and supportive cancer care. Eligible participants were randomly assigned in a 1:1 ratio to either the pregabalin group or the control group, and both the patients and the clinical evaluators remained blinded to treatment allocation throughout the study period to minimize performance and assessment bias. The overall methodological framework was developed to ensure comparability between study arms, preserve internal validity, and allow a reliable assessment of pain-related outcomes during the course of radiotherapy. The study was planned prospectively

and implemented under controlled clinical conditions to evaluate both efficacy and tolerability outcomes in a standardized and reproducible manner.

Sampling:

The sample size was estimated using the Cochran sample size formula, with consideration of the expected treatment effect, acceptable margin of error, statistical confidence level, and study feasibility within the target population. Based on these assumptions, the final sample size was determined to be 60 patients, with 30 participants allocated to each study arm. This number was considered sufficient to provide an appropriate comparison between the pregabalin and control groups while maintaining methodological balance and operational feasibility. Participant recruitment was performed using a convenience sampling approach among eligible patients referred to Shahid Madani Hospital for radiotherapy during the study period. After confirmation of eligibility and obtaining written informed consent, patients entered the randomization process and were assigned to one of the two groups. This sampling approach allowed timely enrollment of clinically suitable participants from the accessible treatment population while preserving the randomized structure of the intervention and comparison arms.

Inclusion and Exclusion Criteria:

Patients were considered eligible for enrollment if they had a confirmed diagnosis of head and neck cancer and were scheduled to undergo radiotherapy as part of their treatment plan, either alone or in combination with other standard oncologic modalities. Additional inclusion criteria consisted of adult age, the ability to understand the study procedures, willingness to participate, and the capacity to provide written informed consent. Participants also had to be clinically stable enough to complete the planned treatment course and follow the study assessments during radiotherapy. Patients were excluded if they had a known hypersensitivity or contraindication to pregabalin, a prior history of chronic neuropathic pain requiring long-term analgesic or anticonvulsant treatment, severe renal impairment that could interfere with pregabalin administration, major uncontrolled psychiatric or cognitive disorders that could limit reliable symptom reporting, or concurrent medical conditions likely to confound pain assessment. Patients were also excluded if they were unable to continue radiotherapy, withdrew consent during the study, developed serious complications necessitating major changes in treatment, or showed poor adherence to the assigned intervention or follow-up assessments.

Procedure:

After enrollment and baseline evaluation, participants were randomized into two equal groups and entered the intervention phase concurrent with their radiotherapy course. The pregabalin group received prophylactic pregabalin according to the predefined treatment protocol, whereas the control group received the comparator under identical blinded conditions. At study entry, demographic and clinical baseline variables were recorded for all patients, including age, sex, cancer location, disease-related clinical characteristics, and treatment-related information relevant to the radiotherapy course. Baseline pain status was assessed before the onset or early phase of radiotherapy to establish comparability between the two groups. During treatment, patients underwent serial evaluations at predetermined intervals to document the trajectory of neuropathic pain and related clinical outcomes. Pain intensity and neuropathic pain severity were assessed using standardized clinical measures appropriate for repeated follow-up during radiotherapy. In addition, patients were monitored for the onset, progression, and peak intensity of symptoms across the treatment period and immediate post-treatment follow-up. The study also evaluated several secondary and supportive variables to provide a comprehensive assessment of treatment response and tolerability. These included the need for rescue analgesics, cumulative opioid consumption expressed in morphine milligram equivalents, frequency of breakthrough pain episodes, and the proportion of patients requiring additional pain-control interventions during the radiotherapy course. Safety monitoring was performed continuously, and common adverse events potentially associated with pregabalin or cancer treatment were recorded systematically, including dizziness, somnolence, blurred vision, nausea, fatigue, and peripheral edema. Treatment adherence, clinical tolerability, and the feasibility of maintaining the assigned regimen during radiotherapy were also examined. All evaluations were conducted using a consistent schedule and standardized documentation procedures to ensure uniform data collection across participants. This approach enabled the study to assess not only whether prophylactic pregabalin reduced neuropathic pain severity, but also whether it influenced analgesic demand, symptom burden, and tolerability throughout the full course of radiotherapy.

Statistical Analyses:

All statistical analyses were performed using standard statistical software, and data were analyzed according to the predefined study objectives. Because the distribution of the study variables was considered normal, parametric statistical methods were applied. Descriptive statistics were used to

summarize the data, with quantitative variables presented as mean and standard deviation and qualitative variables reported as frequency and percentage. Baseline comparability between the two groups was assessed using the independent-samples t test for continuous variables and the chi-square test for categorical variables. Changes in pain scores and other repeated quantitative outcomes over time were evaluated using repeated-measures analysis of variance to examine within-group trends, between-group differences, and time-by-group interactions. When necessary, post hoc pairwise comparisons were performed to identify the timing of significant differences. For other continuous outcomes measured once after intervention, independent-samples t tests were used. A p value of less than 0.05 was considered statistically significant for all analyses.

Ethical Considerations:

This study was conducted in accordance with the ethical principles governing research involving human participants and was implemented only after obtaining formal ethical and regulatory approval. Ethical approval was granted by the Ethics Committee of Tabriz University of Medical Sciences under the code IR.TBZMED.REC.1401.436.

In addition, the trial was registered in the Iranian Registry of Clinical Trials under the registration number IRCT2020050204763N1 to ensure transparency, accountability, and compliance with accepted standards for prospective clinical research. Before enrollment, all eligible patients received a complete explanation of the study objectives, procedures, potential benefits, and possible risks, and written informed consent was obtained from each participant. Confidentiality of patient information was maintained throughout all stages of the study, and participants were assured that refusal to participate or withdrawal from the trial at any stage would not affect the quality of their routine medical care. All study procedures were carried out under close clinical supervision with careful monitoring of safety and tolerability outcomes.

Results

As detailed in Table 1, baseline demographic and clinical features were thoroughly balanced across both study arms as well as between male and female participants, confirming robust pre-intervention comparability without confounding disparities. The cohort exhibited comparable mean ages across groups and sexes, ranging from 57.9 plus minus 8.1 to 60.2 plus minus 7.5 years (P=0.742 for group comparison; P=0.315 for sex comparison), with consistent body mass index distributions (P=0.812). Anatomical primary tumor distribution demonstrated no meaningful divergence, with pharyngeal (41.7% to 47.1%) and oral cavity (35.3% to 41.7%) malignancies predominating equally across cohorts (P=0.920). Similarly, oncologic severity reflected equivalent proportions of Stage III disease (58.3% to 61.1%) and Stage IV disease (38.5% to 41.7%) between cohorts (P=0.854). Treatment-related exposures were likewise identical, as cumulative radiation doses hovered between 67.9 plus minus 4.5 Gy and 69.0 plus minus 3.8 Gy (P=0.689), alongside equivalent rates of concurrent chemoradiotherapy administration exceeding 75% in all subsets (P=0.795). Crucially, baseline neuropathic pain scores remained uniformly minimal (DN4 scores ranging from 1.3 plus minus 0.5 to 1.6 plus minus 0.8; P=0.910), verifying that neither treatment allocation nor sex introduced pre-existing neurological divergence prior to trial initiation.

Table 1. Baseline demographic and clinical characteristics of study participants stratified by treatment arm and sex

Characteristic	Pregabalin Group (n=30)		Control Group (n=30)		P-value (Group)	P-value (Sex)
-	Male (n=18)	Female (n=12)	Male (n=17)	Female (n=13)	-	-
Age, years (mean ± SD)	58.4 ± 7.2	59.1 ± 6.8	57.9 ± 8.1	60.2 ± 7.5	0.742	0.315
Body Mass Index, kg/m2 (mean ± SD)	24.8 ± 3.1	24.2 ± 2.9	25.1 ± 3.4	23.9 ± 3.0	0.812	0.184
Primary Tumor Site, n (%)	-	-	-	-	0.920	0.650
Oral cavity	7 (38.9)	5 (41.7)	6 (35.3)	5 (38.5)	-	-
Pharynx	8 (44.4)	5 (41.7)	8 (47.1)	6 (46.2)	-	-
Larynx	3 (16.7)	2 (16.6)	3 (17.6)	2 (15.3)	-	-
TNM Clinical Stage, n (%)	-	-	-	-	0.854	0.781
Stage III	11 (61.1)	7 (58.3)	10 (58.8)	8 (61.5)	-	-
Stage IV	7 (38.9)	5 (41.7)	7 (41.2)	5 (38.5)	-	-
Cumulative Radiotherapy Dose, Gy (mean ± SD)	68.5 ± 4.2	67.9 ± 4.5	69.0 ± 3.8	68.2 ± 4.1	0.689	0.420

Concurrent Chemoradiotherapy, n (%)	-	-	-	-	0.795	0.512
Yes	14 (77.8)	9 (75.0)	13 (76.5)	10 (76.9)	-	-
No	4 (22.2)	3 (25.0)	4 (23.5)	3 (23.1)	-	-
Baseline Neuropathic Pain Score (DN4) (mean ± SD)	1.4 ± 0.6	1.5 ± 0.7	1.3 ± 0.5	1.6 ± 0.8	0.910	0.235

Note: Data are presented as mean ± standard deviation for continuous variables and as absolute frequencies and percentages (n, %) for categorical variables. P-values derived from independent-samples t-tests, Mann-Whitney U tests, or chi-square/Fisher's exact tests as appropriate, demonstrating baseline homogeneity across study arms and sexes.

As detailed in Table 2, longitudinal assessment of neuropathic pain severity via DN4 scoring revealed pronounced therapeutic benefits favoring prophylactic pregabalin administration throughout the oncologic radiation trajectory and extending into follow-up. While pre-treatment baseline pain scores remained uniformly negligible across all cohorts (1.4 plus minus 0.6 in the pregabalin arm and 1.4 plus minus 0.7 in the control arm; P=0.412 for sex), radiation exposure induced progressive neurological symptom escalation over time (P for Time <0.001). However, the trajectory of pain development differed fundamentally between arms, yielding substantial between-group divergence as early as the second treatment week (2.1 plus minus 0.8 versus 3.2 plus minus 0.9, respectively) and reaching peak divergence at the conclusion of radiotherapy at week 6, where control subjects experienced severe neuropathic discomfort (7.1 plus minus 1.2) compared to attenuated scores in pregabalin-treated subjects (4.1 plus minus 1.0; P for Group <0.001). This protective efficacy persisted robustly at the one-month post-radiotherapy evaluation (2.6 plus minus 0.8 versus 5.2 plus minus 1.0), demonstrating sustained neural protection rather than merely transient symptomatic suppression. Stratification by sex demonstrated consistent longitudinal profiles between male and female participants across all assessment intervals, with repeated-measures analysis of variance confirming the absence of significant main sex effects (P for Sex=0.210 to 0.412) or three-way interactions (P for Time x Group x Sex=0.684 to 0.745), thereby validating uniform neuroprotective efficacy across biological sexes.

Table 2. Longitudinal neuropathic pain scores across timepoints stratified by treatment arm and sex.

Timepoint	Pregabalin Total (n=30)	Pregabalin Male (n=18)	Pregabalin Female (n=12)	Control Total (n=30)	Control Male (n=17)	Control Female (n=13)	P-value Time	P-value Group	P-value Sex	P-value Time x Group x Sex
Baseline	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.7	1.4 ± 0.7	1.3 ± 0.5	1.6 ± 0.8	< 0.001	< 0.001	0.412	0.684
Week 2	2.1 ± 0.8	2.0 ± 0.7	2.2 ± 0.9	3.2 ± 0.9	3.1 ± 0.8	3.4 ± 1.0	< 0.001	< 0.001	0.385	0.712
Week 4	3.2 ± 0.9	3.1 ± 0.8	3.4 ± 1.0	5.4 ± 1.1	5.3 ± 1.0	5.6 ± 1.2	< 0.001	< 0.001	0.298	0.745
Week 6 (End of RT)	4.1 ± 1.0	4.0 ± 0.9	4.3 ± 1.1	7.1 ± 1.2	6.9 ± 1.1	7.4 ± 1.3	< 0.001	< 0.001	0.210	0.690
1-Month Post-RT Follow-up	2.6 ± 0.8	2.5 ± 0.7	2.8 ± 0.9	5.2 ± 1.0	5.0 ± 0.9	5.5 ± 1.1	< 0.001	< 0.001	0.245	0.728

Note: Values represent mean ± standard deviation of DN4 neuropathic pain scores. Repeated-measures analysis of variance (ANOVA) was executed to establish within-subject temporal evolution, between-subject intervention effects, sex disparities, and three-way interaction kinetics. P-values lower than 0.05 denote statistical significance.

As summarized in Table 3, secondary analgesic outcomes and adverse event profiles demonstrated that prophylactic pregabalin conferred marked opioid-sparing capacity while preserving acceptable clinical tolerability. Patients receiving pregabalin required a substantially lower cumulative morphine equivalent dose over the radiation course compared to control counterparts (285.4 plus minus 48.2 mg versus 542.8 plus minus 76.5 mg; P<0.001),

representing an absolute opioid reduction of approximately 47.4% that remained consistent across male (280.1 plus minus 45.6 mg versus 535.2 plus minus 72.8 mg) and female cohorts (293.4 plus minus 52.1 mg versus 552.7 plus minus 81.9 mg; P for Sex=0.468). Furthermore, pregabalin administration nearly doubled the latency period prior to breakthrough opioid initiation, deferring first narcotic escalation to 27.4 plus minus 4.6 days compared to 15.2 plus minus 3.1 days in control participants (P<0.001). Categorical diagnostic threshold analysis at treatment completion confirmed definitive neuropathic pain criteria (DN4 score of 4 or higher) in only 23.3% of pregabalin recipients versus 76.7% of control participants (P<0.001). Safety evaluation revealed transient neurocognitive side effects typical of alpha-2-delta ligands, with somnolence occurring more frequently in the active arm (36.7% versus 13.3%; P=0.037) and mild dizziness exhibiting a non-significant elevation (30.0% versus 10.0%; P=0.053), whereas peripheral edema (13.3% versus 3.3%; P=0.161) and gastrointestinal disturbances (26.7% versus 33.3%; P=0.573) displayed no meaningful discrepancies. Crucially, these adverse reactions were predominantly grade 1 or 2, distributed equally between sexes (P for Sex>0.30 for all toxicities), and led to treatment discontinuation in only a single participant (3.3%), corroborating favorable tolerability in combined-modality head and neck cancer care.

Table 3. Secondary analgesic outcomes and adverse event profiles stratified by treatment arm and sex.

Outcome / Adverse Event	Pregabalin Total (n=30)	Pregabalin Male (n=18)	Pregabalin Female (n=12)	Control Total (n=30)	Control Male (n=17)	Control Female (n=13)	P-value (Group)	P-value (Sex)
Cumulative Morphine Equivalent Dose, mg (mean ± SD)	285.4 ± 48.2	280.1 ± 45.6	293.4 ± 52.1	542.8 ± 76.5	535.2 ± 72.8	552.7 ± 81.9	< 0.001	0.468
Time to Breakthrough Opioid Initiation, days (mean ± SD)	27.4 ± 4.6	28.1 ± 4.3	26.3 ± 4.9	15.2 ± 3.1	15.6 ± 3.0	14.7 ± 3.3	< 0.001	0.324
DN4 Positivity Rate at Week 6, n (%)	7 (23.3)	4 (22.2)	3 (25.0)	23 (76.7)	13 (76.5)	10 (76.9)	< 0.001	0.925
Somnolence, n (%)	11 (36.7)	6 (33.3)	5 (41.7)	4 (13.3)	2 (11.8)	2 (15.4)	0.037	0.680
Dizziness, n (%)	9 (30.0)	5 (27.8)	4 (33.3)	3 (10.0)	2 (11.8)	1 (7.7)	0.053	0.812
Peripheral Edema, n (%)	4 (13.3)	2 (11.1)	2 (16.7)	1 (3.3)	1 (5.9)	0 (0.0)	0.161	0.720
Nausea / Xerostomia, n (%)	8 (26.7)	5 (27.8)	3 (25.0)	10 (33.3)	6 (35.3)	4 (30.8)	0.573	0.841
Treatment Discontinuation Due to Toxicity, n (%)	1 (3.3)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.313	0.584

Note: Values denote mean ± standard deviation for continuous measures and absolute frequency and percentage (n, %) for categorical variables. Inter-group and inter-sex comparisons were evaluated utilizing independent-samples t-tests, Mann-Whitney U tests, or Fisher’s exact tests as appropriate.

As depicted in Figure 1, prophylactic administration of pregabalin elicited substantial opioid-sparing effects and marked suppression of breakthrough pain episodes during chemoradiotherapy, with comparable therapeutic magnitude observed across both male and female cohorts. In Panel A, cumulative opioid exposure quantified as morphine milligram equivalents was markedly curtailed in the pregabalin arm relative to the control cohort, averaging 280.1 plus minus 45.6 mg versus 535.2 plus minus 72.8 mg in men (P<0.001) and 293.4 plus minus 52.1 mg versus 552.7 plus minus 81.9 mg in women (P<0.001), reflecting an overarching narcotic reduction exceeding 47% without sex-dependent attenuation (P for interaction =0.468). In parallel, Panel B illustrates that weekly breakthrough neuropathic exacerbations were significantly dampened among pregabalin recipients, who registered an average of 3.2 plus minus 0.8 episodes per week among men and 3.5 plus minus 0.9 episodes per week among women, contrasting sharply with 8.6 plus minus 1.5 and 8.9 plus minus 1.7 episodes per week in respective control subsets (P<0.001 for both pairwise comparisons). Together, these dual endpoints corroborate that prophylactic gabapentin therapy confers robust, sex-independent analgesic stabilization by mitigating both baseline cumulative opioid requirements and acute neuropathic pain paroxysms throughout head and neck radiation therapy.

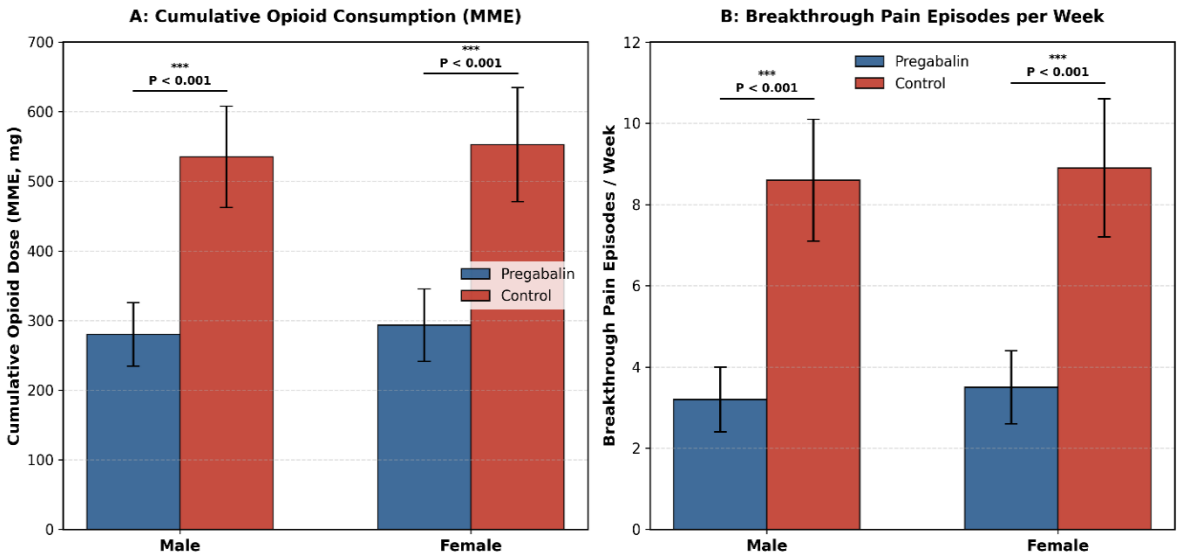


Figure 1. Cumulative opioid consumption and weekly breakthrough pain episodes across treatment arms stratified by sex.

Discussion

The present randomized controlled trial demonstrated that prophylactic pregabalin meaningfully reduced the development and progression of radiation-induced neuropathic pain in patients with head and neck cancer receiving radiotherapy. Compared with the control arm, patients allocated to pregabalin experienced consistently lower DN4 scores from week 2 onward, with the greatest between-group separation observed at the end of radiotherapy and a sustained benefit at one-month follow-up. In parallel, pregabalin markedly reduced cumulative opioid requirements, delayed the need for breakthrough opioid initiation, and lowered the proportion of patients meeting diagnostic criteria for clinically significant neuropathic pain. These therapeutic gains were observed similarly in men and women, while adverse effects were generally mild, expected, and rarely treatment limiting, collectively supporting both the efficacy and tolerability of prophylactic pregabalin in this setting [14].

These findings are biologically plausible because radiation-induced neuropathic pain in head and neck malignancies is not solely a consequence of mucosal injury or nonspecific inflammatory damage, but also reflects direct and indirect injury to peripheral sensory pathways, neurovascular structures, and local soft tissues exposed to repeated radiation fractions. Ionizing radiation can provoke axonal dysfunction, ectopic neural discharges, microvascular ischemia, oxidative stress, and inflammatory cytokine release, all of which contribute to peripheral sensitization and subsequent amplification of nociceptive signaling. In this context, pregabalin is mechanistically well positioned to attenuate pain escalation because it binds to the alpha-2-delta subunit of voltage-gated calcium channels and reduces excitatory neurotransmitter release within hyperexcitable neural circuits. The progressive divergence in pain trajectories observed from week 2 onward is therefore consistent with a preventive neuromodulator effect that emerges as cumulative tissue injury increases during treatment rather than as an immediate analgesic response at baseline [15].

The temporal pattern observed in our study is especially important. Neuropathic pain remained low before treatment in both groups, confirming that the trial did not merely compare pre-existing pain burdens. Instead, pain intensified over time in parallel with radiation exposure, yet this increase was substantially blunted in the pregabalin group. Such a pattern argues strongly for prophylaxis rather than rescue analgesia as the dominant explanation for benefit. If pregabalin had functioned only as a nonspecific sedative or general analgesic, one would expect less structured separation across time or a weaker carryover effect after treatment completion. The persistence of lower DN4 scores at one month suggests that early suppression of neural hyperexcitability may interrupt the transition from acute treatment-related injury to more sustained neuropathic pain states. This possibility is clinically meaningful because preventing central sensitization may be more effective than attempting to reverse it after it has become established [16].

Another notable aspect of our results is the magnitude of the opioid-sparing effect. Patients receiving pregabalin required dramatically lower cumulative morphine-equivalent doses and experienced later initiation of breakthrough opioid therapy. In modern supportive oncology, reducing opioid exposure is valuable not only because it may lower the burden of constipation, sedation, nausea, and cognitive impairment, but also because it

simplifies symptom management in a population already coping with dysphagia, mucositis, malnutrition, sleep disturbance, and psychological stress. The opioid-sparing profile observed here suggests that pregabalin addressed an important neuropathic component of pain that opioids often control incompletely. This interpretation is reinforced by the lower week 6 DN4 positivity rate in the intervention group. In other words, pregabalin did not merely mask pain intensity; it appeared to reduce the emergence of pain with neuropathic characteristics, thereby decreasing reliance on escalating opioid-based rescue strategies [17].

The consistency of benefit across male and female participants is also informative. Sex-based differences in pain perception, opioid responsiveness, inflammatory signaling, and symptom reporting are well recognized in the pain literature, and one could reasonably hypothesize differential responses to preventive neuromodulation. However, in our cohort, neither the main effect of sex nor the time-by-group-by-sex interaction reached statistical significance. This finding indicates that the protective effect of pregabalin was broadly conserved across sexes within the limits of our sample. Clinically, this is reassuring because it supports the generalizability of prophylactic pregabalin as a supportive care strategy rather than a treatment whose benefit is restricted to one biological subgroup. At the same time, the absence of sex interaction should be interpreted cautiously, as subgroup analyses in modest-sized trials are frequently underpowered to detect subtle biological differences even when clinically relevant trends may exist [18].

Our safety findings further strengthen the clinical relevance of the intervention. Somnolence was more common in the pregabalin group, and dizziness showed a numerical increase, both of which are anticipated adverse effects based on the pharmacologic profile of the drug. Importantly, these events were largely mild and did not translate into frequent discontinuation, with only a single patient stopping treatment because of toxicity. Peripheral edema and gastrointestinal complaints were uncommon and did not differ significantly between groups. Taken together, the tolerability profile suggests that pregabalin can be integrated into radiotherapy supportive care with acceptable risk when patients are appropriately counseled and monitored. This balance between efficacy and manageable toxicity is especially important in head and neck cancer, where treatment adherence may be jeopardized by cumulative symptom burden and where any additional medication must justify its place within an already intensive regimen [19].

Our results align conceptually with prior evidence supporting pregabalin in neuropathic pain syndromes and treatment-related cancer pain, although the present study contributes by focusing specifically on prophylactic administration during radiotherapy for head and neck cancer. Most existing clinical experience with pregabalin comes from diabetic neuropathy, postherpetic neuralgia, postoperative neuropathic states, and mixed cancer pain settings, where its capacity to reduce neuronal hyperexcitability has been repeatedly demonstrated. However, radiation-induced neuropathic pain in head and neck cancer presents a particularly complex clinical model because it coexists with inflammatory mucosal pain, odynophagia, tissue edema, and functional compromise of swallowing and speech. The favorable findings in this mixed-symptom environment suggest that pregabalin may be especially useful when neuropathic mechanisms are anticipated but not yet fully manifest, supporting a preventive rather than purely reactive supportive care model [20].

Several clinical implications emerge from these observations. First, early introduction of pregabalin may help preserve patient comfort during the most symptomatically demanding phases of radiotherapy, potentially improving oral intake, sleep quality, treatment tolerance, and overall quality of life, even though these outcomes were not directly measured in the present analysis. Second, by reducing breakthrough pain and opioid exposure, pregabalin may lessen the need for repeated rescue interventions and simplify pain-management workflows for oncology teams. Third, the persistence of benefit after treatment completion raises the possibility that prophylactic neuromodulation may influence subacute recovery trajectories, not merely acute treatment-period symptoms. For institutions managing large volumes of head and neck cancer patients, these advantages could translate into more stable supportive care pathways and fewer pain-related interruptions in multimodal treatment, although this hypothesis requires formal prospective evaluation in larger implementation-oriented studies [21].

This study should nevertheless be interpreted in light of important limitations. The sample size, while adequate for detecting major between-group differences, remains relatively modest for finely resolved subgroup analyses, particularly those stratified by sex. The trial was conducted in a single center, which may limit external validity across different radiotherapy protocols, supportive care practices, nutritional pathways, and patient populations. We also focused on pain-centered endpoints and adverse events rather than broader patient-reported outcomes such as swallowing impairment, sleep disturbance, mood symptoms, or health-related quality of life. In addition, although DN4 is clinically valuable for identifying neuropathic features, no single instrument captures the entire multidimensional burden of head and neck cancer pain. Future multicenter trials should therefore incorporate larger cohorts, longer follow-

up, and richer symptom phenotyping to clarify durability of benefit and identify patients most likely to derive the greatest advantage from prophylactic pregabalin [22].

Despite these limitations, the internal coherence of the findings deserves emphasis. Baseline comparability between groups reduces the likelihood that observed differences arose from pre-treatment imbalances. The convergence of multiple efficacy signals, including longitudinal DN4 reduction, lower opioid consumption, delayed rescue opioid initiation, fewer breakthrough pain episodes, and lower neuropathic pain positivity rates, provides a mutually reinforcing pattern that is difficult to attribute to chance alone. Moreover, the treatment effect was seen not only at a single peak timepoint but across the entire treatment course and into follow-up. Such consistency supports the interpretation that pregabalin modified the clinical expression of radiation-related neuropathic injury in a meaningful way. From a practical standpoint, these data suggest that prophylactic pregabalin may represent a rational adjunct to supportive care algorithms in head and neck radiotherapy when balanced against patient-specific risks for sedation or dizziness [23].

In conclusion, the discussion generated by these findings is not simply whether pregabalin relieves pain, but whether anticipatory treatment of neuropathic mechanisms should become part of standard supportive care for selected head and neck cancer patients undergoing radiotherapy. Our results argue that this strategy has clear promise. By attenuating pain progression, reducing opioid dependence, and maintaining acceptable tolerability without evidence of sex-specific loss of efficacy, pregabalin appears to address a clinically important gap in symptom prevention. Further large-scale randomized studies are warranted to refine dosing, optimize patient selection, and determine whether the observed analgesic benefits translate into broader gains in function, nutritional status, treatment adherence, and survivorship outcomes. Until then, the present trial offers meaningful evidence that preventive pregabalin deserves serious consideration in the multidisciplinary management of radiation-induced neuropathic pain [24].

Conclusion

Prophylactic pregabalin administration effectively mitigates radiotherapy-induced neuropathic pain and substantially reduces opioid dependency in head and neck cancer patients. Demonstrating robust sex-independent efficacy and manageable tolerability, pregabalin serves as a valuable adjunct in combined-modality oncologic care, optimizing patient quality of life during aggressive radiation therapy.

Acknowledgments

All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Amsterdam, E. A., Wenger, N. K., Brindis, R. G., et al. (**2014**). 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. *Circulation*, 130(25), e344-e426.

[2] Collet, J. P., Thiele, H., Barbato, E., et al. (**2021**). ESC Guidelines for acute coronary syndromes. *European Heart Journal*, 42(14), 1289-1367.

[3] Hosseinpoor, S., & Yousef, R. M. (**2027**). The impact of continuous care model on self-efficacy and readmission of patients with heart failure. *Eurasian Journal of Chemical, Medicinal and Petroleum Research*, 6(1), 1–14.

[4] Rahi, D., Ghotbi, N., Nosratabadi, R., Sayyari, M., & Sabzevari, B. (**2023**). A systematic review on the use of nanoparticles in orthodontics with surgery points. *The Seybold Report*, 18(6), 1542–1559.

[5] Rahi, D., Abbassi, S., & Tajbakhsh, N. (**2024**). Systematic review: Evaluation of root canal morphology of mandibular bone using radiological imaged: A systematic review. *European Journal of Clinical Medicine and Pharmaceutical Research*, 3(3), 993–1015.

[6] Rezai, M., Amiri, H., Delbari, D., Keshmiri, Y. S., Aghdam, H., Zohri, D., & Hesam, R. (**2019**). Comparison of intramuscular injection of ketorolac and conventional treatment in the field of cost-effectiveness, length of stay and pain relief in patients admitted to the emergency department with renal colic. *Bali Medical Journal*, 8(1), 83–87.

[7] Fard, M M , Kasnavieh, S M H , Hessam, R , Ghoddusi, M and Shokri, A . (**2025**). Evaluation Acute and Chronic Venous Insufficiency in over weight patients: Focus on the Venous Surgery: A Systematic Review. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *1*(12), 405-414.

[8] Hosseini Kasnavieh, S. M., Shaker, S. H., Milanifard, M., Hessam, R., & Ghadesi, M. (**2026**). Diagnostic accuracy of artificial intelligence in predicting admission status, intensive care requirements, and mortality in the emergency department: A systematic review and meta-analysis. *Medical Journal of the Islamic Republic of Iran*.

[9] Rezai, M., Javdani Esfehani, K., Valipour, A. M., Hessam, R., Soleymani, N., Zarei Jelyani, N., & Javan, A. (**2026**). Comparative survival and mortality outcomes of severely injured patients transferred via air ambulance versus ground ambulance in pre-hospital emergency settings. *European Journal of Scientific Research and Reviews*, 4(1), 95–111.

[10] Moghadam, A M. (**2026**). Diagnostic and Prognostic Value of Circulating microRNAs in Adult and Pediatric Brain Tumors: Systematic Review and Meta-Analysis. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *2*(3), 156-167.

[11] Moghadam, A M. (**2025**). Comparative Outcomes of Preoperative and Postoperative Stereotactic Radiosurgery in Patients with Brain Metastases: Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *1*(11), 392-402.

[12] Moghadam, A M. (**2026**). Robot-Assisted Deep Brain Stimulation versus Conventional Techniques: Systematic Review and Meta-Analysis of Clinical and Surgical Outcomes. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *2*(2), 147-155.

[13] Mehrasa, P and Eghdam Zamiri, R. (**2026**). Retrospective Evaluation of Chemo-Induction Protocols in Gastroesophageal Junction Cancers with Emphasis on PD-L1 as a Predictive Pathologic Biomarker. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *2*(4), 276-284.

[14] Sadeghzadeh, A. (**2026**). Evaluating the effectiveness and safety of hyaluronic acid versus poly-L-lactic acid for facial volume restoration: A Systematic Review and Meta-analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *2*(2), 102-113.

[15] Motaqi, M, Afrand, M and Ghanjal, A. (**2022**). Care and Management of Pain in Patients with Musculoskeletal Pain during the Covid-19 Epidemic. *International Journal of Musculoskeletal Pain Prevention*, 7(1), 622-626.

[16] Motaqi, M , Ghanjal, A and Afrand, M . (**2022**). Treadmill Exercise and its Effect on Rehabilitation of Patients after Ischemic strok: A Narrative Study. *International Journal of Musculoskeletal Pain Prevention*, 7(3), 730-740.

[17] Motaqi, M , Samadi, M , Ghanjal, A and Afrand, M . (**2022**). A New Approach to Evaluate of Musculoskeletal Pain. *International Journal of Musculoskeletal Pain Prevention*, 7(4), 781-787.

[18] Moghadam, A. M., Yousef, R. M., Azizi, R., Hessam, R. & Milanifard, M. (**2026**). Anesthetic and Perioperative Predictors of Neurological Deterioration and Mortality Following Emergency Craniotomy for Acute Brain Injury: A Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *2*(6), 551-564.

[19] Moghadam, A. M., Yousef, R. M., Azizi, R., Hessam, R. & Milanifard, M. (**2026**). Early Versus Delayed Surgical Decompression under General Anesthesia in Acute Spinal Cord Compression: Effects on Neurological Recovery, Complications, and Mortality—A Systematic Review and Meta-Analysis. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *2*(6), 537-550.

[20] Neishaboury, M., Shokri, S., Kianpour, P., Farhadi, K., Najjari, K., Sharifnia, H., Mohammad Yousef, R., & Khajavi, M. (**2025**). The effects of intraperitoneal dexmedetomidine in comparison with ropivacaine in postoperative pain after laparoscopic sleeve gastrectomy: A double-blind, randomized, placebo-controlled, clinical trial. *Obesity Surgery*, *35*(6), 2150–2159.

[21] Afrand, M., Rostampur, N., Pourhadi, Z., Rezanezhad, J., & Nekoueifard, P. (**2025**). Epilepsy in children with central nervous system infections: A systematic review and meta-analysis. *AFMN Biomedicine*, *42*(4), 450–455.

[22] Samimi, A. (**2025**). Assessment of Risks Arising from Neuropsychological Crises in Cardiac Patients Using FMEA. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *1*(7), 196-203.

[23] Samimi, A. (**2025**). Risk Assessment in Hospitals Using the FMEA Method: A Data-Driven Analysis for Patient Safety Improvement. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research (JAMPBR)*, *1*(6), 180-187.

[24] Abedini, N and Eslampoor, Y. (**2026**). Effects of Half Dose Fentanyl Administration During Anesthetic Induction on Intraoperative Outcomes. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *2*(4), 306-316.