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Review

Immunotherapy Combined With Standard Therapies in Head and Neck Squamous Cell Carcinoma – A Meta-analysis

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Abstract. *Head and neck squamous cell carcinoma (HNSCC) is a deadly disease with a poor prognosis due to late diagnosis and limited treatment options. Immunotherapy (IT) is emerging as a promising approach, especially after the failure of standard of care therapies (STs). The objective of this systematic review and meta-analysis was to evaluate whether the addition of IT to STs improves outcomes for patients with HNSCC, including overall survival (OS), progression-free survival (PFS), and quality of life (QoL). This review employed the Population Intervention Comparison and Outcome (PICO) framework to identify relevant search terms in electronic databases, and also included supplementary hand searches. Six primary research articles were selected using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow chart, and were critically appraised. Data extraction from these studies was conducted, and a meta-analysis was performed to aid in the generation of forest plots. The addition of IT to standard anticancer therapies was found to enhance patient outcomes, such as OS, PFS, and QoL. The toxicity profile of IT was acceptable, with minimal treatment-related deaths. The most frequently observed adverse events (AE) were related to the skin, followed by hematological toxicities. Based on our analysis, the addition of IT to STs is a suitable treatment option and is supported by current research. However, further studies are needed to investigate factors that influence treatment effectiveness and to develop*

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optimal therapies. To achieve this, we recommend a comprehensive treatment approach that involves the multidisciplinary team (MDT) and patient assessment tools.

Head and neck cancer (HNC) comprises 5% of all malignancies worldwide, with head and neck squamous cell carcinoma (HNSCC) being the most common subtype (1). Approximately 650,000 new cases of HNC are diagnosed annually, resulting in 350,000 deaths (2). The primary risk factors for HNC are smoking, alcohol consumption, and Human Papilloma Virus (HPV) infection (3). Diagnosing HNSCC is challenging, and it is often detected when the disease is locally advanced or metastatic (4). The standard treatments (STs) for HNC depend on the primary tumour's location and traditionally include surgery, radiotherapy (RT), and chemotherapy (5). In the early stages (I and II), surgery and RT have high cure rates, with one- and two-year survival rates of 88.7% and 79.8%, respectively. However, relapses can still occur despite intensive treatment, leading to a poor prognosis (6). For cases where relapse occurs or upfront metastatic tumors are present, the aim of treatment is palliative rather than curative (7). For the last three decades, platinum-based chemotherapy has been the standard of care for these patients, with a median overall survival (OS) of approximately seven months (8). Immune checkpoint inhibitors (ICIs) were initially evaluated after frontline therapies failed, and have since transformed the outcomes for these patients (9).

Recent studies have suggested that combining ICIs with STs may improve patient outcomes compared to chemotherapy-based regimens (10). Research has also demonstrated that incorporating ICIs into radiotherapy (RT) enables modified fractionation, thereby decreasing the radiation dose delivered to the circulating blood supply (11). This technique preserves proximal lymphocytes while still promotes anti-programmed death-ligand 1 (PD-L1) antibody activity, thereby enhancing the effects of ICIs (11). Additionally, research has indicated that the combination of RT and ICIs can induce an abscopal effect. In this phenomenon, local treatment triggers a systemic anti-tumor immune response, affecting distant metastatic lesions that were not directly exposed to radiation (12, 13). This systematic literature review and meta-analysis aims to provide current evidence on the use of ICIs in combination with STs for patients with HNSCC, evaluating whether it improves survival outcomes and patients' quality of life (QoL).

Methods

This study utilized a literature review methodology to gather data, following the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The research question was formulated using the Population Intervention Comparison and Outcome (PICO) framework (14). The rationale for using PICO is that it helps create a clear, focused research question, which assists in the database search process by highlighting relevant keywords (15). The refined PICO question for this study was, "Does adding immunotherapy (I) to standard therapies (C) improve outcomes (O) for patients with head and neck squamous cell carcinoma (P)?".

To identify eligible primary research articles, we conducted a comprehensive search of four electronic databases. We selected Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete and MEDLINE Complete for their wide range of nursing, medical, and health-related topics. We included Embase and the Cochrane Central Register of Controlled Trials (CCRCT) for their specific focus on drug therapy research. The use of CCRCT can be criticized because it does not contain full-text articles, which limited our ability to gather studies. However, we included it because it provided valuable data to facilitate our understanding of the efficacy of immunotherapy (IT) and encourage further reading and research relevant to the review question.

Using different databases with various specialties and entering the keywords ensured a broad range of research was obtained (16). We performed four searches to gather a wealth of information on the effects of combining IT and STs on the outcomes of HNSCC patients. We began by conducting searches using different variations of the PICO keywords combined with the Boolean operator 'OR' and truncations to broaden the search (Table I). We then combined these searches with the Boolean operator 'AND' Table I), yielding 349 results before applying limiters (Table II).

Hand searching was employed to supplement the database searches as research has shown that this method can help locate up-to-date articles, enabling a broader yet efficient search (17). In total, five studies were found through hand searching, and after applying filters, a total of 39 articles were identified, which were reduced to 32 after removing duplicates. The abstracts of these articles were screened using inclusion and exclusion criteria (Table II) to determine their eligibility for review. After duplicates were removed and limiters, inclusion, and exclusion criteria were applied, the articles were refined to six. These six full-text papers were critically evaluated for eligibility, and the methods were assessed using critical appraisal tools (Appendix I). For this review, the Critical Appraisal Skills Programme (CASP) for cohort studies and the Centre for Evidence-Based Medicine (CEBM) for prognostic studies appraisal tools were used (Appendix I) (18, 19). These tools are useful as they provide structured checklists allowing the simplified breakdown of research. The CASP was selected because four of the six studies evaluated were retrospective cohort reviews, making it the most appropriate appraisal tool (18). The CEBM tool was chosen because it analyzes studies that consider chosen variables and how these impact the outcome of a disease; thus, it was the most applicable for the non-randomized clinical trials examining the impact of IT plus or minus ST (19).

Data was extracted from the selected articles, including the

Table I. *Outline of PICO search strategy and results.*

Boolean operator	P	I	C	O	MEDLINE complete	CINAHL complete	Embase	CCRCT
OR	"HNSCC"	IT	CT	"PFS"	29,628	6,613	41,349	1,924
OR	"HNC"	Biological therapy	Anti-cancer therapy	Palliate	251,376	14,122	205,027	6,045
OR	"Oral cancer"	Biotherapy	5-FU	Remission	349,372	47,049	518,533	30,861
OR	"Oropharyngeal cancer"	Biological response modifier therapy	Platinum CT	"QoL"	417,538	123,463	661,477	72,615
OR		Monoclonal antibodies cetuximab			103	41	186	19
OR and Total						349		

PICO: Population Intervention Comparison and Outcome; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CCRCT: Cochrane Central Register of Controlled Trials; HNSCC: head and neck squamous cell carcinoma; IT: immunotherapy; CT: chemotherapy; PFS: progression-free survival: HNC: head and neck cancer; 5-FU: 5-fluorouracil; QoL: quality of life.

Table II. *Inclusion, exclusion and limiting factors for research articles.*

	Factors	Rationale
Limiters	Full text with references available	To allow them to be thoroughly analysed for inclusion in the review.
	Peer reviewed	To reduce bias and ensure they were high quality.
	Patients must be adults (18+)	To ensure relevance to field of practice. HNSCC is most likely to develop in adults due to the environmental nature of its aetiology
	English language	Translation is beyond the scope of this review.
	Research must be published after 2008	To guarantee the most current evidence is reviewed.
Inclusion	Primary research critiquing the use of IT in conjunction with STs (RT/CT) or IT when ST has failed	To ensure relevance to the aims and objectives set by this dissertation. • To ensure a baseline histology for all patients from which to make comparisons
	Patients must have HNSCC	• Because HNSCC is the most common histological type of HNC
	Use objective measurements of patient outcomes (PFS, OS, symptom palliation, adverse effects, QoL)	• To minimise risk of experimenter bias • To ensure results are valid and generalisable to target population
Exclusion	Systematic reviews	To ensure primary, peer reviewed research is analysed
	Study protocols	Due to lack of generalisability to the target population.
	Case studies	
	Lacking a strong link of IT to patient outcomes	To ensure relevance to the PICO key terms

HNSCC: Head and neck squamous cell carcinoma; ST: standard therapy; RT: radiotherapy; CT: chemotherapy; IT: immunotherapy; CT: chemotherapy; PFS: progression-free survival: OS: overall survival; QoL: quality of life; PICO: Population Intervention Comparison and Outcome.

authors, year of publication, country of origin, study design, sample size, methods of patient recruitment, and outcomes. A meta-analysis was performed using the extracted data. This review considered quantitative data, with all studies containing statistics regarding overall survival (OS) and progression-free survival (PFS). A forest plot was generated to visualize the data, facilitating the identification of statistical and clinical significance from the summarized evidence (20).

Results

The methodology for screening the selected articles is demonstrated using the PRISMA framework, as shown in Figure 1 (21). The 32 articles found through database and hand searches were initially screened by title and abstract for eligibility. Of these, eight full-text articles were assessed for eligibility for appraisal, and six articles were deemed appropriate for review. A summary of these articles can be seen in Table III.

Study characteristics. The studies included in this meta-analysis were conducted in various countries, including one in the USA (22), one in France (23), one in Germany (24), one multicentre study in France and Belgium (25), one in Spain (26), and one conducted internationally (27). Among the selected articles, four used a retrospective cohort study

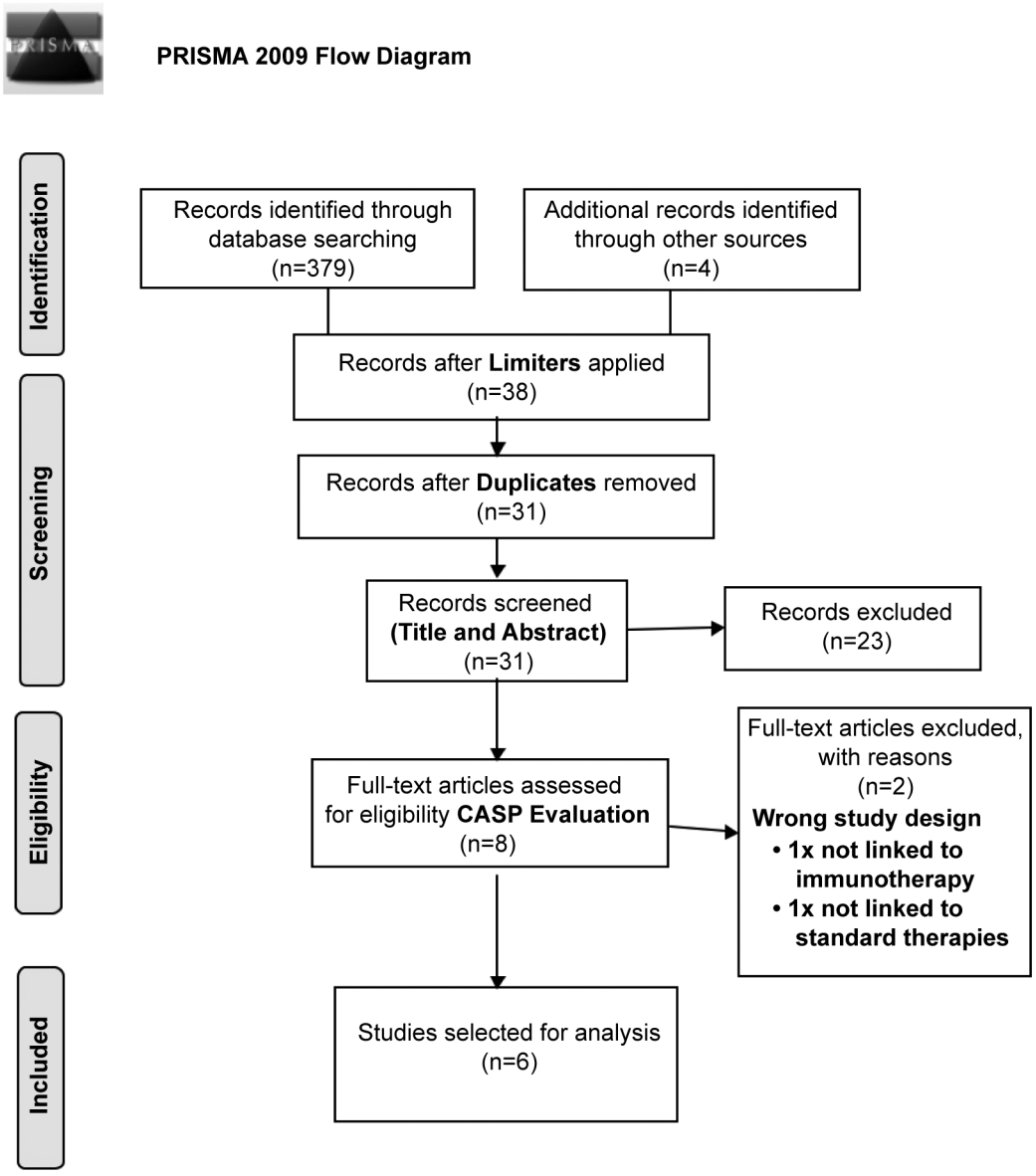

Figure 1. *The PRISMA flowchart illustrates the method used to select references through the search process. Revised from Moher et al. (21).*

design (22-24, 26) and two were prognostic, non-randomised phase II studies (25, 27). Three studies employed mixed methods (22, 26, 27) and three used quantitative methods (23-25).

Table III presents the sample sizes, sex distribution, and median age of the participants in the reviewed studies. Vargo *et al*. (22) included 28 patients, Burgy *et al*. (23) included 59 patients, Milanovic *et al*. (24) included 23 patients, Guigay *et al*. (25) included 54 patients, Sosa *et al*. (26) included 33 patients, and Zandberg *et al*. (27) included 112 patients. The sex distribution and median age of the participants varied among the studies.

Small sample sizes in research can be problematic when attempting to generalize findings to the larger population. However, in the studies by Burgy *et al*. (23) and Sosa *et al*. (26), the authors acknowledged the issue of small sample sizes. Sosa *et al*. (26) justified their small sample size by highlighting how their results were consistent with other similar studies. Burgy *et al*. (23) excluded certain patients from their study in order to prioritize patients' safety, as there is currently no standard care for elderly HNSCC patients. Although Burgy *et al*. (23) specifically studied an elderly population, this should not be viewed as a limitation, as older adults are a group with a higher risk of developing HNSCC,

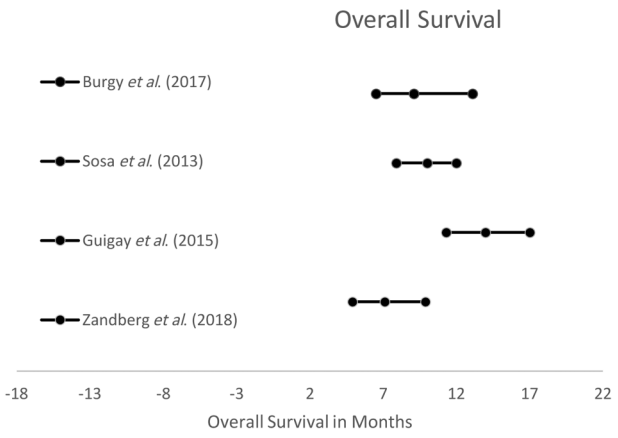

Figure 2. *Forest plot displaying the overall survival data.*

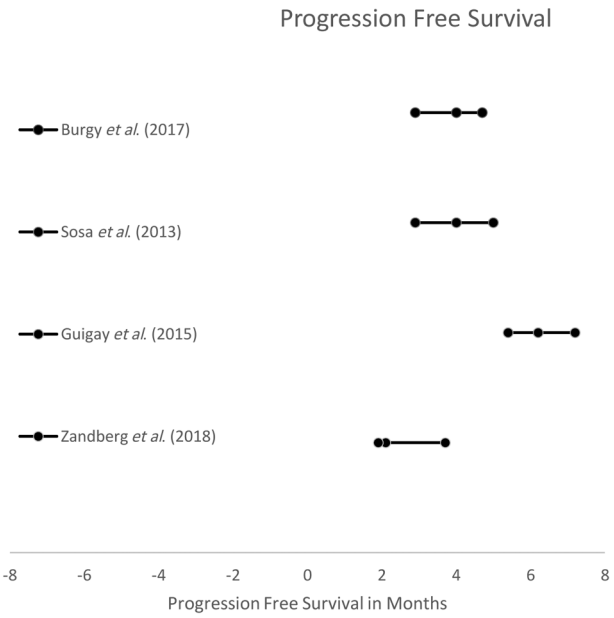

Figure 3. *Forest plot displaying the progression-free survival data.*

thus identifying appropriate treatments for this population is critical.

An additional weakness of the reviewed research is that it did not account for patient characteristics such as socioeconomic status and ethnicity. These factors can play a significant role in the development of HNSCC, treatment effectiveness, and patient QoL (28, 29), which can impact the validity and generalizability of the findings to the entire HNSCC patient population.

Considering the PICO question (14), all six studies reviewed in this meta-analysis assessed the population of HNSCC patients who received IT interventions and evaluated the outcomes such as OS and PFS. In terms of comparison, two studies examined the effect of cetuximab as an adjuvant to chemotherapy (23, 25). Two studies investigated the impact of cetuximab with RT (22, 24), and Zandberg *et al*. (27) studied the IT agent durvalumab, a monoclonal antibody that targets the PD-L1 receptor. However, it can be argued that Zandberg *et al*.'s (27) study did not fully address the PICO question of this review as it did not assess the addition of IT to STs. Nonetheless, evaluating the efficacy of IT monotherapy may indicate whether IT is a useful addition to ST or if it could be used as a treatment alone. A limitation of this review is that the reviewed articles did not include a control ST arm for comparison with the IT and ST combination. Hence, the selected studies alone do not address the PICO question of this review.

All six reviewed articles employed data and statistical analysis methods to determine outcomes such as OS and PFS, using the Kaplan–Meier method (as detailed in Table III) (22-27). Two of the mixed methods studies utilized questionnaires to obtain qualitative data on patient QoL (22, 27). Vargo *et al*. (22) used the validated University of Washington Quality of Life Revised (UW-QoL-R) questionnaire, which measures patient-reported QoL (PR-QoL) with 12 head and neck and three global domain Likert-type questions. Zandberg *et al*. (27) employed the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire, containing 30 core and HNC-specific symptoms, with the corresponding HNC EORTC module used throughout treatment to give researchers a comparison point. Sosa *et al*. (26) informally asked participants about their perceptions of their pain and anxiety (whether they felt more, equal, or less) regarding their tumors at every three-week follow-up, evaluating adverse events (AE).

Key findings and themes. Efficacy. To determine whether adding IT to ST improves outcomes, it is important to establish efficacy. This meta-analysis measured OS and PFS, as shown in Table III, by using patient baseline values when treatment started. Forest plots for OS and PFS were created for Burgy *et al*. (23), Guigay *et al*. (25), Sosa *et al*. (26), and Zandberg *et al*. (27) (Figure 2 and Figure 3), while Vargo *et al*. (22) and Milanovic *et al*. (24) were excluded. Vargo *et al*. (22) measured the percentage of OS and PFS at different patient follow-up intervals, and Milanovic *et al*. (24) did not include confidence intervals, making their data incompatible. The forest plots show point estimates and interquartile range (IQR) for OS and PFS, with the studies using median and IQR data rather than standard deviation and means. This method is resilient to outliers and normal data, making it easier to identify anomalies (30).

The forest plot for OS, which is measured from patient baseline (before treatment) until death or the Kaplan–Meier

Table III. *Summary of the reviewed papers*.

Study	1	2	3	4	5	6
author and reference	Vargo *et al*. (22)	Burgy *et al*. (23)	Milanovic *et al*. (24)	Guigay *et al*. (25)	Sosa *et al*. (26)	Zandberg *et al*. (27)
Year	2014	2017	2013	2015	2013	2018
Country	America	France	Germany	France and Belgium	Spain	International
Number of participants and median age	28 (M=16, F=12) 66 years Adjuvant therapy (7) ST alone (21)	59 (M=52, F=11) 70 years	23 (M=21, F=2) 60.9 years	54 (M=52, F=2) 57.7 years	33 (M=30, F=3) 65 years	112 (M=80, F=32) 60 years
Design	Retrospective, mixed methods single centre, cohort review of a 2 arm study	Retrospective, single institution quantitative cohort study	Retrospective, single institution quantitative cohort study	Single arm, non-randomised phase II, quantitative multicentre clinical trial	Retrospective, mixed methods, cohort study	Single arm, phase II non-randomised single centre, mixed methods study
Aims	Evaluation on whether SBRT +/– cetuximab improves tumour control whilst reducing treatment related toxicity post salvage-surgery	Investigation of the efficacy, toxicity profile, outcome and safety of cetuximab plus platinum-based CT regimen in patients >65 years with recurrent or metastatic HNSCC	Assessment of the feasibility, toxicity and outcome of reirradiation, combined with EGFR blockade	Assessment of the safety and efficacy of 4 cycles of docetaxel plus cisplatin and cetuximab, followed by 2-weekly maintenance cetuximab in patients with recurrent/ metastatic HNSCC	Evaluation of the efficacy of weekly paclitaxel and cetuximab as a second line treatment	Assessment of the safety and efficacy of durvalumab monotherapy in patients with PD-L1 high tumour expression, metastatic/ recurrent HNSCC that progressed after platinum CT
IT agent, ST, and target receptor	Cetuximab and SBRT	Cetuximab and platinum based CT	Cetuximab and external beam re-RT	Cetuximab and docetaxel and cisplatin	Cetuximab and paclitaxel	Durvalumab
Data and statistical analysis	All statistics were performed using SPSS version 19.0 The RECIST was used to identify locoregional control The Kaplan–Meier method was used to estimate tumour control and survival, whilst comparisons between groups were achieve using log-rank *t*-tests QoL analysis was done using UW-QoL-R and compared with Wilcoxon signed rank test baselines	The RECIST 1.0 was used as a secondary endpoint along with PFS AEs were classified according to CTCAE version 4.0 guidelines OS and PFS were concluded using the Kaplan–Meier method Qualitative variables were analysed using a log-rank test, whereas quantitative using the Cox model All analyses were done with R 3.1.0 software and the survival package	All statistical analyses performed using the open statistical analyses software environment (survival time from completing treatment was the dependent variable) The relationship between prognostic factors and survival was measured using the Cox proportional hazards model Survival rates were estimated using the Kaplan–Meier method, side effects were scored using the CTCAE v3.0	Toxicities were graded using the NCI-CTCAE v3.0 Tumours were graded using the RECIST 1.0 The Simon's two-stage optimal design for phase II clinical trials was utilised for statistical analyses	The RECIST 1.1 was used to document disease progression The NCI-CTCAE v3.0 toxicity scale was utilised to rank toxicity All statistical analyses were performed using the PASW Statistics package version 20.0.0 Survival was estimated by the Kaplan–Meier product-limit method and the log rank test was used to compare the two survival curves Patients were assessed for AEs every 3 weeks and asked about any pain and anxiety variations (more, equal, less so)	Blinded independent central review measured using the RECIST 1.1 CTCAE v4.3 was used to assess AE occurrence PFS and OS distributions were measured using Kaplan–Meier methodology QoL was measured using EORTC QoL questionnaire, whilst any HNC specific symptoms were measured using the corresponding module.

Table III. *Continued*

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OS (median)	Median follow up of 14 months Both groups: 64% Adjuvant subgroup 67%	9.1 months	9 months	14 months	10 months	7.1 months
PFS (median)	Median follow up of 14 months Both groups 49% Adjuvant subgroup 53%	4 months	4.3 months	6.2 months	4 months	2.1 months

M: Males; F: females; ST: systemic treatment; RT: radiotherapy; HNSCC: head and neck squamous cell carcinoma; IT: immunotherapy; CT: chemotherapy; EGFR: epidermal growth factor receptor; PD-L1: programmed death ligand 1; SBRT: stereotactic body radiotherapy; RECIST 1.1: Response Evaluation Criteria in Solid Tumours (version 1.1); NCI-CTCAE v3.0: National Cancer Institute-Common Terminology Criteria for Adverse Events (version 3.0); AEs: adverse events; QoL: quality of life; PFS: progression-free survival: OS: overall survival; EORTC: European Organisation for Research and Treatment of Cancer; HNC: head and neck cancer; UW-QOL-R: University of Washington Quality of Life Revised.

estimation of this, indicates outcome homogeneity (*i.e.*, consistency in the results across the studies) as the IQR overlap.

The forest plot for PFS, which measures the time from patient baseline until disease progression or the Kaplan–Meier estimate of this, also demonstrates consistency in the results of the four studies.

The consistency of outcomes observed between the reviewed studies indicates a high level of internal validity and reproducibility, making the findings applicable to the general population. However, a limitation of these studies is the absence of a comparison arm to compare the outcomes of IT combined with ST *versus* ST alone. Therefore, in the discussion section, it is necessary to compare the results of the reviewed articles with similar current research that has a comparison arm. This leads to data indirectness, which can affect data quality and applicability. However, since the reviewed articles have clinical homogeneity, meaning they assess similar population groups using similar treatment protocols that are not different enough to affect the results, a "similarity assumption" can be made. Nonetheless, data quality still needs to be downgraded accordingly (31).

The risk of bias can affect the grade and applicability of research findings. Among the reviewed studies, Vargo *et al*. (22), Burgy *et al*. (23), Milanovic *et al*. (24), and Sosa *et al*. (26) have low to moderate risk of bias (see Appendix II), while Guigay *et al*. (25) and Zandberg *et al*. (27) have low risk of bias (see Appendix III). This suggests that the findings of the reviewed articles are valid and transferable to the HNSCC patient population.

Quality of life. The six papers reviewed have highlighted determinants of QoL, which is a holistic assessment of patients' overall wellbeing. Two key determinants identified were AE and treatment regimen, which impact attrition rate. Three studies used qualitative assessments of patients' QoL (22, 26, 27) and all showed improvements in patients' QoL. For example, Sosa *et al*. (26) found that "all responding patients improved the feeling of local pain and anxiety caused by the tumour". Zandberg *et al*. (27) found clinically significant improvements in global health status, physical functioning, and fatigue. The increase in global and physical functioning is particularly meaningful as it suggests an overall improvement in the patient's health status. Clinically meaningful improvements were also seen in HNC-specific symptoms such as taste and smell, swallowing, mouth pain, and speech.

Furthermore, Vargo *et al*. (22) found that 56% of patients reported that their QoL had improved or remained the same throughout the trial. PR-QoL remained stable throughout the entirety of the head and neck-specific and general health-related criteria for the duration of survey examination. Mean scores obtained from UW-QoL-R responses were compared, using the Wilcoxon signed-rank test, to patient baseline scores and a p-value of less than 0.05 was deemed statistically significant. Thus, the specific UW-QoL-R result for pain (p=0.034) and activity ($p \leq 0.41$) when compared from patient baseline to one year showed a statistically significant improvement, which is arguably clinically significant. This suggests that the combination of IT and ST may improve patients' QoL.

Adverse events. All six articles reviewed reported on AE and treatment-related adverse events (TRAE). Three studies reported treatment-related deaths (23-25). Burgy *et al*. (23) had the highest percentage of treatment-related deaths (5%), all due to sepsis. Milanovic *et al*. (24) reported a patient death due to anaphylaxis during initial intravenous administration of cetuximab. Guigay *et al*. (25) reported a death of unknown attribution. The impact of TRAE and treatment-related death on study attrition rates needed to be better addressed by the

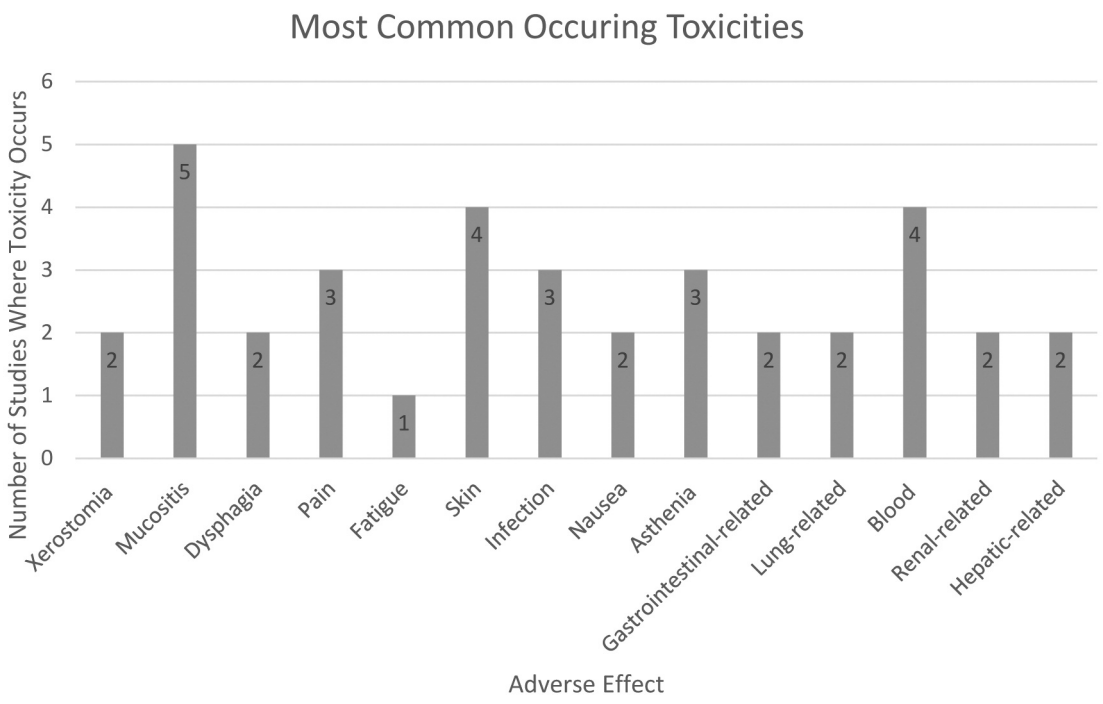

Figure 4. *Most commonly occurring grade 1-4 adverse events.*

reviewed articles, as this may consequently bias results, reducing the reliability of the research findings.

Four of the studies utilized the Common Terminology Criteria for Adverse Events (CTCAE) to evaluate adverse events and toxicities (23, 24, 26, 27), while Vargo *et al*. (22) and Guigay *et al*. (25) employed the National Cancer Institute's CTCAE v3.0 to grade AE. However, Vargo *et al*.'s (22) AE were recorded by physicians rather than patients at baseline, which they acknowledged as a limitation as it may lead to an underestimation of toxicity. To mitigate potential bias, Vargo *et al*. (22) also used PR-QoL to assess AE.

One limitation of this review is that it compares studies that use different grading systems for AE. This is problematic because there may be differences in the standardized terms used for each tool to record and grade the AE, and research has shown that grading tools such as CTCAE are often misused (32). However, Zhang *et al*. (32) concluded that this is clinically insignificant because, despite variations, the reader's ability to understand the treatment toxicity profile is not affected. Figure 4 depicts the most frequently occurring AE of any grade, which include mucositis (22-26), skin (22, 24, 25), and haematological toxicities (23, 25-27).

Common grade 3 and 4 toxicities reported in the reviewed studies were related to blood (23, 25-27), infection (22, 23, 25), and skin (24-26) and are illustrated in Figure 5. According to the Cancer Therapy Evaluation Program's (33) CTCAE, grade 3 and 4 toxicities are classified as "severe AE" and "life-threatening or disabling AE", respectively, indicating a significant impact on patient QoL. Therefore, it is promising to note the relatively low occurrence of these toxicities in the 6 studies. For instance, in Vargo *et al*.'s (22) study, 57% of patients experienced no acute and 80% had no late toxicities, whereas in Milanovic *et al*. (24), no grade 4 toxicities were reported.

Treatment regimen and attrition. Table IV summarizes the treatment regimens and attrition rates observed in the included review articles. Noting inconsistencies in the treatment regimes for the analysed studies is essential as this affects validity. Clinical homogeneity, which refers to the similarity and comparability of the method of intervention implementation and outcome measurement, can be observed between the six studies, thus suggesting that their findings are reliable and replicable.

Considering attrition rates, Vargo *et al*. (22) and Milanovic *et al*. (24) had the best attrition rates, with all patients completing the regimen; 20 out of 23 patients completing the ST element, and 23 out of 23 completing the IT part of the regimen, respectively. Both studies had the same adjuvant therapy (RT and cetuximab). Two of the studies showed that patients had an allergic response to cetuximab (24, 26). The most common reason for discontinuation of the treatment was disease progression, followed by adverse events and

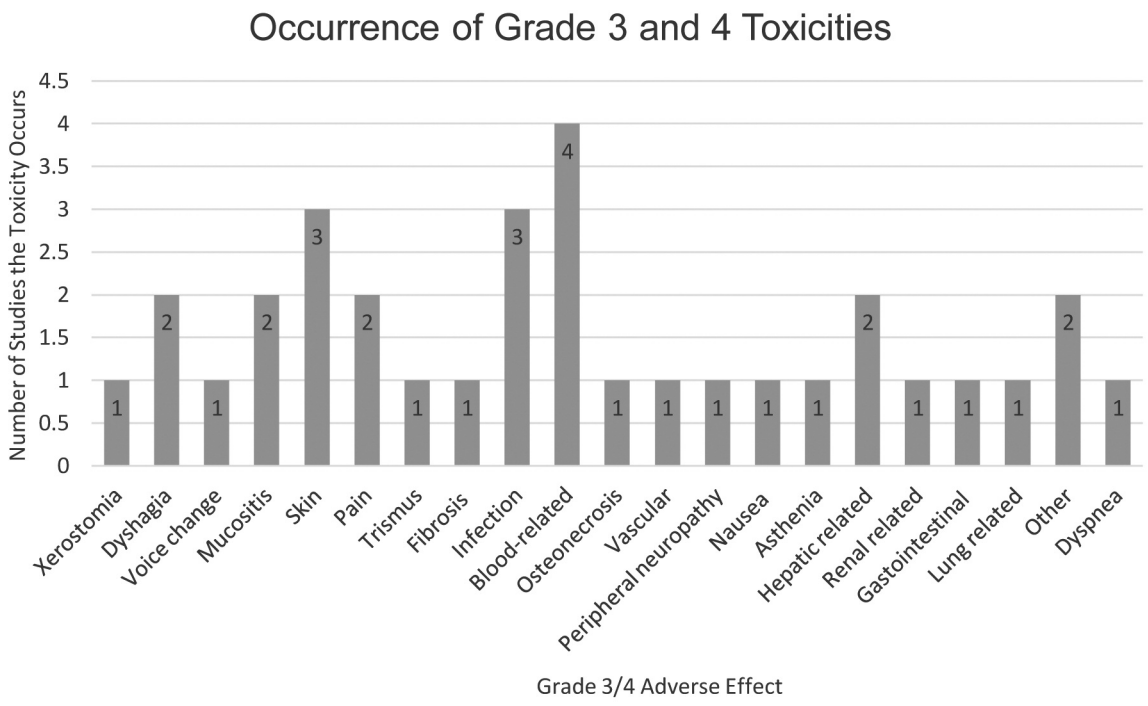

Figure 5. *Grade 3 and 4 toxicities*.

unacceptable treatment toxicity, treatment-related death, and personal decision.

Discussion

The findings of this review can be grouped into four main discussion points, namely efficacy, QoL including AE, treatment regimen, and attrition. Additionally, recommendations for practice, research, and education are evaluated.

The four reviewed articles that assessed the combination of IT and ST (23-26) showed similar values for OS and PFS as current research that evaluated the same combination (34). Vermorken *et al*.'s research (34) also found significant improvements in OS and PFS between adjuvant therapies *versus* the ST alone arm, providing further support for the combination of IT and ST. Figure 6 illustrates a statistically significant difference in OS between the combination of IT and ST compared to ST alone in four of the reviewed studies and the EXTREME trial. Conversely, Zandberg *et al*. (27) found no significant difference in OS. They only examined IT monotherapy, suggesting that the improvement in OS is due to the combination of IT and ST rather than single modality ST or IT.

The majority of the reviewed studies on adjuvant ST and IT showed an improvement in PFS compared to ST alone, as depicted in Figure 7. However, Zandberg *et al*. (27) reported a decrease in PFS compared to ST alone. Both Szturz *et al*.'s (35) EXTREME trial and Guigay *et al*. (25) showed statistically significant improvements in PFS compared to ST. While Burgy *et al*. (23) and Sosa *et al*. (26) also demonstrated improvement, it was not statistically significant.

It is crucial to differentiate between statistical and clinical significance, especially in the context of survival data (36). This is because a patient adding a month to their overall survival may not be statistically significant, but the clinical benefit of gaining this extra month to spend with their loved ones outweighs this statistical insignificance. Moreover, a treatment that leads to a statistically significant increase in overall survival may not be appropriate if it is accompanied by intolerable toxicity that diminishes the patient's QoL (37). Hence, a comprehensive evaluation of significance is necessary while making treatment recommendations.

Burgy *et al*. (23) and Guigay *et al*. (25) investigated the use of adjuvant cetuximab and chemotherapy, with Guigay *et al*. (25) reporting the longest OS (14 months) and PFS (6.1 months) among all the reviewed studies. The National Institute for Health and Care Excellence (NICE) also recommends this combination and suggests the use of cetuximab and platinum-based chemotherapy followed by maintenance cetuximab until disease progression for recurrent HNSCC (38). Therefore, the review's findings are consistent with NICE's treatment recommendation, indicating that adding IT to the ST regimen can improve patient outcomes.

Table IV. *Attrition rates and treatment regimens of the reviewed papers.*

Study	1	2	3	4	5	6
author and reference	Vargo *et al.* 2014 (22)	Burgy *et al.* 2017 (23)	Milanovic *et al.* 2013 (24)	Guigay *et al.* 2015 (25)	Sosa *et al.* 2013 (26)	Zandberg *et al.* 2018 (27)
Attrition	All patients completed adjuvant SBRT at a median of 68 days, following salvage surgery	8/59 treatment permanently interrupted due to toxicity 3/8 developed grade 3 infusion-related reaction to cetuximab first dose 1/8 developed 5-FU-induced unstable angina 3/8 developed grade 3 asthenia 1/8 developed grade 3 thrombo-cytopenia and neutropenia 3/59 treatment-related deaths (sepsis) 39/59 stopped CT regime, due to progression and occurrence of AE	20/23 completed prescribed course of re-RT 23/23 received the prescribed cetuximab 1/23 death due to cetuximab induced anaphylaxis on initial administration 2/23 discontinued upon their own request after receiving part of the re-RT regime	No patients were lost to follow up One patient remained on maintenance cetuximab >22 months after the study AEs led to CT or cetuximab discontinuation in 9.2% of patients 6/54 patients could not be evaluated at week 12, due to toxicities leading to treatment discontinuation 4/54 patients died prior to evaluation	1/33 had an allergic reaction within minutes of first cetuximab administration and was not included in analysis 1/33 had half dose of cetuximab, due to cutaneous toxicity 1/33 had reduced paclitaxel due to peripheral neuropathy 28/33 disease progression 2/33 end of programmed treatment 2/33 toxicity 1/33 patient decision	21/112 completed treatment 27/112 remained on the study on treatment or on follow up 91/112 discontinued treatment (69.6% disease progression, 7.1% AE and 4.5% patient decision) Median treatment duration was 3.5 months 9/112 had TRAE that led to durvalumab dose interruptions but no TRAE led to death
Regime	All patients had surgical salvage with curative intent and an R0/1 resection Prior to each treatment and on follow up the patients were given the UW-QoL-R questionnaire SBRT was administered in 5 fractions on alternating days over 1 to 2 weeks Patients were considered for concurrent cetuximab (400 mg/m^2 day-7 and 250 mg/m^2 days 0 and +8) and they did not have to be cetuximab-naïve	Carboplatin (AUC 5 on day 1) + 5-FU CT (1,000 mg/m^2/day from day 1-4) and cetuximab (initial dose 400 mg/m^2, followed by weekly dose 250 mg/m^2) regime for ≥6 cycles plus or minus cetuximab monotherapy	Prescribed total dose of 50.4 and 66 Gy at daily fractions of 1.8 Gy on 5 successive days per week In 22/23 patients, cetuximab (400 mg/m^2) administered 2 days prior to re-RT and then weekly throughout the re-RT at 250 mg/m^2 1/23 received 400 mg/m^2 of cetuximab after re-RT at 10.8 Gy Patients seen weekly for FBC and metabolic-panels Toxicity recorded at baseline, every week through treatment and then 3 monthly Follow up 6 weeks after regime completion and then 3/4 monthly	Day 1: IV docetaxel (75 mg/m^2), cisplatin (75 mg/m^2) and cetuximab (400 mg/m^2 week 1 and 250 mg/m^2 on subsequent administrations), as well as day 8 and 15 Cycles were repeated every 3 weeks for 4 cycles with systematic granulocyte colony-stimulating factor support at each cycle After 4 cycles, cetuximab 500 mg/m^2 was administered every 2 weeks as maintenance therapy	Weekly paclitaxel at 80 mg/m^2 plus cetuximab (initial 2h infusion of 400 mg/m^2 followed by 1×weekly 1h infusion of 250 mg/m^2) All patients were visited 3/52 to search for AEs and were questioned about pain and anxiety Preliminary evaluation of tumour response in 6 weeks and final in 12 weeks In responders, treatment continued for a further 12 weeks and then stopped	10 mg/kg durvalumab every 2 weeks, up to a year or until disease progression, initiation of an alternative anti-cancer therapy, unacceptable toxicity or consent withdrawal Upon any progression, patients were given the option to continue durvalumab for an additional year

ST: Systemic treatment; RT: radiotherapy; CT: chemotherapy; SBRT: stereotactic body radiotherapy; AEs: adverse events; 5-FU: Fluorouracil; AUC: area under the curve; TRAE: Treatment Related Adverse Effects; FBC: full blood count; UW-QOL-R: University of Washington Quality of Life Revised.

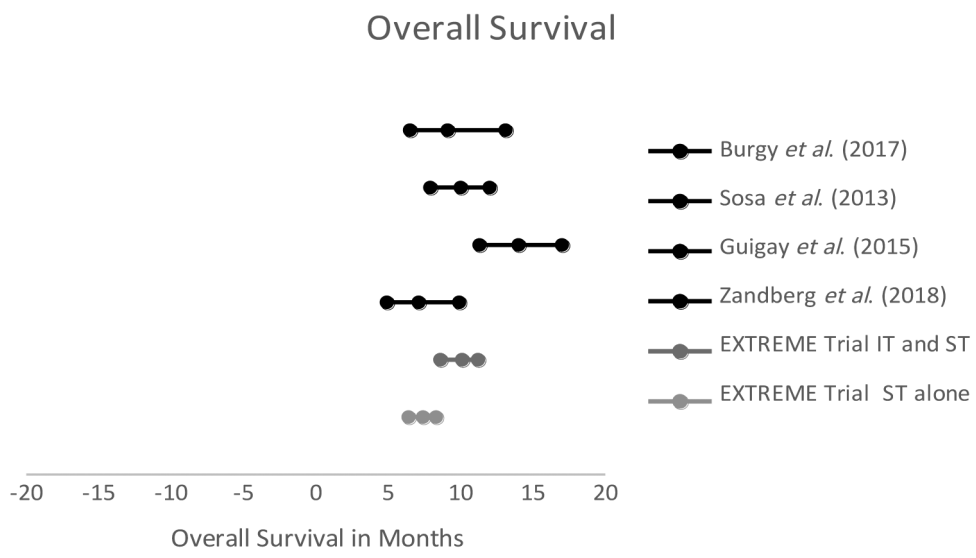

Figure 6. *Forest plot showing overall survival in reviewed studies versus current research.*

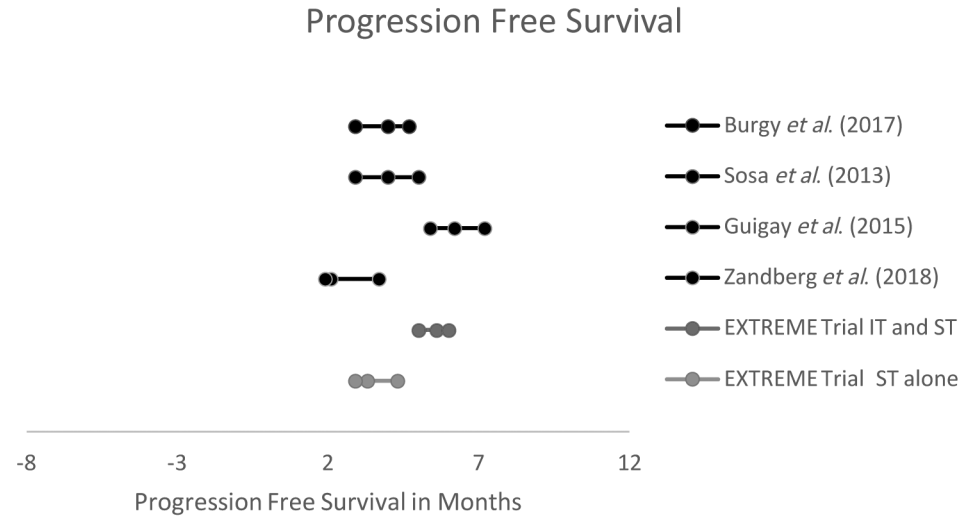

Figure 7. *Forest plot showing progression-free survival in reviewed studies versus current research.*

Additional support for the use of adjuvant IT and ST comes from a case report of a patient who participated in the EXTREME trial and achieved a disease-free survival of eight years, with a relatively low to moderate incidence of adverse events except for grade 3 stomatitis (39). However, it is important to note that case studies have limitations as their findings may not be generalizable to the larger population due to individual differences (40).

The findings from the two reviewed articles on combination RT and IT (22, 24) show promise, but there is currently limited clinical guidance on the use of this approach for palliating HNSCC. Palliative RT and IT can be justified by a case study results of a patient with inoperable salivary gland mucoepidermoid carcinoma who underwent re-RT and cetuximab, resulting in a complete response after 25 months with good tolerability (41). However, the transferability of these findings to HNSCC is difficult due to differences in individual cell types' responses to therapy, such as differences in oxygen supply, tumour proliferation, and density (42, 43). This highlights a weakness in the reviewed articles' methodology as tumour sites with potentially different responses to treatments were not distinguished between. This

could affect the reliability and replicability of the review findings. Nonetheless, all the tumours in the reviewed studies were of the same histological type, which reduces this bias.

Zandberg *et al*.'s (27) study on IT alone had the lowest median OS (7.1 months) and PFS (2.1 months) among the reviewed studies, indicating that the combination of IT and ST is more effective than either IT or ST monotherapy. However, this contradicts the findings of NICE (44) that single IT increased OS by 2.6 months compared to chemotherapy, upon which their recommendation for nivolumab as a second-line treatment for patients who recurred after platinum-based chemotherapy was based. Similarly, the United States Food and Drug Administration recommends second-line nivolumab and pembrolizumab (45), but concerns have been raised about nivolumab's efficacy in low-PD-L1-expressing HNSCC. Zandberg *et al*.'s (27) methodology highlighted the PD-L1 tumor expression issue since only patients with highly expressed PD-L1 tumors were included in their research on durvalumab treatment, making the research focused on the sub-group most likely to respond to this therapy. Therefore, their results may be biased, unrepresentative, and lack generalizability.

Prioritizing patient well-being is a nursing care standard, and preserving QoL is an essential outcome of anticancer therapy (46, 47). In the case of HNSCC, symptom relief (6), improving QoL, and disease control are often the main objectives for patients (48). Thus, addressing these outcomes is necessary for adjuvant immunotherapy to be appropriate and improve patient outcomes. Three reviewed studies demonstrated increased patient QoL (22, 26, 27). These functional improvements are supported by the findings of Harrington *et al*. in their Phase III study Checkmate 141, who found both statistically and clinically significant improvements in role and social functioning, fatigue, appetite, pain, and sensory problems, among others, in the immunotherapy *versus* standard therapy arm (49). Zandberg *et al*. (27) and Harrington *et al*. (49) had similar results using the same assessment and treatment method, suggesting these findings are generalizable. However, the EXTREME trial – contradictory to Vargo *et al*. (22) and Zandberg *et al*. (27) – found non-statistically significant improvement compared to baseline in the immunotherapy and standard therapy arm compared to standard therapy alone for general QoL (50). However, the HNSCC-specific symptoms of pain, swallowing issues, speech, and social eating were significantly improved, which was supported by the review findings (22, 26, 27). In conclusion, this suggests that adding immunotherapy to standard therapy specifically improves HNSCC-related symptoms and patient QoL compared to standard therapy alone.

When considering the benefits of IT on patient outcomes, efficacy is a crucial factor. However, a treatment may be effective, but if it is not safe, then it may not be suitable (51). Three of the reviewed studies reported treatment-related deaths, but grade 3 and 4 toxicities were relatively infrequent (23-25). Vargo *et al*. (22), Burgy *et al*. (23), and Sosa *et al*. (26) all concluded that IT is an acceptable addition to ST in the treatment of HNSCC patients, who are often immunocompromised and thus vulnerable (52). Guigay *et al*. (25) also supported the tolerability of the IT and ST safety profile for HNSCC. Their findings are consistent with those of Vermoken *et al*. (6), who commented on the satisfactory adverse event profile in the EXTREME trial, noting no cetuximab-related deaths. These findings suggest that the addition of IT to ST may reduce toxicity compared to ST alone.

None of the reviewed articles stated that patients discontinued treatment due to the intensive treatment regimen (Table IV). However, the effect of treatment plans on patient QoL should not be ignored, as decreased quality of life can affect patients' treatment adherence and, consequently, treatment effectiveness. It could also potentially lead to a waste of limited healthcare resources (53-55).

The results regarding treatment attrition rates for IT plus ST *versus* ST alone are conflicting. Milanovic *et al*. (24) reported that all 23 patients completed the prescribed IT, but only 20 out of 23 received the ST However, Vargo *et al*. (22) had a 100% completion rate. Mésia *et al*. (50) also support the reviewed studies' findings, reporting higher dropout rates in their chemotherapy arm compared to the IT and chemotherapy combination. However, Lee *et al*. (56) found that the addition of IT to induction chemotherapy reduced completion rates. The impact of IT on ST completion rate requires further study to determine a causal link that could potentially improve treatment attrition rates and optimize patient outcomes.

Vargo *et al*. (22) described how their treatment plan, which used target RT and took advantage of radiobiological benefits, resulted in a more effective regimen that delivered fewer large fractions, thereby reducing treatment time and acute toxicities compared to standard RT. Addeo *et al*. (57) also supported the use of IT for treatment optimization, as they found that the use of maintenance IT after adjuvant IT and chemotherapy improved effectiveness, convenience, tolerance, and compliance with the treatment plan. However, further research is necessary to weigh the costs and benefits of optimizing treatment.

The review findings, along with current research, have identified areas for development in practice, education, and further study. Table V summarizes the strength of the recommendation to implement IT as an adjuvant to ST in the treatment of HNSCC (58). The analysis of these findings suggests that IT as an adjuvant to ST can address the issue of poor outcomes for HNSCC patients compared to ST alone by improving OS, PFS, and QoL. Although IT is expensive (59), the unit cost per benefit is low. Therefore, this review argues that the addition of IT to ST is appropriate.

More data is required to comprehend why some patients respond better to treatment than others and how to overcome

Table V. *GRADE evidence to decision; the approach used for making a healthcare recommendation – Adapted from Alonso-Coello et al (59).*

	Criteria	Judgements	Explanation/Research Evidence
Problem	Is the problem a priority?	Yes	HNSCC, especially that which is recurrent/metastatic, has a poor prognosis and limited ST options.
Benefits and harms of the options	Are the anticipated desirable effects large?	Yes	IT plus ST shown statistically significant improvements to OS and PFS compared to ST alone (see Figures 6 and Figure 7). Research has shown large improvements in patient QoL with patients reporting reductions in tumour-related pain and anxiety.
	Are the anticipated undesirable effects small?	Varies	Research states an acceptable toxicity profile for IT and minimal treatment related deaths. Grade 3 and 4 toxicities were observed, most commonly skin-related.
	What is the overall certainty of the evidence of effects?	Moderate	Statistically and clinically significant improvements in OS and PFS seen in the adjuvant IT and ST compared to ST. Statistical and clinical improvements seen in patient QoL. However, none of the studies reviewed having comparison groups; their findings have had to be compared to other existing literature.
	Is there important uncertainty or variability about how much people value the main outcomes?	Probably no	No known publication bias or withheld data.
	Do the desirable effects outweigh the undesirable effects?	Yes	The weight of the desirable effects of adjuvant IT and ST (improved OS, PFS and patient QoL) are larger than the undesirable effects (small toxicity profile, minimal treatment-related deaths).
Resource Use	Are the resources required small?	Uncertain	IT is expensive and it may cost more to implement than current standards of care (58). However, it may save financial resources due to improved treatment attrition rates, thus healthcare resources are not wasted (55). More clinicians may be required to facilitate IT and provide an MDT approach, however whether the cost of this for IT and ST compared to ST alone is unknown.
	What is the certainty of resource requirements?	No important uncertainty	
	Are the net benefits worth the incremental cost?	Yes	The cost per unit of benefit is low which makes the option a priority.
Equity	What would the impact be on health equity?	Uncertain	Interculturally, due to the high cost of IT it may be a treatment better suited to westernised cultures where there are more financial and healthcare resources compared to other, non-western cultures (58). In the UK where there is a national health service, there is little impact on health equity. In the USA where healthcare is covered by insurance, there may be issues with what insurances will or will not cover which may impact on the health equity of IT.
Accessibility	Is the intervention/option acceptable to key stakeholders?	Yes	Patients Physicians Employers Insurance Companies Pharmaceutical firms Government
Feasibility	Is the intervention feasible to implement?	Yes	There are no obvious barriers or difficulties to overcome to implement IT adjuvant therapy.

Combined IT and ST (cetuximab and platinum based CT) has been applied in first line palliative care in the UK. HNSCC: Head and neck squamous cell carcinoma; ST: systemic treatment; IT: immunotherapy; OS: overall survival; PFS: progression-free survival; QoL: quality of life; MDT: multidisciplinary team; CT: chemotherapy.

potential barriers such as drug resistance (60). Investigations into the impact of HPV status, which has been shown to be a confounding variable for positive treatment outcomes, may help identify ways to increase treatment efficacy, such as survival and response rates. This is supported by Zandberg *et al*. (27), who reported a 29.4% response rate in HPV-positive tumors compared to 10.8% in non-HPV-positive tumors. Similar results were published by Lee *et al*. (56). Additionally, further research into utilizing the IT and ST regimen to improve HNSCC patients' QoL and functionality would aid them in continuing to participate in activities of daily living, which is a primary nursing goal (61).

Two of the studies reviewed in this analysis used a multidisciplinary team (MDT) approach for treatment and assessment (22, 24). Research in oncology suggests that MDT input can improve outcomes and overcome barriers to patients receiving holistic care (48, 62). An MDT approach is particularly important for the treatment of HNSCC, which is complex and requires a range of expertise (63). Therefore, the utilization of an MDT approach is recommended in this review. Additionally, the implementation of systematic assessment tools for patients, such as the PR-QoL (22), could streamline the treatment process, ensure holistic assessments, and improve patient outcomes. These tools could be incorporated through nursing education and training.

One weakness of this review is the limited number of studies included, with only six selected in total. This was due to strict inclusion and exclusion criteria, such as study design, which meant that most of the available research did not meet these criteria. Furthermore, four of the studies were retrospective in design, which can lead to selection bias and small sample sizes. Retrospective studies like those reviewed in this article are more susceptible to selection bias because the participants must be representative of the same population, such as having HNSCC (64). However, retrospective cohort study designs have the benefit of using archived data, making them quicker and cheaper to conduct than follow-up prospective cohort studies (65). Moreover, they validate evidence and confirm relationships between treatment, such as IT, and data, like OS and PFS, from other weaker studies, which then safely facilitates further prospective research (65).

A general limitation of this study is that it only reviewed research published up to 2019, which threatens the comparability and applicability of the findings to current treatment recommendations (66). Since then, subsequent research has been published, including the EAGLE and Keynote-048 phase III studies by Ferris *et al*. (67) and Harrington *et al*. (68), respectively, which discuss the impact of IT and ST in the treatment of HNSCC. Ferris *et al*. (67) found no statistically significant differences in OS in IT monotherapy (durvalumab and dervalumab-tremelimumab) *versus* ST alone, similar to Zandberg *et al*. (27). However, they noted increased response and survival rates between 12 and 24 months for patients receiving durvalumab, indicating its clinical activity. Both Zandberg *et al*. (27) and Ferris *et al*. (67) examined IT monotherapy alone, suggesting that the significant improvement in OS in the other studies evaluated in this paper is due to the combination of IT and ST rather than single modality ST or IT. This deduction is supported by Harrington *et al*.'s Keynote-048 study, which found that pembrolizumab monotherapy and pembrolizumab-chemotherapy improved OS and PFS compared to ST second-line taxanes alone (68). Evaluating this current research against the original studies analysed in this review allows for comparison of findings across different conditions, interventions, and time, which enables a discussion of whether one can be confident in the initial conclusions drawn. The homogeneity of subsequent research findings with the original evidence analysed demonstrates its quality, as the outcomes are clearly replicable over time, and thus have external validity. Therefore, it is fair to infer that these results are reliable despite the latest research (69).

Lastly, a potential limitation of this review is that all the studies analysed were conducted in high-income countries, which may limit the generalizability of the findings to low and middle-income countries (70). This is particularly problematic since IT is expensive (59) and may not be affordable or appropriate in resource-limited settings. Additionally, none of the included studies were conducted in the UK. Vargo *et al*.'s (22) study was conducted in the USA, which could be a concern given the differences in healthcare policies and guidelines between countries. For instance, in the USA, cetuximab is approved as a first-line monotherapy for HNSCC, whereas in the UK, it is approved as a first-line combination therapy with platinum chemotherapy (8). However, since these studies focused solely on the effects of IT on patient outcomes, the findings are still relevant.

It is worthy to be mentioned that sex-specific medicine, an evolving field in healthcare, has garnered substantial recognition and significance in recent years. In a retrospective case-matched analysis, there was an observed tendency for female patients to exhibit a higher 5-year OS probability compared to their male counterparts across different therapeutic regimens for HNSCC (71). Furthermore, real-world data have been recently published regarding the efficacy and safety of palliative first-line ICIs in platinum-sensitive patients with recurrent or metastatic HNSCC treated outside of a clinical trial, thus closely mirroring clinical practice. The data revealed a disease control rate of nearly 50% and a response rate of approximately 20% in a disease with a historically unfavourable prognosis. Notably, these treatments were relatively well-tolerated by patients with multiple comorbidities (72).

Finally, we should report that no direct comparison has been made so far to determine the superiority between pembrolizumab monotherapy and pembrolizumab combined with chemotherapy for treating recurrent or metastatic HNSCC.

Patients who experience adverse events with ICIs, specifically immune-related adverse events, tend to exhibit more favorable prognoses and may also demonstrate long-term maintenance of efficacy. In a recently published study, the addition of chemotherapy did not contribute to an improvement in prognosis (73). Therefore, when contemplating the long-term treatment of patients with recurrent or metastatic HNSCC, opting for pembrolizumab monotherapy may be more favourable than combination therapy. Moreover, the use of monotherapy has the potential to mitigate additional adverse effects associated with combination therapy.

Conclusion

Based on the selected articles, it can be concluded that IT is a useful adjunct to ST in the treatment of HNSCC. This conclusion is supported by current research and guidelines that suggest combining IT and ST leads to improved patient outcomes such as OS and PFS. Moreover, the results indicate that IT is a safe and appropriate addition to ST, with acceptable adverse effects and toxicities observed and minimal treatment-related deaths.

Furthermore, incorporating IT into HNSCC treatment has been demonstrated to enhance patient QoL by improving general function and addressing head and neck specific symptoms such as tumour-related pain and anxiety, swallowing difficulties, and appetite issues. Therefore, from a patient-centred perspective, the combination of IT and ST provides a clinically significant benefit.

However, additional research is required to understand the reasons for variations in patients' responses to treatment and to identify and overcome any potential barriers to therapy success. The implementation of policies related to patient assessment and multidisciplinary team collaboration will also enhance the approach to HNSCC treatment.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

DE – conceptualization, writing – original draft preparation, writing – review and editing; AG – conceptualization, data curation, writing – review and editing, visualization; MM – methodology, validation, resources; JAPF – software, formal analysis, project administration; ER – validation, investigation; SB – conceptualization, validation, writing – review and editing, supervision, funding acquisition.

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