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Systematic Review

The effects of continued smoking in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis

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ABSTRACT

Purpose: To determine the effects of continued smoking in head and neck cancer (HNC) patients undergoing radiotherapy on overall survival (OS), locoregional control (LRC), quality of life (QoL) and acute and late toxicities.

Methods: Articles from January 1990 to August 14, 2018 were searched in PubMed, MEDLINE (Ovid), Embase, Scopus, The Cochrane Library, CINAHL and AUSThealth. Articles were included if majority of patients were treated with radiotherapy and smokers were defined as those who continued to smoke during or after radiotherapy. Data extraction and risk of bias assessment was performed by three independent co-authors using summary data of original studies. A meta-analysis using a random effects model was conducted for OS and LRC. In addition, a qualitative synthesis was performed for toxicities and quality of life as only a limited number of articles were available.

Results: The initial search identified 2217 studies, with 24 articles comprising 6332 patients eligible for inclusion. Analysis demonstrated that continued smoking was associated with approximately two times the risk of mortality (RR = 1.85, 95% CI 1.55–2.21, $p < 0.0001$, $I^2 = 43\%$) in HNC patients. Similarly, the risk of locoregional failure was more than two times greater in HNC patients who continued smoking (RR = 2.24, CI 1.42–3.52, $p = 0.0005$, $I^2 = 64\%$). The qualitative synthesis indicates that continued smoking may contribute to an elevated incidence of late but not acute toxicities.

Conclusions: This review provides evidence that continued smoking is associated with a lower OS and LRC and a higher incidence of late toxicities. Therefore, clinicians should strongly encourage smoking cessation amongst all head and neck cancer patients.

Head and Neck cancer (HNC) is the ninth most common malignancy in the world and includes tumours within the oral cavity, nasal cavity, pharynx and larynx [1,2]. More than 90% of these malignancies are squamous cell carcinomas, with smoking, alcohol and human papilloma virus (HPV) being the major recognised risk factors [1–3]. Prognosis for these patients has largely remained unchanged, with a 5-year overall survival rate of 66% [4]. Current treatment options for HNC include various combinations of radiotherapy, surgery, and chemotherapy, depending on the stage and location of the tumour. Early stage disease (I or II) is often treated with surgery or radiation alone, whilst advanced stage disease (III or IV) usually involves multimodality treatment [2]. Radiotherapy (RT) is an integral component of the clinical management of HNC, with up to 80% of patients receiving RT as part of their treatment [5]. Smoking after a diagnosis of HNC is relatively common, with 55% of patients who were smokers at diagnosis found to be still smoking at 1-year follow-up [6]. This has significant prognostic implications for patients undergoing RT, where continued smoking has been suggested to reduce the efficacy of this treatment modality through the induction of chronic hypoxia [7,8].

A number of studies [9–11] have investigated the prognostic value of smoking status at diagnosis in HNC patients, but few have evaluated the effects of continued smoking after diagnosis. From a clinical perspective the period after a diagnosis is critical as it represents a "teachable moment" in which health professionals can encourage smoking cessation [12]. Only one systematic review has previously been conducted to assess the effects of continued smoking in HNC patients [13]. However, this review included

Abbreviations: HNC, head and neck cancer; OS, overall survival; LRC, locoregional control; QoL, quality of life.

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studies with up to 50% of patients treated with surgery alone and did not specifically evaluate the potential interaction of continued smoking with RT or its effects on toxicities and quality of life. Furthermore, this review included limited studies and did not perform a meta-analysis due to reported heterogeneity. The aim of the current review was to investigate the effects of continuing to smoke during or after RT on overall survival (OS), locoregional control (LRC), quality of life (QoL) and acute and late toxicities in patients with HNC.

Methods

This study followed the PRISMA and MOOSE guidelines for systematic reviews and meta-analyses. A study protocol was registered with the PROSPERO database (registration number CRD42018087473).

Eligibility criteria

This systematic review included studies that complied with the following criteria.

Inclusion criteria:

1. Patients with squamous cell carcinomas of oral cavity, larynx and pharynx.
2. Patients were treated with radiotherapy (as the sole modality or in conjunction with chemotherapy or surgery).
3. Smokers were defined as those who continued to smoke during or after radiotherapy.
4. Reported data for a continuing and ceased smoking group for at least one of the following outcomes:
   - Primary: OS and LRC
   - Secondary: Acute and late toxicities and QoL
5. Early and late toxicities were graded as per standardised criteria – Radiation Therapy Oncology Group (RTOG), European Organisation for Research and Treatment of Cancer (EORTC) or Common Terminology Criteria for Adverse Effects (CTCAE).
6. Quality of life measured using a validated tool.

Exclusion criteria:

1. Inadequate definition of smoking status provided.
2. Abstract only articles with no full text publication available.

Information sources and searches

Using the search strategy outlined below, the following databases were searched: PubMed, MEDLINE (Ovid), Embase, Scopus, The Cochrane Library, CINAHL and AUSThealth. The citations of the articles selected for inclusion were analysed to identify further relevant studies. For the most relevant studies, a Google Scholar 'cited by' search of the first 50 results was performed. Searches were limited to those published in English and between January 1990 until the date the search was conducted (April 19th, 2018). A second search was conducted on August 14th, 2018 to identify articles that may have been published whilst the manuscript was being prepared. The search strategy for PubMed can be found in Appendix A, with alterations made for use in alternative databases.

Study selection

The retrieved articles were initially screened based on their titles and abstracts by the first author (JS) who created a list of articles for full text analysis. These articles were then independently screened in full text by a second review author (DN) and assessed for suitability. Disagreements were resolved by consultation with a third reviewer (MC).

Data collection process

Three authors (JS, DN, RT) piloted the initial data extraction form and agreed upon any required alterations. These researchers then conducted the data extraction independently. Disagreements were resolved with an additional researcher (MC). The corresponding authors of original studies were contacted for additional data if required. One author [14] provided raw data from their study, which was used to calculate the QoL scores for continuing and ceased smokers.

Data items

Data were extracted for each included study relating to participant characteristics, study methodology and outcomes. Further details are demonstrated in Appendix B.

Risk of bias in individual studies

The risk of bias in the included studies was conducted using a modified Newcastle–Ottawa quality assessment scale. Studies were rated as low, medium or high quality using a modified version of this scale (Appendix C). Low quality articles were those with a score of 0–3, whilst a score of 4–5 was considered moderate quality, and 6–7 high quality. The quality assessment was conducted independently by the co-authors (JS, DN, RT) with another co-author (MC) consulted if there were any disagreements. Only articles deemed of a moderate or high quality were included in the meta-analysis.

Summary measures

A meta-analysis was performed for OS and LRC, which is presented as an overall risk ratio (RR) with 95% confidence intervals (95% CI). Given substantial variations in reporting of toxicities, the results of this outcome are presented as the percentage of events occurring. As only one study reported on QoL a quantitative synthesis was also not possible for this outcome.

Synthesis of results

A random effects model was used in the quantitative synthesis to account for expected heterogeneity amongst the studies. All computations were performed using "RevMan 5" software and statistical significance was defined at the conventional 5% level. The heterogeneity was evaluated through I^2 and Tau^2 tests. Whilst the outcome of interest was LRC, papers reporting local control [17–22] were also included in the meta-analysis as these studies included only early laryngeal cancers with a low risk of regional failure.

Risk of bias across studies

Funnel plots were created in RevMan 5 and grey literature such as conference abstracts were examined to allow assessment of publication bias. To minimise selective reporting bias, articles which reported the absence of an association were also screened and their stated findings discussed.

Sensitivity analysis

A sensitivity analysis was performed to determine the robustness of the observed outcomes. In particular, a leave-one-out method was used to repeat the full set analysis to determine whether these changes have any effect on the combined outcome estimate. A sub-group analysis was performed to assess the influence of quality of studies on the results.

Results

Study selection

The initial search across all databases identified 3452 studies (Appendix D). After duplicates were removed, this number was reduced to 2217. A title and abstract screen was then conducted, with 73 articles selected for full text analysis. Fifty-two of these articles were later excluded, with 16 due to insufficient data for continuing and ceased smokers. Three [23–25] of the 16 articles with no data stated the presence or absence of an association but did not report actual values. These articles are mentioned below in the relevant paragraphs, with their stated findings. Eight were excluded as the majority of patients did not receive RT, 14 because the outcomes reported weren't relevant and 13 because the smoking status definition was inadequate. Another study was excluded [26] as its results were duplicates of an included study [17]. Three studies [22,27,28] were added in based on the reference lists of the initially included studies, which left 24 studies for inclusion in the review. Nine articles [7,15–20,22,29] were included in the quantitative analysis for OS or LRC, with two of these studies [7,17] having data on both outcomes.

Study characteristics

The study characteristics for the included articles are summarised in Appendix E. Sixteen studies (67%) reported on smoking status during RT [7,15–17,20,22,28–37] and eight (33%) investigated smoking status post-RT [14,18,19,27,38–41]. Of these, only three studies (12.5%) performed an analysis on current smokers at baseline (pre-treatment) who either continued or ceased smoking [31,35,41]. There were significant variations in the types and locations of cancers involved, with some studies analysing low stage glottic tumours only [17–19,22,34]. There were two studies which did not have all patients receiving RT as part of their management [40,41]. Both of these studies had greater than 80% of participants undergoing RT and were included in the qualitative synthesis.

Risk of bias within studies

The results of the quality assessment using the modified Newcastle Ottawa tool are shown in Appendix C. Ten studies (42%) were determined to be of moderate quality [14,17–20,22,28,33,34,37], thirteen studies (54%) of high quality [7,15,16,27,29–32,35,36,38,40,41] and one study (4%) of low quality [39]. Only one study utilised biochemical verification to ascertain smoking status [16]. Eight studies (33%) had more than 20% of their cohort with no smoking status recorded [17,18,20,22,28,31,34,39].

Overall survival

The OS rates for ceased and continuing smokers are presented in Table 1. Five studies reported OS rates and were included in the meta-analysis [7,15,17,21,29]. Analysis revealed that patients who continued smoking had almost two times greater risk of mortality when compared with those who ceased smoking (RR = 1.85, 95% CI 1.55–2.21, $p < 0.0001$, $I^2 = 43\%$; Fig. 1). Platek et al. reported a 5-year OS for continuing and ceased smokers for both a HPV + and HPV- group, with continuing smokers having an increased risk of mortality irrespective of HPV status [29]. Browman et al. did not report data for a continuing and ceased smoking group but reported combined 2-year survival values for a "lighter" (abstainers and ≤1 cigarette/day) and "heavier" (>1–10/day, 11–20/day and >20/day) smoking group [16]. These figures were included in the meta-analysis as 71.4% of the "light smoking" group were abstainers confirmed on biochemical verification. Three studies [30,32,41] reported hazard ratios only and could not be included in the meta-analysis but found that continuing to smoke during RT resulted in a significant reduction in overall OS. Choi et al. reported hazard ratios for continuing smokers, quitters (those who smoked at diagnosis but quit) and former smokers in comparison to never smokers [41]. This study demonstrated that the highest hazard ratio was for continuing smokers (HR = 2.71, $p = 0.001$) with a reduced hazard ratio (HR = 2.38, $p = 0.005$) for patients who quit smoking after their diagnosis.

Locoregional control

Incidences of LRC for included studies are presented in Table 2. Quantitative synthesis (Fig. 2) revealed that patients with HNC who continued to smoke had more than two times greater risk of locoregional failure when compared with those who ceased smoking (RR = 2.24, CI 1.42–3.52, $I^2 = 64\%$, $p = 0.0005$). Two studies [28,31] reported LRC rates but did not state the numbers of continuing and ceased smokers and therefore could not be included in the meta-analysis. Both articles found that continuing smoking was associated with significantly lower 5-year LRC rates [28,31].

Acute & late toxicities

Data reported for acute and late toxicities in each of the relevant studies is described in Table 3. There were substantial variations in the outcomes used for quantifying these toxicities and therefore a quantitative analysis was not possible. A qualitative synthesis of these data suggests that continued smoking is associated with an increase in late but not acute toxicities.

As shown in Table 3 only one study by Rugg et al. found a statistically significant association between continued smoking and acute toxicities [33]. Subsequent studies found higher rates of acute toxicities, but these differences did not reach statistical significance [36,37]. Another study by Chen et al. reported that ceased smokers had higher rates of acute toxicities, but this association was not statistically significant [7]. Four articles describing correlations between smoking and acute toxicities did not provide adequate data for inclusion in the review [15,16,23,30]. Porock et al. was the only study which found a positive correlation between continued smoking and acute toxicities, reporting a statistically significant correlation between number of cigarettes smoked and severity of mucositis [23]. Skin toxicities were also increased in continuing smokers in this study [23]. Other studies with insufficient data all reported a negative correlation [15,16,30]. Browman et al [15] analysed stomatitis and skin toxicities but found no differences between continuing and ceased smokers, and in the associated follow-up study found no association between smoking and radiation-induced mucositis [16]. Gillison et al. also found no differences in rates of severe mucositis (grade ≥3) between continuing and ceased smokers [30].

Two studies reported late toxicities as an incidence of Grade III or higher toxicity (Table 3) [7,36]. These studies measured multiple toxicities such as fibrosis, laryngeal oedema, dysphagia, trismus and osteoradionecrosis (ORN). Five articles presented data for specific late toxicities, with four on ORN [7,27,35,38] and one for chondroradionecrosis [39] All these studies demonstrated higher rates of late toxicities in continuing smokers, but only two were found to be statistically significant [27,35].

Quality of life

Only one study (Silveira et al.) reported on the QoL of ceased and continuing smokers [14]. This study utilised the QoL in Swallowing Disorders (SWAL-QoL) and found that patients who continued to smoke after RT had a poorer QoL. Whilst values for each of the groups was not published, the authors provided this additional

Table 1
Overall survival (OS) data from included studies.

First Author (Year)	Follow-Up Period (Years)	OS Ceased Smokers (%)	OS Continuing Smokers (%)	*p* value
Studies Included in Meta-Analysis				
Browman (1993) [15]	2	66	39	0.005
Browman (2002) [16]	2	Light – 63.4	Heavy – 54.8	NR
Chen (2011) [7]	5	55	23	<0.001
Al-Mamgani (2013) [17]	10	68	33	<0.001
Platek (2016) [29]	5	70.7	32.1	NR
Studies not in Meta-Analysis				
Gillison (2012) [30]	9.3*	HR – 2.19		<0.01
Choi (2016) [41]	4.5*	HR** – 2.71 (Continuing), 2.38 (Ceased), 1.68 (Former)		All < 0.05
Descamps (2016) [32]	2*	HR – 1.51		0.03

NR – Not recorded.
* Reported as median follow-up.
** Hazard ratios were reported in comparison to never smokers.

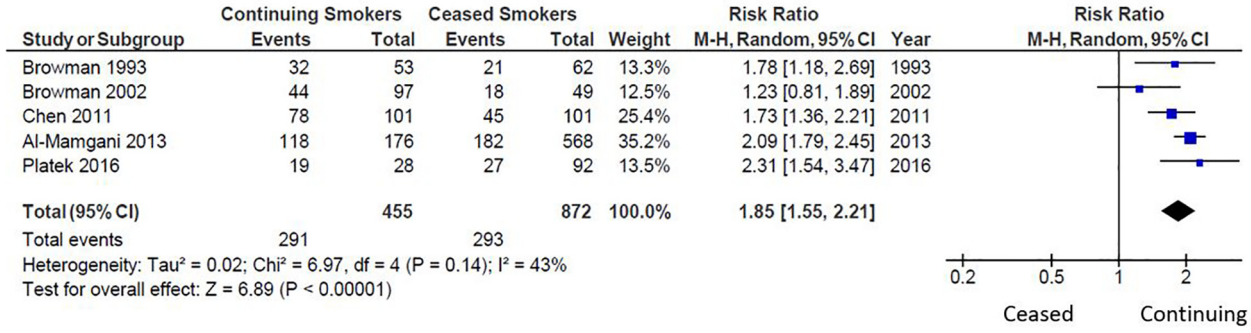

Fig. 1. Forest plot of relative risk for OS: a comparison of continuing and ceased smokers.

Table 2
Locoregional control (LRC) data from included studies.

First Author (Year)	Follow-Up Period (Years)	LRC Ceased Smokers (%)	LRC Continuing Smokers (%)	*p* value
Studies Included in Meta-Analysis				
Terhaard (1991) [18]	3	96	85	<0.05
Benninger (1994) [19]	6.2*	89.1	58.8	0.012
Colasanto (2004) [20]	16.6*	91	90	0.30
Sjogren (2009) [22]	5	89	81	0.12
Chen (2011) [7]	5	69	58	0.03
Al-Mamgani (2013) [17]	10	89	66	<0.001
Studies not in Meta-Analysis				
Garden (2013) [31]	5	78	67	0.08
Zackrisson (2015) [28]	5**	71.2	57.1	<0.001

* Reported as mean [19] and median [20] follow-up.
** Kaplan–Meier's estimate.

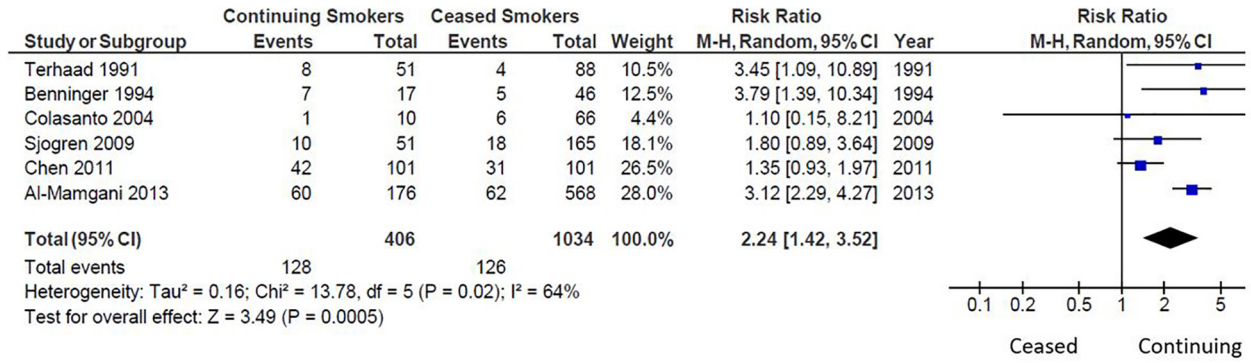

Fig. 2. Forest plot of relative risk for LRC: a comparison of continuing and ceased smokers.

Table 3
Acute and late toxicities for ceased and continuing smokers.

First Author (Year)	Outcome Measured	Acute Toxicity Rate Ceased Smokers (%)	Acute Toxicity Rate Continuing Smokers (%)	*p* value
Acute Toxicities				
Rugg (1990) [33]	Mucositis*	13.6wks	23.4wks	0.014
Zevallos (2009) [35]	Skin ≥ Grade II	43.2	31.8	0.29
	Mucositis ≥ Grade II	56.8	72.7	0.13
Chen (2011) [7]	≥Grade III	60	55	0.74
Meyer (2012) [36]	≥Grade III	22.3	24.1	0.65
Szeszko (2015) [37]	Mucositis ≥ Grade III	42	46	0.71
Late Toxicities				
Van der Voet (1998) [34]	10 yr Laryngeal Complications	14	28	NR
Chen (2011) [7]	≥Grade III	31	49	0.01
Meyer (2012) [36]	≥Grade III	3.5	4.5	0.61
Specific Late Toxicities – ORN/CRN				
Katsura (2008) [27]	ORN	3.8	38.5	0.011
Zevallos (2009) [35]	ORN	2.7	20.5	0.02
Chen (2011) [7]	ORN	4	5	NR
Raguse (2016) [38]	ORN	22.9	30.2	0.051
Sathasivam (2017) [40]	ORN	11	35.1	<0.001
Gessert (2017) [39]	CRN**	1.2	5.7	0.067

NR – Not recorded.
* Reported as weeks to resolution of mucositis.
** Chondroradionecrosis.

information. Continuing smokers were found to have reduced mean scores when compared to ceased smokes across each of the 'burden' (40.1 vs 60.4, $p = 0.003$), 'mental health' (48.6 vs 63.2, $p = 0.030$) and 'fatigue' (61.4 vs 73.1, $p = 0.028$) domains. Another study did not provide adequate data for inclusion but stated that continued smoking during radiotherapy reduced QoL [25].

Risk of bias across studies

Funnel plots were created for OS and LRC, as seen in Appendix F. No evidence of publication bias was observed by visual inspection of these figures.

Sensitivity analysis

Exclusion of studies from the meta-analysis which were rated as medium quality on the modified Newcastle–Ottawa scale did not result in significant changes in the effect estimates. A leave-one-out sensitivity analysis revealed that no single study substantially affected the overall risk ratios, or the statistical significance of the effect estimate (Table 4).

Table 4
Leave-one-out sensitivity analysis: relative risk (RR), 95% confidence intervals (CI) and p value when one study was removed from the meta-analysis.

Study Removed from Analysis	RR	95% CI	*p* value
Overall Survival			
Browman (1993) [15]	1.85	1.50–2.29	<0.0001
Browman (2002) [16]	1.99	1.76–2.24	<0.0001
Chen (2011) [7]	1.87	1.48–2.37	<0.0001
Al-Mamgani (2013) [17]	1.73	1.39–2.15	<0.0001
Platek (2016) [29]	1.78	1.46–2.17	<0.0001
Locoregional Control			
Terhaard (1991) [18]	2.13	1.29–3.51	0.003
Benninger (1994) [19]	2.08	1.26–3.42	0.004
Colasanto (2004) [20]	2.32	1.44–3.73	0.0005
Sjogren (2009) [22]	2.36	1.37–4.09	0.002
Chen (2011) [7]	2.89	2.22–3.77	< 0.0001
Al-Mamgani (2013) [17]	1.85	1.21–2.83	0.004

Discussion

The main finding of this systematic review is that continued smoking during and after RT is associated with an increased mortality (RR = 1.85) and locoregional failure (RR = 2.24). Whilst deaths unrelated to cancer may contribute to the risk of mortality due to tobacco exposure at diagnosis or after, the increased risk of locoregional failure suggests a possible direct effect of smoking on treatment response and disease control. Prior studies have postulated that smoking may reduce the efficacy of RT through the induction of chronic hypoxia [7,8]. However, without studies investigating smoking behaviour before, during and after treatment; it is difficult to ascertain whether these adverse outcomes are attributed to the effects of smoking on RT, past burden of smoking or the cumulative effects of smoking after treatment. Most studies included in this analysis reported on smoking status during RT, with only some articles analysing those who smoked after the completion of RT. Studies that only investigated smoking during RT could be excluding patients who quit for the duration of treatment and then relapsed afterwards, thus potentially underestimating the effects of continued smoking.

An important clinical question is whether smoking cessation after a HNC diagnosis improves prognosis. Only three studies [31,35,41] reported an analysis on the group of current smokers at baseline who either continued or quit. Patients who ceased smoking after diagnosis demonstrated improved LRC [31], reduced mortality [41] and a decrease in ORN [35]. Choi et al. determined that continuing smokers had the highest hazard ratio for all-cause mortality (HR = 2.71) when compared with those who ceased at diagnosis (HR = 2.3) and those who were former smokers (HR = 1.68), demonstrating that it is never too late to cease smoking [41]. Browman et al. was another study which investigated the effects of smoking cessation around the time of diagnosis by excluding patients who were smoking more than 12 weeks prior to diagnosis [16]. They concluded that baseline smoking status, and not continued smoking, was an independent predictor of survival. However, this study only reported a 2-year survival estimate, which may not have allowed adequate time for the negative effects of continued smoking to become evident. Most of the included studies compared continuing smokers to a ceased smoking group, which included long-term former smokers and, in some cases, never smokers. Therefore, the results of the meta-analysis may overestimate the effects of continuing smoking when compared to patients who ceased at the time of diagnosis.

This review reports that currently there is limited evidence suggesting a correlation between continued smoking and acute toxicities, with only one paper identifying a statistically significant association [23]. Late toxicities were increased amongst continuing smokers with HNC, with the greatest evidence for osteoradionecrosis [7,27,35,38]. Continued smoking was also found to have a negative influence on quality of life of HNC patients, although this was based on the results of only one article [14]. This was further supported in a study by Jensen et al. which demonstrated that patients who continued smoking had a lower QoL than those who ceased. However, this paper did not meet eligibility criteria due to the inclusion of surgical patients [42]. The correlation between continued smoking and late but not acute toxicities may suggest that the negative effects of smoking are time dependent.

The major limitation of this study is that the analysis was based predominantly on retrospective data, with inadequate recording of smoking history and an absence of biochemical verification of smoking status in most of these studies. The meta-analyses revealed a moderate degree of statistical heterogeneity, possibly due to variations in duration of follow-up, stage and location of cancer and definitions of tobacco usage. Publication bias could have influenced the results, but the grey literature search identified multiple conference abstracts demonstrating a similar negative effect of continued smoking [43–46]. Selective reporting bias is another factor that could have affected the results of this review given that most of the articles did not investigate smoking as their primary variable of interest.

This review suggests that HNC patients who continue to smoke have significant reductions across multiple outcomes. The strength of evidence is sufficient to guide clinicians to pursue smoking cessation amongst these patients. There is a requirement for further high quality prospective studies with biochemical verification of smoking status to accurately determine and quantify the effects of quitting smoking upon and after HNC diagnosis. Additionally, further studies into quality of life amongst continuing smokers are essential, particularly as RT has the potential to cause significant morbidity.

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None to declare.

Conflict of interest

None.

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Appendix A. Supplementary data

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References

[1] Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. Oncology 2016;91(1):13–23. https://doi.org/10.1159/000446117.
[2] Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc 2016;91(3):386–96. https://doi.org/10.1016/j.mayocp.2015.12.017.
[3] Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet 2008;371(9625):1695–709. https://doi.org/10.1016/S0140-6736(08)60728-X.
[4] Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist 2010;15(9):994–1001. https://doi.org/10.1634/theoncologist.2009-0289.
[5] Strojan P, Hutcheson KA, Eisbruch A, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. Cancer Treat Rev 2017;59:79–92. https://doi.org/10.1016/j.ctrv.2017.07.003.
[6] Chen AM, Vazquez E, Courquin J, Donald PJ, Farwell DG. Tobacco use among long term survivors of head and neck cancer treated with radiation therapy. Psychooncology 2014;23(2):190–4. https://doi.org/10.1002/pon.3388.
[7] Chen AM, Chen LM, Vaughan A, et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. Int J Radiat Oncol Biol Phys 2011;79(2):414–9. https://doi.org/10.1016/j.ijrobp.2009.10.050.
[8] Jensen JA, Goodson WH, Hopf HW, Hunt TK. Cigarette smoking decreases tissue oxygen. Arch Surg 1991;126(9):1131–4. https://doi.org/10.1001/archsurg.1991.01410330093013.
[9] Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer 2013;132(2):401–10. https://doi.org/10.1002/ijc.27617.
[10] Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma – a prospective study. Radiother Oncol 2012;103(1):38–44. https://doi.org/10.1016/j.radonc.2012.01.011.
[11] Fortin A, Wang CS, Vigneault E. Influence of smoking and alcohol drinking behaviors on treatment outcomes of patients with squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys 2009;74(4):1062–9. https://doi.org/10.1016/j.ijrobp.2008.09.021.
[12] Sharp L, Johansson H, Fagerstrom K, Rutqvist LE. Smoking cessation among patients with head and neck cancer: cancer as a 'teachable moment'. Eur J Cancer Care 2008;17(2):114–9. https://doi.org/10.1111/j.1365-2354.2007.00815.x.
[13] van Imhoff LC, Kranenburg GG, Macco S, et al. Prognostic value of continued smoking on survival and recurrence rates in patients with head and neck cancer: a systematic review. Head Neck 2016;38(S1):E2214–20. https://doi.org/10.1002/hed.24082.
[14] Silveira MH, Dedivitis RA, Queija DS, Nascimento PC. Quality of life in swallowing disorders after nonsurgical treatment for head and neck cancer. Int Arch Otorhinolaryngol 2015;19(1):46–54. https://doi.org/10.1055/s-0034-1395790.
[15] Browman G, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328(3):159–63. https://doi.org/10.1056/NEJM199301213280302.
[16] Browman GP, Mohide EA, Willan A, et al. Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. Head Neck 2002;24(12):1031–7. https://doi.org/10.1002/hed.10168.
[17] Al-Mamgani A, van Rooij PH, Woutersen DP, et al. Radiotherapy for T1–2N0 glottic cancer: a multivariate analysis of predictive factors for the long-term outcome in 1050 patients and a prospective assessment of quality of life and voice handicap index in a subset of 233 patients. Clin Otolaryngol 2013;38(4):306–12. https://doi.org/10.1111/coa.12139.
[18] Terhaard CH, Snippe K, Ravasz LA, van der Tweel I, Hordijk GJ. Radiotherapy in T1 laryngeal cancer: prognostic factors for locoregional control and survival, uni- and multivariate analysis. Int J Radiat Oncol Biol Phys 1991;21(5):1179–86. https://doi.org/10.1016/0360-3016(91)90274-8.
[19] Benninger MS, Gillen J, Thieme P, Jacobson B, Dragovich J. Factors associated with recurrence and voice quality following radiation therapy for T1 and T2 glottic carcinomas. Laryngoscope 1994;104(3):294–8. https://doi.org/10.1288/00005537-199403000-00009.
[20] Colasanto JM, Haffty BG, Wilson LD. Evaluation of local recurrence and second malignancy in patients with T1 and T2 squamous cell carcinoma of the larynx. Cancer J 2004;10(1):61–6. Accessed May 1, 2018 https://www.ncbi.nlm.nih.gov/pubmed/15000497.
[21] Meyer F, Bairati I, Fortin A, et al. Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: a randomized trial among head and neck cancer patients. Int J Cancer 2008;122(7):1679–83. https://doi.org/10.1002/ijc.23200.
[22] Sjögren EV, Wiggenraad RGJ, Le Cessie S, Snijder S, Pomp J, de Jong RJB. Outcome of radiotherapy in T1 glottic carcinoma: a population-based study. Eur Arch Otorhinolaryngol 2009;266(5):735–44. https://doi.org/10.1007/s00405-008-0803-9.
[23] Porock D, Nikoletti S, Cameron F. The relationship between factors that impair wound healing and the severity of acute radiation skin and mucosal toxicities in head and neck cancer. Cancer Nurs 2004;27(1):71–8. https://doi.org/10.1097/00002820-200401000-00009.
[24] Cooper J, Zhang Q, Pajak T, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;84(5):1198–205. https://doi.org/10.1016/j.ijrobp.2012.05.008.
[25] Egestad H, Emaus N. Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period. Eur J Oncol Nurs 2014;18(4):339–46. https://doi.org/10.1016/j.ejon.2014.04.003.
[26] Al-Mamgani A, van Rooij PH, Mehilal R, Verduijn GM, Tans L, Kwa SL. Radiotherapy for T1a glottic cancer: the influence of smoking cessation and fractionation schedule of radiotherapy. Eur Arch Otorhinolaryngol 2014;271(1):125–32. https://doi.org/10.1007/s00405-013-2608-8.

[27] Katsura K, Sasai K, Sato K, Saito M, Hoshina H, Hayashi T. Relationship between oral health status and development of osteoradionecrosis of the mandible: a retrospective longitudinal study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105(6):731–8. https://doi.org/10.1016/j.tripleo.2007.10.011.
[28] Zackrisson B, Kjellén E, Söderström K, et al. Mature results from a Swedish comparison study of conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma – the ARTSCAN trial. Radiother Oncol 2015;117(1):99–105. https://doi.org/10.1016/j.radonc.2015.09.024.
[29] Platek AJ, Jayaprakash V, Merzianu M, et al. Smoking cessation is associated with improved survival in oropharynx cancer treated by chemoradiation. Laryngoscope 2016;126(12):2733–8. https://doi.org/10.1002/lary.26083.
[30] Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 2012;30(17):2102–11. https://doi.org/10.1200/jco.2011.38.4099.
[31] Garden AS, Kies MS, Morrison WH, et al. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the early 21st century. Radiat Oncol 2013;8(1). https://doi.org/10.1186/1748-717X-8-21.
[32] Descamps G, Karaca Y, Lechien JR, et al. Classical risk factors, but not HPV status, predict survival after chemoradiotherapy in advanced head and neck cancer patients. J Cancer Res Clin Oncol 2016;142(10):2185–96. https://doi.org/10.1007/s00432-016-2203-7.
[33] Rugg T, Saunders MI, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol 1990;63(751):554–6. https://doi.org/10.1259/0007-1285-63-751-554.
[34] van der Voet JC, Keus RB, Hart AA, Hilgers FJ, Bartelink H. The impact of treatment time and smoking on local control and complications in T1 glottic cancer. Int J Radiat Oncol Biol Phys 1998;42(2):247–55. https://doi.org/10.1016/S0360-3016(98)00226-0.
[35] Zevallos JP, Mallen MJ, Lam CY, et al. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer 2009;115(19):4636–44. https://doi.org/10.1002/cncr.24499.
[36] Meyer F, Fortin A, Wang CS, Liu G, Bairati I. Predictors of severe acute and late toxicities in patients with localized head-and-neck cancer treated with radiation therapy. Int J Radiat Oncol Biol Phys 2012;82(4):1454–62. https://doi.org/10.1016/j.ijrobp.2011.04.022.
[37] Szeszko B, Osowiecka K, Rucińska M, Wasilewska-Teśluk E, Gliński K, Kepka L. Smoking during radiotherapy for head and neck cancer and acute mucosal reaction. Rep Pract Oncol Radiother 2015;20(4):299–304. https://doi.org/10.1016/j.rpor.2015.04.001.
[38] Raguse JD, Hossamo J, Tinhofer I, et al. Patient and treatment-related risk factors for osteoradionecrosis of the jaw in patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2016;121(3):215–21. https://doi.org/10.1016/j.oooo.2015.10.006.
[39] Gessert TG, Britt CJ, Maas AMW, Wieland AM, Harari PM, Hartig GK. Chondroradionecrosis of the larynx: 24-year University of Wisconsin experience. Head Neck 2017;39(6):1189–94. https://doi.org/10.1002/hed.24749.
[40] Sathasivam HP, Davies GR, Boyd NM. Predictive factors for osteoradionecrosis of the jaws: a retrospective study. Head Neck 2018;40(1):46–54. https://doi.org/10.1002/hed.24907.
[41] Choi SH, Terrell JE, Bradford CR, et al. Does quitting smoking make a difference among newly diagnosed head and neck cancer patients? Nicotine Tob Res 2016;18(12):2216–24. https://doi.org/10.1093/ntr/ntw189.
[42] Jensen K, Jensen AB, Grau C. Smoking has a negative impact upon health related quality of life after treatment for head and neck cancer. Oral Oncol 2007;43(2):187–92. https://doi.org/10.1016/j.oraloncology.2006.02.006.
[43] Boeje CR, Lassen P, Hoff C, Overgaard J. The influence of comorbidity, smoking behaviour and human papillomavirus on overall survival in 1091 patients with oropharyngeal carcinoma: the DAHANCA experience [abstract 131]. Radiother Oncol 2011;99(S1):S49. https://doi.org/10.1016/S0167-8140(11)70253-5.
[44] Chan AW, McBride SM, Cianchetti M, Busse PM, Ali NN, Wang JJ. Tobacco smoking during radiation treatment predicts for decreased survival in patients with oropharyngeal carcinoma [abstract]. Int J Radiat Oncol Biol Phys 2011;81(2):S487. https://doi.org/10.1016/j.ijrobp.2011.06.783.
[45] Dhanireddy B, Mourad WF, Patel S, et al. The impact of smoking on laryngeal preservation in locally advanced laryngeal cancer treated with definitive chemoradiation therapy [abstract]. Int J Radiat Oncol Biol Phys 2014;90(1):S540. https://doi.org/10.1016/j.ijrobp.2014.05.1641.
[46] Møller P, Primdahl HCAK, et al. Effect of continued tobacco smoking during radiotherapy on loco-regional control for carcinoma of the larynx [abstract 1129]. Radiother Oncol 2015;115(S1):S613–4. https://doi.org/10.1016/S0167-8140(15)41121-1.