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Abstract

Post-radiotherapy head and neck cancer patients are at increased risk of dental caries due to radiotherapy-induced salivary gland hypofunction and radiation damage to tooth structure. Dental caries causes pain and discomfort and is likely to have a detrimental impact on patients' quality of life. This systematic review appraised and synthesised best available evidence regarding the incidence and severity of post-radiotherapy dental caries in head and neck cancer patients. Six databases and two trial registries were searched from their inception to May 2019. A total of 22 papers met the inclusion criteria. The pooled percentage of patients that developed dental caries post-radiotherapy was 29% (n=15 studies; 95% CI 21%, 39%; $I^2=88.0\%$). Excluding studies with longer than two years follow-up, the pooled percentage was 37% (n=9 studies; 95% CI 25%, 51%; $I^2=88.6\%$). Meta-regression analysis revealed that studies with a higher mean/median radiotherapy dose exposure had an increased incidence of dental caries ($p=0.02$). Furthermore, studies with a higher proportion of patients treated with chemotherapy had an increased incidence of dental caries ($p=0.02$) after the exclusion of an outlier. It is important to be mindful of the high degree of observed heterogeneity and the inclusion of a large number of non-randomised studies. Data regarding the number of carious teeth, the number of carious tooth surfaces, and the number of carious lesions that developed post-radiotherapy were unsuitable for meta-analysis. There is a need for well-designed studies to improve understanding about dental caries-risk in post-radiotherapy head and neck cancer patients.

Highlights

- This review summarised the incidence of post-radiotherapy dental caries.
- Pooled estimates for post-radiotherapy caries ranged from 29-37%.
- A narrative review of the severity of post-radiotherapy caries is also presented.
- Comprehensive oral care is needed for head and neck cancer patients.

Keywords

Head and neck neoplasms
Radiotherapy
Dental caries
Chemotherapy
Oral health

Abbreviations:

CI – confidence intervals
CM – Ciaran Moore (reviewer)
CML – Conor McLister (reviewer)
DMFS – decayed, missing, or filled tooth surfaces
DMFT – decayed, missing, or filled teeth
DNA – deoxyribonucleic acid
GMK – Gerry McKenna (reviewer)
HANC – head and neck cancer
IMRT – intensity modulated radiation therapy

ORN – osteoradionecrosis

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

SD – standard deviation

Introduction

Head and neck cancer (HANC) is defined by tumour location as a group of malignancies that principally affect the oral cavity, nasal cavity, sinuses, salivary glands, pharynx, and larynx.[1] Over 550,00 new cases of HANC are diagnosed worldwide every year,[2] and in the United Kingdom (UK), approximately 12,000 people are diagnosed per annum.[3–7] The incidence of disease among people under the age of 50 appears to be increasing.[8,9] Survival rates from HANC are variable depending on the site of the primary tumour. Five-year survival rates have been shown to range from 27.8% for hypopharyngeal cancers to 67.0% for salivary gland cancers.[10]

Radiotherapy and surgery are the most commonly employed treatment modalities for HANC.[1] Either may be used alone for the treatment of early stage disease.[1,11,12] For more advanced tumours, however, a combination of surgery and post-operative radiotherapy; or chemotherapy and radiotherapy; may be warranted.[1,11,12] Between 42 to 84% of HANC patients are treated by radiotherapy depending on the location of the cancer.[13]

Radiotherapy stimulates cellular destruction by deoxyribonucleic acid (DNA) damage.[14,15] Increasing the radiation dose to the tumour increases the probability of cure, however, higher radiation doses are constrained by the potential to cause damage to surrounding normal tissues.[14,15] The adverse side effects of head and neck radiotherapy have been well documented and may include mucositis,[16] trismus,[17] xerostomia or salivary gland hypofunction,[18] dental caries,[19] periodontal disease,[20] and osteoradionecrosis[21].

Dental caries, or tooth decay, is a localised destructive disease of dental hard tissue that entails the demineralisation of enamel and dentine by cariogenic plaque bacteria.[22] Behind an advancing front of acid-demineralisation, bacterial ingress and infection triggers a series of inflammatory and immunological pulpal reactions within the tooth.[22,23] Patients with a high frequency of sugar intake, low fluoride exposure, poor plaque control, and dry mouth, have been shown to be at increased risk of developing dental caries.[22–24]

Head and neck radiotherapy patients are also at increased risk of tooth decay.[25,26] The prevalence of dental caries has been estimated at 24% for cancer patients treated with radiotherapy, and 21% for cancer patients treated with chemo-radiotherapy.[19] In Northern Ireland, 57% of HANC patients diagnosed between 2004 and 2014 developed dental caries following radiotherapy, with a mean of 3.6 teeth affected.[27] Rampant, aggressive dental caries may develop as early as three months post-radiotherapy and can result in the complete devastation of a previously healthy dentition within one year of treatment.[28–30] The aetiology of this increased risk is multifactorial,[31] and is summarised in Figure 1.

Figure 1: Summary of the multifactorial aetiology of the increased risk of dental caries among head and neck radiotherapy patients.

Radiotherapy-induced salivary gland acinar degeneration and interstitial fibrosis,[25,32,33] in combination with the other indirect effects of radiotherapy,[34–41] are suspected to be the major causative factors for an increased risk of tooth decay.[25,26] Changes to the composition of dental hard tissue, however, such as loss of enamel prism structure, the degeneration of odontoblast processes, the obliteration of dentinal tubules, and gap formation at the enamel-dentine junction, may also be important contributory factors.[42–46]

Oral ill-health can negatively impact on patients' quality of life.[47–49] Patients with active tooth decay may choose to avoid social interaction with others, for example, conversing, laughing, smiling, or engaging in relationship-behaviours such as kissing, due to a perceived embarrassment regarding the appearance of their teeth.[49,50] Basic oral functions such as mastication and speech may also be hindered, and this can impinge on a patient's ability to sustain and build friendships and intimate relationships.[50] Furthermore, the progression of dental caries may be associated with severe oro-facial pain including reversible pulpitis, irreversible pulpitis, and acute apical periodontitis.[22,23]

The aim of this systematic review was to quantify the overall incidence and severity of dental caries in post-radiotherapy head and neck cancer patients.

Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[51] The study's protocol was registered in advance on the International Prospective Register of Systematic Reviews (PROSPERO CRD42017052622).[52]

Study selection

This systematic review included randomised controlled trials and observational studies that had investigated the incidence of dental caries in head and neck radiotherapy

patients. Caries may have been diagnosed clinically and/or radiologically, and studies must have followed-up patients for a minimum of three months. Study participants must have been dentally assessed and treated prior to radiotherapy. Studies involving patients with recurrent head and neck cancer, or receiving a repeat course of radiotherapy, were excluded. In contrast, studies involving radiotherapy combined with surgery and/or chemotherapy were eligible for inclusion. Primary outcome measures included: the percentage of patients developing one or more carious lesions post-radiotherapy, the mean number of teeth affected by caries post-radiotherapy, and the mean number of tooth surfaces affected by caries post-radiotherapy.

Search strategy

The electronic databases of MEDLINE, EMBASE, and CENTRAL, as well as the grey literature databases of ProQuest, Scopus, and Web of Science, were searched from their inception to May 2019 using a search strategy developed for the OVID interface (MEDLINE/EMBASE) and revised as appropriate for each database (appendix 1). The trial registries of the World Health Organisation (ICTRP) and the US National Institutes of Health (ClinicalTrials.gov) were also searched. The reference lists of all included studies were also reviewed for additional possible studies. Non-English language papers were excluded.

Data extraction

The titles and abstracts of articles gleaned from the search were independently reviewed by two researchers (CM and CML). Full manuscripts were obtained for potentially relevant articles, for articles with no abstract available, or for articles whose abstracts provided insufficient information to allow for a definitive decision regarding inclusion. Discrepancies were resolved by discussion, with a third reviewer (GMK) available for arbitration. The following data was independently extracted by CM and CML from all of the included studies: year of publication, study design, and details of participants, interventions, and outcomes.

Statistical analysis

A random-effects model was used to pool proportions of patients with post-radiotherapy dental caries from the included studies.[53,54] Each proportion was converted to a log-odds and then the standard error of the log-odds was calculated. This data was then pooled and back converted to give an overall proportion. Based on the log-odds, a standard chi-squared test of study heterogeneity (Q-statistic) was undertaken to investigate between-study heterogeneity, and the I^2 statistic was calculated to determine the degree of heterogeneity in proportions across studies.[55] For one study with no events,[56] a separate analysis adding 0.5 to the numerator and denominator, was conducted and revealed identical results (data not shown). Publication bias was assessed via the construction of a funnel plot (Supplementary Figure 1). Meta-regression (based on the log-odds and the standard error of the log-odds) was undertaken to investigate correlations between the proportion with dental caries, and radiation dose, chemotherapy, the site of HANC (all pre-specified), as well as other relevant variables identified from the screening process.[57] Pooled proportions were also calculated using the logistic-normal random-effects model via STATA routine “metaprop_one”, which has been shown to have improved performance.[53,54] The results were almost identical to those obtained using the log-odds method and are

therefore not shown. All analyses were conducted using STATA version 14 (StataCorp LLC, United States of America).

Results

As shown in Figure 2, a total of 847 papers were identified through the search strategy. After 104 duplicates were removed, 743 titles and abstracts were independently reviewed by CM and CML. Full manuscripts were obtained for 85 potentially relevant articles. Data was extracted from 22 studies that met the inclusion criteria. The characteristics of these studies are summarised in Table 1. The reasons for the exclusion of 63 articles are summarised in Supplementary Table 1.

Figure 2: PRISMA flow diagram for studies retrieved through search, identification, and screening.

Of the 22 included studies, 3 were randomised or quasi-randomised controlled trials. 19 observational studies were included, of which 7 were retrospective studies. 15 articles reported on the number of HANC patients who developed dental caries or had a documented increase in DMFT (decayed, missing, or filled tooth) or DMFS (decayed, missing, or filled surface) post-radiotherapy. 6 studies reported data regarding the number of 'cariou teeth' developed post-radiotherapy. 5 studies reported on the number of 'cariou tooth surfaces' developed post-radiotherapy and 4 studies reported on the number of 'cariou lesions' developed post-radiotherapy.

Author	Type of study	Year of Publication	Number of patients	Follow-up (months)	Caries (outcome) data	Caries assessment	Site of head and neck cancer	Age (years)	Gender - male (%)
<i>Al-Nowas & Grotz</i> [58]	Prospective cohort study	2006	22	12	Mean increase in DMFS of 7.8 at 12 months	Clinical	All regions of the head and neck	47.9 (mean)	68
<i>Almstahl et al.</i> [59]	Prospective cohort study	2018	32	24	37% developed dental caries at 2 years. Mean no. carious lesions at 2 years: 2.1 (+/- 5.9)	Clinical and radiographical	All regions of the head and neck	-	70
<i>Bachok et al.</i> [60]	Quasi-randomised controlled trial	2018	30	3	Mean increase in DMFT of 1.55	Clinical	All regions of the head and neck	46.7 (mean)	70
<i>Bonan et al.</i> [61]	Prospective cohort study	2006	9 at least 3 months	3-42 (mean 22.3 months)	11% developed dental caries	Clinical	All regions of the head and neck	47.9 (mean). 34-62 (range)	89
<i>Dholam et al.</i> [62]	Retrospective cohort study	2013	190	15	Mean increase in DMFT of 1.02 at 15 months	Clinical	All regions of the head and neck	46.5 (mean). 16-77 (range)	73
<i>Dreizen et al.</i> [63]	Randomised controlled trial	1977	42	Mean of 16 months	Mean increase in DMFT of 4.8 and DMFS of 9.4	Clinical	All regions of the head and neck	51.8 (mean). 17.6-76.5 (range)	64
<i>Duarte et al.</i> [64]	Retrospective cohort study	2014	158	12	17% developed dental caries	Clinical	All regions of the head and neck	62.4 (mean). 24-91 (range)	99
<i>Frydrych et al.</i> [65]	Retrospective cohort study	2017	116 at least 12 months	12-108 (mean 45 months)	17% developed caries during follow-up	Clinical	All regions of the head and neck	56.7 (mean). 17-88 (range)	73
<i>Hey et al.</i> [66]	Prospective cohort study	2013	70	24	57% had sporadic or generalised carious lesions at follow-up	Clinical	All regions of the head and neck	Approximately 58 (median). 26-77 (range)	73
<i>Jham et al.</i> [67]	Retrospective cohort study	2008	109 at least 3 months	3-33 (mean 4 months)	Radiation caries found in 11% of patients	Clinical	All regions of the head and neck	57.8 (mean). 14-87 (range)	79
<i>Joyston-Bechal et al.</i> [68]	Prospective cohort study	1992	25	12	Mean increase of 2.4 in DMFS at 12 months. Mean decrease of 0.08 in DMFT at 12 months	Clinical and radiographical	All regions of the head and neck	55.6 (mean). 16-84 (range)	64
<i>Meng et</i>	Prospective	2005	10	6	Mean increase in DMFT	Clinical	Nasopharynx	41 (mean). 20-67	40

<i>al.[69]</i>	cohort study					and DMFS of 1.1 at 6 months. 80% of patients developed new carious lesions.	Clinical	All regions of the head and neck	56.8 (mean). 24-84 (range)	84
<i>Mougeot et al.[70]</i>	Prospective cohort study	2019	20	18	35% had increase in DMFS at 18 months. Mean decrease in DMFS of 0.15 at 18 months		Clinical	All regions of the head and neck	56.8 (mean). 24-84 (range)	84
<i>Regezi et al.[71]</i>	Retrospective cohort study	1976	130 at least 12 months	12-120	New carious lesions developed in 20% of patients		Clinical	All regions of the head and neck	52 (mean). 7-86 (range)	68
<i>Rocha et al.[56]</i>	Prospective cohort study	2017	5 at least 39 months	39-60 (mean 53 months)	0 patients developed caries		Clinical	Lip	60.4 (mean). 47-72 (range)	40
<i>Rudat et al.[72]</i>	Retrospective study of a subgroup of patients from a previous RCT (longitudinal assessments performed)	2000	35	12	37% developed caries at 1 year		Clinical	All regions of the head and neck	Approximately 49 (median). 28-68 (range)	77
<i>Schuurhuis et al.[73]</i>	Prospective cohort study	2018	51 at least 11 months	11-24	25% developed one or more carious lesions		Clinical and radiographical	Oral cavity and oropharynx	59 (mean)	63
<i>Stala et al.[74]</i>	Retrospective cohort study	2014	239 at least 35 months	35-176 (median 111 months)	35% developed dental caries		Clinical	Nasopharynx	43 (mean). 10-75 (range)	67
<i>Spak et al.[24]</i>	Randomised controlled trial	1994	37	12	62% had caries at 12 months. Mean of 4.8 carious lesions at 12 months		Clinical and radiographical	All regions of the head and neck	58.1 (mean)	70
<i>Sun et al.[75]</i>	Prospective cohort study	2010	19	6	New carious lesions found in 11% of patients		Clinical	Nasopharynx	57.6 (mean). 45-65 (range)	-
<i>Wang et al.[76]</i>	Retrospective cohort study	2008	84 at least 3 months	3-12	Mean of 2.14 carious teeth at follow-up		Clinical	Nasopharynx	-	78
<i>Wescott et al.[77]</i>	Longitudinal study	1975	15 at least 39 months	39-55 (mean 45 months)	Mean of 13.7 carious lesions developed		Clinical	All regions of the head and neck	-	-

Table 1: Characteristics of 22 included studies.

Incidence of dental caries

15 studies were included in the meta-analysis as shown in Figure 3. The pooled estimate obtained for the proportion of patients who developed dental caries post-radiotherapy was 0.29 (95% CI 0.21,0.39). The figure should be interpreted with caution, however, given the high heterogeneity observed ($p < 0.001$, I^2 88.0%).

Figure 3: Forest plot of post-radiotherapy dental caries incidence in HANC patients (drawn using binomial exact confidence intervals).

Sensitivity analyses were also undertaken. After excluding 6 studies on the basis of follow-up greater than two years, a pooled estimate of 0.37 (95% CI 0.25,0.51) was calculated for the proportion of patients who developed dental caries within two years of radiation treatment. Again, this figure should be interpreted with caution given the high heterogeneity determined ($p < 0.001$, I^2 88.6%). Excluding the randomised controlled trial conducted by Spak et al.[24] due to a perceived high risk of bias, as well as observational studies by Rocha et al.,[56] Duarte et al.[64], Frydrych et al.,[65] Jham et al.,[67] Sun et al.,[75] Meng et al.,[69] Siala et al.,[74] and Mougeot et al.[70] on the basis of lower Newcastle-Ottawa Scale scores,[78] a pooled estimate of 0.30 (95% CI 0.19,0.44) was calculated for the proportion of patients who developed dental caries post-radiotherapy. Heterogeneity, however, was only marginally reduced after the exclusion of these studies ($p < 0.001$, I^2 87.2%). The 'risk of bias' assessment for each of the included studies is summarised in Supplementary Tables 2 and 3.

Meta-regression was undertaken to determine possible associations between the percentage of patients diagnosed with post-radiotherapy dental caries and: 1) the

prescribed fluoride regime per study (%), 2) the percentage of patients treated with intensity-modulated radiation therapy (IMRT) per study, 3) the mean or median radiation dose exposure of patients per study (Gray), 4) the percentage of patients diagnosed with an oral tumour per study, 5) the percentage of patients diagnosed with a lower pharyngeal (e.g. laryngeal or hypopharyngeal) tumour per study, 6) the percentage of patients treated with chemotherapy per study, 7) the percentage of male patients per study, 8) the mean or median age of patients per study (years), and 9) the mean post-radiotherapy stimulated salivary flow rate of patients per study (ml/min). Analyses are summarised in Table 2. The relationship between the percentage of patients diagnosed with post-radiotherapy dental caries and the mean/median radiation dose exposure of patients per study is illustrated graphically in Figure 4. Similarly, the relationship between the percentage of patients diagnosed with post-radiotherapy dental caries and the percentage of patients treated with chemotherapy per study is illustrated in Figure 5.

Studies with an increased mean/median radiation dose exposure had an increased incidence of post-radiotherapy dental caries ($p=0.02$). An increase in mean/median radiation dose exposure of 1 Gray was associated with a 20% increase in the odds of post-radiotherapy dental caries.

Initially, no significant association was found between the percentage of patients diagnosed with post-radiotherapy dental caries and the percentage of patients treated with chemotherapy per study ($p=0.61$, odds ratio = 1.01). After exclusion of the study by Meng et al.[69] as an outlier (see Figure 5), however, meta-regression demonstrated that studies with a higher proportion of patients treated with chemotherapy had an increased incidence of post-radiotherapy dental caries ($p=0.02$). A 1% increase in the percentage of patients treated with chemotherapy was associated with a 2% increase in the odds of post-radiotherapy dental caries per study.

No statistically significant associations were found between the percentage of patients diagnosed with post-radiotherapy caries per study and: the prescribed fluoride regime per study; the percentage of patients treated with IMRT per study; the percentage of patients diagnosed with an oral cavity tumour per study; the percentage of patients diagnosed with a lower pharyngeal tumour per study; the percentage of male patients per study; the mean/median age of patients per study; and the mean post-radiotherapy stimulated salivary flow rate per study.

	Number of studies	Odds ratio	95% Confidence intervals	p-value
<i>Fluoride (%)</i>	10	0.82	0.36, 1.88	0.60
<i>IMRT (%)</i>	4	1.00	0.93, 1.07	0.97
<i>Radiation dose exposure (Gray)</i>	9	1.20	1.04, 1.38	0.02*
<i>Oral cavity tumours (%)</i>	13	0.98	0.96, 1.00	0.11
<i>Lower pharynx tumours (%)</i>	13	1.00	0.94, 1.06	0.94
<i>Chemotherapy (%)</i>	10	1.01	0.98, 1.03	0.61
<i>Chemotherapy (with Meng et al.[69] removed - %)</i>	9	1.02	1.00, 1.03	0.02*
<i>Gender – male (%)</i>	13	1.00	0.93, 1.01	0.09
<i>Age (years)</i>	13	0.94	0.85, 1.04	0.23
<i>Stimulated saliva (ml/min)</i>	5	0.19	<0.01, 15.1	0.32

Table 2: Summary of meta-regression analysis (*statistically significant at the 5% level).

Figure 4: Graphical representation of the relationship between the percentage of patients diagnosed with post-radiotherapy caries and the mean/median radiation dose exposure per study.

Figure 5: Graphical representation of the relationship between the percentage of patients diagnosed with post-radiotherapy caries and the percentage of patients treated with chemotherapy per study.

Number of carious teeth/surfaces/lesions developed post-radiotherapy

The authors felt that there was an inadequate number of studies available and sufficient differences in the definitions of 'carious teeth', 'carious surfaces', and 'carious lesions', to preclude the combination of data through meta-analysis. Therefore, a narrative review only is presented.

In a randomised controlled trial comparing the anti-caries efficacy of Oral 7® mouthwash versus sodium chloride/sodium bicarbonate mouthwash by Bachok et al., DMFT increased by an average of 1.55 for all patients from pre-radiotherapy assessment to three months post-radiotherapy.[60] DMFT was shown to have increased from a mean of 13.7 pre-radiotherapy to a mean of 15.2 post-radiotherapy.[60] There was no statistically significant difference in mean change in DMFT score between the two comparative groups.[60] In a study of 10 patients with nasopharyngeal carcinoma, Meng et al. found that DMFT increased from an average of 4.00 (SD 3.65) pre-radiotherapy to an average of 5.10 (SD 3.72) six months post-radiotherapy.[68] Similarly, DMFS increased from a mean of 16.70 (SD 18.34) pre-radiotherapy to a mean of 17.80 (SD 18.36) six months post-radiotherapy.[68] Changes in DMFT and DMFS over time, however, were not found to be statistically significant.[68] In a retrospective study of 190 HANC patients by Dholam et al., a statistically significant increase in mean DMFT score was observed from pre-radiotherapy assessment to fifteen months post-radiotherapy ($p=0.002$).[61] Mean DMFT increased from 4.12 (SD 4.35) pre-radiotherapy to 5.14 (SD 5.36) fifteen months post-radiotherapy.[61] In a study of 22 HANC patients by Al-Nawas and Grotz, an increase in mean DMFS was observed from pre-radiotherapy assessment to twelve months post-radiotherapy.[57] DMFS increased from an average of 80.7 pre-radiotherapy to 88.5 post-radiotherapy, respectively.[57] In contrast, Mougeot et al. found that mean DMFS decreased by 0.15 among 20 HANC patients eighteen months post-radiotherapy, even though 35% of patients had an increase in DMFS over the same time period.[69] DMFS decreased from an average of 46.01 pre-radiotherapy to an average of 45.86 post-radiotherapy.[69] In a prospective cohort study of 25 HANC patients by Joyston-Bechal et al., mean DMFS increased from 86.16 (SD 37.6) at pre-radiotherapy assessment to 88.56 (SD 37.21) twelve months post-radiotherapy.[68] DMFT, however, decreased from an average of 22.80 (SD 7.47) pre-radiotherapy to 22.72 (SD 7.31) twelve months post-radiotherapy.[68]

Dreizen et al. compared the effects of oral hygiene instruction; oral hygiene instruction and daily use of 1% fluoride gel; and oral hygiene, daily use of 1% fluoride gel, and adoption of a sucrose-restricted diet; on three-year caries incidence in 42 head and neck radiotherapy patients via a three-arm randomised controlled trial.[62] They found increases in mean DMFT of 11.00 and mean DMFS of 22.21 post-radiotherapy for the oral hygiene-only group.[62] Increases in mean DMFT of 1.77 and mean DMFS of 3.23 post-radiotherapy were observed for the oral hygiene and daily fluoride group, and increases in mean DMFT of 0.45 and mean DMFS of 0.55 post-radiotherapy were observed for the oral-hygiene, daily fluoride, and sucrose-restricted group.[62] Statistically significant differences in the changes in DMFT and DMFS scores were found between the oral hygiene-only group and the oral hygiene/daily fluoride group ($p<0.001$), as well as the oral hygiene-only group and the oral hygiene/daily fluoride/restricted sucrose group ($p<0.001$).[62]

In a prospective cohort study by Almstahl et al., post-radiotherapy HANC patients were found to have developed an average of 2.1 carious lesions (SD 5.9 carious lesions) two years after treatment.[59] 8 patients (25%) were found to have carious lesions on 1-4 surfaces, and 4 patients (12%) were found to have carious lesions on more than 4 surfaces (range of 5-33 surfaces).[59] Meng et al. found that 8 out of 10 nasopharyngeal carcinoma patients developed 1 to 3 carious lesions six months post-radiotherapy.[69] Joyston-Bechal et al. found that a total of 3 new carious lesions developed among 25 post-radiotherapy HANC patients at twelve months follow-up.[68] In a randomised controlled trial comparing the anti-caries efficacy of daily 0.42% fluoride gel, and daily 0.42% fluoride gel in combination with four-week daily application of 1.23% fluoride gel, by Spak et al., 23 out of 37 patients developed dental caries at twelve months (62.2%).[24] The mean number of carious lesions developed was 4.8 (SD 8.6).[24] There was no significant difference in the mean number of carious lesions developed between the two groups.[24] In a study of 84 nasopharyngeal carcinoma patients by Wang et al., the average number of carious teeth developed within three to twelve months post-radiotherapy was 2.14 (range 0-4).[76] Wescott et al. followed up 15 head and neck radiotherapy patients for an average of forty-five months and found that 9 patients who were classified as being uncooperative with oral hygiene and fluoride had a total of 57 crowns amputated due to caries, as well as 75 additional carious tooth surfaces.[77] In contrast, six oral hygiene- and fluoride-cooperative patients were found to have 0 crowns amputated and only 1 carious tooth surface at follow-up.[77]

Discussion

Summary of the evidence

This is the first systematic review to have investigated the incidence of post-radiotherapy dental caries in HANC patients. The results indicate that dental caries occurs in approximately 29% of post-radiotherapy HANC patients. Furthermore, the risk of developing dental caries within two years of head and neck radiotherapy is approximately 37%. Mean/median radiation dose exposure per study, as well as the percentage of patients treated with chemotherapy per study (after the exclusion of an outlier), were both associated with an increase in the percentage of patients diagnosed with dental caries. There was, however, a high degree of observed heterogeneity. Data regarding the number of carious teeth, the number of carious tooth surfaces, and the number of carious lesions developed post-radiotherapy, was deemed unsuitable for meta-analysis and a narrative review was presented.

A systematic review by Hong et al. in 2010 determined a weighted overall prevalence of dental caries in post-treatment cancer survivors of 28.1%.[19] The weighted prevalence of caries in cancer patients who received chemotherapy-only was 37.3%.[19] In contrast, the weighted prevalence of dental caries in cancer patients who were treated with radiotherapy-only, and in cancer patients who received chemo-radiotherapy, were 24.0% and 21.4% respectively.[19] Combined estimates for DMFT and DMFS in post-treatment cancer survivors were calculated as 9.19 and 11.8 respectively.[19] The review by Hong et al., however, included a large proportion of patients diagnosed with haematological malignancies (34%), and 24 out of the 61 (39%) included studies recruited paediatric patients only.[19] These factors may have accounted for the lower combined DMFT and DMFS scores calculated in comparison to those observed in this study's narrative review.

Susceptibility to post-radiation dental caries has been shown to persist in the long-term.[62,74,79] In a 2014 retrospective study of 314 patients, Siala et al. found that the prevalence of dental disease among nasopharyngeal cancer patients escalated from 16% at one-year post-radiotherapy to 36%, 55%, and 74%, at three, five, and seven years post-radiotherapy respectively.[74] Dholam et al. also found significant increases in mean DMFT score at 9, 12, and 15 months post-radiotherapy.[62] These findings are somewhat contradictory to those of this review, however, in which the pooled estimate calculated by the exclusion of studies with longer than two years follow-up (37%) was higher than the overall pooled estimate (29%).

Meta-regression analysis demonstrated a linear association between mean/median radiation dose exposure per study and the percentage of patients diagnosed with dental caries. This relationship may be explained by the multifactorial aetiology of post-radiotherapy dental caries, specifically an increase in radiation-damage to salivary gland and dental structures at higher doses of radiotherapy.

Post-radiotherapy HANC patients are primarily at an increased risk of dental caries due to radiation-induced salivary gland hypofunction.[25,26] At doses of less than 30 Gray, functional salivary gland damage has been shown to be reversible.[80] At cumulative doses above 75 Gray, however, extensive damage to salivary gland secretory tissue occurs in combination with interstitial fibrosis.[80] Mean radiation doses in excess of 20-39Gy have been associated with the development of clinical hyposalivation.[81–88] A dose-response relationship has also been elicited through clinical research, with a salivary gland's quantitative salivary output shown to be inversely associated with its radiation dose exposure.[84] Below a dose of 26-40 Gray, parotid salivary gland function has been shown to recover over time.[18,84] Most of this recovery occurs within the first two years of radiation treatment, however, the repair process can take up to a total of five years post-radiotherapy.[18,83,84,89]

Hey et al. explored the effect of parotid gland 'sparing' on radiation damage to the dentition and concluded that parotid gland radiation doses below 20 Gray could be protective of dental hard tissue.[66] They found that 30 patients with no carious lesions at two years of follow-up had a mean radiation dose exposure of 21.2 Gray to the 'spared' parotid gland, compared to 18 patients with sporadic carious lesions and 22 patients with generalised carious lesions, who had mean radiation dose exposures of 26.5 Gray and 33.9 Gray to the 'spared' parotid gland respectively.[66] The mean radiation dose exposure of the 'spared' parotid gland was found to be significantly lower for patients with no dental caries at follow-up compared to patients with generalised carious lesions at follow-up ($p < 0.001$).[66] Moreover, patients with no dental caries at follow-up had a significantly higher mean stimulated salivary flow rate post-radiotherapy compared to patients with generalised carious lesions at follow-up ($p < 0.01$).[66] Rudat et al. also showed that amifostine, a drug protective of post-radiotherapy salivary gland function, may reduce the incidence of post-radiotherapy dental caries. [1,31,72] The drug's routine use has not been recommended, however, given the risk of serious adverse side effects.[1,31,72]

A dose-effect relationship for post-radiotherapy dental caries has yet to be elicited through clinical research and a paucity of well-designed studies persists in this

field.[31,90] Walker et al. and Liang et al. both explored the effects of dental radiation dose on dental hard tissue.[91,92] In a retrospective study of head and neck radiotherapy patients, Walker et al. found that teeth exposed to greater than 60 Gray were more likely to have tooth damage - defined as moderate to severe enamel loss - by odds of greater than 10 in comparison to teeth exposed to 0 Gray.[91,93] The odds of tooth damage for teeth exposed to 30-60 Gray was 2-3 times higher than the odds of tooth damage for teeth exposed to 0 Gray.[91,93] In a cross-sectional study of nasopharyngeal carcinoma patients treated with IMRT, Liang et al. found that sites on premolar teeth exposed to 30-60 Gray had a 12-200 times increase in the odds of tooth damage - defined as slight, moderate, or severe enamel loss - compared to sites exposed to 0-19 Gray.[92] Walker et al. and Liang et al. speculated that the observed tooth damage between doses of 30-60 Gray was mainly as a result of radiation-induced salivary gland hypofunction.[91,92] For teeth exposed to greater than 60 Gray, however, a greater amount of tooth damage could be attributable to radiation-induced changes to the properties of enamel and dentine including decreased hardness, reduced elastic moduli, decreased tensile strength, and increased susceptibility to enamel shear fracture.[91,92]

The percentage of patients treated with chemotherapy per study was also found to be linearly associated with the percentage of patients diagnosed with dental caries, after the exclusion of the study by Meng et al.[69] There are only a small number of papers in the literature that have explored the effect of chemotherapy on the incidence of dental caries.[94] A systematic review by Busenhart et al. in 2018 revealed that childhood cancer patients treated with chemotherapy had had a greater amount of caries experience in comparison to control patients.[94] The strength of the overall evidence was deemed to be low, however, given the inclusion of non-randomised studies only.[94] Furthermore, the generalisability of the results may be limited given that all of the included studies assessed caries-risk among paediatric patients.[94] Proposed reasons for an increased risk of dental caries in chemotherapy patients include: salivary gland dysfunction, oral mucositis, poorer oral hygiene practice, and disturbances in orodental development e.g. incomplete dental calcification, enamel hypoplasia, delayed or arrested root development, premature closure of apices, and microdontia.[94-98] The impact of chemotherapy on salivary gland function has also yet to be fully determined through clinical research.[18] Based on the small number of studies available, however, it is believed that chemotherapy-induced xerostomia is entirely reversible upon the cessation of treatment.[18,86,99-102]

It is difficult to determine precisely the true relationship, if any, between radiotherapy dose, chemotherapy, and caries-risk in HANC patients, given the large number of potential confounding variables. For example, in radiotherapy and chemotherapy populations, compliance with oral hygiene has been shown to be poor.[65,94] Furthermore, studies with a higher percentage of patients treated with chemotherapy are likely to have included a greater proportion of patients with advanced stage disease.[1] Nevertheless, the findings of this review synthesise current best available evidence and point to the need for well-designed studies in this field.

Strengths and limitations

One obvious drawback of this systematic review is the high heterogeneity determined across included studies. Combined with disparities in methods for assessing the

presence of dental caries, together with variable follow-up times, different sites of head and neck cancer, and the inclusion of a large number of retrospective observational studies likely to introduce bias, the findings of this review are limited. The review highlights the need for well-designed research. The reviewers reduced bias in the review by excluding studies that failed to document participants as having a dental assessment and treatment prior to radiotherapy. Thirty-three out of sixty-three (52%) studies were excluded for this reason. In four of the twenty-two studies (18%) included in this review, radiographic evidence of post-radiotherapy dental caries was counted in addition to clinically diagnosed caries, and therefore the incidence of tooth decay sourced from these studies may be relatively inflated. At least seven studies assessed for the presence of dental caries through a change in DMFS or DMFT score, and for two studies the method of caries assessment was not clearly described.[56,74] Ten of the included studies had a high drop-out rate. The search strategy was restricted to only English-language publications and this may have excluded potentially relevant studies published in other languages. The screening process, however, suggested that this was unlikely and previous investigations have found little effect on combined effect estimates from meta-analyses after the exclusion of trials published in languages other than English.[103]

Clinical implications

Teeth that are extensively affected by dental caries in HANC patients may necessitate tooth extraction.[104] Extractions performed in irradiated patients increase the risk of osteoradionecrosis (ORN). ORN is defined as an area of irradiated, devitalised bone exposed through overlying skin or mucosa, that has failed to heal within three to six months and is present in the absence of local neoplastic disease.[21,105–107] It is considered the most serious complication of radiotherapy excluding tumour recurrence. Symptoms of ORN can be extremely severe for patients and its development may have a significant detrimental impact on patients' quality of life.[108–111]

In the prospective cohort study by Schuurhuis et al., 4 out of 51 (7.8%) patients required at least one tooth extraction within two years of radiation treatment due to deep dental caries.[73] Frydrych et al. determined a statistically significant association between the development of post-radiotherapy dental caries and the need for tooth extractions ($p < 0.001$).[65] They found that 23 out of 116 (19.8%) patients needed at least one post-radiotherapy tooth extraction within a follow-up period of twelve to one hundred and eight months.[65] Duarte et al. found that 12 out of 59 (20.3%) patients treated with IMRT, and 28 out of 99 (28.3%) patients treated with conventional radiotherapy, required at least one tooth extraction within twelve months of the completion of radiotherapy.[64] The difference between the groups was not found to be statistically significant.[64]

Keys and McCasland demonstrated that the implementation of a comprehensive dental care program for HANC patients entailing pre-radiotherapy stabilisation of oral disease, daily fluoride exposure, regular dietary-counselling, regular oral hygiene advice, and close post-radiotherapy follow-up, resulted in significantly decreased levels of dental caries three years post-radiotherapy.[79] Sennhenn-Kirchner et al. also demonstrated that improvements in the preventive and therapeutic dental care of head and neck radiotherapy patients, including the provision of stents for fluoride application, were associated with improved levels of oral hygiene, lower values of Community

Periodontal Index of Treatment Need, and fewer carious teeth at follow-up.[112] Unfortunately, however, post-radiotherapy patients' long-term compliance with fluoride-application trays has been shown to be poor.[113–115] Indeed, Frydrych et al. demonstrated that non-compliance with: regular dental attendance, oral hygiene instruction, dietary advice, and daily fluoride use, were all associated with an increased risk of developing tooth decay post-radiotherapy.[65]

The results have important implications for the clinical dental management of patients with HANC. Head and neck radiotherapy patients should receive intensive oral hygiene instruction and dietary advice, and be recalled at regular intervals during and after treatment, to prevent the onset of tooth decay, to reduce the need for post-radiotherapy tooth extractions, and to minimise the risk of osteoradionecrosis and reduced quality of life.[1,31] The need for an improved understanding of the dental side-effects of radiotherapy is also exemplified by the current lack of consensus among dental professionals on how best head and neck radiotherapy patients should be treated, particularly in relation to pre-radiotherapy dental extractions.[116–118]

Conclusion

This systematic review demonstrated that the incidence of dental caries in post-radiotherapy head and neck cancer patients is approximately 29%. The incidence of dental caries in head and neck cancer patients within two years of the completion of radiotherapy is approximately 37%. The dental caries burden experienced by post-radiotherapy HANC patients appears to be substantial. There is a need for well-designed clinical studies aimed at improving understanding about the risk of dental caries in head and neck radiotherapy patients.

Conflict of interest

None declared

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Author	Type of study	Year of Publication	Number of patients	Follow-up (months)	Caries (outcome) data	Caries assessment	Site of head and neck cancer	Age (years)	Gender - male (%)
<i>Al-Nowas & Grotz</i> [58]	Prospective cohort study	2006	22	12	Mean increase in DMFS of 7.8 at 12 months	Clinical	All regions of the head and neck	47.9 (mean)	68
<i>Almstahl et al.</i> [59]	Prospective cohort study	2018	32	24	37% developed dental caries at 2 years. Mean no. carious lesions at 2 years: 2.1 (+/- 5.9)	Clinical and radiographical	All regions of the head and neck	-	70
<i>Bachok et al.</i> [60]	Quasi-randomised controlled trial	2018	30	3	Mean increase in DMFT of 1.55	Clinical	All regions of the head and neck	46.7 (mean)	70
<i>Bonan et al.</i> [61]	Prospective cohort study	2006	9 at least 3 months	3-42 (mean 22.3 months)	11% developed dental caries	Clinical	All regions of the head and neck	47.9 (mean). 34-62 (range)	89
<i>Dholam et al.</i> [62]	Retrospective cohort study	2013	190	15	Mean increase in DMFT of 1.02 at 15 months	Clinical	All regions of the head and neck	46.5 (mean). 16-77 (range)	73
<i>Dreizen et al.</i> [63]	Randomised controlled trial	1977	42	Mean of 16 months	Mean increase in DMFT of 4.8 and DMFS of 9.4	Clinical	All regions of the head and neck	51.8 (mean). 17.6-76.5 (range)	64
<i>Duarte et al.</i> [64]	Retrospective cohort study	2014	158	12	17% developed dental caries	Clinical	All regions of the head and neck	62.4 (mean). 24-91 (range)	99
<i>Frydrych et al.</i> [65]	Retrospective cohort study	2017	116 at least 12 months	12-108 (mean 45 months)	17% developed caries during follow-up	Clinical	All regions of the head and neck	56.7 (mean). 17-88 (range)	73
<i>Hey et al.</i> [66]	Prospective cohort study	2013	70	24	57% had sporadic or generalised carious lesions at follow-up	Clinical	All regions of the head and neck	Approximately 58 (median). 26-77 (range)	73
<i>Jham et al.</i> [67]	Retrospective cohort study	2008	109 at least 3 months	3-33 (mean 4 months)	Radiation caries found in 11% of patients	Clinical	All regions of the head and neck	57.8 (mean). 14-87 (range)	79
<i>Joyston-Bechal et al.</i> [68]	Prospective cohort study	1992	25	12	Mean increase of 2.4 in DMFS at 12 months. Mean decrease of 0.08 in DMFT at 12 months	Clinical and radiographical	All regions of the head and neck	55.6 (mean). 16-84 (range)	64
<i>Meng et</i>	Prospective	2005	10	6	Mean increase in DMFT	Clinical	Nasopharynx	41 (mean). 20-67	40

<i>al.[69]</i>	cohort study					and DMFS of 1.1 at 6 months. 80% of patients developed new carious lesions.	Clinical	All regions of the head and neck	56.8 (mean). 24-84 (range)	84
<i>Maugent et al.[70]</i>	Prospective cohort study	2019	20	18	35% had increase in DMFS at 18 months. Mean decrease in DMFS of 0.15 at 18 months		Clinical	All regions of the head and neck	56.8 (mean). 24-84 (range)	84
<i>Regezi et al.[71]</i>	Retrospective cohort study	1976	130 at least 12 months	12-120	New carious lesions developed in 20% of patients		Clinical	All regions of the head and neck	52 (mean). 7-86 (range)	68
<i>Rocha et al.[56]</i>	Prospective cohort study	2017	5 at least 39 months	39-60 (mean 53 months)	0 patients developed caries		Clinical	Lip	60.4 (mean). 47-72 (range)	40
<i>Rudat et al.[72]</i>	Retrospective study of a subgroup of patients from a previous RCT (longitudinal assessments performed)	2000	35	12	37% developed caries at 1 year		Clinical	All regions of the head and neck	Approximately 49 (median). 28-68 (range)	77
<i>Schuurhuis et al.[73]</i>	Prospective cohort study	2018	51 at least 11 months	11-24	25% developed one or more carious lesions		Clinical and radiographical	Oral cavity and oropharynx	59 (mean)	63
<i>Stala et al.[74]</i>	Retrospective cohort study	2014	239 at least 35 months	35-176 (median 111 months)	35% developed dental caries		Clinical	Nasopharynx	43 (mean). 10-75 (range)	67
<i>Spak et al.[24]</i>	Randomised controlled trial	1994	37	12	62% had caries at 12 months. Mean of 4.8 carious lesions at 12 months		Clinical and radiographical	All regions of the head and neck	58.1 (mean)	70
<i>Sun et al.[75]</i>	Prospective cohort study	2010	19	6	New carious lesions found in 11% of patients		Clinical	Nasopharynx	57.6 (mean). 45-65 (range)	-
<i>Wang et al.[76]</i>	Retrospective cohort study	2008	84 at least 3 months	3-12	Mean of 2.14 carious teeth at follow-up		Clinical	Nasopharynx	-	78
<i>Wescott et al.[77]</i>	Longitudinal study	1975	15 at least 39 months	39-55 (mean 45 months)	Mean of 13.7 carious lesions developed		Clinical	All regions of the head and neck	-	-

	Number of studies	Odds ratio	95% Confidence intervals	p-value
<i>Fluoride (%)</i>	10	0.82	0.36, 1.88	0.60
<i>IMRT (%)</i>	4	1.00	0.93, 1.07	0.97
<i>Radiation dose exposure (Gray)</i>	9	1.20	1.04, 1.38	0.02*
<i>Oral cavity tumours (%)</i>	13	0.98	0.96, 1.00	0.11
<i>Lower pharynx tumours (%)</i>	13	1.00	0.94, 1.06	0.94
<i>Chemotherapy (%)</i>	10	1.01	0.98, 1.03	0.61
<i>Chemotherapy (with Meng et al.[69] removed - %)</i>	9	1.02	1.00, 1.03	0.02*
<i>Gender – male (%)</i>	13	1.00	0.93, 1.01	0.09
<i>Age (years)</i>	13	0.94	0.85, 1.04	0.23
<i>Stimulated saliva (ml/min)</i>	5	0.19	<0.01, 15.1	0.32

Post-radiotherapy dental caries and radiation dose exposure

Post-radiotherapy dental caries and chemotherapy

Table

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