Head and Neck Cancer Pain: Systematic Review of Prevalence and Associated Factors

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ABSTRACT

Objectives: Pain is a major symptom in patients with cancer; however information on head and neck cancer related pain is limited. The aim of this review was to investigate the prevalence of pain and associated factors among patients with HNC.
Material and Methods: The systematic review used search of MEDLINE, EMBASE and CINAHL databases to December 2011. Cancers of the oral mucosa, oropharynx, hypopharynx and larynx were included in this review with pain as main outcome. The review was restricted to full research reports of observational studies published in English. A checklist was used to assess the quality of selected studies.
Results: There were 82 studies included in the review and most of them (84%) were conducted in the past ten years. Studies were relatively small, with a median of 80 patients (IQR 44, 154). The quality of reporting was variable. Most studies (77%) used self-administered quality of life questionnaires, where pain was a component of the overall scale. Only 33 studies reported pain prevalence in HNC patients (combined estimate from meta-analysis before (57%, 95% CI 43% - 70%) and after (42%, 95% CI 33% - 50%) treatment. Only 49 studies (60%) considered associated factors, mostly tumour- or treatment-related.
Conclusions: The study has shown high levels of pain prevalence and some factors associated with higher levels of pain. There is a need for higher quality studies in a priority area for the care of patients with head and neck cancer.

Keywords: cancer; head and neck cancer; pain; epidemiology; prevalence; review.

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INTRODUCTION

Head and neck cancer is a general name for several types of cancer. The National Cancer Institute defines head and neck cancer as "cancer that arises in the head or neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat or larynx)". Most head and neck cancers are squamous cell carcinomas [1]. Tumours of the salivary glands and the nasopharynx are different from head and neck cancers in their epidemiology, histopathology, and aetiology [2], and therefore are not always included within the head and neck cancer group. Cancer of the head and neck (upper aero-digestive tracts) (oral cavity, pharynx and larynx) is, globally, the ninth most common cancer and cause of cancer mortality, with an estimated 550,319 incident cases and 305,096 deaths worldwide in 2008 [3].

Head and neck cancer remains a potentially disfiguring disease [4]. In the United States and Europe, the five-year survival from cancer of the oral cavity and pharynx is close to 40%, but five-year survival rates are lower in developing countries [5].

The head and neck area is highly sensitive to pain due to rich innervation and the confinement of many anatomical structures to a small space [6]. Therefore persistent pain is a common complaint at presentation and among survivors of head and neck cancer [7]. It has been suggested that the aetiology of cancer-related pain in head and neck cancer patients is multifactorial, and that pain can be due to a direct tumour effect or the result of cancer treatment or factors unrelated to cancer [6,8-9]. Treatment for head and neck cancer patients involves surgery, radiation and chemotherapy, and these treatment methods can cause major structural alteration and chronic pain among survivors of head and neck cancer [6,8]. Jain et al. found head and neck cancers to be the most common cause of neuropathic pain when compared with other common cancers [9]. Thus, this systematic review aimed to examine the prevalence and the associated factors of cancer-related pain among head and neck cancer patients.

MATERIAL AND METHODS

The present systematic review was conducted using, as closely as possible, the general principals described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.2 [10].

Types of participants

Only studies of adults (aged 18 years or over) were used in this review. Studies on head and neck cancer pain due to metastasis to the head and neck were excluded.

Definition of head and neck cancers

Cancers of the oral mucosa, larynx, oropharynx and hypopharynx were considered in this review because of their similarities in epidemiology, treatment, and prognosis [2]. Cancers of the lip, salivary gland, nose, sinuses, middle ear, nerves and bones, thyroid, non-melanoma skin cancers, lymphoma and sarcomas were not considered specifically in this review because of their differences in aetiology and other factors.

Studies were excluded if they combined these tumour sites with cancers of exclusion criteria unless it was possible to extract information for the included types of cancers. Studies were also excluded if it was not clear which types were included in the report.

Stage of cancers

Head and neck being the primary site of cancers, all stages of head and neck cancer were included in this review [11].

Types of publications

The review was restricted to full reports published in the English language up to December 2011. The following publication types were excluded from the review: letters, editorials, post-graduate theses, abstracts, case reports, randomized controlled trials of treatment, qualitative studies and systematic reviews.

Outcome measures

The primary outcome measure of this review was Pain measured using various scales, e.g., Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), pain Numeric Rating Scales (NRS), pain assessment as part of QoL questionnaires administered to head and neck cancer patients before or after treatment and/or for survivors of head and neck cancer.

Associated factors for cancer-related pain such as stage of tumour, type of treatment, time since diagnosis, smoking, alcohol intake, age and gender of the patient and other possible factors were also considered.

We included articles that reported pain domain data or median and inter-quartile range of pain data even though pain proportions were not given. Whenever mean was presented with 95% confidence interval (CI), the CI was converted into standard deviation (SD). If pain prevalence data or pain domain data were not reported but information on association of pain with factors such as

smoking and alcohol intake was presented, those articles were included in the review. If only graphs related to pain data were presented, pain levels were measured to an approximate level.

Mucositis and acute mucosal pain, where the latter could not be differentiated from mucositis, were excluded from this review.

Literature search methods for identification of studies

Search terms used in Cochrane reviews and protocols of head and neck cancer or oral cancer research and research on pain were used in the development of a search strategy for this review [12-17].

Relevant studies were identified by searching the following databases: MEDLINE (1950 to 2011), EMBASE (1947 to 2011) and CINAHL. Detailed search strategies were developed for each electronic database based on the search strategy developed for MEDLINE. The search terms "head and neck, pharynx, oropharynx, hypopharynx, larynx, mouth, oral and tongue" were combined with the words "cancer, carcinoma, neoplasm, malignant or tumour", with different pain classifications and with the term "quality of life". The search strategy was revised appropriately for each database. The search results were imported into the Refworks [18] database; selected results from each database were combined and then duplicates were removed.

The bibliographic references of identified studies and review articles were also checked to find any other studies that were missed during the electronic search. The journals Pain® http://www.elsevier.com/wps/find/journaldescription.cws_home/506083/description#description and Head and Neck http://eu.wiley.com/WileyCDA/WileyTitle/productCd-HED.html were hand-searched for the year 2009 and a basic internet Google search was conducted (Figure 1).

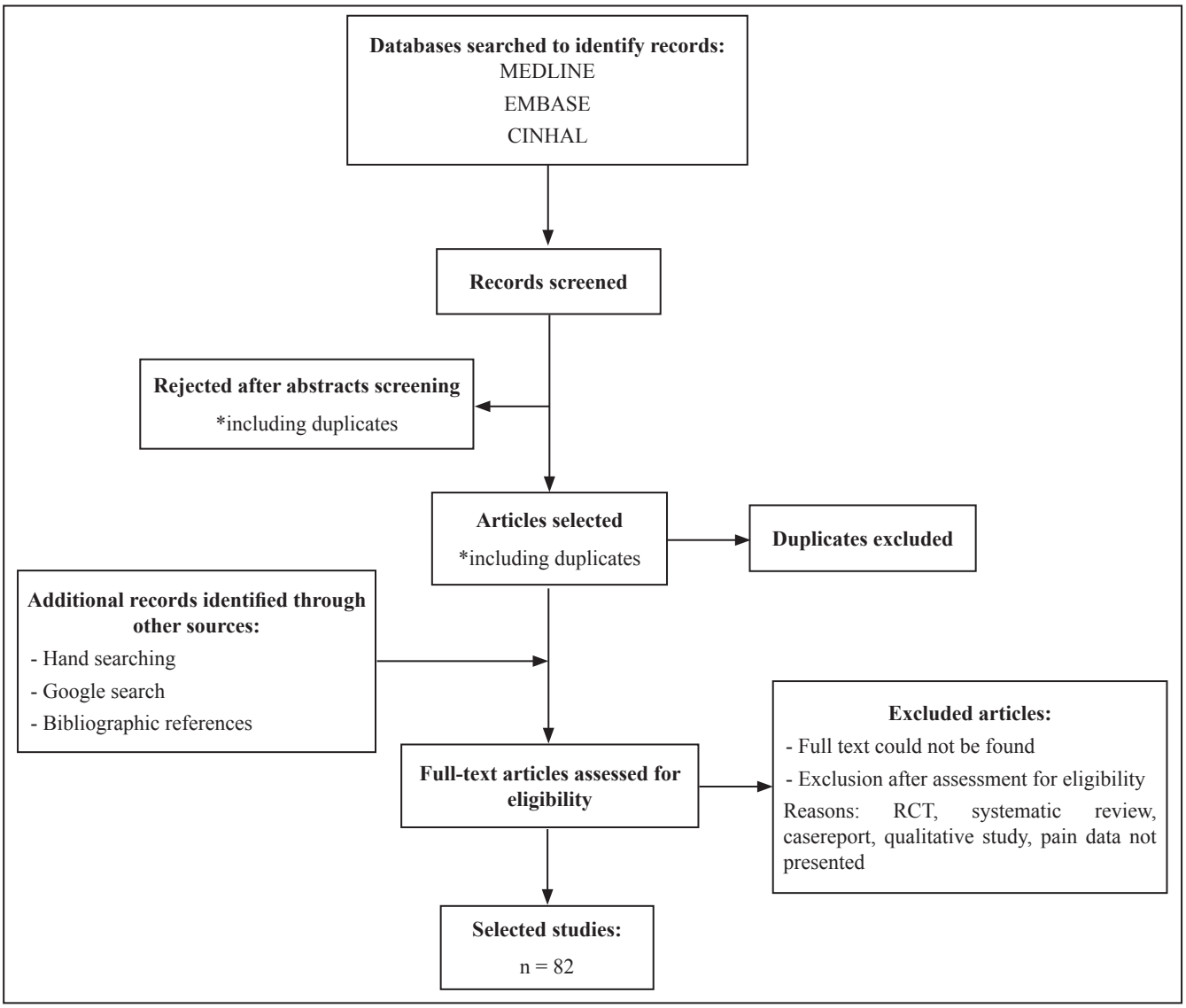


Figure 1. Flow Chart of selection of articles for the review.

Data collection

Two reviewers independently scanned the titles and abstracts of all reports retrieved through electronic searches. Each reviewer classified articles as selected, not selected, or unsure if information from the title and abstract was not sufficient to make a decision. These results were compared between the reviewers and, where there were disagreements, they were discussed and a final decision was made. Full reports were obtained for each study that met the inclusion criteria based on the abstract and these were further assessed for eligibility for inclusion in this review.

Data extraction

For all included studies the following data were extracted using a specially designed data extraction form: first author, year of publication, country of study, ethical clearance approval, source of funding, study design, study duration, number of participants, participation rate, type of cancer, stage of cancer, characteristics of the study population, such as age, gender and ethnicity, study instruments used, time of pain measurement, prevalence of pain as well as information on cancer pain and on associated factors for cancer-related pain. Whenever possible, authors were contacted to clarify information reported in the study.

Quality assessment

Quality assessment of the included reports was carried using a specially designed quality assessment form. This was based on checklists developed by Downs and Black, Crombie and Vandenbroucke et al. [19-21]. The designed form included 16 items. These items were selected to assess the reporting of the aims and objectives of the study, study design, sample size and methods of selecting participants and other methodological issues, such as participation and/or follow-up rate. Further questions were included to assess whether the paper described the statistical methods and main findings of the study, validity and reliability of results, bias, generalisability of study results and limitations. The items were scored as 'yes', 'no', or 'unable to determine'.

Statistical analysis

Information from data extraction forms and quality assessment data were entered in a specially designed spreadsheet for statistical analysis. Meta-analysis was performed for prevalence and mean pain levels separately before and after treatment [22].

RESULTS

Description of studies

There were 82 studies included in the review (Appendix 1, Table 1). Reports of Yoshimura et al. and Karvonen-Gutierrez et al., which did not strictly

Table 1. Description of articles selected for the review

Description	N[a]	%
Head and Neck cancer subtype		
Head and Neck	31	37.8
Oral cavity	14	17.1
Larynx	12	14.6
Oral cavity and Oropharynx	7	8.5
Oropharynx	5	6.1
Tongue	4	4.9
Larynx and Hypopharynx	3	3.7
Oral cavity and Pharynx	2	2.4
Pharynx	1	1.2
Hypopharynx	1	1.2
Oral cavity, Oropharynx and Larynx	1	1.2
Tonsil	1	1.2
Country of study		
Europe	47	57.3
USA and Canada	22	26.8
Asia	10	12.2
Australia and New Zealand	3	3.7
Africa	1	1.2
South America	1	1.2
Gender		
Both males and females	71	86.6
Male only	5	6.1
Not reported	6	7.3
Study Design (as reported by the authors)		
Cross sectional	22	26.8
Prospective	15	18.3
Retrospective	6	7.3
Retrospective chart review	3	3.7
Pilot	2	2.4
Cohort	2	2.4
Case-Control	1	1.2
Case Series	1	1.2
Follow up	1	1.2
Survey	1	1.2
Univariate and correlational descriptive	1	1.2
Study design not reported in methods	27	32.9
Year of publication		
1981 - 1984	3	3.7
1985 - 1990	0	0.0
1991 - 1999	10	12.2
2000 - 2005	31	37.8
2006 - 2011	38	46.3
Sample size		
Minimum, Maximum	13, 1761	
Median (IQR)	80 (44, 154)	

[a]Numbers do not always add up to total (n = 82), because of multiple values.

adhere to the exclusion criteria, were included [23,24]. Yoshimura et al. [23] conducted a study among 56 oral cancer patients with only one lip cancer patient. The study conducted by Karvonen-Gutierrez et al. [24] was also included in this review despite its categorising head and neck cancer patients as "others" together with laryngeal cancer patients. The category "others" could have included any cancer that we would have excluded in this review. However, because the researchers were keen to exclude cancers not arising from the upper aero digestive system such as thyroid, parotid and skin cancers, we included their study in this review.

Because study designs were not reported in a standard manner, study design is presented as reported by the authors (Table 1). In 27 studies the design was not directly reported in the methodology section. The majority of studies were conducted on a mixed group of patients with oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers, whereas few studies were conducted by selecting one particular subsite of head and neck cancer such as oral cavity cancer (17%), laryngeal cancer (15%) or pharyngeal cancer (1%).

Most of the studies were conducted in European countries (57%) and in the Unites States and Canada (27%). Ten studies were conducted in the Asian region, three in Australia and New Zealand, one in Egypt and one in Brazil. The sample size of selected studies ranged from 13 to 1761, with a median of 80 (IQR 44, 154). The majority of the studies were published after the year 2000 (84%). Most studies reported data for men and women combined (Table 1).

Quality assessment

Only 72 articles (88%) clearly described the aim or objective of their study and in addition, only 67% of the articles described and stated the study design in the methodology. The sample size was not justified in any of these articles, besides only 61 (74%) papers described the study setting or location. 71 papers (87%) clearly reported the main outcomes in the introduction or methods sections of the paper. The majority of the papers (84%) did not report any efforts that were taken to address potential sources of bias, but 40% (n = 33) of the papers described the limitations of their study, taking into account sources of bias. 29 articles did not specify the participation rate. In addition, it was difficult to determine the participation rate in seven articles. Out of 29 papers, 20 (69%) mentioned the follow-up rate. Most of the papers (87%) described the statistical methods used. The main findings were clearly described in 68 papers, but not clearly presented in 9 articles. In 72% of the studies the main outcomes measured were valid and reliable. On the other hand, 40% did not discuss the external validity of their study results (Table 2).

Measurement of pain

Tables 3 and 4 show methods of collecting pain data. The selected studies used a variety of methods to collect such data, with most of them utilizing self-administered

Table 2. Quality assessment of studies selected for the review

No	Item	Yes	No	Unable to determine
1	Is the hypothesis/aim/objective of study clearly stated?	72 (87.8)	10 (12.2)	0
2	Is the design of the study described?	55 (67.1)	27 (32.9)	0
3	Is the design appropriate to the stated objectives?	52 (63.4)	0	30 (36.6)
4	Is the sample size stated and justified?	0	82 (100)	0
5	Is the setting/location of the study described?	61 (74.4)	21 (25.6)	0
6	Are the eligibility criteria, and sources and methods of selection of participants described?	59 (72.0)	23 (28.0)	0
7	Are the main outcomes to be measured clearly described in the introduction or methods section?	71 (86.6)	8 (9.8)	3 (3.7)
8	Are the subjects asked to participate in the study representative of the entire population from which they were recruited?	15 (18.3)	5 (6.1)	62 (75.6)
9	Are any efforts to address potential sources of bias described?	13 (15.9)	69 (84.1)	0
10	Is the participation rate stated?	46 (56.1)	29 (35.4)	7 (8.5)
11	Is the follow up rate stated? (if applicable)	20 (69.0)	4 (13.8)	5 (17.2)
12	Are the statistical methods described?	71 (86.6)	11 (13.4)	0
13	Are the main findings of the study clearly described?	68 (82.9)	9 (11.0)	5 (6.1)
14	Were the main outcomes measured used accurate (valid and reliable)?	59 (72.0)	1 (1.2)	22 (26.8)
15	Discuss the generalisability (external validity) of the study results?	32 (39.0)	45 (54.9)	5 (6.1)
16	Discuss limitations of the study taking into account sources of potential bias or imprecision?	48 (58.5)	33 (40.2)	1 (1.2)

Table 3. Quality of Life Questionnaires/Scales used in pain assessment in selected papers

Questionnaire/Scale	N[a]	%
EORTC QLQ-C30	36	43.9
EORTC QLQ-H&N35	31	37.8
UW-QOL	8	9.8
SF-36	6	7.3
UCSF oral cancer pain questionnaire	4	4.9
VAS	3	3.7
Vanderbilt Head and Neck Symptom Survey (VHNSS)	2	2.4
University of Michigan HNQOL	2	2.4
French specific HNQOL	1	1.2
VRS	1	1.2
Brief core set (BCSQ-H&N)	1	1.2
Brief pain Inventory	1	1.2
Common Toxicity Criteria (CTC)	1	1.2
10 point scale	1	1.2
French specific HNQOL	1	1.2
Health Status Q-12	1	1.2
Memorial Symptom Assessment Scale	1	1.2
Oral and Pharyngeal symptom questionnaire	1	1.2
Bochum university questionnaire	1	1.2
RAND-36	1	1.2
SF-12v2	1	1.2
Head and Neck health survey	1	1.2
Xerostomia Questionnaire	1	1.2
Pain data from patient records or no description of pain assessment method	11	13.4

[a]Numbers do not add up to total (n = 82), because some studies used several questionnaires.

questionnaires. The majority of these questionnaires were quality of life questionnaires with pain as a component. These included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC Head and Neck (H&N-35), University of Washington Quality of Life Questionnaire (UWQOL), SF- 36 Health Survey and Visual Analogue Scale (VAS). The most frequently used tool to assess pain domain data was the EORTC QLQ-C30 or the EORTC H&N-35 questionnaire. The UWQOL and SF-36 were the other two commonly used questionnaires in the selected articles, while pain was rarely assed with the VAS.

Dilber et al. [41] used VAS and VRS in an assessment of shoulder pain in selected patients. They evaluated shoulder pain in two stages: at rest and with shoulder movements. In the preoperative evaluation of shoulder pain by VAS, no pain was reported during rest or movements, but mild pain was reported according to VRS. Confusingly, in their discussion the authors observe that "preoperative shoulder pain was absent in our patient group". Majority of studies (61%) reported pain during past week (Table 4) and most (66%) investigated pain after treatment.

Table 4. Method of pain reporting

Description	N[a]	%
Pain data collection method		
Self administered questionnaire	63	76.8
Interview	11	13.4
Patient records	7	8.5
Not clear	1	1.2
Pain data reporting		
As pain domain data	47	57.3
As proportions or percentages	33	40.2
On graphs only	5	6.1
Time period of pain reporting		
Current	2	2.4
Past 24 hours	1	1.2
Past week	50	61.0
Past 4 weeks	11	13.4
Not specified	18	22.0
Timing of pain measurement in relation to treatment		
Before	31	37.8
After	54	65.9
During	1	1.2
Before/After/During	2	2.4
Before and After	2	2.4
During and After	1	1.2
Not specified	4	4.9

[a]Numbers do not always add up to total due to multiple values.

Prevalence of pain

Studies conducted primarily to assess the prevalence of head and neck cancer pain were minimal. 33 articles reported pain as proportions, whereas 47 studies in this review reported pain domain data. The definitions used in describing pain showed considerable variation. Of the studies that reported pain data as proportions, 13 reported pain prevalence data of patients before treatment [25-37] and 18 reported pain after treatment [25,38-54]. Ethunandan et al. [55] examined pain data of patients after treatment one week preceding death. Three studies either included a mixed group of patients or provided no clear information [7,56,57]. In ten studies, pain was specified by severity, e.g. as mild, moderate or severe pain [33,35,37,41,44-46,52,54,57]. 15 studies also defined pain proportions by site, e.g. as bodily pain, head and neck pain, spontaneous or function-related pain, localized pain or referred pain. Studies reporting pain domain data were not subcategorized as studies that gave pain data as proportions unless they reported both pain domain data and percentages.

Gellrich et al. [47] reported that 54% of oral cancer

patients had "some type of pain". A study by Sato et al. in 2010 [28] reported spontaneous pain as 37% and function-related pain as 68% in a sample of 113 oral squamous cell carcinoma patients. Pain prevalence was 86% in another study conducted among squamous cell carcinoma head and neck cancer patients [7]. A study from India by Jagannathan et al. [48] reported that 84% of the head and neck cancer patients had any pain. The prevalence of pre-treatment pain among 13 oropharyngeal cancer patients was 69% [26], and 60% of oral and oropharyngeal cancer patients reported pain as a symptom of cancer [29]. Logan et al. [38] reported pain data among five-year survivors of head and neck squamous cell carcinoma patients, which was 43%. Magne et al. [42] assessed pain in long-term follow-up patients with advanced head and neck cancers; they stated that over a two- to seven-year follow-up after completion of treatment 9% still suffered from pain. One study assessed pain at the week preceding death, putting it at 84% [55].

However, most of the studies reported only mean pain, either with standard deviation, confidence interval or range. Five of them presented their data on graphs, requiring estimation of an approximate value for the given scale [58-62].

Combined estimate of pain prevalence from meta-analysis before treatment was 57%, 95% CI 43% - 70% while combined estimate from meta-analysis after treatment was 42%, 95% CI 33% - 50%, based on 12 and 19 studies respectively (Figures 2 and 3). In contrast, mean level of pain after treatment on scale 0 - 100 was 17, 95% CI 12 - 22, based on 21 studies (Figure 4). There was high level of heterogeneity (I2 > 90 for all three analyses).

Factors associated with head and neck cancer pain

Out of the 82 selected articles, 49 considered factors

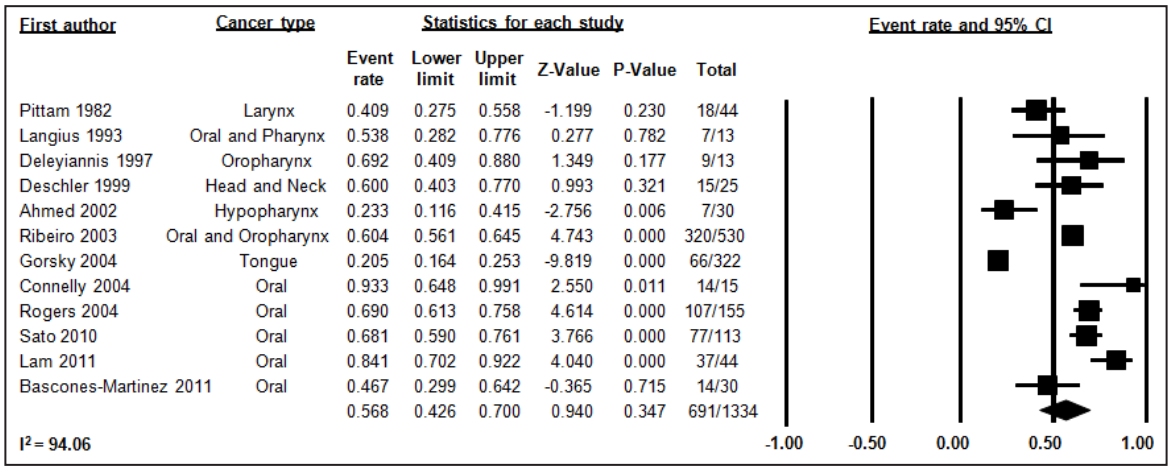


Figure 2. Meta-analysis of pain prevalence before treatment (random effect).

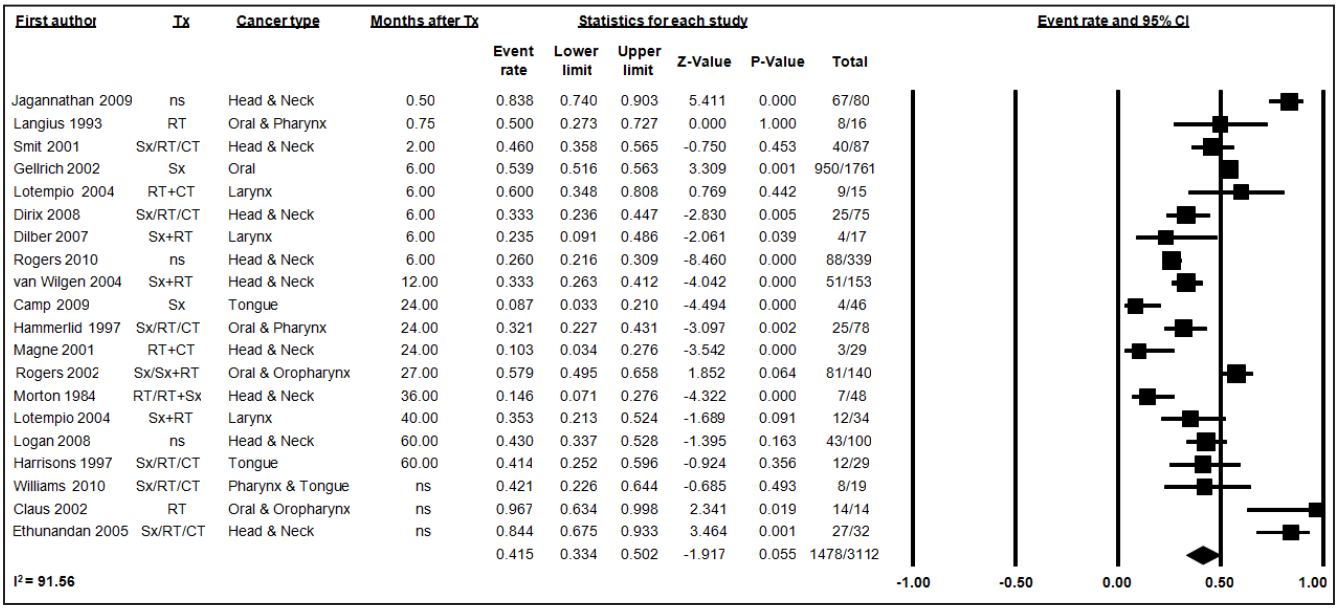
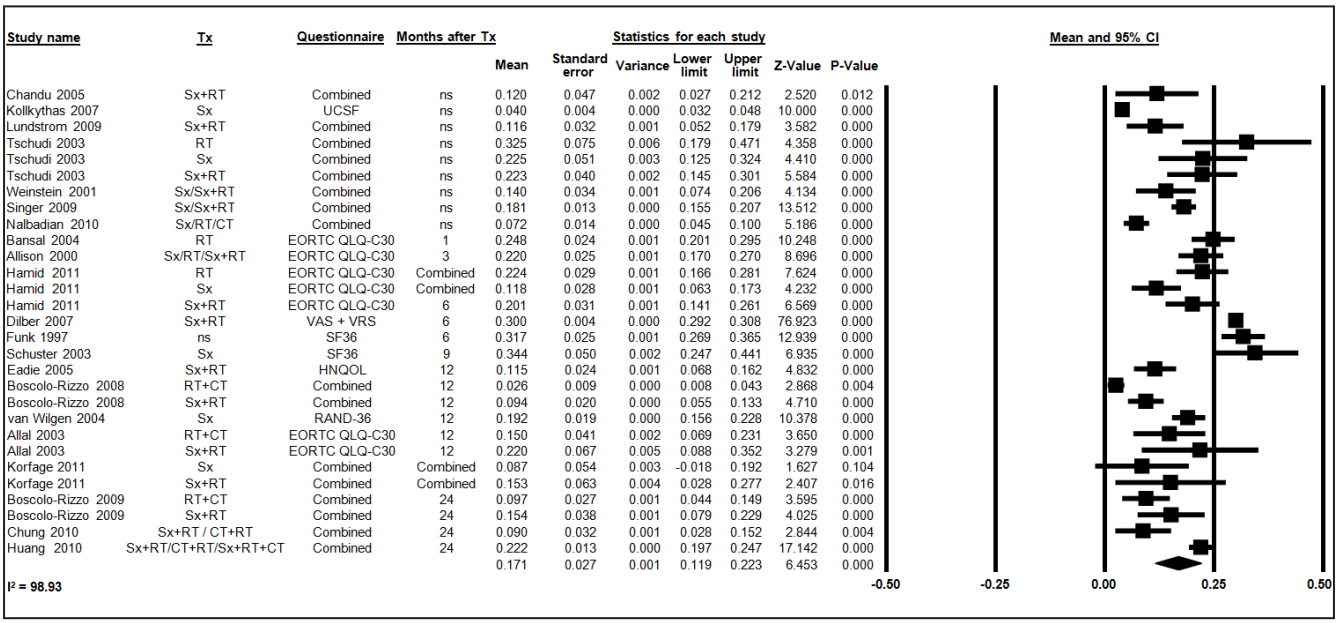


Figure 3. Meta-analysis of pain prevalence after treatment (random effect).



Study name	Tx	Questionnaire	Months after Tx	Statistics for each study						
				Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Chandu 2005	Sx+RT	Combined	ns	0.120	0.047	0.002	0.027	0.212	2.520	0.012
Kollkythas 2007	Sx	UCSF	ns	0.040	0.004	0.000	0.032	0.048	10.000	0.000
Lundstrom 2009	Sx+RT	Combined	ns	0.116	0.032	0.001	0.052	0.179	3.582	0.000
Tschudi 2003	RT	Combined	ns	0.325	0.075	0.006	0.179	0.471	4.358	0.000
Tschudi 2003	Sx	Combined	ns	0.225	0.051	0.003	0.125	0.324	4.410	0.000
Tschudi 2003	Sx+RT	Combined	ns	0.223	0.040	0.002	0.145	0.301	5.584	0.000
Weinstein 2001	Sx/Sx+RT	Combined	ns	0.140	0.034	0.001	0.074	0.206	4.134	0.000
Singer 2009	Sx/Sx+RT	Combined	ns	0.181	0.013	0.000	0.155	0.207	13.512	0.000
Nalbadian 2010	Sx/RT/CT	Combined	ns	0.072	0.014	0.000	0.045	0.100	5.186	0.000
Bansal 2004	RT	EORTC QLQ-C30	1	0.248	0.024	0.001	0.201	0.295	10.248	0.000
Allison 2000	Sx/RT/Sx+RT	EORTC QLQ-C30	3	0.220	0.025	0.001	0.170	0.270	8.696	0.000
Hamid 2011	RT	EORTC QLQ-C30	Combined	0.224	0.029	0.001	0.166	0.281	7.624	0.000
Hamid 2011	Sx	EORTC QLQ-C30	Combined	0.118	0.028	0.001	0.063	0.173	4.232	0.000
Hamid 2011	Sx+RT	EORTC QLQ-C30	6	0.201	0.031	0.001	0.141	0.261	6.569	0.000
Dilber 2007	Sx+RT	VAS + VRS	6	0.300	0.004	0.000	0.292	0.308	76.923	0.000
Funk 1997	ns	SF36	6	0.317	0.025	0.001	0.269	0.365	12.939	0.000
Schuster 2003	Sx	SF36	9	0.344	0.050	0.002	0.247	0.441	6.935	0.000
Eadie 2005	Sx+RT	HNQOL	12	0.115	0.024	0.001	0.068	0.162	4.832	0.000
Boscolo-Rizzo 2008	RT+CT	Combined	12	0.026	0.009	0.000	0.008	0.043	2.868	0.004
Boscolo-Rizzo 2008	Sx+RT	Combined	12	0.094	0.020	0.000	0.055	0.133	4.710	0.000
van Wilgen 2004	Sx	RAND-36	12	0.192	0.019	0.000	0.156	0.228	10.378	0.000
Allal 2003	RT+CT	EORTC QLQ-C30	12	0.150	0.041	0.002	0.069	0.231	3.650	0.000
Allal 2003	Sx+RT	EORTC QLQ-C30	12	0.220	0.067	0.005	0.088	0.352	3.279	0.001
Korfage 2011	Sx	Combined	Combined	0.087	0.054	0.003	-0.018	0.192	1.627	0.104
Korfage 2011	Sx+RT	Combined	Combined	0.153	0.063	0.004	0.028	0.277	2.407	0.016
Boscolo-Rizzo 2009	RT+CT	Combined	24	0.097	0.027	0.001	0.044	0.149	3.595	0.000
Boscolo-Rizzo 2009	Sx+RT	Combined	24	0.154	0.038	0.001	0.079	0.229	4.025	0.000
Chung 2010	Sx+RT / CT+RT	Combined	24	0.090	0.032	0.001	0.028	0.152	2.844	0.004
Huang 2010	Sx+RT/CT+RT/Sx+RT+CT	Combined	24	0.222	0.013	0.000	0.197	0.247	17.142	0.000
				0.171	0.027	0.001	0.119	0.223	6.453	0.000

Figure 4. Meta-analysis of mean pain level after treatment (random effect).

that are potentially associated with head and neck cancer pain (Table 5). Most of them reported tumour-related and treatment-related factors. Less than 50% of these studies examined several factors simultaneously.

There were several studies conducted by the same authors on one study population. All of them were included in the review, because of stating different research questions and varying in data analysis. For example, van Wilgen et al. used the same study sample to first analyze the relationship between neck pain and type of neck dissection, number of dissected levels, radiation therapy and shoulder pain [49] and then to explore the impact of shoulder and neck morbidity after head and neck cancer treatment on patients quality of life [50]. Sato et al. started with elucidating significant factors associated with pain in their patient group [28], to determine afterwards whether cancer pain was predictive of poor prognosis in patients [36].

Non-cancer-related factors

Age

Twelve studies assessed association of pain by age. Nine studies did not show any association with age [36,40,63-69]. Of these nine studies, eight had a sample size of over 50 with both male and female participants. Studies done by Sato et al. [28], Derks et al. [70], and Infante-Cossio et al. [71] reported a significant association between pain and age. All three studies had a sample size of more than 100. In two studies younger patients reported more pain than did the elderly group. Derks et al. [70] compared the 45 - 60 years age group with the over 70 years age group among patients with oral cavity, pharyngeal and laryngeal cancer, while Infante-Cossio et al. [71] compared the below 65 years age group with the over 65 years age group among oral squamous cell carcinoma patients. In the study by Sato et al. [28] the group of patients who reported pain had a significantly lower median age (m = 63) than the group without pain (m = 65).

Gender

Association of pain with gender was assessed in 13 studies [27,28,36,39,40,64-68,71-73]. Three of them found a significant association with pain. The EORTC QLQ-C30 and H&N-35 questionnaires were used in two of these studies [71,72]; the study conducted by Connelly et al. [27] used the UCSF oral cancer pain questionnaire.

The study done by Hammerlid et al. [72] found a significant association with gender, but this association was observed for all head and neck cancer patients, including salivary gland, sinuses, nose and other or unknown primary head and neck cancer tumours. Females reported worse pain scores in this study than men. This is consistent with the results of the study by Infante-Cossio et al. [71], who also found worse pain scores in females. In contrast, Connelly et al. [27] reported significantly higher levels in intensity and sharpness of function-related pain for men in comparison to women.

Other socio-demographic factors

Eight studies considered an association of pain with education level, employment status, income, marital status or cultural groups. A cross-sectional study by

Pourel et al. [64] found no significant association of pain domain data with the marital status, education level and employment status of 113 oropharyngeal cancer patients. Allison [74], however, reported a significant association with pain and employment when comparing unemployed patients with employed or retired patients. Chan et al. [75] examined the medical records of 77 head and neck cancer patients, finding an association of divorced status with poorer pain. A study conducted in France and Canada on a group of oral, larynx and pharynx cancer patients [59] reported that French-speaking Canadians complained of significantly more pain than did English-speaking Canadians and French-speaking French head and neck cancer patients, even when controlled for possible socio-demographic and clinical predictors.

In Taiwan, Huang et al. [76] described a statistically significant trend ($P < 0.05$), that head and neck squamous cell carcinoma survivors with higher annual family income had a better outcome on pain for the EORTC QLQ-H&N35 questionnaire than the ones with lower income.

Consumption of tobacco and alcohol

Pourel et al. [64] evaluated any possible association of tobacco and alcohol consumption with head and neck cancer pain in a sample of male and female oropharyngeal cancer patients of France and found no significant association. A multicenter cross-sectional study of 179 laryngectomised patients conducted by Danker et. al. [77] also resulted in no significant difference on pain scales between alcoholics and non-alcoholics. However, a cross-sectional study done in Canada with a sample of 271 oral, larynx and pharynx cancer patients reported a significant relationship between pain and alcohol drinking ($P = 0.0033$). In this study Allison [74] found that head and neck cancer patients who had consumed at least one alcoholic drink during the last month had significantly less pain scores. This finding goes contrary to the usual belief that continuation of alcohol after diagnosis of head and neck can worsen the pain and quality of life.

Other factors

Twelve studies described an association of pain with presence or absence of co-morbidities, presence or absence of metallic taste, survival and treatment prognosis, dental care, depression and anxiety and optimistic or pessimistic thoughts of patients. The presence or absence of co-morbidities was not significantly associated with pain [39,64]. Logan et al. [38] reported metallic taste as a significant and independent predictor of spontaneous pain. Pain domain scores were significantly associated with survival and prognosis of head and neck cancer patients in two studies [24,65]. Zwahlen et al. [78] found a significant correlation for anxiety with pain and also stated that pain was related to higher levels of depression. In contrast, the prospective cohort analysis by Chan et al. [75] resulted in a significant association of depressive symptoms with poorer pain. However, after controlling for other variables, this association was no longer significant.

A prospective study in France by Allison et al. [79] involving a sample of oral cavity cancer patients described optimistic patients as having significantly less pain than their pessimistic peers in pre-treatment ($P = 0.048$) and post-treatment data ($P = 0.047$).

Cancer-related factors

Site of cancer

Ten studies examined an association of pain with primary cancer site [28,38-40,53,71,76,80-82]. Only Chaplin et al. [80], Infante-Cossio et al. [71], Borggreven et al. [81], Nalbadian et al. [82] and Huang et. al. [76] described a significant association between the two factors. Chaplin et al. [80] reported that patients with laryngeal cancers had significantly less pain at diagnosis than those with tumours in the oral cavity. Infante-Cossio et al. [71] noticed more pain in oropharyngeal cancer patients than in patients with oral tumours. Borggreven et al. [81] found a different association as in their study oral cavity tumour patients had significantly worse pain scores for QOL scales when compared to oropharyngeal tumours.

Tumour stage

A total of eleven studies evaluated the association of pain or pain domain data with tumour stage [27,28,36,38,40,53,65,68,71,75,83]. One study reported no significant association of TNM stage and clinical stage of oral squamous cell cancers with spontaneous pain [28]. The same study revealed that pain in the endophytic group was higher than pain in the exophytic group ($P < 0.05$) and that pain in patients with histological grade II cancers had more pain than grade I patients ($P < 0.05$). Dirix et al. [40] found that TNM classification and clinical stage were not significantly associated with oral pain. The study by Logan et al. [38] also revealed that tumour stage at diagnosis was not associated with pain scores. Schliephake et al. [65] reported a significant association of pain domain data with cancer stage. Another study found that patients with advanced-stage cancers (stage T3 and T4) had significantly more pain

than those with T2 tumours [83]. Infante-Cossio et al. [71] described similar findings. In their study patients with end-stage tumours (stage III and IV) had more pain compared with patients with stage I and II cancers ($P < 0.01$). An increased level of spontaneous pain and functional restriction due to pain was observed in patients with nodal disease in a study by Connelly and colleagues [27].

Tumour size

Only a few studies examined pain data with regard to different tumour sizes. Connelly et al. [27] reported no correlation between the tumour size and pain levels in 16 oral squamous cell carcinoma patients. Lam et al. [35] reported the same result in their cross-sectional study on 44 patients in 2011, but Singer et al. [66] found a significant association with pain and tumour size at the time of surgery ($P < 0.02$) for 323 laryngeal cancer patients.

Treatment-related factors

Overall, 24 studies evaluated the association of different types of treatment with pain severity, with 15 of them finding a significant correlation. In three studies surgically treated patients suffered from more pain than non-surgically treated patients [84-86]. Tschudi et al. [87] found different results where the non-surgically treated group had significantly more pain than the surgically treated group of patients with or without post-operative radiotherapy ($P = 0.004$). This difference was not observed with the EORTC QLQ-C30 scale. Patients with total laryngectomy had higher pain scores than partial laryngectomised patients or patients receiving other types of treatment in three studies [66,88,89]. Two studies reported that the combination of surgery and radiotherapy led to more pain in patients when compared to patients treated with surgery or radiotherapy only [62,90]. Other studies described more pain among patients who were treated with chemoradiotherapy when compared to patients who had undergone other treatment methods [54,82].
In addition, nine studies compared pain levels at different stages of treatment, such as before, during and after treatment or shortly after treatment and after a longer period of time. Six resulted in a significant association. Hamid et al. [62] examined longitudinal changes in the pain scales of a surgical, radiotherapy and combined treatment group. In all groups pain was significant worse during treatment when compared to pretreatment. Moreover, patients in the radiotherapy group had significant worse pain three and six months after completion of treatment than before treatment. A study conducted in the USA included head and neck cancer patients from early recovery (1 - 2 months post treatment), mid recovery (4 - 6 months post treatment) and late recovery (10 - 14 months post treatment). It found that patients in the early stage of recovery had significant higher pain levels than the ones in the middle stage, which means that pain scores declined over time as patients recovered from the toxicities of therapy. However, the symptom did not completely resolve even in the late stage of recovery [67].

DISCUSSION

This systematic review on the prevalence of head and neck cancer pain and associated factors is the first review of its type. Previous reviews had been conducted on the prevalence of pain in patients with cancer [91,92] and two reviews had been done on the prevalence and associated factors of orofacial pain [93,94]. Williams et al. [57] conducted a review of the literature on the prevalence of pain in head and neck cancer patients as part of their study. They presented pain prevalence data of 17 studies, but no data on associated factors.

Literature search and selection of publications

The electronic literature search was conducted using three databases with the intention of retrieving all original reports that meet our aims in this review. It is generally accepted, however, that only a proportion of research projects are published in indexed journals and are readily available for systematic reviews [95]. This results in reporting bias in a review. Sterne et al. [95] further point out that a systematic review of published studies can lead to publication bias as studies with significant results are more likely to be published than studies with negative results. This review was limited to publications in the English language due to a lack of resources to translate articles published in other languages. This might have resulted in language bias in this review. However, the extent and effects of language bias have been recently reduced with the trend of publishing studies in the English language [95]. Out of all citations added to the MEDLINE database in 2008 about 92% were published in English [96].
A number of studies might have been missed in this review during the search and selection process. The electronic search for databases was conducted as broadly as possible. However, if the key search terms were not included in the abstract of a study, that study may have been missed in our search. The selection of

studies was carried out by two reviewers independently to minimize the errors of judgment.

Reporting of pain prevalence data

The results of this systematic review show that few studies have primarily been conducted to assess the prevalence of pain in head and neck cancer patients. The majority of studies only reported pain data as a part of QoL assessment in these patients.

When all the studies with pain prevalence data were considered, irrespective of their methodology, the pain prevalence data ranged from 9% to 98%. There was heterogeneity between studies due to variation in study design, primary site of cancer, stage of cancer, treatment modality, method of pain evaluation, pain definition used and the age of study participants varied greatly in these studies. For example, Camp et al. [44] reported that moderate to severe pain among a sample of base of tongue carcinoma patients was 9%. If mild pain were considered pain as well, the prevalence would have increased further. Ear pain in a group of patients with squamous cell carcinoma of the tongue was 20% [30], and pain in the throat was 23% among 30 hypopharyngeal cancer patients [31]. However, the majority of studies reported pain prevalence of more than 30%. Therefore, it is apparent that pain in head and neck cancer patients is a significant problem.

Systematic reviews conducted on the prevalence of breast cancer pain were confronted with similar problems as this review was. Andersen et al. [97] reported difficulties in exact interpretation of prevalence as studies selected for their review used different questionnaires to assess pain, thus varying in measurement methods and anatomical location. They reported the prevalence of the Post Mastectomy Pain Syndrome (PMPS) at around 25% and the prevalence due to a wider definition of persistent pain after breast cancer treatment at around 50%. A pan-European survey of cancer-related pain [7] reported difference in pain prevalence by cancer type. Patients with the highest prevalence of pain (over 85%) were those with cancers of the pancreas, bone, brain, lymphoma and head and neck.

The heterogeneity of pain prevalence data in studies of this review can be due to several factors. Some studies selected specific head and neck cancer subsites, whereas some studies were conducted on all available head and neck cancer patients. Some studies included all cancer stages, whereas some authors considered early-stage head and neck cancer types only. The selection of participants also varied in studies, with some studies done on a convenient sample of head and neck cancer patients. Study design, sample size, response rate, data collection method, study instrument and other methodological issues can account for the differences in prevalence rates.

On the other hand, several factors can affect pain among head and neck cancer patients. It is a known fact that pain is associated with psychological factors such as anxiety and depression. However, as most of the selected studies were QoL assessment studies, they did not assess the association of pain with psychological factors. Information on pain medication before or during study may be useful in the correct assessment of pain prevalence of head and neck cancer patients unless participants are selected prior to the administration of any treatment. The possible effect of bias and confounding on reported pain data has to be considered. Most of the studies, however, did not report their efforts to minimize bias and adjustments done for possible confounders.

The authors used different tools to assess pain. The data collection tools used in these studies varied from pain intensity scales such as VAS to the use of multidimensional pain instruments like "brief inventory". Most common were QoL questionnaires as the primary goal of many studies was to assess the quality of life of head and neck cancer patients. The discrepancies in reported pain data by different authors may be due to the different pain assessment tools used in data collection. However, van den Beuken-van Everdingen et al. [91] point out that the use of validated or invalidated questionnaires or interviews was not responsible for the heterogeneity of pain prevalence rates in their review. They further suggest using multidimensional tools in pain-related research as these tools facilitate the comparison of studies.

The EORTC QLQ-C30 and H&N35 were common among the studies. EORTC QLQ-C30 uses a Likert scale of 0-100, with a higher score indicating a higher level of symptoms or problems. Chandu et al. [98] mention that these scores can be left as raw scores or can be translated into percentages. When % best score is reported readers can get an idea of the percentage of participants who were pain-free at the time of questionnaire administration and vice versa. However, only a minority of studies that used EORTC QLQC-30 or H&N35 reported % best score and worst score in either tables or texts. The presentation of pain domain data of studies using EORTC QLQ-C30 and H&N35 questionnaires also varied significantly. Some studies report pain domain data by gender, by alcohol consumption, by age group, by tumour site and by presence of co-morbidity. Furthermore, limitations of the questionnaires have to be taken into account. QoL questionnaires contain few questions referring to pain. For example, the EORTC QLQ-C30 and H&N35 only ask for pain in mouth, jaw and throat during the past

week, the interference of pain with daily activities and the use of pain killers [99,100]. The UW-QOL is similarly designed, asking about the severity of pain over the last seven days [46]. Overall 61% of the studies in this review only asked about the pain during the past week. 22% did not even specify the time period of experiencing pain (Table 5). None of them asked about chronic pain lasting for a long period of time and few contained questions addressing the exact site of pain. Therefore, only limited information on pain prevalence and pain characteristics is provided by studies collecting pain data with QoL questionnaires.

Table 5. Number (%) of studies reporting associated factors and showing significant results

Factor	N (%)[a] reporting	N shown significant association
Age	12 (24.5)	3
Gender	13 (26.5)	3
Socio-demographic factors		
Education	2 (4.1)	-
Employment status	2 (4.1)	1
Income	1 (2)	1
Ethnicity	1 (2)	1
Marital status	2 (4.1)	1
Alcohol consumption	3 (6.1)	1
Smoking	2 (4.1)	-
Other factors		
Co-morbidity	2 (4.1)	-
Metallic taste	1 (2)	1
Prognosis	2 (4.1)	2
Dental care	1 (2)	-
Depression or anxiety	5 (10.2)	5
Optimism	1 (2)	1
Site of cancer	10 (20.4)	5
Tumour stage	11 (22.4)	5
Tumour size	3 (6.1)	1
Treatment-related factors		
Type of treatment	24 (49)	15
Stage of treatment or time since treatment	9 (18.4)	6

[a]Numbers do not add up to total (n = 49), because some studies reported several factors.

Reporting of associated factors

Pain can be associated with the tumour itself and treatment modality, but it also may be related to factors such as age, gender, ethnicity, smoking or drinking. We expected to find information on all of the different variables. Education level, consumption of tobacco, co-morbidity and dental care were the only factors for which no study included in the review reported a significant association. Several studies found significant correlations of the other factors with pain. However, this information was not sufficient to reach a reliable conclusion on the aetiological factors of pain in head and neck cancer patients, as their results varied greatly. We could not explain the differences in these findings due to methodological issues in these studies. While some studies used a random sample of head and neck cancer patients, others used a convenient sample of patients. Sample size and participation rate, bias, and confounding factors can also play a role in these findings.

Treatment-related factors were most often shown to be significant associated with head and neck cancer pain. The findings suggest that the type of treatment given to a patient can have a great impact on the pain he or she is experiencing. Moreover, results of this review show that pain values often increase during treatment and stay on high levels in the period following surgery, radiotherapy or chemotherapy. It can take up to six months or even longer until pain reaches levels comparable to the time before treatment. These findings are consistent with the review by Epstein et al. [94], who pointed out that orofacial pain improves following treatment and in many cases does not return to its baseline value. Therefore, a proper management of head and neck cancer pain is an essential part alongside cancer treatment.

Quality assessment

This review was done on observational studies, and quality assessment of selected studies was done based on a checklist designed using available checklists for observational studies.

It was challenging to decide on the study design used in some of the articles as this is not reported in the methodology. Some authors report the study design as a retrospective or a prospective study. The STROBE statement [21] has been developed to strengthen the reporting of observational studies. This is similar to the CONSORT statement of reporting randomized control trials [101], but a recent publication has shown the quality of reporting of observational studies to vary considerably. The STROBE statement recommends that authors refrain from simply stating a study as being "prospective" or "retrospective" because of the ill-defined nature of these terms [21]. It also recommends that authors of observational studies present study design at the end of the introduction or in the methods section.

Methodological problems of definitions used in the selected studies

The pain definitions used in the selected studies varied greatly. Some studies describe "any pain" while some report pain by its intensity, such as "mild, moderate

or severe". Most of the studies do not report the pain assessment duration. Most of the selected studies were not specifically designed to assess pain prevalence and/or associated factors. Most of the studies present pain data as part of a quality assessment study of head and neck cancer patients. It was a limiting factor in this review.

As most studies in this review were not designed to specifically measure pain, they did not report pain descriptors. Study from Norway [114] showed that cancer patients used several pain descriptors, and "aching" was the most frequently used. Although the verbal descriptors provide valuable information regarding the pain experience, it is not possible to differentiate pain mechanisms simply based on pain descriptors.

Another shortcoming observed in this review is the lack of reporting of cancer stage classification. Recent articles use the American Joint Committee on Cancer (AJCC) classification, whereas earlier articles use the International Union against Cancer (UICC) classification for staging. There were articles that report cancer stage but not the classification used for cancer staging. Some articles report only TNM or TN stages.

We selected few studies that report pain in head and neck cancer patients without any subsite specification. When the umbrella term of "head and neck" is used, it may include cancers that we wanted to exclude in this review. So this could have introduced selection bias to this review. Some studies specify head and neck cancers such as pharyngeal and laryngeal and include some cancers under the term "other". Only a few authors describe the cancers included under term "other". We included all hypopharyngeal cancer studies in this review. It was not clear in some studies, however, whether pyriform sinus cancers were included or not when the broad term "hypopharyngeal cancers" was used.

Head and neck cancers include many different types of cancer. The aetiology and histopathology of cancers may vary from each other, making it difficult to go for a direct comparison. Some studies were conducted on a convenient sample of head and neck cancer patients, and they did not consider the differences in cancer type and different cancer stages. Very few studies were conducted selecting a specific group of head and neck cancer patients, paying attention to tumour stage and different treatment modalities and other factors that affect the generalizability of results.

Generalizability

The majority of studies in this review were conducted in European countries, followed by the United States and Canada; only a few studies were conducted in developing countries. A few studies used multiethnic groups but did not report pain prevalence data by ethnic group. Most of the studies did not report the ethnic group of the study sample.

The prevalence of head and neck cancer and cancer-related pain can vary within cultures, and aetiological and geographical changes can also play a role. Allison [59] found a significant association between head and neck cancer pain and cultural groups after controlling for other possible socio-demographic and clinical predictors of health-related quality of life. Therefore, the results of this type of review may not be generalizable to other populations.

With respect to cancer pain mechanisms, cancer and immune cells in the area of tumour release neuroimmune mediators that interact with a variety of receptors. Also, tumours growing in the vicinity of peripheral nerves can compromise the integrity of the nerve, inducing a neuropathic condition accompanied by persistent pain [115]. Both of these actions of tumours on peripheral nerve can result in central sensitization. Systematic review of prevalence and aetiology of neuropathic pain in cancer patients, which aimed to identify the prevalence of neuropathic mechanisms in patients with cancer pain, highlighted the need for a standardised approach or taxonomy used for assessing neuropathic pain in patients with cancer in order to improve treatment outcomes [116]. The review also showed that the proportion of pain caused by cancer treatment was higher in neuropathic pain compared with all types of cancer pain.

This review did not consider studies of head and neck cancer pain management. However the review of oral cancer pain by Dios and Lestón [117] showed that the literature on oral cancer pain management was sparse. Oral cancer pain management requires multimodal approach but there is no evidence of the efficacy of non-pharmacological methods such as acupuncture or transcutaneous nerve stimulation.

Future research on the prevalence of pain in head and neck cancer patients should pay attention to the selection of a representative sample of patients and to obtain an adequate sample size, in order to reach adequate study power. The authors should justify the sample size and report participation rate and pain-related data, including severity of pain, type of pain, pain descriptors and possible aetiological factors. In addition, information on pain management should be also collected. It would be useful if authors follow proper guidelines or recommendations in the reporting of their studies to increase the quality of publications.

CONCLUSIONS

It is apparent from the available data that pain in head and neck cancer is a significant problem. Even though minimal research has been done regarding pain in cancer survivors of five years or more and the pain of patients dying of cancer, the available data suggest that a significant percentage of patients suffer from pain after completion of treatment. With advanced cancer treatment methods, the numbers of head and neck cancer survivors are increasing but their quality of life would be affected significantly if pain is not properly addressed. Therefore, screening programmes for timely identification of pain in patients with head and neck cancer are necessary. Questionnaires assessing cancer pain can be effective components of such a programme and can provide clinicians with a screening tool for targeting and treating pain at an early point of the treatment period [67].

This review has also shown the need for good-quality epidemiological studies directed at the assessment of head and neck cancer pain and associated factors. Future studies should pay much attention to methodological issues in study conduct and reporting.

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Appendix 1.

Publication Year	First Author	Country	Study design	Gender	Cancer type	Measure time	Treatment	Follow up time	Questionnaire	Pain time period	% with pain	N total	Prevalence (%)	Mean[a]	SD[a]	Pain site	Pain severity
1982	Pittam	UK	ns	M+F	Larynx	Before	na	na	ns	ns	18	44	41	-	-	Ear	ns
1982	Robertson	New Zealand	Retrospective	M+F	Oral Oropharynx Hypopharynx Supraglottis Head and Neck	ns	ns	ns	UWQOL	past week	68 14 6 1 89	117 85 54 52 308	58 16 11 2 29	-	-	ns	ns
1984	Morton	UK	Pilot	M	Head and Neck	After	RT/RT+Sx	within 3 years	10 point scales	current	7	7	15.4	-	-	ns	Moderate to severe
1992	Jones	UK	Retrospective	M+F	Head and Neck	After	Sx	ns	EORTC core quest. + H&N module	ns	-	15	-	0.3 (scale 0 - 3)	-	Operation site	-
1993	Langius	Sweden	Univariate and correlational deceptive	M+F	Oral and Pharynx	Before After	na RT	na 3 weeks	OPSQ	ns	7 8	13 16	54 50	-	-	ns	ns
1997	Hammerlid	Sweden	ns	M+F	Oral and Pharynx	Before and after	RT	na	EORTC H&N-37	past week	15	29	51.7	-	-	Mouth	Quite a bit or very much
1997	Gliklich	USA	Cross sectional	M+F	Head and Neck	Before and after	Sx	na	SF36	past 4 weeks	-	37	-	33.20	32.60	Body	ns
1997	Harrisons	USA	ns	M+F	Tongue	After	SX/RT/CT	ns	MSAS	past week	12	29	43	-	-	ns	ns
1997	Funk	USA	ns	ns	Head and Neck	Before After	na 6 months	na	SF36	past 4 weeks	-	180 109	-	40.62 31.72	26.05 25.56	Body	ns
1997	Deleyiannis	USA	Prospective	M+F	Oropharynx	Before	na	na	UWQOL	past week	9	13	69.23	-	-	ns	ns
1999	Deschler	USA	ns	M+F	Head and Neck	Before	na	na	SF36	past 4 weeks	15	25	60	-	-	Body	ns
1999	Graeff	Netherlands	Prospective	M+F	Oral and Oropharynx	Before After	na Sx/Sx+RT	na 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	75	-	21.60 27.90 14.00 21.20	-	ns	ns
1999	Chaplin	New Zealand	Prospective	M+F	Glottis Oral and Oropharynx Supraglottis and Hypopharynx	Before	na	na	VAS	past 4 weeks		30 27 20		10.00 14.00 20.00		ns	ns
2000	Allison	France	Prospective	M+F	Head and Neck	Before	na	na	EORTC QLQ-C30	past week	-	88	-	25.20	29.10	ns	ns
2001	Mueller	Germany	Cross sectional	M+F	Larynx	After	Sx/RT/Sx+RT	3 months	QLQ-C30 + H&N35	past week	-	124	-	22.00	23.70	Body	ns
2001	Major	USA	Retrospective chart review	M+F	Larynx and Hypopharynx	After	Sx+RT RT+CT	ns	Health status Q-12	past 4 weeks	-	6 15	-	32.00[c]	-	Body	ns
2001	Hammerlid	Norway and Sweden	Prospective	M	Larynx Tongue Oral Floor of mouth Gingival Tonsil Hypopharynx	Before	na	na	EORTC QLQ-C30	past week		86 54 23 27 31 37 28		18.00 26.00 28.00 26.00 28.00 28.00 27.00		ns	ns
2001	Allison	France and Canada	Cross sectional	M+F	Head and Neck	After	Sx/RT/Sx+RT	3 - 6 months	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	91[13] 79[14] 101[15] 91[13] 79[14] 101[15]	-	20.00[c,3] 33.00[c,4] 22.00[c,3] 20.00[c,3] 40.00[c,4] 18.00[c,3]	-	ns Head and Neck	ns
2001	Magne	France	ns	M+F	Head and Neck	After	RT+CT	End of treatment	French H&N cancer QOL	ns	25	29	86	-	-	Head and neck	ns
2001	Smit	Netherlands	Retrospective	M+F	Head and Neck	After	SX/RT/CT	2 - 7 years within 2 months	ns	ns	3 40 22	29 87 87	9 46 25.3	-	-	Head and neck Localized Referred	ns ns ns
2001	Weinstein	USA	Prospective	M+F	Larynx	After	Sx/Sx+RT	ns	SF36 HNQOL	past 4 weeks	-	31	-	13.10 14.90	19.50 18.20	Body ns	ns ns
2002	Pourel	France	Cross sectional	M F	Oropharynx	After	RT/RT+Sx	at least 2 years	EORTC QLQ-C30	past week	-	97 16	-	25.00 35.00	27.00 28.00	ns	ns
2002	Schliephake	Germany	Prospective	M+F	Oral	Before After	na Sx	na 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	45	-	31.10 32.40 24.40 16.70	-	ns	ns
2002	Allison	Canada	Cross sectional	M+F	Head and Neck	After	Sx/RT/Sx+RT	ns	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	78[1] 113[2] 78[1] 113[2]	-	13.30[1] 26.10[2] 18.70[1] 23.70[2]	21.02[1] 30.30[2] 23.67[1] 26.87[2]	ns Head and Neck Head and Neck	ns
2002	Gellrich	Germany, Switzerland and Austria	Follow up	M+F	Oral	After	Sx	at least 6 months 6 - 12 months 6 - 12 months 6 - 12 months 6 - 12 months 6 - 12 months	BUQ	ns	950 40 5 6 9 2	1761 138 138 138 138 138	54 29 3.7 4.3 6.5 1.4	-	-	ns Shoulder Neck TMJ Oral Face	ns
2002	Claus	Belgium	ns	ns	Oral and Oropharynx	After	RT	ns	Common Toxicity Criteria	ns	14	14	100	-	-	ns	Mild to severe
2002	Ahmed	Pakistan	Prospective	M+F	Hypopharynx	Before	na	na	ns	ns	7	30	23	-	-	Throat	ns
2002	Rogers	UK	Cross sectional	M+F	Oral and Oropharynx	After	Sx/Sx+RT	ns	UWQOL	past week	81	140	57.9	-	-	ns	Mild to severe
2003	Schuster	Germany	Cross sectional	M	Larynx	After	Sx	at least 9 months	SF36	past 4 weeks	-	25	-	34.40	24.80	Body	ns
2003	Ribeiro	Brazil	ns	M+F	Oral and Oropharynx	Before	na	na	ns	ns	320	530	60.4	-	-	ns	ns
2003	Tschudi	Switzerland	Retrospective chart review	M+F	Oropharynx	After	Sx+RT Sx RT Sx+RT Sx RT	ns	EORTC QLQ-H&N35 EORTC QLQ-C30	past week		49 31 19 49 31 19		18.7 (Median 8.3) 16.90 (Median 0) 32.5 (Median 25) 25.9 (Median 16.7) 28 (Median 16.7) 32.50 (Median 16.7)	22.1 24.30 30.9 33.2 31.9 34.5	ns	ns
2003	Allal	Switzerland	Retrospective cross sectional	M+F	Oropharynx	After	RT+CT Sx+RT	at least 1 year	EORTC QLQ-C30	past week	-	40 20	-	15.00 22.00	26.00 30.00	ns	ns
2004	Gorsky	Canada	Case series	M+F	Tongue	Before	na	na	ns	ns	66	322	20	-	-	Ear	ns
2004	Derks	Netherlands	Prospective	M+F	Head and Neck	Before After	na na	na na	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	105[1] 78[2] 105[1] 78[2]	-	31.00[c] 28.00[c] 39.00[c] 38.00[c]	-	ns	ns
2004	Connelly	USA	ns	M+F	Oral	Before	na	na	UCSF	past week	14	15	93.3	-	-	Function-related	ns
2004	Van Wilgen	Netherlands	Cross sectional	ns	Head and Neck	After	Sx	at least 1 year	RAND-36	past 4 weeks	-	154	-	19.20	23.00	Body	ns
2004	van Wilgen	Netherlands	ns	M+F	Head and Neck	After	Sx+RT	at least 1 year	VAS	past week	51 57 61	153	33 37 40	-	-	Neck Shoulder Joint	ns
2004	Banal	India	ns	M+F	Head and Neck	Before After	na RT	na 1 month	EORTC QLQ-C30	past week	-	45 44	-	10.17 24.82	9.11 16.03	ns	ns
2004	Rogers	UK	Cohort	M+F	Oral	Before	na	na	UWQOL	past week	107	155	69	29	24.9	ns	ns
2004	Lotempio	USA	ns	M+F	Larynx	After	RT+CT Sx+RT Sx+RT/CT/+RT	Median 6 months Median 40 months Median 27 months	UWQOL	past week	9 12 21	15 34 49	60 35.3 42.9	-	-	ns	Mild to severe
2005	Derks	Netherlands	ns	M+F	Head and Neck	After	na	na	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	98[1] 54[2] 98[1] 54[2]	-	31.00[c] 32.00[c] 38.00[c] 40.00[c]	-	ns	ns
2005	Ethunandan	UK	Retrospective case note analysis	M+F	Head and Neck	After	SX/RT/CT	week preceding death	ns	past week	27	32	84	-	-	ns	ns
2005	Eadie	Canada	ns	M	Larynx	After	Sx+RT	at least 1 year	HNQOL	past 4 weeks	-	30	-	11.46	13.04 (min 0, max 43.75)	ns	ns
2005	Chandu	Australia	Cross sectional pilot trial	M+F	Oral	After	Sx+RT	ns	UWQOL EORTC QLQ-C30	past week	-	22	-	12.50 11.40	20.00 24.30	ns	ns
2007	Kollkythas	USA	ns	M+F	Oral	Before After	na Sx	na ns	UCSF	past week	-	16	-	20.00[c] 49.60[c] 4.00[c] 8.80[c]	3.20[c] 5.60[c] 1.60[c] 4.00[c]	Spontaneous Function-related Spontaneous Function-related	ns
2007	Borggreven	Netherlands	Prospective	M+F	Oral and Oropharynx	Before After Before After	na Sx na Sx	na 1 year na 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	44	-	29.20 12.10 33.00 19.50	28.60 - - -	ns ns	ns
2007	Dilber	Turkey	Prospective	M+F	Larynx	After	Sx+RT	6 months	VRS VRS VAS + VRS VRS VRS VAS + VRS	current	14 3 17 13 4 17	17 17 17 17 17 17	82.4 17.7 100 76.5 23.5 100	- - 30.00 - - 40.00	- - 1.60 - - 1.80	Shoulder at rest Shoulder at rest Shoulder at rest Shoulder function Shoulder function Shoulder function	Mild Moderate Mild to moderate Mild Moderate Mild to moderate
2007	Borggreven	Netherlands	ns	M+F	Oral and Oro-pharynx	Before	na	na	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	32 48 32 48	-	22.4[c] 37.8[c] 27.1[c] 41.5[c]	25.3 31.8 17.6 25.5	ns	ns
2008	Logan	USA	Case-control	M+F	Head and Neck	After	ns	5 years	UCSF	past week	43	100	43	-	-	ns	ns
2008	Zwahlen	Switzerland	ns	M	Oral	After	SX/RT/CT	At least 6 months	EORTC QLQ-H&N35	past week	-	31	-	13.60 (Median 30)	IQR 25.00	ns	ns
2008	Boscolo-Rizzo	Italy	Retrospective cross sectional	M+F	Larynx	After	Sx+RT RT+CT Sx+RT RT+CT	at least 1 year	EORTC QLQ-C30 EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-H&N35	past week	-	39 28 39 28	-	12.40 11.80 6.40 3.30	19.05 5.13 12.10 4.23	ns	ns
2008	Dirix	USA	ns	M+F	Head and Neck	After	SX/RT/CT	At least 6 months	XQ	ns	25	75	33	-	-	Oral	ns
2008	Karvonen-Gutierrez	USA	ns	M+F	Head and Neck	Before/after/ during	SX/RT/CT	na	HNQOL	past 4 weeks	-	491	-	38.0	26.1 (min 0, max 100)	ns	ns
2009	Lundstrom	Sweden	ns	M+F	Larynx	After	Sx+RT	ns	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	43	-	13.60 9.50	24.20 17.60	ns	ns
2009	Brevik	Europe and Israel	Cross sectional	ns	Head and Neck	ns	ns	ns	ns	ns	183	213	86	-	-	ns	ns
2009	Camp	USA	Retrospective chart review	M+F	Tongue	After	Sx	2 years	UWQOL	past week	4	46	9	-	-	ns	Moderate to severe
2009	Jagannathan	India	Cross sectional	M+F	Head and Neck	After	ns	ns	ns	ns	67	80	83.8	-	-	ns	ns
2009	Yoshimura	Japan	Prospective	M+F	Oral	Before After Before After	na RT na RT	na 1 year na 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	20	-	17.00 11.00 14.00 5.00	-	ns	ns
2009	Singer	Germany	ns	M+F	Larynx	After	Sx/Sx+RT	ns	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	323	-	23.60 12.60	28.60 18.60	ns Mouth	ns
2009	Infante-Cossio	Spain	ns	M+F	Oral Oropharynx	Before	na	na	EORTC QLQ-C30	past week	-	72	-	Median 33.3 Median 50	IQR 8.9 IQR 33.3	ns	ns
2009	Boscolo-Rizzo	Italy	Cross sectional	M+F	Oropharynx	After	Sx+RT RT+CT Sx+RT RT+CT	at least 2 years	EORTC QLQ-C30 EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-H&N35	past week	-	26 31 26 31	-	21.80 9.60 9.00 10.70	23.60 13.64 14.28 16.15	ns	ns
2010	Sato	Japan	ns	M+F	Oral	Before	na	na	ns	ns	42 77	113 113	37 68	-	-	Spontaneous Function-related	ns
2010	Yang	China	ns	M+F	Tongue	Before After	na SX/RT/CT	na 3 months 6 months 1 year	UWQOL	past week		231		23.38 19.92 11.47 10.18		ns	ns
2010	Murphy	USA	Survey	M+F	Head and Neck	ns	ns	ns	VHNSS	past week	-	235	-	19.80 (Median 0)	27.20	ns	ns
2010	Maciejewski	Germany	Cross sectional	M	Oral	After	Sx	ns	EORTC QLQ-C30	past week		31[16] 23[17] 27[18] 27[17]		(Median 33) (Median 33) (Median 50) (Median 33)	IQR 33.7 IQR 67.0 IQR 83 IQR 50	ns	ns
2010	Lee	UK	Cross sectional	M F M F	Larynx	After	Sx+RT	at least 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	22 23 22 21	-	12.10 17.50 9.10 8.70	18.70 26.60 11.80 13.30	ns	ns
2010	Chung	South Korea	Historical cohort	ns	Tonsil	After	Sx+RT/CT+ RT	at least 2 years	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	35	-	8.50 9.50	18.60 18.90	ns	ns
2010	Silveira	Portugal	ns	M+F	Head and Neck	Outpatients	ns	ns	EORTC QLQ-C30 EORTC QLQ-H&N35	past week		102		33 25	28 22	ns	ns
2010	Rogers	UK	Cross sectional	M+F	Head and Neck	After	ns	at least 6 months	BCSQ-H&N	past 4 weeks	88	339	26	-	-	ns	ns
2010	Nalbadian	Greece	Cross sectional	M+F	Pharynx	After	SX/RT/CT	ns	EORTC QLQ-C30 EORTC QLQ-H&N35	past week		109		6.27 8.18	14.49 14.61	ns	ns
2010	Huang	Taiwan	Cross sectional	M+F	Head and Neck	After	Sx+RT/CT+ RT/ Sx+RT+ CT	at least 2 years	EORTC QLQ-C30 EORTC QLQ-H&N35	past week		307		23.10 21.30	22.90 22.50	ns	ns
2010	Williams	UK	ns	M+F	Pharynx Tongue	Before/after/ during	SX/RT/CT	na	Brief pain Inventory	past 24 hours	5 3	11 8	45 37.5	-	-	ns	Mild to severe
2011	Horney	UK	Cross sectional	M+F	Pharynx and Tongue Head and Neck	Before	na	na	SF-12v2	ns	8 -	19 103	42.1 -	33.01	31.93	Body	ns
2011	Hamid	Egypt	Prospective	M+F	Larynx	Before During After Before During After During After After During After After During	na Sx+RT Sx RT	na 3 months 6 months na 3 months 6 months na 3 months 6 months Sx+RT Sx RT	EORTC QLQ-C30	past week	-	20	-	29.10 75.00 34.00 20.10 12.50 73.30 16.80 6.80 8.40 62.50 28.00 16.70 67.00[c] 78.0[c] 78.0[c]	15.00 21.00 14.80 13.70 17.80 22.50 9.30 15.00 11.80 20.00 14.20 11.90 -	ns	ns
2011	Bond	USA	Cross sectional (5 studies)	M+F	Head and Neck	During and after	ns	na	VHNSS	past week	-	211	-	26.2 (Median 22.5)	IQR 42.5	ns	ns
2011	Chan	USA	Prospective	M+F	Oral, Larynx and Oropharynx	Before	na	na	UWQOL	past week		77		27.7	27.20	ns	ns
2011	Basconcu-Martinez	Spain	Retrospective	M+F	Oral	Before	na	na	ns	ns	14	30	47	-	-	Function-related	Symptom prompting hospital admission
2011	Danker	Germany	Cross sectional	M+F	Larynx and Hypopharynx	After	Sx/Sx+RT	ns	EORTC QLQ-C30	past week		167[7] 137[8]		23.40 25.80		ns	ns
2011	Guibert	France	Retrospective	M+F	Larynx Hypopharynx	After	Sx+RT conservative Sx+RT conservative Sx+RT conservative Sx+RT conservative	at least 1 year	EORTC QLQ-C30 EORTC QLQ-H&N35 EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	46 17 46 17 24 13 24 13	-	Median 0[c] Median 15[c] Median 0[c] Median 8.00[c] Median 24.00[c] Median 0[c] Median 16.00[c] Median 0[c]	Min 0, Max 65[c] Min 0, Max 100[c] Min 0, Max 34[c] Min 0, Max 75[c] Min 0, Max 65[c] Min 0, Max 32[c] Min 0, Max 75[c] Min 0, Max 50	ns	ns
2011	Korfage	Netherlands	Prospective	M+F	Oral	After	Sx+RT Sx Sx+RT Sx Sx+RT Sx Sx/Sx+RT	1 year 5 years 1 year 5 years 5 years	EORTC QLQ-C30 EORTC QLQ-H&N35	past week	-	9 11 9 11 9 11 9 11 9 11 14[c]	-	13.00 10.60 13.00 9.10 15.70 6.10 19.40 9.10 16.70 8.30	16.20 25.00 22.20 15.60 22.60 9.90 11.80 17.30 18.30 19.30	ns	ns
2011	Lam	USA	Cross sectional	M+F	Oral	Before	ns	na	UCSF	past week	37	44	84	13.00	-	ns	Moderate to severe
2011	Sato	Japan	ns	M+F	Oral	Before	na	na	ns	ns	40 72	109 109	37 66	-	-	Spontaneous Function-related	ns

[a]Unless otherwise specified.
[1]Data obtained from graphs.
[2]Age 45 - 60 years.
[3] > 70 years.
[4]Consuming alcohol.
[5]Consuming no alcohol.
[6]English speaking Canadians.
[7]French speaking Canadians.
[8]French speaking French.
[9]Scale used is not clearly stated.
[10]age < 60 years.
[11]age ≥ 60 years.
[12]Not alcohol dependent.
[13]Alcohol dependent.
[14]With comorbidity.
[15]Without comorbidity.
[16]Males.
[17]Females.

BUQ = Bochum University Questionnaire; OPSQ = Oral and Pharyngeal Symptom Questionnaire; XQ = Xerostomia Questionnaire; MSAS = Memorial Symptom Assessment Scale; na = Not applicable; ns = not specified; Sx = surgery; RT = radiotherapy; CT = chemotherapy.