

Eligibility Restrictiveness and Generalisability in Radiation Immunotherapy Trials for Head and Neck Squamous Cell Carcinoma: A Systematic Review of Trial Protocols

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ABSTRACT

Introduction: Head and Neck Squamous Cell Carcinoma (HNSCC) commonly affect older patients who often have multiple co-morbidities. With the growing use of Radiation Immunotherapy (RT-ICI) combinations in head and neck malignancies, concerns have emerged regarding the representativeness of trial populations.

Aim: The present study aimed to evaluate the prevalence and cumulative burden of restrictive eligibility criteria in contemporary Phase II-III RT-ICI trials.

Materials and Methods: This systematic review of trial protocols was conducted using ClinicalTrials.gov as the primary data source, following a registry-based cross-sectional analytical approach. Interventional Phase II-III radiation immunotherapy trials in Head and Neck Squamous Cell Carcinoma (HNSCC) registered between January 1, 2020 and December 31, 2025 were included. While the search parameters were confined to this period, final data extraction and clinical audit were performed in 2026. Eligibility criteria were reviewed across selected domains, including age limits, performance status, renal function, autoimmune disease, prior malignancy, steroid use, cardiac disease, and investigator discretion. Trials were excluded if they were early-phase (Phase I or Phase I/II), focused exclusively on non-head and neck malignancies, included mixed tumour populations without

separate HNSCC analysis, or evaluated immunotherapy without concurrent radiation therapy. A Composite Restrictive Index (CRI), based on age restriction, Eastern Cooperative Oncology Group (ECOG) 0-1 status, creatinine clearance ≥ 60 mL/min, and autoimmune exclusion, was proposed and used to assess the combined effect of major eligibility criteria. The distribution of these criteria across domains was evaluated using Chi-square testing, and effect size was measured using Cramér's V.

Results: Thirty-two eligible trials were identified. Restrictive eligibility criteria were highly prevalent, with 84.4% of trials limiting enrollment to ECOG 0-1 patients and 87.5% excluding individuals with autoimmune disease. Age restrictions were present in 56.3% of trials, while 43.8% required a creatinine clearance ≥ 60 mL/min. Additional exclusions included prior malignancy (81.3%), chronic steroid use (71.9%), and significant cardiac disease (65.6%). Subjective exclusion criteria were noted in 81.3% of protocols. The mean CRI was 2.72 (SD 1.08), with 31.3% of trials applying all four restrictive domains. No significant clustering of restrictive criteria across domains was observed ($p=0.091$).

Conclusion: Modern RT-ICI trials in HNSCC tend to apply multiple eligibility restrictions across key clinical domains. This may limit the applicability of their results to the wider, more diverse patient population encountered in everyday practice.

Keywords: Autoimmune diseases, Chemotherapy, Co-morbidity, External validity, Oral cancers

INTRODUCTION

The HNSCC remains a critical global health challenge; according to 2022 GLOBOCAN estimates, there were approximately 940,000 new cases and 480,000 deaths attributed to head and neck malignancies annually [1]. Despite advances in multidisciplinary care, outcomes remain suboptimal, particularly in patients presenting with locally advanced disease [2,3]. Importantly, HNSCC predominantly affects older adults, with Surveillance, Epidemiology, and End Results (SEER) data indicating a median age at diagnosis of approximately 66-67 years [4]. While previous estimates suggested a peak in the oldest cohorts, some population-based analyses suggest that incidence is highest in the sixth decade of life [5]. Furthermore, clinical outcomes are notably poorer in the elderly specifically in patients aged 75 years or older [6]. This demographic shift reflects broader global population aging trends, often described as the "Silver Tsunami," with the proportion of individuals ≥ 65 years projected to double by 2050 [7].

For decades, concurrent chemoradiotherapy has represented the standard approach for locally advanced HNSCC [8]. However, the therapeutic landscape has evolved with the emergence of Immune

Checkpoint Inhibitors (ICIs), including anti-PD-1 antibodies such as nivolumab and pembrolizumab, which have demonstrated survival benefits in recurrent or metastatic settings [9-11]. There is also some preclinical and translational evidence suggesting that radiation and immunotherapy may work better together, possibly through mechanisms like increased antigen presentation and what is known as the "abscopal effect" [12,13]. Because of this, there have been a growing number of Phase II-III trials looking at radiation immunotherapy (RT-ICI) combinations in the head and neck cancers.

Yet a critical question remains: Are the patients enrolled in these trials representative of the real-world HNSCC population? Historically, older adults and patients with co-morbidities have been systematically underrepresented in oncology clinical trials [14-16]. Regulatory analyses have confirmed that strict eligibility criteria, particularly performance status thresholds, organ function requirements, and co-morbidity exclusions, disproportionately exclude elderly and patients with multiple co-morbidities [17,18]. Because of this, the findings from these trials may not fully reflect what is seen in routine clinical practice [19].

The issue is particularly salient in immuno-oncology. Patients with preexisting autoimmune disease are frequently excluded due to concerns regarding immune-related adverse events, despite emerging data suggesting that many such patients can be treated safely under careful monitoring [20,21]. Similarly, rigid performance status cutoffs (ECOG 0-1 only) disproportionately exclude frail elderly individuals, despite the high prevalence of co-morbidity and functional limitation in HNSCC populations [22-24]. Renal function thresholds (e.g., creatinine clearance ≥ 60 mL/min) may further restrict access for older adults experiencing age-related nephrosclerosis, even when radiation-based therapies remain clinically feasible.

Collectively, these patterns raise the possibility of a structural “eligibility gap” between the demographic and co-morbidity profile of real-world HNSCC and the populations represented in contemporary RT-ICI trials. If trials mostly include patients who are physiologically fit, efficacy and toxicity outcomes may not accurately reflect results achievable in routine practice.

To date, however, the restrictiveness of eligibility criteria in modern Phase II-III RT-ICI trials for HNSCC has not been systematically quantified. The authors therefore conducted a structured audit of eligibility criteria in contemporary trials to evaluate the prevalence, clustering, and cumulative burden of major restrictive domains. By applying a CRI and domain-level heterogeneity testing, the authors sought to characterise the magnitude of the eligibility gap and assess its implications to see how well the evidence applies to patients routinely seen in current head and neck oncology practice.

MATERIALS AND METHODS

The present study was conducted as a systematic review of trial protocols with a methodological audit, in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. A structured, protocol-driven approach was used to evaluate the design characteristics of contemporary Phase II-III RT-ICI trials in HNSCC.

The primary objective was to quantify the prevalence and cumulative burden of restrictive eligibility criteria. A pooled analysis of protocol-level variables was performed by aggregating eligibility criteria across trials to estimate the overall “selection pressure” exerted by these criteria. This approach enabled a quantitative assessment of the potential generalisability gap between trial populations and the more heterogeneous, co-morbid patient population encountered in routine clinical practice. This study was based on publicly available registry data and did not involve patient-level information. Therefore, institutional review board approval was not required.

Data Source and Search Strategy

A systematic search of ClinicalTrials.gov was performed to identify interventional trials evaluating radiation therapy combined with ICIs in HNSCC. The search strategy included “HNSCC”, “radiation” or “radiotherapy”, “immunotherapy”, “PD-1”, “PD-L1”, “checkpoint inhibitor”. The search was restricted to trials registered between January 1, 2020 and December 31, 2025. While the search parameters were confined to this period, final data extraction and clinical audit were performed in 2026.

Inclusion criteria: Trials were included if they were Phase II or Phase III studies with an interventional therapeutic design evaluating a combination of radiation therapy and immune checkpoint inhibition in patients with HNSCC and related head and neck malignancies.

Exclusion criteria: Trials were excluded if they were early-phase studies (Phase I), included mixed solid tumour populations without separate analysis of head and neck cancers, or evaluated immunotherapy without concurrent radiation therapy. After applying these criteria, a total of 32 trials were included in the final analysis.

Eligibility Audit and Coding Framework

Eligibility criteria were manually extracted from publicly available trial protocol sections. Each trial was assessed across predefined domains, including age limits, performance status (ECOG), renal function thresholds, autoimmune disease exclusion, prior malignancy restrictions, chronic steroid use, cardiac disease exclusion, and the presence of subjective exclusion criteria.

Subjective exclusion criteria were defined as the use of non-specific language such as “investigator discretion,” “unsuitable for participation,” or similar statements without clearly defined clinical thresholds. These criteria were analysed separately, as they represent a non-standardised component of patient selection.

Each domain was coded as either restrictive: (1) or non-restrictive (0).

Composite Restrictive Index (CRI)

To assess the combined effect of key eligibility criteria, a four-domain CRI was constructed using age restriction, ECOG 0-1 status, creatinine clearance ≥ 60 mL/min, and autoimmune exclusion. The CRI ranged from 0 to 4. These domains were selected to represent major clinical factors related to age, functional status, organ function, and immune-related co-morbidity. Other domains, including prior malignancy, cardiac disease, steroid use, and subjective exclusion criteria, were analysed separately.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarise eligibility criteria across trials. Categorical variables were reported as frequencies and percentages. The CRI was summarised using mean, standard deviation, 95% confidence interval, median, interquartile range, and range. To assess the distribution of restrictive criteria across domains, a chi-square test was performed for the four primary domains (age, ECOG, renal function, and autoimmune exclusion). Effect size was measured using Cramér's V and interpreted as small (0.1), moderate (0.3), or large (≥ 0.5). A p-value < 0.05 was considered statistically significant.

Data Synthesis

A combined approach was used for data synthesis, incorporating both quantitative analysis and a qualitative review of trial eligibility criteria.

1. Quantitative synthesis: The quantitative synthesis involved aggregation of protocol-level variables across the 32 included trials to estimate the overall prevalence of restrictive eligibility criteria. The primary outcome was the proportion of trials applying each specific restrictive threshold.

To assess cumulative restrictiveness, the CRI was calculated for each study. Comparisons of CRI scores between Phase II and Phase III trials were performed using the Mann-Whitney U test, treating CRI as an ordinal variable. To explore whether certain eligibility criteria tended to co-occur, Chi-square testing was applied across the four primary domains (age, ECOG performance status, renal function, and autoimmune exclusion), with the strength of association quantified using Cramér's V. This aggregated approach provides insight into whether restrictive criteria are applied independently or in combination across trials. Pooled proportions were calculated for each eligibility domain based on the number of trials applying the respective restriction.

2. Qualitative assessment of eligibility criteria: A qualitative assessment was conducted to examine patterns in the application and wording of eligibility criteria across included trials. In addition to objective clinical thresholds, subjective exclusion criteria (e.g., “investigator discretion,” “unsuitable for participation,” or similar language) were identified and categorised. These criteria were grouped into predefined categories, including clinical safety-related considerations and operational or protocol-related considerations.

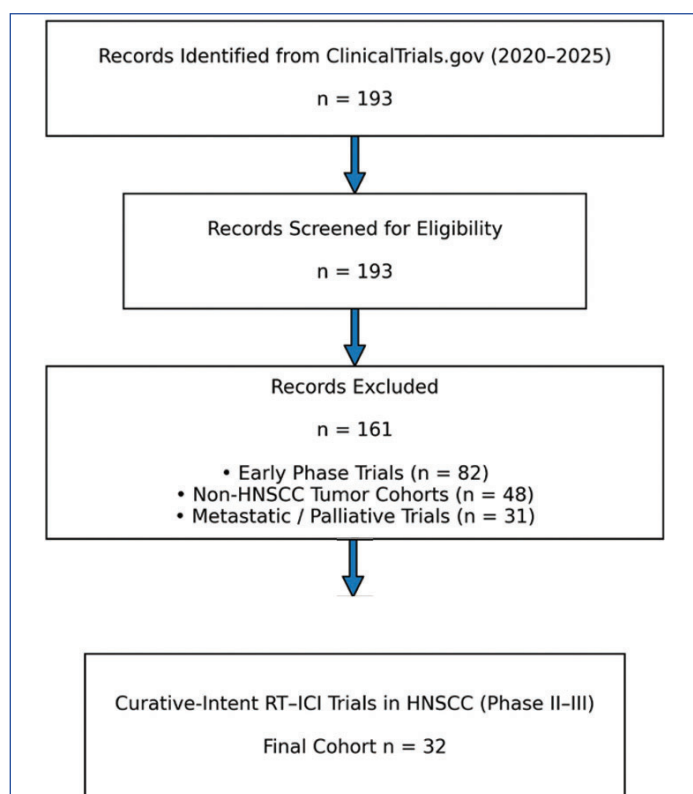
The wording of eligibility criteria was further evaluated to distinguish between standardised phrasing and trial-specific language. The classification of qualitative criteria was reviewed and agreed upon by all authors to ensure consistency.

This assessment complements the quantitative analysis by providing structured insight into how discretionary eligibility criteria may influence patient selection beyond predefined objective thresholds. The classification and interpretation of qualitative eligibility criteria were independently reviewed and subsequently discussed among all authors to achieve consensus and ensure consistency.

RESULTS

Trial Selection and Landscape of Research

The selection funnel: A total of 193 interventional trials were identified through ClinicalTrials.gov (2020-2025). After applying predefined eligibility criteria restricting inclusion to Phase II-III radiation immunotherapy trials in HNSCC, 32 studies (16.5%) constituted the final analytic cohort [Table/Fig-1] (Supplementary [Table/Fig-S1,S2]) The majority of excluded trials were early-phase studies (Phase I), mixed solid tumour studies without HNSCC-specific cohorts, or studies evaluating non-radiation immunotherapy approaches. This selection pattern suggests a degree of narrowing within the available evidence base; although immuno-oncology is a broad field, the number of late-phase, RT-ICI trials in HNSCC remains relatively limited. This constrained cohort highlights the relevance of the present aggregated analysis, as these trials collectively form the current evidence landscape in this setting.



[Table/Fig-1]: PRISMA Flow Diagram: Systematic selection of curative-intent RT-ICI trials in HNSCC (2020-2025).

Pooled Analysis of Eligibility Criteria

A pooled analysis of protocol-level eligibility variables across the 32 included trials demonstrated a high prevalence of restrictive criteria across multiple domains as seen below [Table/Fig-2]. Functional status restriction, defined as limitation to ECOG 0-1, was observed in 84.4% of trials, while 87.5% excluded patients with autoimmune disease. Age-based upper limits were applied in 56.3% of studies. Renal function thresholds, most commonly creatinine clearance ≥ 60 mL/min, were present in 43.8% of trials. Additional exclusion criteria included prior malignancy (81.3%), chronic steroid use (71.9%), and

significant cardiac disease (65.6%). Subjective exclusion criteria, such as investigator discretion or similar discretionary language, were identified in 81.3% of protocols. Overall, these findings indicate that restrictive eligibility criteria are frequently applied across multiple domains and often coexist within the same trial population.

Prevalence of Chronological and Performance Status Restrictions

Age limits: Explicit upper age limits were present in 18 of 32 trials (56.3%). The median age cap was 70 years (range: 65-80 years), and five trials imposed an upper age limit of 65 years, representing the most restrictive threshold. Given that the median age at diagnosis for HNSCC is approximately 67 years, these caps structurally limit enrollment of a substantial segment of the real-world disease population.

Domain	Criterion	Trials Applying Restriction (n)	Percentage (%)
Functional status	ECOG 0-1 only	27	84.4%
Renal function	CrCl ≥ 60 mL/min	14	43.8%
Autoimmune disease	Exclusion present	28	87.5%
Age	Upper age limit applied	18	56.3%
Prior malignancy	Exclusion present	26	81.3%
Steroid use	Exclusion present	23	71.9%
Cardiac disease	Exclusion present	21	65.6%
Subjective criteria	Investigator discretion	26	81.3%

[Table/Fig-2]: Pooled prevalence of restrictive eligibility criteria across included trials (n=32).

Performance Status Requirements

Twenty-seven of 32 trials (84.4%) restricted enrollment to ECOG performance status 0-1, while only five trials (15.6%) permitted inclusion of patients with ECOG 2. This high prevalence of functional status restriction narrows trial populations to physiologically robust individuals.

Renal Thresholds

A creatinine clearance (CrCl) ≥ 60 mL/min was required in 14 of 32 trials (43.8%), while the remaining 18 trials (56.2%) did not specify this threshold or allowed more flexible renal function criteria. This indicates that renal restrictions were applied in a substantial but not universal proportion of studies. Such requirements may limit participation of older patients with age-related renal decline, even when they may otherwise be suitable for radiation-based treatment.

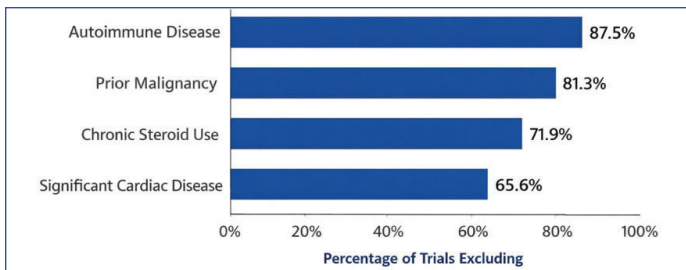
Co-morbidity Clusters

High rates of exclusion were observed across major co-morbidity domains. Autoimmune disease was excluded in 28 of 32 trials (87.5%), while only four trials allowed inclusion. Prior malignancy restrictions were present in 26 trials (81.3%), with six trials not applying this criterion. Chronic steroid use and cardiac disease were excluded in 23 (71.9%) and 21 (65.6%) trials, respectively, indicating that these restrictions were common but not universal.

Although these criteria were not uniformly applied across all studies, their high frequency suggests a consistent tendency to limit enrollment of patients with coexisting medical conditions. This pattern indicates that trial populations are preferentially composed of individuals with lower co-morbidity burden, which may reduce the representation of patients commonly encountered in routine clinical practice [Table/Fig-3].

Subjective Gatekeeping and Investigator Discretion

Subjective exclusion criteria, such as "investigator discretion" or "unsuitable for inclusion," were present in 26 of 32 trials (81.3%). While these clauses may allow clinical flexibility, they can also

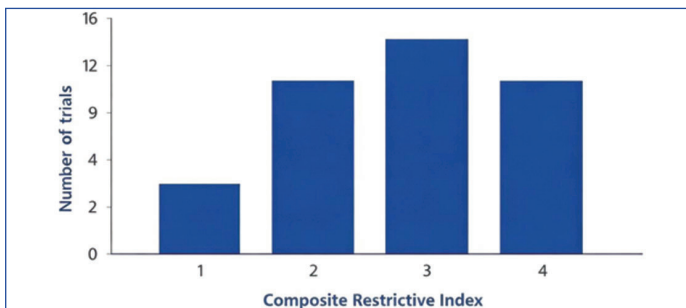


[Table/Fig-3]: Distribution of co-morbidity-based eligibility restrictions in phase II-III RT-ICI trials for HNSCC. Bar graph illustrating the proportion of trials excluding patients based on major co-morbidity domains, including autoimmune disease (87.5%), prior malignancy (81.3%), chronic systemic steroid use (71.9%), and significant cardiac disease (65.6%). The figure demonstrates the high prevalence of multimorbidity-related exclusions across contemporary trial protocols.

introduce variability in patient selection and may contribute to differences in access across institutions.

The Cumulative Restrictive Burden (Composite Analysis) A four-domain CRI, incorporating age restriction, ECOG 0-1 status, creatinine clearance ≥ 60 mL/min, and autoimmune exclusion, was used to assess cumulative eligibility filtering. The mean CRI score was 2.72 (SD 1.08; 95% CI: 2.35-3.09), with a median of 3 (IQR: 2-4) and a range from 1 to 4.

These findings indicate that most trials applied multiple restrictive criteria simultaneously, with the typical study requiring patients to meet at least three of the four physiologic eligibility conditions. Notably, 31.3% (10/32) of trials imposed all four restrictive domains concurrently, representing the most exclusionary tier [Table/Fig-4].



[Table/Fig-4]: Composite restrictive index distribution in phase II-III curative-intent RT-ICI trials for HNSCC. Histogram illustrating the distribution of Composite Restrictive Index (CRI) scores among 32 trials based on the presence of four major physiologic eligibility restrictions: age cap, ECOG performance status 0-1, renal function (CrCl ≥ 60 mL/min), and autoimmune exclusion. The median trial had a CRI score of 3

Comparison of Restrictiveness by Trial Phase

The median CRI did not differ significantly between Phase II and Phase III trials (median 3 vs 3; $p=0.84$), indicating a similar degree of eligibility restrictiveness across trial phases.

This suggests that restrictive eligibility criteria are consistently applied across both early- and late-phase trials rather than being confined to later-stage study designs.

Distribution of Restrictive Eligibility Criteria across Domains

To evaluate whether restrictive criteria were evenly distributed across physiologic domains, four primary filters were compared [Table/Fig-5].

Domain	Restrictive (n)	Restrictive (%)	Non-restrictive (n)	Non-restrictive (%)
ECOG 0-1 only	27	84.4%	5	15.6%
Autoimmune exclusion	28	87.5%	4	12.5%
Age cap present	18	56.3%	14	43.7%
CrCl ≥ 60 mL/min	14	43.8%	18	56.2%

[Table/Fig-5]: Distribution of restrictive eligibility criteria across major physiologic domains in Phase II-III radiation immunotherapy trials for HNSCC (2020-2025).

Performance status and autoimmune exclusions were the most prevalent restrictive domains.

Chi-square Analysis of Domain-level Heterogeneity

A chi-square test was performed to assess whether restrictive criteria were uniformly distributed across the four physiologic domains. The analysis showed no statistically significant difference in distribution ($\chi^2=6.47$, $df=3$, $p=0.091$). This suggests that restrictive criteria were applied across domains without strong clustering in any single domain. The effect size, measured using Cramér's V, was 0.26, indicating a moderate level of variation. Under the assumption of uniform distribution, each domain would be expected to have a similar number of restrictive instances. However, some variation was observed, with higher frequencies of performance status and autoimmune restrictions and lower use of renal thresholds. Despite this, the differences were not statistically significant.

Integrated Interpretation

Collectively, these findings demonstrate a substantial cumulative burden of restrictive eligibility criteria across contemporary Phase II-III RT-ICI trials. Although no statistically significant clustering was observed across domains, the high prevalence of performance status and immune-related exclusions combined with composite multi-domain filtering indicates a trial landscape that preferentially enrolls physiologically robust patients.

The cumulative effect of these layered eligibility filters supports the presence of a measurable "Eligibility Gap" between trial populations and the broader real-world HNSCC population. An integrated quantitative-qualitative synthesis of key eligibility domains is summarised in [Table/Fig-6].

Domain	Quantitative prevalence (%)	Qualitative interpretation
Functional Status (ECOG 0-1)	84.4%	Strong selection toward fitter patients; may underrepresent frail and elderly populations commonly seen in practice
Autoimmune exclusion	87.5%	Reflects safety concerns but excludes a clinically relevant subgroup frequently encountered in real-world settings
Age restriction	56.3%	Suggests partial exclusion of older patients despite disease predominance in elderly populations
Renal function (CrCl ≥ 60)	43.8%	May disproportionately exclude patients with age-related renal decline rather than true treatment intolerance
Prior malignancy	81.3%	Restricts inclusion of cancer survivors, limiting applicability in multimorbid populations
Steroid use	71.9%	May exclude patients with chronic inflammatory conditions requiring baseline immunosuppression
Cardiac exclusion	65.6%	Potentially limits inclusion of older patients with stable cardiovascular disease
Subjective criteria	81.3%	Introduces non-standardised "investigator discretion", adding variability and implicit selection bias
Cumulative restrictiveness (Mean CRI=2.72)	-	Indicates multiple overlapping filters, leading to systematically enriched trial populations

[Table/Fig-6]: Integrated quantitative-qualitative synthesis of eligibility restrictiveness.

DISCUSSION

This analysis demonstrates that modern Phase II-III RT-ICI trials in HNSCC are structurally restrictive across multiple physiologic domains. Although immunotherapy has transformed the management of advanced head and neck cancers [25,26], the eligibility architecture of contemporary trials appears selectively enriched for biologically robust patients.

Chronological-epidemiologic Mismatch

The HNSCC predominantly affects older adults, with a median age at diagnosis of approximately 66-67 years [27]. Despite this, 56.3% of trials in the study cohort imposed explicit upper age limits, most commonly around 70 years and five protocols limited enrollment to patients aged ≤ 65 years.

The use of age-based eligibility criteria remains controversial in oncology research. Current guidelines suggest that treatment decisions should be guided more by physiologic rather than chronological age [28,29], yet age-based restrictions continue to be applied across oncology trials [30]. In the context of HNSCC, where co-morbidity, frailty, and treatment tolerance are closely linked to age, such exclusions may limit the applicability of trial findings.

According to population-level data from the Surveillance, Epidemiology, and End Results (SEER) program, the median age at diagnosis for HNSCC is approximately 66-67 years, with a significant burden of disease seen in older age groups [31]. In contrast, more than half of contemporary Phase II-III RT-ICI trials impose explicit upper age limits, and most of the trials restrict enrollment to patients with ECOG 0-1. This contrast between the older age profile of patients with HNSCC and the selective nature of trial eligibility highlights a gap between trial populations and routine clinical practice, where older and more medically complex patients are commonly encountered.

Functional Selection and the “Athletes with Cancer” Phenomenon

Performance status emerged as the dominant structural barrier. An 84.4% of trials restricted enrollment to ECOG 0-1 patients. Only 15.6% permitted ECOG 2. ECOG performance status is strongly associated with survival, treatment tolerance, and immunotherapy responsiveness [32]. However, strict exclusion of ECOG ≥ 2 patients systematically filters out frail, elderly, and co-morbid individuals who comprise a substantial proportion of real-world HNSCC cases [33]. Previous studies across oncology trials have shown that performance status restrictions are among the most common and significant barriers to patient enrollment [34]. As trials tend to select patients who are more physically fit, their findings may overestimate both efficacy and tolerability. In contrast, real-world data suggest higher rates of toxicity and less favourable survival outcomes [35].

Immune and Co-morbidity Exclusion Clusters

Autoimmune disease exclusion was present in 87.5% of trials. Chronic steroid exclusion occurred in 71.9%, and significant cardiac disease exclusion in 65.6%. Prior malignancy restrictions were observed in 81.3%.

Checkpoint inhibitors carry known risks of immune-related adverse events [36], justifying caution in patients with pre-existing autoimmune disease. However, growing evidence indicates that carefully selected patients with controlled autoimmune conditions may be able to tolerate immunotherapy without significant issues [37]. As a result excluding all such patients may be overly cautious and could limit how well trial findings apply to routine clinical practice.

Similarly, restrictive prior malignancy criteria have been criticised for lacking strong evidence-based justification in many contexts [38]. Exclusion of patients with cardiac co-morbidities, although reasonable in some situations, may still end up excluding many older patients who otherwise have stable cardiovascular disease [39]. Together, these exclusion patterns suggest that trials tend to include patients with fewer co-morbidities rather than those typically seen in routine clinical practice.

Renal Function Thresholds and Geriatric Physiology

A Creatinine Clearance (CrCl) ≥ 60 mL/min threshold was required in 43.8% of protocols. Age-related nephrosclerosis frequently reduces estimated CrCl below this threshold in otherwise functional older adults [40]. While cisplatin eligibility has historically required

preserved renal function, modern RT-ICI regimens may not uniformly necessitate strict nephrotoxicity thresholds. Strict renal function cutoffs may therefore act less as safety requirements and more as a barrier to including geriatric patients in these trials.

The Gatekeeper Effect: Subjective Discretion as a Structural Filter

Subjective exclusion language “investigator discretion” or “unsuitable for participation” was present in 81.3% of trials. Although such clauses provide flexibility in clinical decision-making, they may introduce variability and potential bias in patient selection. Prior analyses of oncology trial enrollment have demonstrated that non-biologic barriers including socioeconomic factors, transportation, caregiver support, and clinician perception affect participation [41,42]. These kinds of discretionary exclusions may affect underserved groups more and can further widen existing differences in access to clinical trials. Importantly, subjective gatekeeping can act as an additional filter alongside objective clinical criteria.

Structural Imbalance in Restrictive Domains

Chi-square analysis demonstrated no statistically significant heterogeneity across the four primary restrictive domains ($\chi^2=6.47$, $df=3$, $p=0.091$), although a moderate effect size was observed (Cramér's $V=0.26$). Restrictive criteria were therefore relatively distributed across domains rather than sharply clustered within a single physiologic barrier. While ECOG 0-1 requirements and autoimmune exclusions were numerically more prevalent than renal thresholds, the overall distribution did not meet conventional thresholds for statistical significance. This suggests that eligibility restrictions in contemporary RT-ICI trials are applied across multiple domains, including performance status, co-morbidity, and organ function, rather than being concentrated in any single area.

The Cumulative Restrictive Burden

The mean composite restrictive Score was 2.72 (95% CI 2.35-3.09), with 31.3% of trials imposing all four major restrictive filters simultaneously. Thus, the typical Phase II-III RT-ICI trial requires patients to satisfy three major physiologic criteria concurrently. Although domain-level clustering was not statistically significant, the cumulative multi-domain structure creates a substantial eligibility barrier. Applying multiple eligibility criteria across age, functional status, renal function, and immune conditions likely results in a more selected group of patients, which may differ from the more diverse population seen in routine clinical practice. Comparable analyses across oncology disciplines have identified similar patterns of cumulative eligibility narrowing, contributing to what has been termed the “trial-practice gap” [43].

Implications for Generalisability

As immunotherapy is increasingly being used in head and neck cancer settings, it becomes more important that trial populations reflect real-world patients. Regulatory agencies and cooperative groups have also suggested that eligibility criteria should be updated to improve inclusion while still maintaining patient safety [44]. The present study findings suggest that, despite existing recommendations, restrictive eligibility practices continue to be used in RT-ICI trials for HNSCC. As a result, evidence is often generated in fitter patient populations, and clinicians may need to apply these findings to older and more co-morbid patients without direct supporting data. This may lead to both overtreatment and undertreatment in routine clinical practice.

Limitation(s)

This analysis was based on publicly available registry data and may not reflect protocol amendments or detailed eligibility clarifications. The authors assessed structural eligibility criteria rather than actual enrollment or screen failure rates, and therefore could not determine how many real-world patients would be ineligible. The classification of eligibility domains involved investigator judgment, which may introduce some degree of bias. In addition, the relationship between eligibility restrictiveness and trial outcomes was not examined.

CONCLUSION(S)

Modern radiation immunotherapy trials in HNSCC apply multiple eligibility restrictions across functional status, organ function, and immune-related conditions, with frequent use of performance status criteria and subjective exclusion language. Although no significant clustering of restrictions was observed, the overall pattern suggests that multiple criteria are often applied together. As HNSCC increasingly affects older and more co-morbid patients, reconsidering current eligibility practices may help improve how well trial findings apply to real-world clinical settings.

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