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REVIEW

Burning mouth in oncology care: a systematic review

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Abstract

Burning mouth, also referred to as oral dysesthesia, is an underreported condition among cancer patients that may represent an early symptom of cancer or an adverse effect of treatment. This review sought to characterize this symptom in oncology care where burning symptoms may occur. A systematic review of the literature was performed based on the PRISMA statement, and the protocol was registered at PROSPERO database. A structured search was done using eight databases. The process of study selection was conducted in two distinct phases. The JBI Critical Appraisal Tools were utilized to evaluate the risk of bias in the studies included. Of the total number of studies assessed, sixteen met the eligibility criteria. Of these studies included, 7 were case reports, 7 cross-sectional studies, and 2 non-randomized clinical trials. Most studies presented low risk of bias ($n=9$), while the remaining studies were evaluated and scored as moderate ($n=5$) or high ($n=2$) risk of bias. Burning mouth was reported as a first symptom of cancer in three studies, and as an adverse event of radiotherapy ($n=2$), chemoradiotherapy ($n=2$), and chemotherapy ($n=9$). Burning mouth was a first symptom in 0.62% of oral squamous cell carcinoma (OSCC), and 3.3% of patients with pain as chief complaint. Oral dysesthesia prevalence was 13.6% in patients experiencing chemotherapy-induced oral adverse events. The symptom of burning mouth should be examined in oncology care, as it may be underreported and therefore undertreated. New therapies may be related to a higher risk of oral burning and studies assessing approach to management are needed. Current management borrows from the current management of burning mouth in the non-cancer setting.

Keywords Burning mouth · Oral dysesthesia · Cancer · Oncology · Systematic review

Introduction

Cancer is a global issue with over 19.3 million emerging cases and nearly 10 million deaths worldwide in the year of 2020 [1]. The global burden of cancer incidence and mortality is escalating at a rapid pace, reflecting a combination of factors, including the aging population, population growth, and shifts in the prevalence and distribution of key cancer risk factors, many of which are linked to socioeconomic development [2, 3]. Also, quality of life parameters have been demonstrated to deteriorate after a cancer diagnosis as it typically induces intense anxiety, a feeling of threat and uncertainty, and may lead to depression [4].

Cancer patients are usually treated by surgery, chemotherapy, radiotherapy, or combinations of these treatments, and may face oral complications during and after treatment [5]. The complications may be acute or chronic. The most common include oral mucositis, dysgeusia, hyposalivation, dysphagia, and osteonecrosis [5]. However, there are other underrecognized signs and symptoms that may affect cancer patients, such as orofacial and oropharyngeal pain [6]. Oral pain can be attributed to the presence of primary, recurrent or metastatic and systemic cancers of the oral cavity or in the head and neck region, as well as due to treatment modalities for cancer [6].

Oral pain is a broad term that include a variety of types of pain that may arise in the oral cavity, including different sites, symptoms, and intensities [7]. Oral dysesthesia is one of the forms of pain which can affect cancer patients and is described as a burning or tingling perception in any areas of the oral cavity or oropharynx (CTCAE v5.0) [8]. Burning

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mouth symptom in oncology care is more often recognized recently probably due to newly developed chemotherapeutic agents, although it is suggested to be underreported [9]. In addition to appearing as an adverse event of cancer treatment, whether radiotherapy or chemotherapy, the symptom of burning mouth has also been described as the first complaint of an undiagnosed cancer [7, 10]. A total of twelve different types of initial pain complaints have been identified among patients diagnosed with oral cancer, and burning mouth represented 3.3% of such pain complaints [7]. Burning pain has also been reported as first symptom of oral squamous cell carcinoma, resembling a burning mouth syndrome [10]. In this sense, somatic symptom disorders should raise suspicion of malignant conditions as well.

Burning mouth syndrome, or burning mouth disorder (BMD), may manifest with symptoms similar to those of chemotherapy-induced oral dysesthesia [11]. BMD is a chronic condition that is defined by the presence of a persistent burning sensation in the oral mucosa, that despite clinical examination, no apparent causative lesions can be identified [12]. BMD in oncology care can manifest even without clinically detected injuries. While the causes of oral dysesthesia and BMD may have an identifiable cause in the therapy provided, the absence of mucosal lesion in the presence of pain suggests that oral dysesthesia and BMD may be similar in presentation and potentially management [13]. Thus, the objective of this systematic review was to evaluate the mouth burning symptoms in oncology care, characterizing this symptom, and examining the therapeutic approaches recommended for management.

Methods

Eligibility criteria

The review question was "Are mouth burning symptoms part of the spectrum of oral events in oncology care?". In order to answer this question, the components of the PICOS framework were utilized to formulate the inclusion criteria for this review: 1) population: cancer patients experiencing burning mouth symptoms; 2) intervention: oncology care (chemotherapy, radiotherapy, transplantation, targeted therapy); 3) comparison: none specific; 4) outcomes: characterization of the burning mouth symptoms in oncology care in terms of symptomatology, time of onset, severity, and management; 5) studies: clinical trials and observational studies.

The following criteria led to the exclusion of studies from the review: 1) no burning mouth symptoms reported; 2) assessment of burning symptoms but not in cancer patients; 3) language restriction; 4) reviews, short communications, protocols, letters to the editor, personal opinions, book chapters, conference abstracts, in vitro or in vivo animal studies; 5) full-text not available for assessment of eligibility and data collection.

Information sources and search strategy

Customized search strategies were implemented in each of the designated databases: PubMed, Scopus, Embase, Web of Science, LILACS, and Cochrane Library. Furthermore, the grey literature was searched using Google Scholar and ProQuest. Additionally, the reference lists of the studies included in the systematic review were thoroughly manually examined to identify any possible additional papers. The searches in all databases were conducted on January 14th, 2023. The complete search strategies for all databases, including the filters applied, are presented on Supplementary Material 1. The studies obtained from all databases were imported into Endnote Web, a reference manager software, which automatically eliminated any duplicated references. The search strategy did not impose any restrictions based on publication date.

Selection process

The process of study selection was carried out in two distinct phases During the initial phase, two reviewers (AGCN and ARSS) independently assessed the titles and abstracts of the retrieved studies and verified their eligibility based on the predefined criteria. The first phase was conducted using Rayyan® software [14], where any remaining duplicate references were manually removed. The studies that appeared to meet all the inclusion criteria proceeded to the second phase of the selection process. In this phase, the same two reviewers independently confirmed the inclusion criteria by assessing full texts of all screened references. The reviewers resolved any disagreements during both phases through discussion and reaching a mutual agreement.

Data collection process and data items

One reviewer (AGCN) gathered data from the included reports, while the other reviewers verified the accuracy of the data. The collection of data from reports was manually performed by reading each included study and extracting relevant data for an Excel spreadsheet. Collected data were defined based on the most relevant information to characterize the publication, the sample, the methods, the results, and the conclusions of each report. For publication characterization we collected the last name of the first author, the publication year, journal name, and the country where the study was conducted, study design, and objective of the research. To characterize the sample, it was collected the sample size, gender, age, cancer diagnosis, cancer site, stage, and cancer treatment. In the methods section, it was collected data

regarding cancer treatment details, in cases of clinical trials, in addition to data regarding quality of life or toxicities assessment. Results included all relevant data according to the outcomes of the review.

Study risk of bias assessment

Two calibrated reviewers (AGCN and ARSS) independently assessed the risk of bias of individual studies using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for Case Reports, Analytical Cross-sectional and Non-randomized experimental studies [15]. Briefly, the assessment of the methodological quality of all included studies was conducted by directed questions according to each study design, to address the risk of bias in its methods, conduction, and analysis. The risk of bias score was calculated by dividing the frequency of "yes" answers by the total number of questions. Studies were categorized as having a high risk of bias when they scored up to 49% "yes," as moderate risk when the score ranged from 50 to 69% "yes," and as a low risk of bias when the score exceeded 69% "yes."

Effect measures

The main outcome of the review was to assess the burning mouth symptoms in oncology care. In this instance, the prevalence of such adverse event among the sample of each included study was defined and presented in the results as proportions.

Synthesis methods

A qualitative analysis was conducted by grouping the studies by etiology of the burning mouth symptom, i.e., whether a first symptom of the cancer or an adverse event of chemotherapy, radiotherapy or chemoradiotherapy. This grouping method allows synthesizing and analyzing which chemotherapy drugs and doses caused this symptomatology, as well as the scheme and dose of radiation.

Results

Study selection

The database search yielded 1,194 references, which were imported into Endnote Web. After automatic removal of 414 duplicates, 780 records remained, and their titles and abstracts were evaluated at Rayyan. In this phase, a total of 748 references were excluded as they did not meet the eligibility criteria, resulting in 32 remaining references that progressed to the second phase of selection process. Five studies could not be retrieved as full texts were not available. Thus, 27 studies were fully read to confirm eligibility criteria, of which 12 were excluded due to not meeting all the inclusion criteria (Supplementary Material 2). The review incorporated 15 studies obtained from the database searches. From grey literature and list of reference of included studies, another 154 reports were screened. Out of these, a total of 137 studies were excluded after reading their titles and abstracts, and the remaining 17 were sought for retrieval. Four studies could not be retrieved, so 13 reports were assessed for eligibility by full text reading. Twelve studies were excluded as they did not meet the eligibility criteria, remaining one study that was included with the other 15 previously selected by database search. Finally, a total of 16 studies were included in the qualitative synthesis, and their data were extracted [7, 10, 13, 16–28]. The study selection process is described in the flow diagram (Fig. 1).

Study characteristics

The included studies were published in English between 1988 and 2022, with most having been published in the last decade ($n = 13$, 81.2%). The studies were performed in the USA [17, 18, 21, 25, 28], Japan [10, 13, 22, 23], Poland [26, 27], Austria [16], Belgium/Lebanon [20], Brazil [7], Greece [24], and Switzerland [19]. Among the 16 included studies, there were seven case reports, seven cross-sectional studies and two non-randomized clinical trials. In the case reports, most reported only one case of oral dysesthesia/oral burning, while one study reported three cases of burning symptom among cancer patients [10]. Cross-sectional studies included 1,362 cancer patients to assess oral dysesthesia as chief complaints before cancer diagnosis or as oral toxicity during/after radiotherapy or chemotherapy. The two clinical trials presented a sample size of 28 patients in conjunction, of which 13 with relapsed or refractory peripheral T-cell lymphoma [18] and 15 diagnosed with breast cancer with brain metastases [16].

The patients evaluated in the included studies presented a variety of diagnoses, including oral squamous cell carcinoma [7, 10, 19, 21], head and neck cancer [20, 22, 25], colon adenocarcinoma [17, 26], breast cancer [16, 23], metastatic renal cell carcinoma [24, 28], lung adenocarcinoma [23, 28], acute myeloid leukemia [27], peripheral T cell lymphoma [18], among others [13, 28].

Risk of bias in studies

The seven case reports were scored as having low ($n = 5$) and moderate ($n = 2$) risk of bias. The most problematic item was regarding identification and description of adverse events (harms) or unanticipated events. Four out of 7 case reports did not clearly report adverse or unanticipated events after management of the burning sensation. Also, two studies did

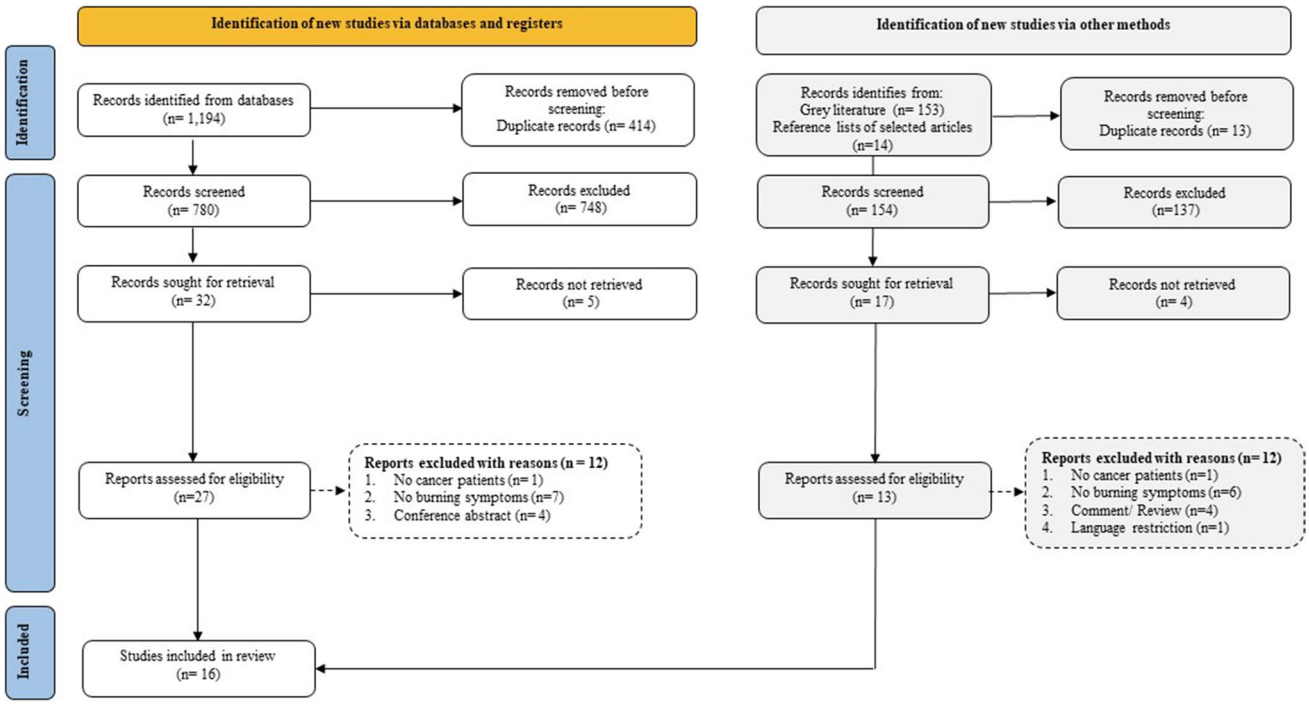

Fig. 1 The flow diagram depicting the process of literature search and selection criteria (adapted from PRISMA 2020 [44])

not clearly describe the post-intervention clinical condition nor presented the patient's history in the form of a timeline.

Among cross-sectional studies, three studies were scored as having low risk of bias, as the other four studies were scored as having moderate ($n=2$) and high ($n=2$) risk of bias. The question concerning statement of strategies to deal with confounding factors was the most negatively scored, since the studies did not clearly state the strategies. Likewise, detailed description of study subjects and study setting, in addition to measurement of the exposure and outcome in a valid and reliable way were also usually missing among cross-sectional studies.

Finally, the two non-randomized experimental studies were scored as having low ($n=1$) and moderate ($n=1$) risk of bias. Both studies were not considered to have included similar participants as different histologies among the same cancer diagnoses were considered for inclusion in the trials. Additionally, none of the clinical trials presented a control group as both were designed as single-arm studies, which also impacted on risk of bias assessment.

Assessment of risk of bias in case reports, cross-sectional and non-randomized experimental studies are summarized in Fig. 2 and detailed in Supplementary Material 3.

Results of individual studies

Among the 16 included studies that evaluated the symptom of burning mouth in oncology care, three described this symptom as the first manifestation of cancer [7, 10, 17]. The other 13 studies reported the burning mouth symptom as an adverse effect of radiotherapy [19, 20], chemoradiotherapy [21, 25] and chemotherapy [13, 16, 18, 22–24, 26–28]. Details of the results of individual studies are presented in Table 1 and summarized in Fig. 3.

Burning mouth as the first symptom of cancer

Cuffari et al. reviewed a large series of oral cancer patients that presented pain as their chief complaint [7]. Among 1,412 reviewed charts, the study found that 271 patients (19.2%) stated pain as their chief complaint, of which 9 presented burning mouth as one of the types of initial pain complaints. Patients reporting this type of pain had tumors located on the palate ($n=2$), tongue/mouth floor ($n=3$), and tongue ($n=4$), and with TNM staging of 3 ($n=5$) and 4 ($n=4$). However, no statistical correlation was found between burning symptom and tumor site or TNM staging. Suga et al. reported three rare cases of OSCC with the first symptom of burning tongue [10]. One of the reported cases was initially treated as Burning Mouth Disorder (BMD), as the symptoms started 8 years earlier, but as the symptom persisted, incisional biopsy of a leukoplakia in the margin of the tongue revealed OSCC. In the other two cases, the burning symptom was present for a shorter period of time, one for 6 months and the other for 1 year. Both cases presented during first examination, an induration on the floor of the

Fig. 2 Summary of risk of bias: the review authors' assessments of each risk of bias item are presented as percentages for (**a**) case reports, (**b**) cross-sectional studies, and (**c**) non-randomized experimental studies

mouth that were promptly assessed by magnetic resonance imaging (MRI) and biopsied. MRI revealed the masses accompanied by enlargement of lymph nodes in one case and bone resorption in the other case. Biopsies confirmed the diagnosis of OSCC [10]. Gallagher et al. also reported a case of oral burning symptom in a previously healthy patient [17]. The patient had complaints of dry mouth and burning tongue, and by intraoral examination, a general pale, vaguely yellowish appearance of the mucosal tissues was revealed. Laboratory results disclosed iron deficiency anemia and soon after, the patient evolved with lower abdominal pain that revealed a colon adenocarcinoma [17].

Table 1 Summary of results of individual studies ($n = 16$)

References	Study Design	Cancer Diagnosis	Sample Size	Oral Burning Cases	Cancer Treatment	Results
Cancer first symptom						
Cuffari et al., 2006 [7]	Cross-sectional	OSCC	271	9	NR	271 of 1440 patients (19.2%) presented pain as chief complaint of OSCC. Burning mouth was reported as first symptom in 9 patients (3.3%) with OSCC lesions in the palate ($n = 2$), in the tongue/mouth of floor ($n = 3$), and in the tongue ($n = 4$). Burning mouth symptom were present only in advanced tumors TNM 3 ($n = 5$) and TNM 4 ($n = 4$). The results suggest the need to include oral cancer in the differential diagnosis of BMD
Gallagher et al., 1988 [17]	Case Report	Colon cancer	1	1	Surgery	The patient's chief complaints were dry mouth and burning tongue. Adequately maintained dentition, slight-to-moderate xerostomia and a smooth tongue with slight atrophy of the anterior papillae. Mucosal tissues were generalized pale and slightly yellowish. Oral signs and symptoms were suggestive of xerostomia and glossodynia, secondary to medication (diazepam for 1 month), hormonal imbalance, or anemia. A diagnosis of iron deficiency anemia was made. Shortly thereafter, the patient felt lower abdominal pain and a colonoscopy disclosed a colon adenocarcinoma
Suga et al., 2021 [10]	Case Report	OSCC	3	3	1. Surgery 2. Radio-chemotherapy 3. No treatment (patient refusal)	Case 1: burning and allodynia-like pain on the left lingual margin, worsened by talking and eating, started 8 years previously, and its severity fluctuated daily. Leukoplakia on the left lateral border of the tongue was found. Diagnosed with BMD and treated with amitriptyline, 5 mg/day. After 2 weeks, the symptom of burning pain improved while allodynia-like pain remained. The burning pain recurred inducing loss of appetite. Incisional biopsy from the white lesion yielded a diagnosis of OSCC Case 2: burning sensation and paralysis on the right side of the tongue for over 6 months. Complaining of taste disturbance and dysphasia. Tongue with decreased mobility and sensory loss. An induration in the right side of the floor of the mouth was detected. The biopsy confirmed a carcinoma in the right sublingual region Case 3: burning sensation on the tip of the tongue for almost 1 year. Four months earlier diagnosed with stomach cancer. During examination, an induration was found under the midfloor of the mouth. A biopsy confirmed the diagnosis of OSCC
Radiotherapy Adverse Event						
El Mobadder et al., 2019 [20]	Case Report	HNC	1	1	Radiotherapy	The patient underwent intensified HNC RT and presented a chief complaint of complete loss of taste function and sensation of mouth burning. The diagnosis was a taste alteration due to direct neurological toxicity of the taste buds cells. For the management of burning mouth sensation, it was used a diode laser 635 nm with an energy density of 3 J/cm^2. A significant improvement of taste perception and a significant decrease in the burning mouth sensation was noticed after 10 sessions of PBMT (VAS scale went from 7 to 0)
Lübbers et al., 2014 [19]	Case Report	OSCC	1	1	Radiotherapy	The patient had experienced dry mouth since he had undergone RT 14 years earlier. The chief complaint was pain when eating spicy food or when consuming hot or acidic fluids. He described his pain as a burning sensation throughout the oral cavity that was not triggered by consumption of mild foods or cold drinks. The oral mucosa appeared pink, slightly atrophic and dry, with no signs of candidiasis. Postradiation xerostomia was diagnosed

Table 1 (continued)

References	Study Design	Cancer Diagnosis	Sample Size	Oral Burning Cases	Cancer Treatment	Results
Chemoradiotherapy Adverse Event						
Oberoi-Jassal et al., 2018 [21]	Case Report	OSCC	1	1	Hemiglossectomy, neck lymph node dissection, and adjuvant chemoradiation	The patient described a severe (9 out of 10 on pain scale) continuously painful "fire" sensation of the anterior tongue and burning tingling, and numbness of the base of the tongue. Pain was modestly improved with opioids and exacerbated with oral intake. Other symptoms included dysgeusia, xerostomia, and metallic taste. Treatment with Gabapentin, transdermal fentanyl and liquid oxycodone did not improve symptoms. Dose of Gabapentin was increased and a-lipoic acid was added, as well as rinse with clonazepam. Improvement of tongue pain to 7 out of 10 on the pain scale was reported. Methadone was added to the regimen, and fentanyl and gabapentin were reduced. Over the following months, the patient reported ongoing improved pain control and functionality
Sharp et al., 2008 [25]	Cross-sectional	HNC	9	6	CT: Gefitinib and Paclitaxel RT: External beam RT (66.6 to 72 Gy)	Six of the 9 patients (67%) developed grade 3 "burning" quality generalized oral dysesthesia. The dysesthesia was exacerbated by the ingestion of neutral pH liquids such as water. Patients with dysesthesia also developed some dysarthria. These 6 patients received at least 50 Gy (range 50–70 Gy) to the oral tongue whereas the other 3 patients received less than 50 Gy. Oral dysesthesia began in the second week of radiation treatment, preceding the development of mucositis by 7 to 10 days. Dysesthesia did resolve in all patients by the 3- to 6-month follow-up. Two patients were empirically treated with gabapentin (Neurontin) for their painful mucosal dysesthesia and both patients had near resolution of the symptoms
Chemotherapy Adverse Event						
Bartsch et al., 2022 [16]	Clinical Trial (Phase II)	Breast cancer with brain metastases	15	1	Trastuzumab deruxtecan	All 15 patients experienced at least one adverse event (AE) (100%). Most AEs were mild and moderate. Grade 1 oral dysesthesia was observed in one patient (6.7%) and Grade 1 dysgeusia was observed in one patient (6.7%)
Hino et al., 2021 [13]	Cross-sectional	Peritoneal = 1 Lymphoma = 3 Pancreatic = 1 Rectal = 1 Ovarian = 1 Colorectal = 3 Gastric = 2 Leukemia = 1	180	13	Cytarabine, Carboplatin, Cyclophosphamide, Irinotecan, Docetaxel, Doxorubicin, Fluorouracil, Oxaliplatin, Prednisolone, Paclitaxel, Tegafur / Gimeracil/ Oteracil, Vincristine	All cases of oral dysesthesia were mild according to the CTCAE (v5.0). The most common symptom of oral dysesthesia was tingling of the tongue (8/13) (61.5%, $p = 0.5000$). One patient presented tingling of the lips, 3 patients presented hyperesthesia of entire oral mucosa and 1 patient hyperesthesia of the tongue apex. 12 cases had concomitant peripheral neuropathy (PN) (92.3%) and 9 cases had dysgeusia (69.2%). The onset of oral dysesthesia was at the same time of peripheral neuropathy in 4 cases (30.8%) and after PN in 8 cases (61.6%). Symptoms of oral dysesthesia continued after CT in 9 of 15 cases with the continuation of PN and/ or dysgeusia (66.7%) ($p = 0.1509$) and persisted > 6 months in 4 cases (30.8%)
Krishnan et al., 2022 [18]	Clinical Trial (Phase I)	Relapsed or refractory PTCL	13	2	Carfilzomib	Oral dysesthesia was observed in 2 patients (16%), grades 1 to 2. No grades 3 to 4 oral dysesthesia were observed. Overall, the drug was well tolerated; most of observed toxicities were manageable with supportive strategies and dose reduction
Okamoto et al., 2022 [22]	Cross-sectional	HNC	9	1	Photoimmunotherapy (PIT), using cetuximab sarotalocan sodium with a laser system	No significant decrease or improvement in any of the QOL endpoints with HN-PIT. The responses to treatment were as follows: complete response (two patients), partial response (six patients), and stable disease (one patient). Oral dysesthesia occurred in one patient (11%)

Table 1 (continued)

References	Study Design	Cancer Diagnosis	Sample Size	Oral Burning Cases	Cancer Treatment	Results
Otsu et al., 2022 [23]	Case Report	Lung and Breast cancer	1	1	Entrectinib	Five days after entrectinib administration, the patient developed oral dysesthesia (grade 1 according to CTCAE v5.0), and her blood creatinine increased (grade 2). These findings gradually worsened, and entrectinib was temporarily discontinued. 14 days later the symptoms improved, and treatment with entrectinib was continued at a reduced dose. 19 days later, the patient presented heart failure. Entrectinib was again interrupted, and the cardiac function restored in about one week after
Papadopoulou et al., 2022 [24]	Case Report	Metastatic Renal Cell Carcinoma	1	1	Pazopanib	Patient with a chief complaint of oral bleeding and burning mouth sensation 5 months after starting CT with pazopanib. Clinically, local spontaneous gingival bleeding on the right anterior maxilla, and enlarged and erythematous gingiva associated with poor oral hygiene. The patient also reported xerostomia. Pazopanib administration was interrupted. Oral hygiene instructions were delivered, including rinses with chlorhexidine 0.2% and warm chamomile mouthwash. Within one week, the patient reported regression of the bleeding and the burning sensation
Szmidt et al., 2015 [26]	Cross-sectional	Colon cancer	66	9	Adjuvant chemotherapy with leucovorin and 5-FU	14% of patients complained of either burning sensation in the mouth or stomatalgia. Among female patients, 16% ($n=4$) complained of burning sensation in the mouth, whereas 12% of male patients ($n=5$) presented this symptom ($p=0.662$). Regarding the number of CT cycles there was also not difference in terms of burning mouth sensation
Wysocka-Słowik et al., 2021 [27]	Cross-sectional	Acute myeloid leukemia	80	25	Allogeneic hematopoietic cell transplantation preceded by myeloablation therapy (MAC) or reduced-intensity therapy (RIC)	The burning sensation of the oral mucosa was reported by 25 (31%) patients during the 1st examination and by 29 (36%) during the 2nd examination. Prior to transplantation, this complaint occurred in 7 (9%) patients, including 4 (7%) in the MAC group and 3 (12%) in the RIC group. In the 1st week after transplantation, the burning sensation was reported by 20 (37%) patients in the MAC group and 5 (19%) in the RIC group. During the 2nd examination, the incidence of burning sensation increased to 46% (25 patients) in the MAC group, while in the RIC group, it decreased to 15% (4 patients) ($p=0.0068$)
Yuan et al., 2015 [28]	Cross-sectional	Metastatic renal cell carcinoma = 98 Gastrointestinal = 112 Lung = 159 Other = 378	747	99	Sorafenib = 172 Sunitinib = 161 Bevacizumab = 159 Imatinib = 144 Pazopanib = 132 Cabozantinib = 23 Regorafenib = 15	The two most frequent adverse events were mucosal sensitivity/pain and dysgeusia/hypoguesia. Concurrent mucosal sensitivity and dysgeusia were reported in 24% of cases, most frequently associated with sunitinib. Approximately 40% of patients experiencing mucosal sensitivity/pain received intervention for AE management, including magic mouthwash (diphenhydramine/ lidocaine/ MaaloxTM swish and spit; 26% of cases), clonazepam solution (0.1 mg/mL swish and spit; 21% of cases), and over-the-counter palliative rinses (Biotene, salt water, and/or baking soda; 15% of cases)

AE adverse events; *CT* chemotherapy; *CTCAE* Common Terminology Criteria for Adverse Events; *HNC* head and neck cancer; *NR* not reported; *OSCC* oral squamous cell carcinoma; *PBMT* photobiomodulation therapy; *PTCL* peripheral T cell Lymphoma; *QOL* quality of Life; *RT* radiotherapy

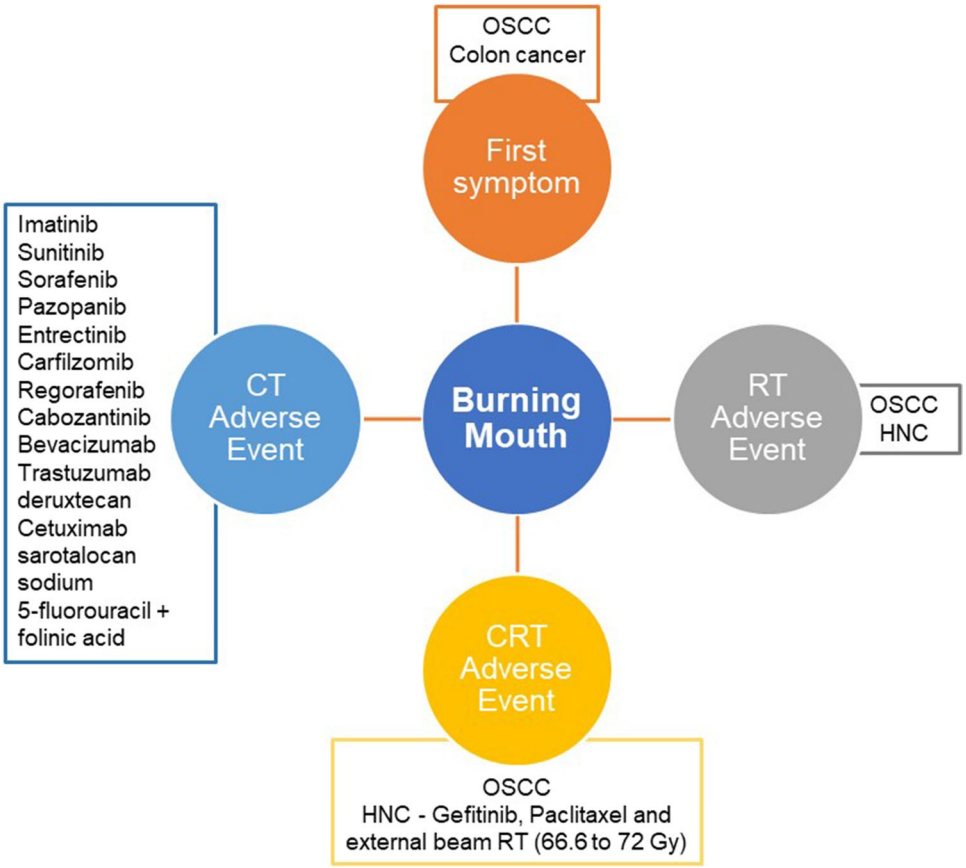

Fig. 3 Summary of findings regarding burning mouth as cancer first symptom, or as adverse event of radiotherapy, chemoradiotherapy, and chemotherapy

Burning mouth as adverse event of radiotherapy

El Mobadder et al. reported a case of a patient who had undergone head and neck radiotherapy (RT) and presented a chief complaint of complete taste loss and a sensation of burning in the mouth, possibly due to direct neurological toxicity [20]. A 635-nm diode laser was utilized for the management of the taste alteration and burning mouth sensation, with an energy density of 3 J/cm^2, as proposed elsewhere [29]. There was significant improvement in taste perception, accompanied by a notable decrease in the sensation of burning in the mouth after 10 sessions of PBMT, suggesting potential utility in the management of these symptoms. Lübbers et al. also reported a case of a patient who had experienced dry mouth following RT as primary treatment for OSCC 14 years earlier and presented a burning sensation throughout the oral cavity [19]. The patient complained of pain when consuming spicy food, hot liquids, or acidic fluids but the burning sensation did not occur when consuming mild foods or cold beverages. Clinically, the oral mucosa exhibited a pink, somewhat atrophic, and dry appearance, with no indications of candidiasis, and post-radiation xerostomia was diagnosed [19].

Burning mouth as adverse event of chemoradiotherapy

Oberoi-Jassal et al. presented a case of a patient with a history of recurrent OSCC treated by hemiglossectomy, lymph node neck dissection and adjuvant chemoradiation [21]. The patient presented uncontrolled severe pain (9 of 10 on visual pain scale), described as a persistent painful "fire" sensation on the anterior tongue, accompanied by a burning, tingling, and numbness sensation at the base of the tongue. The management consisted of gabapentin, transdermal fentanyl and liquid oxycodone. As severe pain persisted, the dose of gabapentin was increased, a-lipoic acid and clonazepam were added. With this, the patient reported improvement of tongue pain and function. Sharp et al. also reported the occurrence of burning tongue pain, referred as oral dysesthesia, in locally advanced head and neck cancer patients treated by oral gefitinib combined with paclitaxel and radiotherapy [25]. Among 9 treated patients, six (67%) developed grade 3 "burning" quality generalized oral dysesthesia, beginning in the second week of radiotherapy. It was noticed that oral dysesthesia occurred 7 to 10 days prior to the development of mucositis, persisted after resolution of the mucositis, and resolved during the follow-up of 3- to 6-months. Gabapentin was administered to two patients to

manage their painful mucosal dysesthesia, that resulted in near resolution of the symptoms [25].

Burning mouth as adverse event of chemotherapy

Two studies reported cases of burning sensation after treatment with entrectinib and pazopanib, which are targeted therapies for metastatic lung adenocarcinoma and metastatic renal cell carcinoma, respectively [23, 24]. Otsu et al. reported a case of entrectinib-induced heart failure that was preceded by grade 1 oral dysesthesia occurring 5 days after the administration of the medication, and that was resolved by discontinuation of the therapy. Papadopoulou et al. presented a case of a patient with oral bleeding and burning mouth sensation after 5 months under chemotherapy with pazopanib [24]. The medication administration was interrupted, and oral hygiene instructions were delivered, as well as prescription of chlorhexidine 0.2% and warm chamomile mouthwash. Amelioration of the oral symptoms were observed within 2 weeks.

Yuan et al. also reported oral adverse events observed in patients treated by target-specific anti-neoplastic agents such as sunitinib, regorafenib, pazopanib, sorafenib, imatinib, cabozantinib, and bevacizumab [28]. Among 747 patients, 99 patients experienced mucosal sensitivity/pain (13.2%), which was largely associated with sorafenib and sunitinib, with median times to adverse event of 1.4 and 1.1 months, respectively. There was a significant difference in the median duration of mucosal sensitivity among the agents, ranging from 0.4 to 2.8 months ($p = 0.019$). Another drug associated with oral dysesthesia was the carfilzomib, which was tested in a phase 1 trial in relapsed or refractory peripheral T cell lymphoma (PTCL) patients [18]. In total, 30 adverse events of grade ≥ 3 were observed and among thirteen included patients, two patients (16%) presented grades 1–2 oral dysesthesia [18].

The phase 2 clinical trial performed by Bartsch et al. aimed to assess efficacy and safety of trastuzumab deruxtecan, a HER2-directed monoclonal antibody, in HER2-positive breast cancer with brain metastases [16]. Fifteen patients were included in the trial and all patients experienced at least one adverse event (100%), of which most were mild or moderate. Oral dysesthesia was reported in one patient (6.7%), as well as dysgeusia (6.7%) [16]. Another monoclonal antibody associated with oral dysesthesia was the cetuximab sarotalocan sodium, which was used in a combination with a laser system to treat unresectable locally advanced or locally recurrent head and neck carcinoma [22]. In the study by Okamoto et al., nine patients were treated with this drug and one patient (11%) presented grade 1 oral dysesthesia [22].

Two cross-sectional studies aimed to identify the prevailing oral complaints among patients undergoing chemotherapy for colon cancer and conditioning for acute myeloid leukemia after allogeneic hematopoietic cell transplantation [26, 27]. Szmidt et al. assessed 66 colon cancer patients receiving 5-fluorouracil and folinic acid (leucovorin) and found that only 14% of patients ($n = 9$) complained of either burning sensation in the mouth [26]. No significant difference was observed among male and female patients, as well as according to the number of cycles of chemotherapy [26]. Wysocka-Słowik et al. compared two conditioning protocols in allogeneic hematopoietic cell transplantation for acute myeloid leukemia patients: myeloablation therapy (MAC) and reduced-intensity therapy (RIC) [27]. In the MAC group, burning sensation progressively increased from preliminary examination preceding transplantation ($n = 4$; 7%), to first ($n = 20$; 37%) and second ($n = 25$; 46%) examinations after transplantation [27]. In the RIC group burning sensation was present in 3 patients (12%) before transplantation, increased after first examination ($n = 5$, 19%) and then decreased after second examination ($n = 4$, 15%) [27].

Finally, Hino et al. found among 180 patients who were referred due to oral adverse events associated with cancer chemotherapy, 13 cases of oral dysesthesia [13]. Two cases showed both oral dysesthesia and toothache. The symptoms were referred as tingling of the tongue apex ($n = 8$), hypesthesia of the entire oral mucosa ($n = 3$), hypesthesia of the tongue apex ($n = 1$) and tingling of the lips ($n = 1$) [13].

Results of synthesis

Among the clinical trials which assessed safety of different chemotherapeutic agents, the proportion of patients experiencing oral dysesthesia ranged from 6.7 [16] to 16% [18], with a mean prevalence of 11.1%. For cross-sectional studies, burning mouth was a first symptom in OSCC patients in 0.62% of cases, and amongst patients with pain as chief complaint, burning mouth corresponded to 3.3% of the cases [7]. As a chemoradiotherapy adverse event, oral burning was reported in 6 of 9 (67%) HNC patients treated by a combination of paclitaxel, gefitinib, and external beam radiation therapy [25]. Finally, as a chemotherapy adverse event, oral dysesthesia prevalence ranged from 7.2 to 31.25%, with a mean prevalence of 13.6% in patients experiencing chemotherapy-induced oral adverse events [13, 26–28].

Discussion

Burning mouth symptoms have been explored and reported in cases of burning mouth disorder. Patients suffering from this disorder experience an intraoral burning defined as recurring daily for at least 2 h per day over 3 months, with no evidence of causative lesions during clinical examination [12]. Differently, in the oncological context, the patients

present causative lesions that may be due to the OSCC itself or more commonly as an adverse event of therapeutic strategies. In both situations, cancer patients do not fit the diagnostic criteria for BMD, especially when the symptom appears associated with the diagnosis of malignant disease or when oral burning occurs during treatment and with mucosal lesions or infections. In any case, there are similarities between the two conditions regarding the main symptom, the burning sensation. In oncology practice, there are adverse effects that are well known and have a range of guidelines for prevention and treatment. Burning mouth in cancer patients, in turn, is a symptom rarely reported, likely under-reported and little discussed and likely represents small fiber neuropathy. Thus, this systematic review sought to compile the literature, in order to understand the main oncological treatments associated with this symptom, possible preventive and therapeutic methods, in addition to exploring this symptom as the chief complaint prior to diagnosis.

As stated, the causes of burning symptom in oncology care and BMD are different, but the mechanical process of both entities may be closely associated. Different hypotheses have been developed to explain the etiology of BMD [30]. There is growing evidence that BMD is a neuropathic pain condition, supported by studies demonstrating peripheral small fiber damage or signs of decreased inhibition within the central nervous system [31]. Burning mouth symptoms in oncology care may share similar abnormalities caused by the tumor, by the radiation or by the chemotherapeutic and/or targeted agent. The oral mucosa, particularly the tongue, appears to be a site highly sensitive to neurological stimuli, characterized by a reduced count of small diameter nerve fibers. The remaining fibers demonstrate an upregulation of the transient receptor potential subfamily member V1 (TRPV1) ion channel, as well as an upregulation of P2X3 receptors and nerve growth factor (NGF) [32].

Oral squamous cell carcinoma presenting as first symptom of burning tongue has been reported, raising the concern regarding malignant lesions that may mimic somatic symptom disorder such as BMD [10]. OSCC lesions may appear as exophytic or endophytic growths, with the endophytic OSCC usually accompanied by spontaneous pain before treatment, which can rarely resemble a typical burning pain of BMD without any apparent clinical evidence [10, 33]. A retrospective study found that almost 20% of OSCC patients stated pain as chief complaint at the time of initial presentation prior to the treatment of oral cancer [7]. Interestingly, among these patients indicating pain as chief complaint, the burning mouth was among the twelve types of reported pains, comprising 3.3% of the cases [7]. In this sense, although likely rare, oral cancer should be included in the differential diagnosis of BMD, with a thorough head and neck examination, investigation of the medical history, and appropriate imaging techniques, including computed tomography and MRI, especially when endophytic OSCC is suspected on palpation [7, 10].

Besides oral cancer, burning mouth symptom should also raise the concern regarding other malignancies, such as gastrointestinal malignancy [17]. Gallagher et al. reported a rare case of colon adenocarcinoma in a patient presenting as chief complaint dry mouth and burning tongue [17]. At first, it was suspected that the xerostomia and burning symptom were due to the use of diazepam prescribed one month earlier. However, the pale oral mucosa led to the investigation and diagnosis of iron deficiency anemia that was closely followed by abdominal pain. A colonoscopy revealed a mass in the ascending colon grossly consistent with adenocarcinoma [17]. As burning sensation is among the oral manifestations of iron deficiency anemia, it can be hypothesized that in this case the anemia was caused by the colon tumor, and the mouth burning sensation was probably a symptom associated with anemia [34, 35]. Glossodynia has also been reported as initial symptom of metastatic gastric adenocarcinoma, although the nature of the pain has not been described as burning sensation [36].

It is well-known that cancer patients commonly experience oral complications related to treatment of the primary disease, mainly mucositis, hyposalivation, and dysgeusia [5, 37]. Less frequently reported, the burning mouth symptom seems to be an unusual or underreported symptom among patients submitted to cancer therapy [37]. El Mobadder et al. reported a case of a HNC patient submitted to intensified radiotherapy that presented ageusia and sensation of mouth burning [20]. The symptoms were managed by photobiomodulation and after 10 sessions, a notable reduction in the sensation of burning mouth was observed [20]. Photobiomodulation has been proven to be effective in reducing pain and improving the quality of life in patients with BMD, thus, its use in oncology care seems a promising strategy to manage the burning symptoms [38, 39].

Gabapentin is a strategy used for pain relief in BMD patients, that may be combined alpha-lipoic acid, that has also been used in the management of burning symptoms in oncology care [21, 25, 40, 41]. Oberoi-Jassal et al. reported a case of a OSCC patient who experienced a severe constantly painful burning sensation of the tongue after adjuvant chemoradiation and was managed with a combination of medications, including gabapentin [21]. Gabapentin dose in this case was 1,200 mg three times a day, associated with twice-daily 300 mg of alpha-lipoic acid, and 1mg clonazepam to be retained orally and subsequently expectorated three times a day [21]. With this regimen the patient reported improved pain control [21]. Similarly, Sharp et al. described treatment of oral dysesthesia with gabapentin in locally advanced HNC patients treated by concurrent chemoradiation therapy [25]. Among the nine assessed patients,

6 presented oral dysesthesia, of which 2 of them received empirical treatment with gabapentin for their painful oral mucosa dysesthesia [25]. The patients receiving gabapentin experienced considerable resolution of the oral dysesthesia, demonstrating that this treatment, that may be used in BMD patients, seems to be promising in controlling oral burning in patients undergoing chemoradiotherapy.

Significant advances in understanding the mechanisms of oncogenesis have resulted in the emergence of numerous targeted therapies and immune checkpoint inhibitors (ICI) for anti-neoplastic treatment in the last years [9, 28]. Oral toxicities induced by these novel therapies are not uncommon and frequently exhibit very characteristic features, although limited attention have been given in clinical trials [9]. Oral dysesthesia has been reported in patients treated by agents targeting the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), such as cetuximab and trastuzumab, respectively [16, 22]. The sample size of both studies was small, and the symptom of oral dysesthesia was only mentioned among countless other adverse effects, but with prevalence varying between 6.7% and 11%, which already draws attention to this symptom associated with these treatments [16, 22]. A records review has also observed that 24% of patients receiving ICI were identified with oral neuropathy [42].

Angiogenesis inhibitors is a category of targeted therapies distinguished by their inhibitory impact on tumor neoangiogenesis [9]. Papadopoulou et al. reported a case of burning

Table 2 Summary of potential approaches for management of burning mouth in oncology care*

Approaches	Dose	Evidence	References
Photobiomodulation			
Low-level laser 630—685 nm	2–3 J/cm2, 10–58 s, 30–100 mW, continuous and contact mode, applied at: tongue dorsum (10 points), lateral tongue (4 points), buccal mucosa (8 points), labial mucosa (5 points), hard palate (8 points), soft palate (3 points), and 3 points by sextant on the gingiva	Red laser protocols resulted in improvement in pain and in quality of life – SR Burning sensation severity and quality of significantly different from placebo ($p=0.004$)—RCT	[20, 38, 45, 46]
Neurologically active medications			
Topical Clonazepam	0.5 – 1 mg, 1-3x/day to retain orally for 3 min and then expectorate	Decrease in pain scores compared to placebo group ($p=0.014$) – 2 RCT and Cochrane SR	[47–49]
Systemic Clonazepam	0.5 mg daily	Significantly improvement in pain ratings ($p<.001$)—RCT and Cochrane SR	[48, 50]
Gabapentin	300 mg daily	OR of presenting positive changes (or total resolution) 5.7 × higher than placebo ($p<0.001$); best results when combined with ALA – RCT and SR	[40, 41]
Pregabalin	50–150 mg daily	Significant decrease in mean VAS score ($p<0.001$) – RCT and SR	[45, 51]
Amitriptyline	10–50 mg daily (increase dosage by 10 mg every 4 to 7 d until oral burning is relieved)	RCT with high risk of bias and low quality of evidence Significant reduction in the mean VNS pain score ($p=0.007$)—Retrospective Cohort and Review	[52–54]
Duloxetine	20 mg once daily to a maximum of 40 mg once daily (gradual increase can be done 2 weeks or more after initiation)	Significant decrease on VAS ($p<0.01$)—NRCT	[55]
Supplements			
Alpha-lipoic acid (ALA)	400–600 mg daily	Improvement in the pain score but not significant—SR of RCTs Significant improvement in symptomatology compared to placebo ($p=0.009$)—RCT	[41, 56–58]
n-acetyl cysteine (NAC)	400–1200 mg daily	60% positive response rate but more effective when combined with Clonazepam – NRCT Ameliorate the inflammatory and pain status—Review	[59, 60]

*Based on BMD management

OR odds ratio; *NRCT* non-randomized clinical trial; *RCT* randomized clinical trial; *SR* systematic review; *VAS* Visual Analog Scale; *VNS* Verbal Numerical Scale

mouth sensation in a patient treated by pazopanib, an angiogenesis inhibitor, due to a metastatic renal cell carcinoma [24]. The medication was interrupted for two weeks and resumed after the patient reported complete regression of the symptom [24]. The study by Yuan et al. further explored the prevalence and clinical characteristics of oral adverse events among cancer patients receiving angiogenesis inhibitor [28]. Among the reported oral adverse events, oral dysesthesia was the most commonly observed, affecting 12% of patients, often without accompanying clinical findings and largely associated with sunitinib and sorafenib [28]. Prospective studies should be performed to better characterize effective management strategies for oral dysesthesia, with the ultimate purpose of preventing dose reductions or interruption of antiangiogenic agents as reported. Potential approaches to management are summarized in Table 2.

It is important to acknowledge limitations of the current systematic review. First, most included studies cited burning mouth/oral dysesthesia as an adverse event but did not further explore the symptom in terms of severity, location, time of onset and duration, revealing that there is still a lack of a more accurate evaluation of this symptom. Furthermore, the heterogeneity of the studies regarding study design, tumor diagnosis, and oncological treatment precluded a quantitative analysis by means of a meta-analysis. Hence, studies with larger sample size specifically exploring the symptom of burning mouth should be carried out, especially in patients undergoing treatment with anti-neoplastic targeted therapies and immune checkpoint inhibitors.

To the best of our knowledge, this study is the first review of oral burning sensation in oncology care. The symptom may represent the chief complaint of an incipient tumor; therefore, it should be among the diagnostic hypotheses of psychosomatic disorders such as the burning mouth disorder. Oral burning sensation represents an important adverse effect of oncological therapies, especially targeted therapies and immune check point inhibition, and may be a factor leading to treatment interruption and impact quality of life. We believe that the symptom is underreported and therefore undertreated. With changes in oncology care, multiple chemotherapeutics and development and increasing use of targeted chemotherapeutics and immune check point inhibitors as induction, active and potentially ongoing/maintenance therapy, oral burning in cancer therapy may increase in presentation and impact patient quality of life. Therefore, preventive and therapeutic strategies must be pursued. Current management is directed by approach to management of burning mouth in non-cancer patients. Continuing study of this symptom, impact upon quality of life, and directed approach to management is needed.

Other information

Registration and protocol

The present systematic review was planned preceding its commencement and the protocol derived from PRISMA-P [43] was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the registration number CRD42022303546. Furthermore, this systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [44].

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Author contributions A.G.C.N. and A.R.S.S. did the data curation and formal analysis. A.G.C.N. wrote the original draft and A.R.S.S and J.B.E. reviewed and edited the manuscript. J.B.E. performed the conceptualization of the study, as well as administred the project.

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Declarations

Ethics approval This study represents a systematic review of the literature. The Research Ethics Committee from Piracicaba Dental School, University of Campinas, Brazil, has confirmed that ethical approval is unnecessary for this investigation.

Consent to participate As this study is a systematic review of the literature, it did not involve the inclusion of human subjects. Consequently, the absence of informed consent from patients for study participation is justified.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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